University Hospitals Case Medical Center
Department of Anesthesiology
Division of Pain Medicine
Short Study title: ***"Determining the Prognostic Value of Continuous intrathecal infusion prognostic infusion test"***

Protocol Title:
"A randomized double blind cross-over trial of continuous intrathecal infusion for assessing patients with chronic non-cancer pain who would benefit from treatment with intrathecal drug delivery system (IDDS) implant"

ABSTRACT

2.1 Purpose:
The purpose of this study will be to determine the efficacy and the prognostic value of a continuous intrathecal prognostic infusion test in an in-hospital setting for selecting patients who would have better long term outcomes for treatment with intrathecal implantable devices. We will compare the primary outcomes [changes in pain intensity score (NRS), patient global impression of change (PGIC)] before and after intrathecal infusion of an admixture of bupivacaine and fentanyl versus normal saline.

2.2 Research Design:
Randomized, double blind placebo controlled cross over study

2.3 Methodology /Technical Approach:
The study will include 36 patients with intractable chronic low back pain in the setting of lumbar post-laminectomy syndrome or vertebral compression fracture who failed conservative management and are considered candidates for IDDS.

As per usual clinical care prior to the implant, the patients will undergo an intrathecal prognostic infusion test with an externalized catheter. An intrathecal catheter will be placed in the outpatient procedure suite and intrathecal infusion will be started using an external pump once patient is in the PACU. The research component is to perform the intrathecal test with saline (inactive placebo solution) in addition to a test with fentanyl and bupivacaine (active solution). Patients will be randomly assigned to two groups:

Group I will be trialed with continuous infusion of intrathecal bupivacaine 0.625 mg/ml and fentanyl 1 mcg/ml at a rate of 0.5-1.0 ml/hr for approximately 14-18 hours followed by a washout period of 4-6 hours, before resuming intrathecal infusion for testing with continuous normal saline for another 14-18 hours.

Group II will be trialed with intrathecal normal saline for approximately 14-18 hours followed by a washout period of 4-6 hours, before resuming intrathecal infusion with a solution of bupivacaine 0.625 mg/ml and fentanyl 1 mcg/ml for another 14-18 hours.

Baseline numerical rating scale pain scores (NRS; an 11-point pain scale whereby 0 signifies no pain and 10 the worse pain ever) will be assessed and documented on all patients upon admission to the preoperative area. Intrathecal catheters will be placed in the

operating room as per usual clinical care at the appropriate level for target dermatomes. The needle entry point will occur in the upper lumbar spine and catheter tip will be placed in the lower thoracic spine (most commonly T7-T11), under local anesthesia with the patient awake and with minimal or no sedation. In PACU, patients will be started on an infusion rate of 0.5 ml/hr and titrated to pain relief greater than 50% of baseline or up to 0.8-1.0 ml/hr within 6-8 hrs after start of the infusion on the day of the intrathecal prognostic infusion test.

A clinician blinded to the treatment arm will assess NRS and PGIC on the patients after around 12 hours (around 6-7am/morning of the following day). Assessment will include changes in pain intensity score at rest and upon ambulating or performing maneuvers that normally elicit patient's low back pain. A 4-6-hour washout period will be allotted with infusion of preservative-free normal saline at a rate of 0.2 ml/hr, after which the physician will document a return of the NRS to baseline before switching therapies (cross over).

3. OBJECTIVES AND RATIONALE

Continuous infusion intrathecal tests are prognostic clinical procedures routinely employed to select patients who would benefit from implantable intrathecal drug delivery systems. Intrathecal prognostic infusion tests are often criticized as subjective and proceeding with an implant after a questionable intrathecal test can only lead to frustration of both patient and provider. Compared to normal saline, bupivacaine and fentanyl actively function as analgesics and therefore should reveal a difference compared to preservative-free normal saline.

The objectives of this clinical trial would be:

a) To determine the benefits of a continuous intrathecal prognostic infusion test with a mixture of fentanyl and bupivacaine for selecting patients that will benefit from an implantable therapy
b) To examine the long-term effectiveness as determined by satisfaction and improvement in function of patients treated with IDDS and selected by a continuous infusion intrathecal prognostic test.

4. MEDICAL APPLICATION

Targeted intrathecal drug delivery is an established interventional modality in managing different chronic pain conditions, especially post laminectomy syndrome, also known as failed back surgery syndrome (FBSS) and vertebral compression fractures. Intrathecal delivery of pharmacological agents reduces systemic side effects and the potential for aberrant medication use (1).

The success of the treatment with an implantable device is strictly dependent on patient selection. Currently, there are no unified standard protocols for intrathecal tests which are

considered prognostic procedures for future implants (2). Previous clinical studies, but also guidelines, consider acceptable single intrathecal bolus placebo controlled injection or continuous infusion intrathecal test which mimic somewhat closely the continuous intrathecal infusion from an implantable device. The proposed study will clearly address the question of placebo controlled continuous infusion tests' utility in prognosis and effectiveness of intrathecal drug delivery systems.

5. BACKGROUND AND SIGNIFICANCE

Chronic low back is a major socioeconomic burden. Despite numerous treatment strategies including rehabilitation, medications, injections, minimally invasive procedures and surgeries, chronic back pain remains a challenge. In particular, patients with back pain persisting after previous lumbar spine surgery (often referred to as post-laminectomy syndrome or failed back surgery syndrome-FBSS) appear to be most resistant to traditional treatment strategies. Neuromodulation in the form of spinal cord stimulation or intrathecal drug delivery, represents the best option at providing effective pain relief in this challenging chronic pain population. While spinal cord stimulation has traditionally been more effective for persistent leg pain, intrathecal drug delivery is more effective in refractory low back pain. Refractory back pain following remote vertebral compression fracture(s) is another clinical entity whereby intrathecal therapy is particularly effective in the absence of alternatives. Prior to implanting an intrathecal drug delivery system, an intrathecal prognostic test is performed. Despite the agreement on the importance of intrathecal testing before the implant, there has been no consensus on the method of testing due to lack of high-quality data. While some clinicians utilize single intrathecal bolus doses of morphine or other opioids, others use continuous infusions especially in the setting of combination therapies (2). Both modalities have been employed with the use of placebo (3, 4). The value of intrathecal testing has been questioned, as it is unclear if it really predicts the long-term success or failure of IDDS. However, it is still advocated as an important initial step before the implant in chronic non-cancer pain (5).

Most of the current data available are derived from prognostic testing with opioids; no prospective randomized trials assessed the effectiveness of bupivacaine combined with an opioid. Our published studies have shown that combination of bupivacaine with intrathecal opioids results in sustained pain relief and blunting of opioid dose escalation (6, 7). However, no studies have been published on the efficacy of prognostic intrathecal infusion testing with a combination of bupivacaine and an opioid. While two studies used placebo saline injections during intrathecal prognostic testing, both involved only opioid boluses (mostly morphine), one in the setting of repeat lumbar puncture(3) and the other with repeat injections through an intrathecal catheter (4).

6. PLAN

6.1 New Investigational Drugs/ Investigational Devices Exemption Status: N/A

6.2 Selection of Subjects

6.2.1 Type of the Subject Population

Patients with refractory chronic low back pain and previous back surgeries or remote compression fractures who are referred to the Division of Pain Medicine at UHCMC for pain management and who failed previous conservative management such as physical therapy, spinal injections and medication therapy with membrane stabilizers.

6.2.2 Inclusion and Exclusion Criteria

a. Inclusion Criteria

- Age 30 years or greater
- Previous lumbar or thoracic spine surgery or lower thoracic/lumbar vertebral compression fracture
- Intractable pain of trunk (more than limbs)
- Patient who passed psychological evaluations as part of the usual clinical care prior to consideration of IDDS and are stable with current pain condition and medications
- Failed more conservative management.

b. Exclusion Criteria

- Untreated coagulopathy or infection.
- Immune compromised state precluding having an implant.
- Allergic reactions to bupivacaine or fentanyl.
- Pregnancy
- Patients using more than 30 mg oral equivalents of morphine daily or who are unable to wean down below that dosage for more than 4 weeks before the prognostic intrathecal infusion test.
- Neurological deficits characterized as weakness in lower extremities with evidence of nerve damage
- Patients with cognitive disorders who would not be able to provide meaningful outcome responses

6.2.3 Recruitment

Subjects will be recruited from patients seen at the University Hospitals Pain Medicine clinics by attending physicians. Screening will be done before obtaining consent by an investigator. If patients are deemed appropriate for an intrathecal device they will undergo normal procedures and guidelines in place prior to being considered candidates for an implantable device. No subject will be compensated for participation.

6.2.4 Consent Process

Subjects will be consented by one of the investigators. An explanation in lay terms for the reasons of the study and the proposed prognostic benefits will be used to promote patient understanding.

If interested, eligible individuals will be given the opportunity to ask and have all questions addressed before signing the informed consent document. The procedure will occur at their next visit, and continued consent of study participation will be confirmed.

6.3 Study Design and Methodology

6.3.1 Study Design

This is a randomized, double-blind, placebo controlled cross over study comparing prognostic intrathecal testing with an admixture of bupivacaine and fentanyl versus saline. None of the procedures in this study deviate from usual clinical care that patients receive at UHCMC or nationally. Baseline scores using the numerical rating scale (NRS) for pain (a scale form 0-10, where 0 signifies no pain at all, and 10 the worst possible pain) will be recorded, both in the sitting or supine position (least pain) and with ambulation or standing (worst pain). Patients will be given weight based cefazolin (or vancomycin if indicated) prior to placing the externalized intrathecal catheter. Placement of the percutaneous intrathecal catheter will be done in the operating room with minimal or no sedation in the prone or lateral decubitus position under fluoroscopic guidance. Needle entry will occur in the mid-upper lumbar spine and through the needle an intrathecal catheter will be advanced until its tip is positioned in the posterior intrathecal space in the lower thoracic spine. The needle is then removed and the catheter is secured in place with steri-strips and a clear sterile bio-occlusive dressing will be placed. Patients will then be transferred to the PACU where they will be initiated on one of two solutions that will be prepared for each patient by the investigational pharmacy staff at UHCMC. The solutions will be labeled as "Intrathecal solution 1" and "Intrathecal solution 2" and will be contained in a sterile 50 ml bag. Solution 1 and 2 may contain either:

a) Preservative-free normal saline
b) Fentanyl 1 mcg/ml and bupivacaine 0.625 mg/ml

The content of Intrathecal solution 1 and 2 will be unknown to all investigators and participants in the study with the exception of the investigational pharmacy. The order of the Intrathecal solution (1 or 2) will be determined by pharmacy using a computer generated random sequence allocation. The intrathecal catheter will be attached to a pump delivering solution 1 or 2 at around noon time, in the recovery area on the day the catheter is placed. A bolus of 1cc will be given through the infusion pump at initiation of therapy and the patient will then be started on an infusion rate of 0.5 ml/hr. After 3-4 hours (around 3-4 pm) hours and similarly around 6-7 pm the rate will be titrated depending on patient's response up to a maximum of 0.8-1.0 ml/hr.

If the patient has achieved > 50% pain relief compared to baseline, no up-titration will occur; i.e. the rate will be increased only if the patient has not had 50% or more reduction in baseline pain on the NRS. The intrathecal rate will be kept the same provided the patient had 50% or greater decrease in pain scores or has reached the 1.0 ml/hr rate (whichever comes first). The rate will be unchanged from 6-7 pm until around 6-7 am the next morning when the infusion will be stopped and the patient will be assessed for pain relief. In the morning, the patient will be asked to rate the pain score at rest (in bed or chair) and with ambulation/standing. The pain scores will be recorded and the catheter will be aspirated at the hub to ensure continued cerebrospinal fluid flow and the patient will be started on a solution of preservative-free normal saline at 0.2 ml/hr to keep the catheter patent. After 6 hours, around noon time, the patient will be crossed over to Intrathecal solution 1 or 2, depending on what she/he had the day before, given 1.0 ml of that solution as a bolus and then infusion will be started at 0.5 ml/hr and the same protocol as the day before will be repeated with the patient discharged the next morning. Patients who experience greater than 50% pain relief (relative to baseline) with either intrathecal solution will be offered the implant of a permanent IDDS that will deliver a combination of bupivacaine and low-dose fentanyl. Patients not responding to both solutions with greater than 50% pain relief will be considered to have failed the intrathecal test and would not proceed to implant. The patients will be asked to pick which solution provided better pain relief: solution 1 or solution 2 and responses will be recorded. Additionally, pain scores obtained periodically as part of patients' usual clinical care vital signs and recorded by the nursing staff on the hospital ward will be collected throughout the study. Un-blinding for patients who had a successful intrathecal prognostic infusion test with greater than 50% pain relief will not occur until 12 months have elapsed since the pump implant.

Outcome measures will include:

1- Baseline prior to commencement of the prognostic infusion test: Pain intensity using the Numerical Rating Scale [NRS], patient global impression of change [PGIC], Oswestry disability index [ODI] and painDETECT.
2- At 14-18 hours: Pain intensity in Numerical Rating Scale [NRS], patient global impression of change [PGIC], complications and side effects.
3- Prior to second infusion: Pain intensity in Numerical Rating Scale [NRS], patient global impression of change [PGIC], complications and side effects.
4- At prognostic infusion test completion: Pain intensity in Numerical Rating Scale [NRS], patient global impression of change [PGIC], complications and side effects, Oswestry disability index [ODI] and painDETECT.
5- At 6 and 12 months post-implant for implanted patients Pain intensity in Numerical Rating Scale [NRS], patient global impression of change [PGIC], Oswestry disability index [ODI] and painDETECT.

6.3.2 Study Methodology/Procedures

The study will include 36 patients with intractable chronic low or mid back pain due to failed back surgery syndrome or vertebral fracture who failed conservative management including epidural steroid injection and medical therapy and were referred to our practice for pain management.

Patient will undergo the usual psychological and medical evaluations before the initiation of the prognostic infusion test.

Patients who are considered candidates for intrathecal pump implant fulfilling the inclusion/exclusion criteria above and who elect to participate in the study will be randomly assigned to receive treatment in one of two counterbalanced conditions.

Group A tested with continuous infusion of intrathecal bupivacaine 0.625 mg/ml and fentanyl 1 mcg/ml for 14-18 hours followed by a trial with normal saline for another 14-18 hours.
Group B tested with intrathecal normal saline for 14-18 hours followed by intrathecal Bupivacaine 0.625 mg/ml and fentanyl 1 mcg/ml for another 14-18 hours.

Note that drugs will be delivered by the pharmacy to a blinded physician and labeled as Intrathecal solution 1 and Intrathecal solution 2 to be administered sequentially, separated by a 4-6-hr infusion of preservative-free saline.

Outcomes will be assessed and documented on all patients upon admission to the preoperative area.

The patients will be taken then to the procedure room and a standardized intrathecal catheter will be placed under fluoroscopic guidance where the tip of the catheter will be placed at the T7-T11 posterior intrathecal interspace. Patients will be discharged to the PACU where they will be started on a rate of 0.5 ml/hr.

Six to eight hours following initiation of the infusion, all the patients will be titrated to 0.8-1.0 ml/hr, provided less < 50% improvement in pain scores occurs. A physician who is blinded to the treatment will assess NRS after approximately 12 hrs (around 6-7 am of the following day). A 4-6 hours washout period will ensue with infusion of preservative-free normal saline at a rate of 0.2 ml/hr after which the physician will document a return of the NRS to baseline before switching therapies or record the value at 6 hrs after infusing normal saline and switch then to solution 2. NRS will be reassessed around 6 am the following morning. Additionally, pain scores documented with usual clinical care vital signs will be captured.

All reported adverse events will be recorded.

No pain medications will be prescribed during the admission. If such medications are needed, the patient will be excluded from continuing on with the study and will be recorded as a prognostic-infusion-test failure.

The intrathecal catheter will be aspirated for confirmation of free cerebrospinal fluid flow (about 1 ml) between all solution changes and at the end of the prognostic infusion test .

After the completion of the prognostic infusion test, the catheter will be removed and patients will be discharged home.

Only patients who report >50% reduction from baseline NRS while receiving either intrathecal solution will be considered for intrathecal drug delivery system implant. It is conceivable that some patients may get >50% reduction in pain scores with both the active solution and saline or have better outcome with the saline solution. The patients will be asked to answer a binary question rating preference to solution 1 vs. solution 2. Patients with pain relief greater than 50% will be implanted with an IDDS and will receive an intrathecal solution of fentanyl and bupivacaine. All subjects with >50% pain relief with either or both intrathecal solutions will be implanted. Even if the patient gets >50% pain relief only from the saline solution, or the patient chooses the saline solution over the active solution (when asked if #1 vs. #2 was better relief) each patient will receive active drug after being implanted. All patients will be compared in long-term outcome (secondary outcome measures) at 6 months and 12 months versus the response to the prognostic test solutions. Unblinding of solution 1 and 2 will not occur until 12 months have elapsed since pump implant. The six and twelve month visits will be coordinated with a pump refill visit.

6.3.3 Collection of the Human Biological Specimens: N/A

6.3.4 Data Collection

Randomization will be performed, and baseline data will collect on admission to the preoperative area. A physician or physician assistant will obtain all data.

Baseline data collected will include name, last 4 digits of social security number, age, sex, race, duration of pain, treatment group, average 0-10 low back numerical rating scale (NRS) pain scores over the past week and analgesic medication consumption.

NRS scores will be collected again around 6am, noon and 6am of the following day, as well as per regular nursing routine on the medical floor. Medication side effects, satisfaction [patient global impression of change-PGIC], complications will also be documented at the completion of each infusion.

At the end of the prognostic infusion test, patients will be asked to specify which infusion they preferred: Intrathecal solution 1 or Intrathecal solution 2. An "assessment of blinding" questionnaire will also be administered. When the data is recorded on the Excel spreadsheet

for statistical analysis, identifying information will be deleted.

6.3.5 Study Time Line

Assessment	Before testing procedure	Testing Procedure; Intrathecal Catheter Placement	Infusion 1 14-18 hours	Wash out 4-6 hours	Infusion 2 14-18 hours	Follow Up 6-months	Follow Up 12-months
Screening Informed Consent	X						
Randomization; Questionnaires; Data Collection; Medication Dose Titration		X	X	X	X		
Data Collection; Questionnaires; Adverse Events			X	X	X		
Long Term Outcomes; Questionnaires; IT Medication Use; Adverse Events						X	X

6.4.1 Data Analysis

For this study, there will be two within-patient experimental groups in a counterbalanced crossover design, such that all patients will receive both treatments. An equal number of patients will be randomly assigned to receive the intrathecal solutions in the order of Treatment 1 followed by Treatment 2, or Treatment 2 followed by Treatment 1.

The primary outcome variable will be the change in pain intensity score [NRS] 0-10 numerical rating scale back pain score at the end of the intrathecal prognostic infusion testing period around 6am between Intrathecal solution 1 and Intrathecal solution 2. That is, the primary outcome will report the degree of change in NRS pain scores between baseline (pre-treatment) and the end of receiving that treatment (post-treatment; approximately 18 hours after treatment initiation), separately for Treatment 1 and for Treatment 2. Changes in NRS pain scores will be considered clinically significant if they result in ≥ 50% pre-treatment/post-treatment NRS scores for pail relief compared to baseline, in either intrathecal solution

Secondary outcome variables will be Oswestry disability score, changes in painDETECT, Patient Global Impression of Change (PGIC) and side effects (medications) and complications (injections). These variables will be recorded at baseline, at the completion of each phase of the prognostic infusion test, and at 6 and 12 months post-implant.

6.4.2-3 Data Analysis and Statistical Plan

Continuous or ordinal data for two groups or conditions will be analyzed using t-tests for paired or independent samples. If the data are non-normally distributed, variations of the t-test for non-parametric distributions will be utilized: Mann-Whitney U test for independent samples. Comparisons of three or more groups will be conducted using a One-Way ANOVA with Bonferroni post-hoc tests to correct for multiple comparisons; alternatively if the data are non-normally distributed a Kruskal-Wallis test will be used. Categorical data will be analyzed using the chi-squared test for categorical data, or using Fisher's exact test, a robust chi-square alternative that is valid for all sample sizes.

6.4.4 Sample Size Estimation

To estimate the sample size we based our calculation on the primary outcome which is change of NRS score from baseline and at 18 hrs and 36 hrs. From the literature we expect 50% in absolute pain score changes with the treatment agent [Δ NRS 1] and that is considered clinically significant. Placebo response is considered 20-30% [Δ NRS 2]. To identify a true effect of treatment, distinguishable from a placebo response, the power analysis should identify an absolute score change from baseline of ≥ 30%; to identify a clinically significant change this score should change by ≥ 50%. The power analysis is conducted to estimate the number of patients required to identify this clinically significant change as also statistically significant.

Power analyses are performed on the primary outcome of interest, the change in NRS scores from baseline to post-treatment. The power analysis software G*Power was used to calculate the sample size for a two-tailed t-test for matched pairs, alpha 0.05, power = 0.8, difference in means = 30%, standard deviation of within-patient differences = 50%. Under these parameters a projected effect size of .5 (Cohen's *d*, moderate effect size) was calculated, and 29 patients were required in total. Under the assumption of a 20% dropout rate, sample size was estimated at 36 patients.

A total of 36 patients will enter this two-treatment crossover study. The probability is 80 percent that the study will detect a treatment difference at 95% confidence that a statistically significant difference would reveal a true effect, if the true difference between treatments is 30 units. This is based on the assumption that the within-patient standard deviation of the response variable is 50.

The final number of patient to be recruited for this study would be 36.

6.5 Reporting Adverse Events

6.5.1 Expected Adverse Events from Research Risks and Reporting
Adverse effects are not expected from this minimal intervention. Other possible side effect would be poor pain control.

All investigators will take the same steps normally taken to minimize adverse events.

6.5.2 Reporting Serious and Unexpected Adverse Events to the IRB
Serious Adverse Events: The PI, within one working day, will report all serious adverse events (SAE) occurring in any subject. This will be accomplished by submitting an adverse event report memorandum to the IRB.

Unexpected (but not serious) adverse events which, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 10 (ten) working days to the IRB using the same procedure.

For all serious and/or unexpected adverse events, the PI will examine the adverse event for relation to the study and report if needed to the IRB.

6.6 Banking of Human Biological Specimens/Tissue (HBS/tissue): N/A

***6.7 Subject Confidentiality Protection:** All treatments received in this study are usual clinical care. No data will be collected that is not relevant to patient care (e.g. treatment, analgesic usage, numerical rating scale pain scores and disability scores), and no data will be shared with any non-investigator. In addition to name and date of birth, patients will also identified by their place on the randomization table (e.g. RT 2, PT 3). This "code" will enable the transfer of study information without mentioning patients' names

6.7.1 Certificate of Confidentiality: N/A

***6.7.2 HIPAA Authorization**

i. Are you intending to collect subject's Protected Health Information (PHI) and any of the following 18 personal identifiers?

___ No – HIPAA does not apply – go to question #**iv**
_x__ Yes – please check which ones:
___ 1. Names
___ 2. Street address, city, county, 5-digit zip code
_x__ 3. Months and dates (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)

_x__ 4. Telephone numbers
_x__ 5. Fax numbers
_x__ 6. E-mail addresses
___ 7. Social security number
___ 8. Medical record number
___ 9. Health plan beneficiary number
___ 10. Account number
___ 11. Certificate/license number
___ 12. Vehicle identification number (VIN) and/or license plate number
___ 13. Device identifiers and serial numbers
___ 14. URLs (Uniform Resource Locators)
___ 15. Internet protocol address number
___ 16. Biometric identifiers, such as finger and voice prints
___ 17. Full face photographic images or any comparable images
___ 18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just dates, city/state/zip, and/or "other unique identifier" (#18 of the above)?
___ Yes – then your dataset may qualify as a Limited Data Set – please complete a Data Use Agreement and attach to your protocol. Then go to question #**iv**.
_x__ No – Go to question #**iii.**

iii. Is obtaining patient Authorization "impracticable"?
___ Yes – Authorization may qualify to be waived by the IRB. Go to *Section 6.7.3* HIPAA Authorization Waiver for the application.
_x__ No – Research subjects will need to sign a HIPAA Authorization. Complete the HIPAA Authorization and attach to this protocol.

iv. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

A randomization table will be developed by a computer generated random number sequence. This "code" and a copy of all data collection sheets will be kept by our research nurse (Karen Arters) in a room in that is locked at night and protected by computer passwords as well as the UHCMC compounding pharmacy that will prepare the solutions labeled as described.

v. When will you destroy the research source documents, data file, and the master code?

The UHCMC research team in the Pain Medicine Clinic will keep the research data for up to six years after the end of the study. Then all the information will be destroyed. The master code will be destroyed as soon as all data collection is completed.

vi. Will research data including Identifiable Protected Health Information be sent outside of UHCMC? No

6.7.3 HIPAA Authorization Waiver: N/A- We will obtain signed HIPAA authorization from each patient.

6.8 Reporting Protocol Deviations

Minor protocol deviations (e.g. minor changes in the consent process, prolonged completion time due to deployments) will be discussed with the investigative team and reported to the IRB on a standard protocol deviation sheet. Any major deviations (e.g. unexpected findings necessitating a change in protocol) may require temporarily stopping the protocol until the steps needed to rectify the deviation are cleared with IRB (e.g. change in protocol).

7.0 Risks, Benefits, Alternatives, Withdrawal

7.1 Risks

All of the medication and equipment being used for this study are considered usual clinical care treatment for back pain. There is a risk for increase in back pain with the normal saline solution.

Questionnaires/Subject Diaries/Research
The questionnaires and subject diaries will be used to compare the outcomes of each week of treatment and pose no risk to the subject.

Possible minimal risks include potential breach of confidentiality of the subject's medical record information and associated privacy. This risk will be minimized by assigning each subject a unique study number. This number will be kept in a locked area with only the study team having access.

Unforeseeable risks
There may be risks or side effects related to the study procedures that are unknown at this time. Subjects will be notified of any significant new findings that become known that may affect their willingness to continue in the study.

7.2 Benefits

Subjects may not receive benefits from participating in this research study. The information that can potentially be gained from this study regarding their condition may be useful to those who suffer from the disease, including the participants.

7.3 Alternatives

If a patient chooses not to participate, they will continue with their current treatment. Any patient may withdraw from the study at any time.

7.4 Withdrawal from Study Participation

Subjects may withdraw from the study at any time. Upon withdrawal, they will return to their usual, usual clinical care treatment and have their IDDS prognostic infusion test and follow up per usual clinical care. Follow up will be per usual clinical care per the investigator's discretion. Data prior to withdrawal may be used, but no further data will be collected. Also, the investigator may choose to withdraw the subject if the investigator deems it is in the best interest of the subject's health and well-being.

References:

1. Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. *Pain physician*. 2011;**14:**219-48.
2. Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation : journal of the International Neuromodulation Society*. 2012;**15:**436-64; discussion 64-6.
3. Dominguez E, Sahinler B, Bassam D, Day M, Lou L, Racz G, et al. Predictive value of intrathecal narcotic trials for long-term therapy with implantable drug administration systems in chronic non-cancer pain patients. *Pain practice : the official journal of World Institute of Pain*. 2002;**2:**315-25.
4. Hamza M, Doleys D, Wells M, Weisbein J, Hoff J, Martin M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med*. 2012;**13:**1304-13.
5. Deer TR, Prager J, Levy R, Burton A, Buchser E, Caraway D, et al. Polyanalgesic Consensus Conference--2012: recommendations on trialing for intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation : journal of the International Neuromodulation Society*. 2012;**15:**420-35; discussion 35.
6. Hayek SM, Veizi E, Hanes M. Intrathecal Hydromorphone and Bupivacaine Combination Therapy for Post-Laminectomy Syndrome Optimized with Patient-Activated Bolus Device. *Pain Med*. 2015.
7. Veizi IE, Hayek SM, Narouze S, Pope JE, Mekhail N. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. *Pain Med*. 2011;**12:**1481-9.