<u>**Proposed Research Protocol Form**</u>

Title: A Prospective Trial of Cooled Radiofrequency Ablation of Medial Branch Nerves versus Facet Joint Injection of Corticosteroid for the Treatment of Lumbar Facet Syndrome

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1.0   Research Aims:

1.1   <u>Research Question:</u>
Does Cooled Radiofrequency Ablation (C-RFA) of the medial branch nerves (MBN) compared to zygapophyseal ("facet") joint injection of corticosteroid result in a greater response rate defined by meaningful relief of low back pain symptoms, functional improvement, and reduction of analgesic medication use in individuals with lumbar facet syndrome?

1.2   <u>Null Hypothesis:</u>
Cooled Radiofrequency Ablation (C-RFA) of the MBNs compared to facet joint injection (FJI) of corticosteroid result does not result in a greater response rate defined by meaningful relief of low back pain symptoms, functional improvement, and reduction of analgesic medication use in individuals with lumbar facet syndrome.

1.3   <u>Specific Aims:</u>
1. Determine the proportion of patients with a successful response (defined as 50% or greater improvement in index pain) to lumbar MBN C-RFA versus facet joint injection of corticosteroid at 3 months, and the duration of relief up to 2 years.
2. Evaluate the functional improvement observed in both groups, as assessed by the Oswestry Disability Index (ODI), the PROMIS Physical Function CAT (PF-CAT), and the Patient Global Impression of Change (PGIC); determine the correlation between reduction in pain and improvement in function, as well as the correlation between the

ODI and the PF-CAT in this specific population, to both the anchor score (PGIC) as well as to each other (ODI vs. PF-CAT).
4. Evaluate changes in opioid and non-opioid analgesic use in both groups, as assessed by the conversions to daily morphine equivalent use and Medication Quantification Scale III score.
5. Evaluate differences in the proportion of patients with a successful treatment response in those who reported 100% relief from dual comparative diagnostic lumbar MBN blocks relative to those with at least 80% improvement but less than 100% relief from the dual comparative blocks.
5. Report immediate, short-term, and long-term adverse effects, using a standardized survey that includes a comprehensive query of known adverse events associated with systemic steroid effects.

2.0 Research significance:

2.1 Background

Chronic, non-neurogenic low back pain (CLBP) is a common condition that affects many individuals across their lives. The lumbar facet joint has been implicated as an important source of CLBP, with a prevalence of 15-45%.[1,2,3,4,5] Elements of clinical history, physical examination, and imaging (radiographs, standard CT scan, standard MRI sequences) provide poor diagnostic specificity for pain of lumbar zygapophysial joint (Z-joint) origin.[6,7] Thus, clinicians have traditionally relied upon MBN blocks to confirm or refute this diagnosis.[8] The reference standard for the diagnosis of lumbar Z-joint pain is a positive response to dual comparative MBN blocks, which requires pain reduction ≥80% of concordant duration to that expected of two different local anesthetics on independent occasions.[9,10] Further, dual comparative MBN blocks have a high positive predictive value for determining the clinical outcome of lumbar MBN RFA for the treatment of lumbar Z-joint pain; when patients are appropriately selected using this reference standard and rigorous MBN RFA technique is implemented according to practice guidelines,[9] studies demonstrate excellent clinical outcomes.[11,12,13]

In additional to MBN RFA, lumbar facet joint injection of corticosteroid is another commonly used treatment strategy for lumbar facet joint pain related to osteoarthritis.[14] While clinical outcome studies of facet joint injection with corticosteroid have generally shown only modest outcome improvements, this literature is generally flawed by invalid selection protocols that do not require dual comparative MBN blocks in order to confirm the diagnosis of pain specific to the lumbar facet joint(s).[9]

Despite the widespread use of these two techniques (lumbar MBN RFA vs. facet joint corticosteroid injection), the two techniques have never been compared in an appropriately-designed head-to-head study. The sole outcome study[15] comparing these two treatment methods used an invalid selection protocol of one positive MBN block, requiring only 50% relief in pain and not of concordant duration with that expected by the local anesthetic used; in addition, a single RFA lesion was applied with a 20g conventional RFA electrode and fluoroscopic images were not published, so it is unclear if parallel electrode technique was used, as is necessary with

conventional RFA. This invalid patient selection and RFA technique protocol is similar to that used in the Mint Trials, which has led to a broad call for improving such standards in research and clinical care by a multitude of experts representing interventional pain, spine, and radiology specialty societies.[13,16,17,18] As such, an appropriately designed head-to-head trial in warranted.

Furthermore, while the conventional RFA modality has been studied extensively for MBN RFA, minimal outcome literature on the effectiveness of C-RFA technology has been published.[19] C-RFA is similar in mechanism to conventional RFA: a thermal lesion is created by applying radiofrequency energy through an electrode placed at a target structure. In C-RFA, a constant flow of ambient water is circulated through the electrode via a peristaltic pump, maintaining a lowered tissue temperature by creating a heat sink. By removing heat from tissues immediately adjacent to the electrode tip, a lower lesioning temperature is maintained, resulting in less tissue charring adjacent to the electrode, less tissue impedance and more efficient heating of target tissue [20,21]. The volume of tissue heated, and the resultant thermal lesion size is substantially larger with C-RFA [22], conferring an advantage over conventional RFA[23]. Further, given the spherical geometry and forward projection the C-RFA lesions beyond the distal end of the electrode, the RFA probe can be positioned at a range of possible angles and still capture the target neural structure, whereas more fastidious, parallel positioning is required with conventional RFA.[9] These technical advantages increase the probability of successful denervation of neural pain generators that have variability in anatomic location, as is the case with facet syndromes in which significant osteoarthritis is present, which is associated with joint hypertrophy and osteophyte formation. Additionally, a longer lesion of the MBN may be more reliably achieved with C-RFA compared to conventional RFA, potentially resulted in greater treatment durability, as the recurrent of facetogenic pain after successful denervation is related to reinnervation by nerve re-growth to bridge the gap created by the lesion.[24] Consistent with this technical advantage, there is preliminary evidence for superiority of C-RFA compared to both conventional RFA and other novel RFA techniques in the treatment of sacroiliac joint-mediated pain.[25,26]

As such, the goal of the proposed study is to determine if individuals with lumbar facet syndrome who are treated with C-RFA of the MBNs compared to facet joint injection of corticosteroid have a greater likelihood of experiencing meaningful relief of low back pain symptoms, functional improvement, and reduction of analgesic medication use at both short and long-term follow-up.

2.2   Significance

Lumbar facet joint pain is a common and costly cause of chronic low back pain. Lumbar MBN RFA and facet joint injection of steroid are two commonly used treatment strategies for lumbar facet-mediated pain, yet the two techniques have never been compared in an appropriately-designed head-to-head trial. Further there is minimal clinical outcome literature describing the effectiveness of MBN C-RFA despite its technical advantages over conventional MBN RFA. We will determine if individuals with lumbar facet syndrome who are treated with MBN C-RFA compared to facet joint injection of corticosteroid have a greater likelihood of experiencing meaningful relief of low back pain symptoms, functional improvement, and reduction of analgesic medication use at both short and long-term follow-up. Answering this clinical question

will help determine which technique is superior, such that patients with lumbar facet syndrome can get be offered the best treatment available.

3.0 Investigational Plan

Study design: Single-blinded, randomized prospective pragmatic comparative trial

Recruitment Process
Participants will be recruited from the practices of the primary investigator and the co-investigators, i.e., the clinics of the University of Utah Orthopaedic Center and the University of Utah South Jordan Health Center. Secondary recruitment from marketing to primary care clinics and local media will also be implemented.

Participant Reimbursement
Participants will be reimbursed $50 at 3-month follow-up, $50 at 1-year follow-up, and $50 at 2-year follow-up.

Enrollment Process
Potential candidates will be approached in clinic or contacted by phone by the investigators or research assistant to introduce the study and proceed to a screening evaluation if the potential candidate agrees. Eligibility is determined by the inclusion and exclusion criteria listed below. Qualifying volunteers will be asked to provide both written and verbal informed consent.

Patients may be compensated for their time and participation upon enrollment and for completion of follow-up intervals.

Inclusion Criteria:
1. Adult patients aged $\geq$ 21 capable of understanding and providing consent in English and capable of complying with the outcome instruments used.
2. Axial (non-radicular) back pain for at least 3 months (i.e. Chronic Low Back Pain) that did not respond to conventional treatment such as physical therapy, oral analgesic agents, and non-invasive adjunctive treatments. The pain can be unilateral or bilateral. The pain can also include referred lower limb pain.
3. Numeric pain rating score (NPRS) for back pain of 5/10 or greater at baseline evaluation.
4. Positive responses to dual diagnostic MBN blocks using 0.5mL of 0.25-0.5% bupivacaine and 2-4% lidocaine, on respective encounters on separate days, at each of the appropriate MBNs. The blocks are administered in a double-blind fashion so that the subject is unaware of the local anesthetic used.

Levels selected for diagnostic procedures will be determined by the treating physician based on the overall clinical picture including the location of pain, pain referral patterns, and imaging findings. All MBN blocks will be performed according to Spine Intervention Society guidelines.[9]

A pain diary with appropriate diagnostic categories of relief will be provided (100% relief, 80% relief, etc.), will be provided. The degree of pain at baseline is recorded and subsequent relief is recorded at 15-minute intervals for six hours.

In order to qualify as a positive block, the subject must experience at least 80% relief from baseline lasting at least one hour with lidocaine and two hours with bupivacaine. The patient is discharged from the recovery suite after 30 minutes, provided there are no adverse effects that require more attention.

The pain relief can include relief in a specified area, e.g. the pain relief can be relief on the right side only. It does not preclude a different diagnosis at a different site, e.g. upper lumbar area.

Exclusion Criteria:
1. Focal neurologic signs or symptoms.
2. Radiologic evidence of a symptomatic herniated disc or nerve root impingement related to spinal stenosis.
3. Active systemic or local infections at the site of proposed needle and electrode placement.
4. Coagulopathy or other bleeding disorder.
5. Receipt of remuneration for their pain treatment (e.g. disability, worker's compensation, auto injury in litigation or pending litigation).
6. History of any lumbar or lower thoracic fusion surgery or placement of other hardware.
7. ≥Grade 2 Spondylolisthesis at an affected or adjacent level.
8. Cobb angle >10 degrees.
9. Sagittal vertical axis angle >5 degrees.
10. BMI >40.
11. Incarceration.
12. Cognitive deficit affecting ability to complete the assessment instruments.
13. Inability to read English and complete the assessment instruments.
14. Allergy to local anesthetics.
15. Chronic widespread pain or somatoform disorder (e.g. fibromyalgia).
16. Prior lumbar MBN radiofrequency neurotomy.
17. Addictive behavior, severe clinical depression, anxiety, or any mental health condition with psychotic features.
18. Possible pregnancy or other reason that precludes the use of fluoroscopy.
19. Daily chronic opiate use of >50 morphine equivalents.

Power Analysis
In the Dreyfuss et al[12] prospective cohort study of conventional RFA for the treatment of chronic lumbar facet joint pain, which used an identical diagnostic/selective MBN block protocol (SIS guidelines[9]), to that of the proposed study, 87% of patients experienced at least 60% reduction in pain at 10-month follow-up. For the present power analysis, we will more conservatively estimate a success rate of 80%, using 50% relief in pain at 3 months as the definition of success.

No study to date has used dual comparative MBN blocks to select patients for facet joint injection of corticosteroid. However, Carette et al. used intra-articular injection of local anesthetic only (>50% relief considered "positive) in order to select patients for a randomized controlled trial of lumbar facet joint injection of corticosteroid versus saline.[27] In this study, a 42% success rate was observed at 3 months. For the present power analysis, we will more conservatively estimate a success rate of 50% at 3 months, as participants will be selected by dual comparative MBN blocks rather than only one intra-articular diagnostic injection.

Given that the primary analysis will be categorical in nature (comparison of the proportion of responders), with an alpha level of 0.05 and a power of 0.80, 39 participants would be needed in each group (total 78 participants) to detect a significant difference in the proportions between the two groups (80% vs. 50%) using a chi-square test. However, in order to improve the power of the study beyond the minimally acceptable standard and to account for anticipated attrition, we propose to enroll 135 patients in the trial.

Outcome Instruments
Baseline Only:
- Demographics (age, sex, BMI), duration of back pain, nature of pain (i.e. bilateral, symmetrical, unilateral), exact anatomic location of lumbar pain based on clinical diagnosis aided by radiologic information, confirmed by MBN blocks.

Baseline & Follow-up:
- Percentage of relief with each of the MBN block procedures (from pain diary)
- NPRS back pain (7-day average)
- Current NPRS
- Oswestry Disability Index score
- PROMIS Physical Function Computer Adaptive Test (PF CAT) score
- PROMIS Global short-form 10 (Global-10) score
- Opioid and non-opioid analgesic use
- Ancillary treatment log

Follow-up Only:
- Patient global impression of change (PGIC)
- Adverse effects. Specifically only: spinal infection, epidural hematoma, and neurological damages to the spinal nerve root(s) at the treated level(s).

Study Timeline
Baseline:
Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving treatment. The baseline examination and all baseline questionnaires will be completed within 8 weeks before the index study treatment procedure (facet joint steroid injection or medial branch radiofrequency ablation) as time is needed to obtain insurance authorization for all study procedures in the present study (all procedures in this

study represent usual care procedures: medial branch blocks, facet joint injections, and medial branch radiofrequency ablation).

Follow-up:
Routine scheduled follow-up will occur at 1 month (+/- 2 weeks), 3 months (+/- 4 weeks), 6 months (+/- 6 weeks), 12 months (+/- 3 months), and 24 months (+/- 3 months), at which times all follow-up measures will be obtained.

The 3-month follow-up will serve as the time point for the primary outcome analysis of the randomized trial and an intention-to-treat analysis will be used to evaluate for differences in outcomes between the two groups. The 3-month time point provides a reasonable timeframe to evaluate the clinical effects of the lumbar MBN C-RFA while also providing a humane timeframe for crossover to active treatment in those randomized to usual treatment. All subsequent follow-up periods are intended to evaluate long-term clinical outcomes of lumbar MBN C-RFA and will be evaluated with an as-treated analysis.

The study start date and the outcome assessment timeline will begin at the date of the participant's initial facet-targeted treatment. After 3 months, patients who have failed treatment (not meeting criteria for success, as described above) can be offered alternative treatment. Those who cross-over will be considered treatment failures of the original treatment, by definition, and continue on the regular follow-up schedule. A new 2-year follow-up period will begin upon cross-over.

This study is intended to monitor outcomes for 2 years following facet joint intervention. Some patients reporting relief at the 3-month follow-up may experience a return of symptoms afterwards. All patients reporting relief at the 3-month follow-up will be instructed to contact their physician if and when they experience a treatment effect that diminishes by >50%. This can occur at any time following the 3-month follow-up, including the regularly scheduled follow-up intervals. Repeating the facet intervention procedure originally assigned beyond the 3-month follow-up does not reset the follow-up schedule. Patients are also free to choose alternative therapies beyond 3 months. Patients may also develop new low back pain that is different from what is being evaluated, which will be noted.
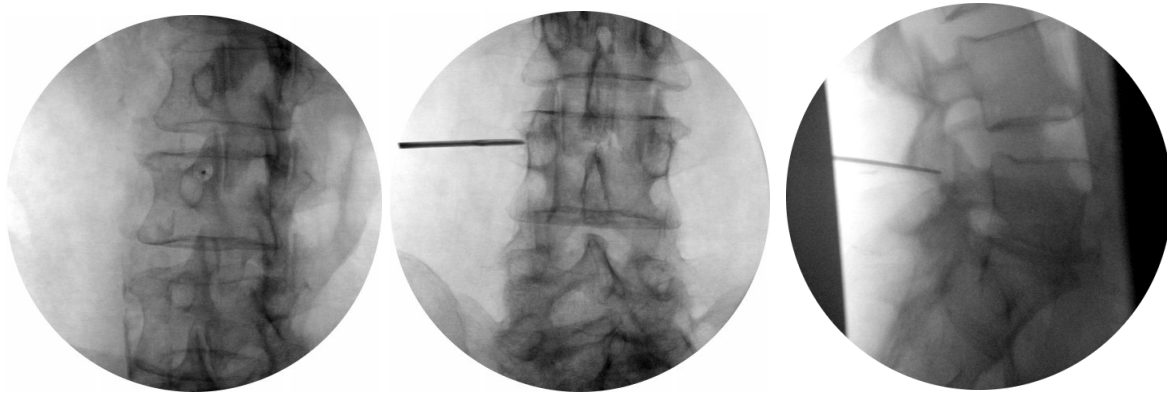

Study Protocol

Treatments Procedures:

C-RFA Procedure (Procedure as performed as standard of care clinical practice)
During the C-RFA procedure, the participant will be positioned prone on a fluoroscopy table. Sterile precautions, including sterile preparation, drapes, and gloves, will be undertaken. A pre-procedure time-out will be performed. Vital signs will be recorded as per usual care for sedation procedures. Patients may be mildly sedated during the procedure, using intravenous midazolam and /or fentanyl. An C-RFA electrode – Coolief® Cooled Radiofrequency Kit (Halyard Health Inc, Alpharetta, GA), will be placed at the junction of the transverse process and the superior articular process in an ipsilateral oblique fluoroscopic view, touching bone, but then with

subsequent withdrawal of the stylet, allowing a 2 mm gap between the electrode tip and the base of the superior articular process given forward projection of the cooled lesion. Appropriate positioning will be confirmed in oblique, anterior-posterior, and lateral fluoroscopic views, as is shown in the below figures per manufacturer guidelines:

Motor testing may be performed at each of the MBNs per physician discretion. Sensory testing is not required, as this technique has been shown to have no influence on treatment outcomes.[28] After appropriate electrode positioning, 1-4 mL of 1-4% lidocaine might need to be used at a given medial branch nerve in order to affectively anesthetize it before lesioning (standard of care range). This is done through an introducer needle for anesthesia during the ablation. The C-RFA lesions will be performed by using the typical C-RFA protocol with lesions performed with the RFA generator (generator is pre-programmed)[29]. Once the procedure is completed, all needles will be removed. Following ablation, 0.25-1 mL of 0.25 -0.5% bupivacaine will be injected at each medial branch nerve to provide post procedure analgesia. No corticosteroids will be injected.

For bilateral low back pain, a maximum of 4 facet joints (two on each side) will be denervated by lesioning of up to 6 MBNs. For unilateral low back pain, up to 3 facet joints will be denervated by lesioning up to 4 MBNs.

FJI Procedure (Procedure as performed as standard of care clinical practice)
During the C-RFA procedure, the participant will be positioned prone on a fluoroscopy table. Sterile precautions, including sterile preparation, drapes, and gloves, will be undertaken.

Using an oblique fluoroscopic view, the image intensifier will be rotated to optimize the posterior joint space opening. A spinal needle will be advanced under fluoroscopic guidance to enter the posterior joint space. The needle position will be confirmed in both AP and oblique views. Approximately 0.2-1 mL of iodinated contrast medium will be injected to confirm intra-articular placement and no vascular uptake. The injection will be then completed with 0.5 mL of 40mg/mL Kenalog and 0.5 mL of 1-4% preservative-free lidocaine. This technique will be repeated for each facet joint injected.

For bilateral low back pain, a maximum of 4 facet joints (two on each side) will be injected. For unilateral low back pain, up to 3 facet joints will be injected.

Group Assignments:
Patients will be randomly assigned to the two treatment groups (C-RFA vs. FJI) at a 1:1 ratio. Participants who reported 50% or more relief of their usual pain (NPRS score compared to baseline) at the 3-month follow-up time point and who subsequently experience a treatment effect that diminishes by > 50% will be offered a repeat procedure. Duration of relief will be considered the time from the provision of the treatment procedure until the participant returns to 50% of their pre-treatment level of pain as reported during scheduled follow-up, or when a repeat treatment procedure is requested and performed.

Crossover:
Any time after the 3-month follow-up, any participant who has not obtained adequate pain relief can ask to cross over to alternative treatment group. In doing so, a new 2-year follow-up will begin for this participant who is now placed in the alternative treatment group for the long-term, as-treated outcomes analysis.

Co-interventions:
Patients are allowed to receive usual care, including co-interventions, as deemed necessary by the treating physician. Treatments related to the participant's spine condition will be reported on the ancillary treatment log.

Primary Outcomes:
The primary outcome for the randomized trial is the proportion of responders, defined by a reduction in NPRS score ≥50% at the 3-month follow-up.

Secondary Outcomes:
   1. Physical function (ODI and PF CAT)
   2. Global function (Global-10)
   3. Analgesic use (MQS III score[30])
   4. Global impression of change (PGIC)
   5. Adverse events (Specifically only: spinal infection, epidural hematoma, and neurological damages to the spinal nerve root(s) at the treated level(s))

Blinding:
Participants cannot be realistically blinded to their intervention. However, all assessors will be independent and blinded. Participants will remain in their allocated groups throughout the study unless they meet the criteria for crossover treatment. In order to provide an unbiased assessment, the treating physician will be different from the outcome assessor, a trained research assistant.

Data Management
Data will be collected on standardized case report forms and entered into a HIPAA-compliant electronic database (REDCap) that provides an appropriate interface with a robust statistical

package (Stata ver. 14.2, StataCorp LLC, College Station, TX, USA). All study-related hard copy materials will be stored in locked file cabinets.

Data Analysis
Results of the randomized comparative trail will be determined by an analysis of categorical data from the 3-month follow-up. At 3-month follow-up, prior to allowing crossover, overall treatment response rates (in the previously defined categories of failure or success) will be calculated for both treatment groups using an intention-to-treat analysis. For time periods beyond 3 months, intention-to-treat and as-treated analyses will be performed with primary reporting based on the as-treated analysis to assess the long-term effectiveness of each treatment. In the intention-to-treat analysis, participants who cross-over will be treated as treatment failures of their original group assignment. In addition, a treatment benefit survival analysis will be performed.

Subgroup analyses will be performed to assess treatment response and long-term effectiveness in patients reporting 100% relief from lumbar MBN blocks as compared with those reporting between 80% relief. Data will also be examined to identify any factors that predict treatment success and need for repeat treatment.

Secondary outcomes will be similarly evaluated. For the assessment of function and global quality of life, the proportions of those achieving and not achieving the established minimal clinically important differences (MCID) will be determined and compared between the two treatment groups at the 6-month follow-up. For long-term analysis of treatment effectiveness, an as-treated analysis will determine the proportion of participants exceeding these response thresholds. In addition to these categorical outcomes, changes in group mean scores will be measured and compared.

Statistical Analysis
Descriptive statistics and graphical displays will be used to examine the central tendency and distribution of each outcome variable. Data will be analyzed using Stata (ver. 14.2, StataCorp LLC, College Station, TX, USA). An alpha level of 0.05 and two-tailed tests will be used for all hypothesis testing.

To illustrate the demographic, radiologic, and procedural characteristics of the study sample, means and standard deviations or medians and interquartile ranges (depending on the distribution of data) will be calculated for continuous variables, and frequencies and proportions will be calculated for categorical variables. Demographic, clinical, and radiologic differences will be compared between the groups (C-RFA vs. FJI) in order to ensure that the two groups are equal in terms of observed as well as unobserved covariates other than the treatment provided to them.

In comparing groups (C-RFA vs. FJI) with regard to categorical variables, Fisher's exact tests will be used. Proportions and 95% confidence intervals will also be calculated in order to confirm that any differences between groups are truly distinguished. A proportion ratio will be calculated as the measure of the effect size. For quantitative variables, independent *t*-tests or Wilcoxon-Mann-Whitney tests will be used to compare means or medians, respectively. An effect size of *r* will be calculated to examine the magnitude of a group difference.

Budget

Please see attached.

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