A Randomized, Prospective Study of Lumbar Transforaminal Epidural Corticosteroid Injection(s) Versus Defined Physical Therapy for the Treatment of Subacute Lumbar Radicular Pain Due to Disc Protrusion

Investigators

Matthew Smuck, MD (PI)          Irina Melnik, MD
Assistant Professor, Stanford University
Department of Orthopaedic Surgery
450 Broadway St., Pavilion C
Redwood City, CA 94063
Office: (650) 721-7627
msmuck@stanford.edu

Irina Melnik, MD
Comprehensive Spine and Sport
591 Redwood Highway Suite 2300
Mill Valley, CA 94941
Office: (415) 388-3808
irinalm@hotmail.com

Research Coordinator

Ma Agnes Martinez Ith
Stanford University, Department of Orthopaedic Surgery
450 Broadway St., Pavilion C
MC 6342
Redwood City, CA 94063
Office: (650) 721-7600
mith@stanford.edu

Research Sites

Medical:
Stanford Spine Center          Comprehensive Spine and Sports
450 Broadway St., Pavilion A          591 Redwood Highway Suite
2300          Mill Valley, CA 94941
Redwood City, CA 94063          (415) 388-3808
(650) 725-5905

Physical Therapy:
Sport and Spine Therapy of Marin          Stanford Outpatient Physical Therapy
165 Rowland Way, Suite 101          450 Broadway St., Pavilion C
Novato, CA 94945          Redwood City, CA 94063
(415) 898-1311          (650) 725-5106

Funding Source

International Spine Intervention Society (ISIS) http://www.spinalinjection.org/
Purpose of the Study

Lumbar radiculopathy/radiculitis is a common problem that can lead to significant disability in an individual, and which has a very substantial economic and productivity impact on western society. In the subacute setting, various physical therapy techniques, medications, patient education programs, home exercise programs, and spinal injection interventions including caudal, transflaval, or transforaminal (TF) corticosteroid injections have been used, alone or in combination, to treat this problem. To date, the comparative effectiveness between these treatment options remains unknown.

The purpose of this study is to evaluate the comparative effectiveness (in terms of pain relief, functional benefits, and cost effectiveness) of TF corticosteroid injections and physical therapy in treating subacute radicular pain, due to disc protrusion.

Synopsis

Patients who have had radicular pain for less than or equal to 12 weeks will be randomized to the Transforaminal Epidural Steroid Injection (TFESI) or Physical Therapy (PT) groups. The primary outcome measure for this study will be reduction in pain as measured by a three day average Visual Analog Scale (VAS). Secondary measures will include: Oswestry Disability Index (ODI), SF-36, a seven point Global Perception of Change (GPC), a three question Patient Specific Activity Questionnaire (PSAQ), and analgesic, outside medical care, and surgical option utilization, as well as physical exam and physical therapy test parameters. (1-11) Qualifying individuals who decline randomization will be asked if they are willing to participate in a concurrent observational cohort study group. Treatment in the observational cohort will be selected by the patient and will include the option to receive TFESI and/or PT.

Background

There is no doubt that lumbar radiculopathy is a prevalent, disabling, and costly entity, both to afflicted individuals and western society. (12-18) As the cost of health care continues to rise, the efficacy of surgery, epidural injections, physical therapy and other treatment modalities for lumbar radiculopathy have come under close review. Recently published reviews have questioned the efficacy of epidural steroid injections for the treatment of lumbar radiculopathy. (19, 20) Armon, et al, representing the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, concluded that: although there is evidence for short term improvement (2-6 weeks) of lumbar radicular pain with epidural corticosteroid injections, these injections “have shown no impact on average impairment of function, on need for surgery, or on long term pain relief beyond 3 months” and their routine use was not indicated. (19) There has been continued discussion regarding pain procedure related costs, guidelines, and policy (see Appendix I). (21-29) The cost effectiveness of TFESIs clearly hinge on their efficacy, in terms not only of pain relief, but increased function and productivity, as well. There is clearly a need for a randomized, controlled, study that assesses the efficacy of TFESI in the treatment of subacute lumbar radicular pain due to disc protrusion.

Epidural steroid injections (ESI) have been used since the 1950s for treatment of back pain (30, 31). Since that time, ESI have changed from blind techniques performed in the office to targeted
injections, performed under fluoroscopic guidance. Recent studies have suggested that targeting steroid medication to specific sites of pathology may lead to better outcomes. Ackerman treated patients with L5/S1 disc herniations with either an interlaminar, caudal, or transforaminal approach and found the transforaminal approach superior in providing pain relief (32). Rosenberg evaluated whether spinal stenosis, post-surgical pain, or disc pathology would respond to a TF injection, and it was found that patients with disc pathology experienced the greatest response. Additional studies have also demonstrated a better effect when the pathology is related to the intervertebral disc (33, 34).

Data has supported the presence and significance of various inflammatory chemicals that are found at the site of disc injury (35-37). Periradicular installation of glucocorticoids may decrease pain by many mechanisms, including: the decrease of prostaglandin and leukotriene synthesis and PMN migration, modulation of peripheral nociceptor neurons, through a direct membrane stabilization mechanism as well as the modulation of spinal cord dorsal horn cells, and may have a slight anesthetic effect (38). These may provide a direct means for pain relief. This, potentially sustained, pain relief may in turn allow a return to a normal functional level.

The treatment of lumbar radicular pain frequently entails a combination of medications, therapies, and injections to manage pain and return patients to their daily living and work activities. Physical therapy can play a role in non-operative care of radicular pain to help restore appropriate movement and function. Saal evaluated patients with herniated discs with radicular pain and found that 90% had good to excellent results with aggressive therapy (39). Not only can specific therapy help reduce pain, but it can also decrease the amount of time away from work (40). Physical therapy plays an important role in treating patients with radiculopathies and is occasionally prescribed to alleviate associated back and leg pain (41). The physical therapy protocol used for this study was designed with specificity and reproducibility in mind, but also serves to provide a comprehensive and evidence based approach. Please see Appendix II for additional background information.

The primary outcome measure for this study will be reduction in pain as measured by a three day average Visual Analog Scale (VAS). Several researchers have studied the numeric rating scale (NRS) and/or the VAS and have found the minimal clinically meaningful change to be a 2 point (or 2 cm) or 30% change, and a ≥ 4 point or 50% change to be substantial. (4, 5, 11) We have chosen the more rigorous and meaningful 50% change as the benchmark for determining a positive or successful outcome in this study. Secondary measures will include: Oswestry Disability Index (ODI), SF-36, a seven point Global Perception of Change (GPC), a three question Patient Specific Activity Questionnaire (PSAQ), and analgesic, outside medical care, and surgical option utilization, as well as physical exam and physical therapy test parameters.(1-11)

**Number of Subjects**

40 subjects will be enrolled in each group (TFESI and PT). An additional 40 subjects will be enrolled into the concurrent observational cohort.

To arrive at a maximum sample size of 30 per group for Study I, one needs to assume a one-sided confidence interval (i.e. ignoring the possibility that the ESI group might be less efficacious than the PT group). In this case, the following statement is generated by the software.

When the sample size in each group is 30, a one-sided 95.0% confidence interval for the difference between a Group 1 proportion, \( \hat{p}_1 \), of 0.500 and a Group 2 proportion, \( \hat{p}_2 \), of 0.750 based on the large sample normal approximation will extend 0.200 from the observed difference in proportions.

This sample size calculation is based on an estimation of 75% of the treatment group reaching a positive outcome status, versus 50% of the control group, which may represent an overestimation of effect. We estimate a 15% drop-out rate in this study by patients electing to undergo surgical intervention, or for other reasons. Thus, 40 was chosen as the per group enrollment sample size.

**Gender of Subjects**

It is expected that an equal distribution of men and women will meet the inclusion/exclusion criteria and be enrolled in the trial.

**Age of Subjects**

Adults aged 18-64 are eligible for enrollment.

**Racial and Ethnic Origin**

The racial and ethnic mix will reflect the patient population of the practice(s) involved with the study, within the greater Denver area.

**Vulnerable Subjects**

No vulnerable subjects will be enrolled in this trial.

**Experimental Treatment**

There are no experimental treatments or testing in this trial. All procedures that are performed in this trial are standard, accepted medical procedures.

**Study Design/Methods:**

Research hypothesis:
Transforaminal epidural corticosteroid/anesthetic injections are more effective in relieving lumbar radicular pain than physical therapy.

**Target Population**

Appropriate study subjects will be identified upon initiation of care (MD evaluation and/or physical therapy). They will have pain of less than or equal to three months duration, within the current pain episode. This may be the initial pain episode or the onset of a most recent episode of pain, preceded by at least a six month pain free interval. They will have focal disc herniation with correlating radicular symptoms and possible radicular/neurological deficits. These radicular symptoms/signs are defined as pain or paresthesias below the knee, pain reproduction with straight-leg-raising and/or extension or quadrant maneuvers, and radicular pattern sensory, reflex or strength changes. These symptoms will be consistent with the level of nerve root impingement. Only subjects with radiculopathy primarily at L5 and/or S1, due to pathology at L4-5 and/or L5-S1 disc levels will be included. Those with canal and foraminal compromise due to disc protrusion at L4-5 with L5 > L4 signs and symptoms WILL be included. Those with predominantly degenerative stenosis, degenerative spondylolisthesis, or spondylolysis will be excluded. Subjects also need to have an eleven point Likert pain scale score greater than or equal to four. They will not have a history of prior epidural steroid injections within the prior year or prior lumbar surgery.

**Inclusion Criteria:**

1. Low back pain episode less than or equal to 12 weeks in duration.
2. Visual analog score (VAS) or screening Likert pain scale score three day average and present pain of at least four/ten at baseline.
3. Age 18 to 64.
4. Subjects will have focal disc herniation with unilateral radicular/neurological deficits or correlating radicular symptoms. These radicular symptoms/signs are defined as pain or paresthesias below the knee, pain reproduction with straight-leg-raising and/or extension or quadrant maneuvers, and radicular pattern sensory, reflex or strength changes. These symptoms will be consistent with their level of nerve root impingement and will primarily involve the L5 and/or S1 roots.
5. Those with canal and foraminal compromise due to disc herniation at L4-5 with L5 > L4 signs and symptoms WILL be included.

**Exclusion Criteria:**

1. Litigation.
2. Workers compensation.
3. Those receiving remuneration for their pain, e.g. disability.
5. Scoliosis of > 15 degrees
6. Those unable to read English and complete the assessment instruments.
7. Spondylolysis, with or without spondylololithesis, degenerative spondylolisthesis, or stenosis due primarily to degenerative bony or soft tissue changes.
8. Systemic inflammatory arthritis (e.g. rheumatoid, lupus).
9. Addictive behaviour, severe clinical depression, or psychotic features.
10. Significant lower extremity pathology that effects gait.
11. Sustained cervical or thoracic pain that is present at a level ≥4/10 on VAS.
12. Possible pregnancy or other reason that precludes the use of fluoroscopy.
13. Prior lumbar surgery
14. Prior epidural steroid injections for treatment of current episode or within the prior year
15. Bilateral radicular signs/symptoms (< 90% laterality of pain intensity or bilateral neurological signs)
16. No more than 4 PT sessions for current episode

Study Patient Identification:

Multiple physicians and physical therapists will be participating in this study. This group will consist only of physicians and physical therapists with specific training and practice emphasis in spine care. These practitioners will be identified prior to the start of the study and their practices will make up the catchment area for the identification of patients appropriate for this study. Community and outside medical practice awareness of the study will be heightened as possible through advertising and personal contact. Potential subjects will be given introductory information regarding this study and referrals to physicians actively participating in the study will be made with a goal of enrolling appropriate candidates and initiating the evaluation and intervention process in a timely manner. They will complete a Likert Pain Scale, and patients with persistent low back pain rated 4 or greater out of 10 on a screening 11 point Likert Pain Scale will be invited to participate in the study.

Study Timeline and Outline

1. Potential research participants identified from clinic population
2. Initial evaluation and study eligibility determination
3. Presentation of study to patient and informed consent obtained
4. Baseline pain and outcome measures evaluation (VAS, SF-36, ODI, GPC, PSAQ, physical exam, work history, analgesic use log, and ancillary treatment log)
5. Randomization to TFESI or PT group, if subject declines then inquire about enrolment in the observational cohort
6. Injection: Anesthetic/corticosteroid (per randomization); repeat 1-3 times if clinically indicated
7. Physical therapy carried out per protocol; 2-3 times per week for a total of 12 treatment sessions (excluding initial evaluation, including exit evaluation, minimum attendance 8/12) to be completed by 6 weeks from initiation of care (within study)
8. MD visit at intake evaluation, 4 weeks, 12 weeks, 6 months, and 12 months (additional phone contact or prn follow up will be logged as additional care)
9. Pain and functional evaluations at: baseline, 4 weeks, 12 weeks, 6 months, 12 months (VAS, SF-36, ODI, GPC, PSAQ, work history, analgesic use log, and ancillary treatment log)
Baseline evaluations:

Upon entry to the study, baseline measurements of the patient's pain and function will be established. The primary outcome measure for this study will be reduction in pain as measured by a three day average Visual Analog Scale (VAS). Secondary measures will include: Oswestry Disability Index (ODI), SF-36, a seven point Global Perception of Change (GPC), a three question Patient Specific Activity Questionnaire (PSAQ) (each patient will list 3 cardinal activities of daily living that are restricted or rendered impossible because of their pain and will score each item), and utilization of analgesic, outside medical care, and surgical options, as well as physician physical exam test parameters (see below).

Treatment Protocol: Physical Therapy (see appendix: Physical Therapy Protocol)

The physical therapy protocol will be divided into 3 phases (See Appendix III for details). The first phase will consist of 1-4 sessions. The first session in phase I will include an initial baseline evaluation of posture, deep tendon reflexes, straight leg raise, sensation, manual muscle testing, range of motion, and stabilization assessment. As phase I continues, the therapist will address core exercises, and protective positioning of the lumbar and sacral area. Phase I will also contain an educational video which includes introduction to study expectations, lumbar anatomy, body mechanics restrictions, protective positioning, and general exercise instruction (provided peripheralization does not occur). This video will also be provided to the TFESI study arm subjects.

Once the patient has completed 5 sessions or has obtained a 50% reduction in leg pain, then the patient will progress to phase II. During the second phase, all first phase core exercises, lateral shift interventions, and protective positioning will be continued as needed. Functional tests and interventions will include squat to lift of a light box from the floor, transfer from supine to sitting, transfer from sitting to standing, reaching overhead to a shelf, and straight back forward bending (bow). Additional core exercises included in this phase are guided by directional preference/tolerance. As in the first phase, the second phase will include leg pain control interventions (traction, shift correction, and protective positioning, and directional preference guidance of exercise prescription). Phase II will continue until 50% reduction in leg pain from the beginning of stage II or the patient has reached the 12th session.

The third phase consists of discharge, final evaluation, and home exercise log maintenance until the 3 month followup. Discharge criteria includes a 90% decrease of back and leg symptoms, independence with a home exercise program, and passing of neurological screens, stabilization exercise level and range of motion testing, and assurance that patients have identified and participated in some form of aerobic cardiovascular exercise. They will maintain an exercise and home therapy log for 6 weeks following discharge, which will be reviewed at the 12 week assessment. At baseline, and again at discharge from Physical Therapy, documentation of physical exam and functional item findings will be carried out. See Appendix IV for details. In short, this will include neurological exam, measurement of SLR and AROM (lumbar), and similar parameters.

Treatment Protocol: Injections
The initial injection(s) will be carried out after baseline physician and outcome assessment tool evaluations are completed. Levels will be selected on the basis of history, exam, and imaging data. Injections will then be done in a staged fashion, beginning with no more than two foraminal levels. For example: subjects with paracentral L4-5 HNP with L5 radiculopathy would receive an L5-S1 transforaminal (subpedicular) injection and, according to whether or not contrast/injectate reaches the L4-5 disc pathology, an L4-5 transforaminal (perhaps retrodiscal) injection might be carried out. Contrast will be injected under live fluoroscopy. Provided that the contrast spread is appropriately epidural, without vascular, thecal, or intraneural uptake, a total of no more than 4.0 cc of injectate will then be injected slowly and cautiously, the dose of injectate being divided between levels if more than one foramen is targeted, with attention to patient comfort and avoidance of over pressurization. The mixture will consist of 1.0% PF lidocaine and 40mg/cc PF triamcinolone acetate or 80mg/cc methylprednisolone acetate (up to a maximum of 80 mg total corticosteroid).

The procedures are performed in a fluoroscopy suite with sterile, surgical technique. The majority of the TF injections will be carried out using 3.5 inch, 25 gauge Quincke needles. In the case of those subjects too large to reach the target foramen/foramina with a 3.5 inch needle, a 4-11/16ths inch or longer 25 gauge Quincke needle will be used. Intravenous conscious sedation may be administered, if patient anxiety level or desire dictates. Fluoroscopic target identification and needle tip entry into the targeted foramina will be carried out using the procedural techniques outlined in Bogduk/International Spine Intervention Society: Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 2004: pp 169-187, for the subpedicular, retroneural, and S1 transforaminal procedures(42), and per Jasper (43) for retrodiscal transforaminal procedures. The choice of approach to the foramina will be dictated by patient anatomy/pathology. The goal of each injection will be to observe the spread of contrast to the location of the pathology observed on the MRI. To achieve this, the needle position may have to be relocated at times.

The patient will be instructed to maintain a pain diary that records the degree and duration of any relief. The pain diary will have an 11 point Likert scale. The left hand end will have the statement “no pain” and the right hand end will have the statement “worst possible pain.” Separate scores will be used for the recording of the level of pain 30 minutes, one hour and then hourly after the diagnostic block for 6 hours. The subjects will mail or fax the completed pain diaries for review by the research coordinator.

A positive response is defined as: lower extremity pain relief greater than or equal to 75% as assessed by patient specific provocation, targeting change in NPR or subjective percentage change [patient estimation]. The patient should rate their pain only after they stand, walk, and move through their normal positions of discomfort or maneuvers that typically cause pain. The response will be considered positive only if there is at least 1.5 hr of relief. Furthermore, while relieved of their pain, patients must be able to regain the activities of daily living that previously had been impeded by their pain. This injection response specific data collection is not germane to the overall study purpose or outcome assessment, but will be collected for sub-group or other analyses.

Study patients will be scheduled for a 2nd injection 2 weeks (12-20 days) after the first injection. This 2nd injection will be cancelled if the patient maintains >90% relief of leg pain following the
1st injection, or if the patient declines further injections. During the study period, all study patients in the injection group will be offered additional (up to a maximum 4 total within the 12 month study timeframe) TFESIs if believed to be clinically indicated or necessary by the attending physician. All repeat injections will be carried out in the same fashion as the initial injection.

**Treatment Protocol: Observational cohort**

Participants in this group will choose their treatment (per-protocol physical therapy, injections, or both) after consulting with their physicians.

**Collection of data**

At the 4 and 12 week, and 6 and 12 month follow-up assessments, patients will complete the same outcome tools used at baseline (VAS, SF-36, ODI, GPC, PSAQ, work history, analgesic use log [through 12 weeks], and ancillary treatment log). Physician and physical therapy examination data, as well as the initial response to TFESI, will be recorded. Thus, data will be collected at baseline, 3 to 5 weeks, 11 to 13 weeks, 5 ½ to 6 ½ months, and 11 ½ to 12 ½ months from entry to the study and initiation of treatment.

If sufficiently disabling pain persists during or beyond the active treatment phase of this study, those individual subjects will undergo their final data collection evaluation and then additional treatment options outside the scope of this study may be offered (i.e. crossover into the alternative treatment group, surgical interventions, etc.).

The data obtained will be entered into a database (e.g. using Microsoft Access) such that there can be an appropriate interface with a statistical package (e.g. SPSS).

**Patient Incentive**

Patients will be provided incentive to participate in the study by reimbursing them for some of their indirect medical costs, time, and travel costs. Reimbursement will be provided at intake ($100), 4 week ($50), 12 week ($50), 6 month ($100), and 12 month ($100) follow-up visits, as well as through direct thanks, by providing them with a high level of care and education, and through their own intrinsic satisfaction of knowing that they have helped further the science of spine care.

**Patient Costs**

The majority of active care rendered in this study will be “medically reasonable and necessary” in the eyes of the subjects’ insurance carriers. Thus, when possible, treatment rendered will be billed to the subjects’ insurance carriers or to the subjects directly. Subjects are financially responsible for any test or treatments for their spinal condition that may be sought outside of the study protocol. These non-study related costs may include, but are not limited to: x-rays, CT scans, bone scans, MRIs, chiropractic care, physical therapy, acupuncture, massage, medications, and second or subsequent lumbar injection sessions.
Transition from Research Participation
Once the subjects are terminated from the trial, they will return to their referring physicians and/or primary care physicians for usual care.

Rescue Treatment and Group Crossover
At the 4 week follow-up, subjects who are not satisfied with treatment will be provided the option to cross-over to the alternate treatment group. All subject crossovers will be documented. In the event of patient crossover, outcome data will continue to be collected at times according to the index treatment. Data will be analyzed by a last observation carried forward (LOCF) and intent to treat (ITT) methodology.

Withdrawal from Treatment Group
Participation in the study is completely voluntary. Subjects will be encouraged to complete the entire research protocol, however, subjects are allowed to withdrawal from the study at will. Furthermore, if at any time during the course of the study the patient and/or the treating physician think that continued participation in the study is not in the best interest of the patient, he or she will withdraw from the study and receive any treatment deemed appropriate by the treating physician. All such treatment outside of the randomized protocol will be documented. In the event of a patient drop, final outcome data will be collected and handled with a last observation carried forward (LOCF) methodology.

Ethical considerations
The randomised, controlled, prospective design is a powerful way of determining the effectiveness of an intervention. Necessarily, this involves giving some participants a control therapy (physical therapy) and therefore exposing them to potential risks of the therapy or lack of benefit resulting from randomization to the control group. In this study the risks of any complications from the control therapy are very small and any discomfort should be mild and of brief duration. All participants will have the active therapy made available to them at the termination of the study if they so desire. The investigators will be available during and after all procedures to ensure that any complications or adverse effects are handled promptly and capably. All participants will receive full and frank appraisals of the benefits and risks attached to the procedures. Participation will be voluntary. There will be no consequences from voluntary withdrawal from the study. Identifying data will not be used in publications and all information separate from the outpatient surgery center records will be in secure storage with access restricted to the investigators.

Risk/Benefit Assessment

Risk Category: Minimal.

Risks: There is the possibility of post-procedural soreness for one to five days after the transforaminal injections. There is a chance (less than 2%) of substantial local bleeding, infection, nerve root injury, or post dural puncture headaches. There is a remote risk of permanent nerve damage to one or more of the spinal nerves. All possible procedural and peri-
procedural safety and comfort measures possible will be employed.

Higher dose of x-ray exposure than what is standard medical practice for fluoroscopic pain management procedures will not occur.

**Potential Benefits:** Subjects enrolled in this trial may obtain substantial and long-lasting relief of their low back and leg pain. Patients will also receive some financial incentive to participate (see Patient Incentive and Patient Cost sections). Furthermore, they will be thanked for, and receive the intrinsic satisfaction of knowing that they have helped further the science of spine care.

**Method of Subject Identification and Recruitment**

Identification of patients for this study will be done as outlined in the Study Design section above. Those patients who fulfil the criteria for this study will be offered participation. Patients that are referred to the clinical practices of physicians participating in the study and their practice partners will be evaluated for this study. If patients fulfil the criteria for this study, they will be offered participation. It will be presented in an unbiased, non-stressed fashion. A quick summary of the study will be presented. If they ask additional questions and remain interested in the study after a quick study summary is presented, discussions will continue and the consent process will begin if they continue to be interested in becoming a research subject. If they decline to enrol in the randomized portion of the study they will be asked if they are interested in participating in an observational study that allows them to choose between physical therapy, injections, or both treatments. If they voice that they are not interested at any point, further discussion regarding the study will cease and usual care will be continued.

The study research coordinator or physicians involved in this study will obtain consent. In a closed quiet room, the potential research subject will be able to ask any questions regarding the trial. Spine models may be used in providing explanations, if appropriate. This process will not be rushed.

The research subject will be provided a copy of the consent, and the consent will remain in the research chart that is available only to the research physicians.

**Data Monitoring**

When 40 subjects (50%) have enrolled in the randomized portion of the study, an interim analysis will be performed. If less than 20% of the active treatment group obtain at least 50% pain relief at the 6 week follow-up, the study will cease on ethical grounds.

**Data Analysis**

The primary outcome measure will be relief of pain. Success is to be defined as reduction of pain by at least 50%, but will additionally be stratified into those patients who obtain complete relief of pain, and those who obtain greater than 30% or greater than 75% relief, as well. The proportions of patients achieving any of these grades of relief will be compared using 95% confidence intervals of the proportions. The study will have a positive result if the 95% confidence intervals do not overlap.
Secondary outcome measures will be used to corroborate success as defined by relief of pain. These include measures of functional improvement, patient satisfaction and economic outcomes (see Appendix I for more details regarding economic outcomes analysis). Within groups, correlations will be calculated between the pain scores before and after treatment, and the scores on each secondary outcome measure. The objective is to test if relief of pain is consistently associated with improvement in function, patient satisfaction, return to work, etc.

For continuous variables, correlation coefficients will be calculated. For categorical variables chi squared analysis will be used. Sensitivity analysis will be used to determine the threshold for significant relationships between categorical variables. Between groups, three types of analysis will be used. For continuous variables, total group data will be compared using means and standards, or median values and interquartile ranges, depending on the nature of the distribution that emerges. The same statistics will be used to compare those subsets of patients in each group who obtain particular grades of relief of pain. For categorical variables, such as return to work and other health care use, chi squared analysis will be used to compare both total group data, and subsets who achieve particular grades of relief. Finally, all continuous variables will be converted to categorical data, according to minimal detectable change and to minimal clinically significant change, and the proportions achieving these grades in each group will be compared using 95% confidence intervals and chi squared analysis.

In the event of a patient drop out or crossover, final outcome data will be collected and handled with a last observation carried forward (LOCF) methodology.

**Storage of data**

Clinical notes of a routine nature will be maintained as part of the medical record. All clinical information related to the study will be stored under the supervision of outcome assessors in a locked cabinet. These research charts will remain separate from routine clinic charts. They will remain in the locked offices of the outcome assessors. They will be available only to the additional research investigators that are serving as outcome assessors. There will be no unauthorized access.

Each patient will be assigned a research number. Their baseline, treatment and outcomes information will then be prospectively entered into a database in reference to this research number. Only the staff involved in the study will have access to this separate database which will be password protected.

All data not routinely kept in the surgery center or clinic medical record will be shredded or erased when research publications have been finalized. The surgery center and clinic records will be subject to the usual laws of access and retention.

**Appendix I:**

There has been continued discussion regarding pain procedure related costs, guidelines, and policy (62). Tosteson reviewed missed work, utilization of resources, and housekeeping days from the SPORT trial and concluded that non-surgical treatment of radiculopathy cost
significantly less than surgical treatment, although surgery held an advantage over conservative care in quality adjusted life years (QALY) of 0.21, at a cost of $69,403 per QALY gained. The non-surgical treatment included physical therapy and epidural injections, but in an uncontrolled and ill-defined manner. Riew found that transforaminal epidural steroid injections, compared to anesthetic alone, reduced the need for surgery. Karppinen, et al. looked at the cost effectiveness of periradicular steroid infiltration for sciatica and found that the surgery prevention rate, and thus cost effectiveness, was greater in the subgroup with contained herniations (saving $12,666 per responder versus the subgroup with disc extrusions (costing $4445 more per injection responder)). The cost effectiveness of TFESIs clearly hinge on their efficacy, not only in terms of pain relief, but also increased function and productivity, as well. Physical therapy is cost effective when adherence to a physical therapy program is maintained. The chapters pertaining to low back and chronic pain in the guidelines by the American College of Occupational and Environmental Medicine have spurred a discussion regarding the use of such guidelines for coverage decisions and their potential for misuse and “mis-guidance” by way of agenda based biases.

To estimate the cost effectiveness of TFESI and PT treatments we will track resource utilization at each study visit. In our analysis, we will distinguish among direct costs and indirect costs. Economic outcomes will include the economic endpoints (resource utilization and days lost from work) that are used to estimate direct medical and indirect costs, and the quality-adjusted life years (QALYs) conversions of the SF-36 and ODI outcomes measures. These data will be used to perform a cost-utility analysis that will include calculations of the cost-utility ratio and the incremental cost-effectiveness ratio.

More specifically, to estimate indirect costs associated with time lost from work, we will use 2010 average income data for the state of California to allow for assigning costs to lost work hours. To identify direct costs associated with treatment, patients are questioned at follow-up visits about treatment since the last study visit. Any inpatient services include both physician and hospital components of costs for each hospital stay experienced during the period of follow-up. Such stays are costed according to DRG (diagnosis-related group) weights and CPT (current procedure terminology) codes using hospital DRG reimbursement by CPT and participating facility national standardized payment amounts. Additional costs incurred during hospitalization include physician and diagnostic service expenses, which are estimated with the resource-based relative value scale (RBRVS). The RBRVS is used by the Centers for Medicare and Medicaid services (Medicare Program Part B schedule for physicians services: Final Rule. 405,413,415 ed: Health Care Financing Administration: Part III. Department of Health and Human Services; 1991.) to reimburse physicians for their services. Under the RBRVS, each CPT code is given a total relative value unit (RVU) weight. To estimate costs associated with physician’s services for each CPT code, unit costs are assigned to each test and procedure based on national allowable payment amounts. For each participant, self-reported medical resource use is multiplied by unit costs to obtain an estimate of resource use at each time point. This approach has the advantage of reflecting national fee schedules and relating them to the RBRVS. We favor this approach over using institution and cost-center-specific cost-to-charge ratios to estimate cost because it can be generalized to the US population. Relevant physician costs for outpatient services are estimated.
using the same approach as for physician inpatient services. These are broken into physician services, other professional services, laboratory and diagnostic testing, and devices. RVU’s for outpatient laboratory and diagnostic services have been derived by dividing the Medicare allowable charge by the appropriate RVU multiplier, as above. To estimate costs of medications or other health care services not routinely covered by Medicare, units of utilization are multiplied by prevailing charges to estimate costs of each item for each patient.

Basic analyses will parallel the procedures used for the primary health status measure. Overall differences in costs and health state values will be calculated on an as-treated basis with appropriate adjustments for differences between the treatment groups. Longitudinal modeling appropriate for repeated measures data will be used to perform inferences for treatment effects at individual time points and for the overall differences in cost and health state values. Estimates for QALYs and cumulative costs will be derived from the longitudinal modeling. The estimates of incremental costs will be done two ways: first, considering only direct medical costs (a perspective of interest for healthcare payors), and second, including indirect costs (i.e., productivity losses which are of interest from a societal perspective).

The goal of the cost-effectiveness evaluation is to estimate the incremental costs associated with TFESI versus PT management of patients relative to the incremental benefit. Thus, the primary outcome measure for the cost-effectiveness evaluation is the incremental cost-effectiveness ratio, which estimates the net change in cost, \( \Delta C \), divided by the net change in effectiveness (QALYs) when interventions are ranked in order of increasing cost. The incremental cost-effectiveness ratio (ICER) = \( \Delta C / \Delta QALY \), allows us to estimate and compare the value of interventions in spinal disease with interventions in other diseases. The primary cost-effectiveness endpoint will be the cost per QALY gained for TFESI relative to PT care.

Appendix II: (considerations regarding physical therapy protocol)

Once a patient has been assessed, the physiotherapist develops a treatment plan targeting the patient’s radiculopathy which includes stabilization and lumbar positioning training. Local stabilizing musculature operates in an anticipatory feed-forward mechanism prior to the actual motion in an effort to aid in the body’s ability to maintain stability. These muscles provide joint protection and support before load occurs and is key for sudden unexpected motions. As described by Comerford, an impairment in the area would present as a dysfunction in the ability of the deep segmental musculature to control a neutral joint position. Local muscles are the deepest layer of muscles that insert segmentally, and/or polysegmentally. They work independent of direction. These muscles include the transverse abdominus, local segmental multifidus, iliopsoas, and deep sacral gluteus maximus. A review of the status of our understanding of the function and clinical significance of the multifidi can be found in MacDonald 2006.

Global stabilization musculature is responsible for controlling the position of the spine through a range of motion. Imbalances or dysfunction in this area occur due to changes in functional length or recruitment of this musculature. The function of these muscles is to generate torque unlike local muscles which maintain a low force continuous activity. These muscles provide eccentric control of end ranges of joint motion. In order to demonstrate sufficient control in the
areas of flexion, rotation, and extension the motion must be performed through a specific range. This must be done without substitution patterns and with relative ease (46).

According to Comerford et al (12), it generally takes about two weeks for the patient to feel decreased symptoms and start to achieve improved motor function. The theory behind this is that if they can learn to control the segment then they can stop the pain(47, 48). The testing of the global stabilizers looks at dissociating movement from one joint to another. It is done in a variety of specific positions in an effort to determine if the stability muscles have efficiency to control direction specific to stress and strain.

O’Sullivan et al found that specific exercises geared toward retraining of the deep abdominals and lumbar multifidus provided statistically significant decreases in pain and an improved level of function as compared to a general exercise group at 30 month follow-up(49). In the American Physical Therapy Association Guide of Physical Therapist Practice it is predicated that the patient should require between 8 and 24 visits to achieve the anticipated goals and expected outcomes(50).

The treatment based classification (TBC) approach to low back syndrome (pain) purposed by Delitto et al (1995) presents several key examination findings that would suggest that a patient would benefit from stabilization exercises. These include a subjective report of frequent prior episodes of LBP, increasing frequency of episodes of LBP, an instability catch or painful arcs during lumbar flexion and extension ROM, hypermobility of the lumbar spine, and a positive prone instability test (51). This classification system also included three other classifications: specific exercise (flexion, extension, and lateral shift patterns), manipulation, and traction. With the extension and flexion classifications the patient’s symptoms centralize when they move in that specific direction. The patient is then given exercises that move them into that direction, have mobilization techniques that promote movement in that direction, and are also instructed on avoiding activities that move them out of that preferred pattern(51). Such directional-based therapies have demonstrated good outcomes in the treatment of back pain with radicular symptoms. Thus, we have incorporated ‘direction of preference’ principles, as elucidated by McKenzie and Sahrmann (57-61), among others, into the physical therapy protocol. These will be used for symptom relief and for guidance in individualizing patients’ home exercise programs.

The treatment based classification (TBC) approach, as described in the preceding paragraph, may have only a limited overlap with the clinical findings of our study subjects. Nevertheless, patients will be guided towards incorporating some stabilization exercises into their programs, to their level of tolerance. Reviews of the literature reveals mixed results regarding the efficacy of specific stabilization exercise verses general exercise (45, 52). Literature that supports general exercises did not, however, take into account the TBC system to determine if the patient population studied would benefit from stabilization exercises (53, 54).

Education on lumbar spine repositioning needed to occur with posture and with specific activities due to lumbar repositioning deficits that are commonly seen in patients with low back pain and to prevent additional neural compression (47, 55). There are studies demonstrating decreased lumbar proprioception in patients with chronic LBP and patients with lumbar spine instability. The study by O’ Sullivan et al. showed the need to address proprioception and repositioning of lumbar neutral because of its potential contribution to ongoing and recurrent pain.(47) There are
also studies showing that trunk muscle recruitment patterns are different in patients with LBP, and that suggests that it is likely that training the stability muscles in this population would have an effect on function and increase spine stability (48). There has been delayed or absence of trunk muscle activation observed in patients with LBP. The abnormal or missing protective reflexes in LBP patients suggests impaired spinal stability. Active physical rehabilitation appears to improve this function (56).
Thanks:

This proposal is based upon the previous work of a few authors. We wish to thank the following for their substantial contributions to this proposal:

Scott Bainbridge, MD – for creating the initial proposal and outcomes instruments that were modified into the existing proposal.

Jonathan Lurie, MD and Kevin McGuire, MD – for sections related to the proposed cost effectiveness analysis, including Appendix I.
Bibliography:


Appendix III: Physical Therapy Protocol

2-3 times per week for a total of 12 treatment visits (excluding initial evaluation) to be completed by 6 weeks; minimum attendance 8/12 treatment visits.

Full evaluation at initial and discharge visits

Discharge criteria: 90% decrease in back and leg pain and independence with home exercise program (HEP) OR 12 visits

Physical Therapy Phases I-III:

Phase I: Sessions 1-4; progress to phase II if 50% reduction leg pain or session 5
Goal: decrease radicular sx/centralization
1. Baseline evaluation/appendix Ia
2. Lateral shift intervention/appendix Ib
3. Introduce CORE exercises, phase I/appendix Ic
4. Protective positioning & LS protection/appendix Id (possible IId)
5. HEP diary: CORE ex, lateral shift interventions
6. Physical modalities prn
7. Educational video #1/appendix Ie
8. Mechanical or manual traction optional

Phase II: continues until 12th session or discharge criteria met
Goal: pass all level I stabilization ex screens & highest possible phase II CORE and more diverse ex per evals at sessions 1 and/or 6
1. Continue phase I ex, lateral shift interventions until corrected, protective positioning as needed
2. Functional tests and interventions/appendix Iia
3. Re-evaluation per appendix Ia @ session 6
4. Supplementary ther ex per findings at sessions 1 or 6/appendix Iib
5. CORE exercises Phase II/appendix IIc
6. Further leg pain control interventions/appendix IId
7. HEP diary: all CORE ex, functional interventions, supplementary ther ex, walking or other tolerated aerobic exercise
8. Cautious mobilization and restoration of gross and segmental range of motion

Phase III: discharge criteria: 90% decrease in back & leg pain; independent in HEP; pass all discharge tests in appendix IIIa
1. D/C criteria achievement or 12th session, I w HEP, whichever met 1st
2. D/C evaluation per appendix Ia administered for comparison to baseline initial physical therapy evaluation
3. Follow-up measures/HEP diary kept & reviewed for 6 weeks post d/c

Physical Therapy Protocol Appendices:

Appendix Ia/Evaluation
1. Posture
   a. identify lateral shift, if present
   b. measure lordosis/kyphosis w dual inclinometry
2. Neurologic screens
   a. Measure SLR w pain described (seated and supine w ankle DF)
   b. LE pinwheel sensation (med leg, dorsal foot, dorsolateral foot)
   c. LE MMT of knee ext/flex, ADF, EHL, Ankle Eversion, Heel and Toe walk, 10 single leg toe raises each side
d. DTRs: patellar, med hamstring, Achilles
3. L/S AROM w dual inclinometry; flex/ext/lateral bend (AMA Guides…)
4. LE flexibility: hip flex/ext/rot, prone knee flex, hip flex tightness, ankle DF
5. Stabilization/strength tests: TA and segmental LM, local iliopsoas, Sahrmann level 1(modified as needed), bridging w single leg extension 15 sec hold x 2, standing, seated bow, and stand to sit demonstrate range w control to pass,

Appendix Ib/Lateral Shift Intervention
1. Active lateral shift correction in prone or standing (position of comfort)
2. Limit trunk motion to neutral until shift corrected
3. Intervention stops when shift corrected; reinstated if shift reappears at any phase

Appendix Ic/CORE Exercises Phase I
1. 2 sets of 10 if patient able, limits based on pain and ROS
2. Based on TBC: ex assuming extension and stabilization classification
   Stabilization: TA & LM local, add LE movements, marching, level 1, seated and standing bow, bridging
   Prone-POE-prone press ups pending LE symptoms
3. Neural mobilization

Appendix Id/Protective Positioning
1. Subjects/therapists identify positions of relief
2. Ex program designed to avoid peripheralization; promote pain relief
3. Back protection education: self ergonomic eval of work station; log roll to get out of bed; no full range trunk rotation, no (kyphotic) unsupported forward bending, no resistive ex w L/S vertical compression

Appendix Ie/Educational Video Contents
1. Includes: introduction to study expectations; body mechanics instruction; protective positioning to control leg pain; proper lifting technique; aerobic and strength training principles including parameters to prevent over fatigue of weak muscle groups; lumbar spine anatomy

Appendix IIa/Functional Tests and Interventions
1. Sum of scores: 2 – correct performance w no cues; 1 – correct but cues needed; 0 – incorrect
2. Intervene until score of 2 achieved for each test score
3. Repetitive practice for 15 repetitions of each activity that is in deficit:
   a. squat to lift empty box from floor
   b. supine to and from sitting
   c. sit to and from stand
   d. forward bow

Appendix IIb/Supplementary Therapeutic Exercises
1. Based on evaluation findings sessions #1 and #6
2. Close observation to avoid increase in lower extremity pain
3. Avoidance of excessive fatigue of muscles (during strength or endurance exercise) with myotomal/focal pattern weakness due to radiculopathy
4. 2 x 10 repetitions for strength and AROM
5. 20-30 sec hold, 3-5 reps for stretching
6. 10 x 10 sec hold for stabilization local re-training exercises

<table>
<thead>
<tr>
<th>Evaluation Finding</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/S AROM AND POSTURE</td>
<td></td>
</tr>
<tr>
<td>a. flexion&lt;50° or extension&gt;35°;lordosis&gt;40°</td>
<td>pelvic tilt; TA activation/control; dying bug; neutral spine w stand/walk; PT ball flexion ex</td>
</tr>
<tr>
<td>b. flexion&gt;70° or extension&lt;15°;lordosis&lt;15°</td>
<td>superman; bird dog; seated/standing bow; prone extension;</td>
</tr>
</tbody>
</table>
c. lateral flexion<15º, >35ºor L/R difference>5º  
   lateral band in standing; PT ball side to side rocking, strength stretch

d. minimum kyphosis>40º  
   wall angels; foam roll exercise/mobs

MYOTOMAL DEFICITS
a. anterior tibialis, EHL, ankle eveter  
   ankle alphabet; stretch band resistance; heel walking
b. plantar flexors  
   double toe raise/single leg lowering; toe walking
c. gluteal/hamstring/TFL/hip flexors/adductors  
   one legged stand/balance; floor/ball w one legged flex/ext/abd/adduct; standing band work

LOWER EXTREMITY FLEXIBILITY
a. any L/R difference >5º  
   specific muscle group stretch
b. single knee to chest <110º  
   hip extensor stretch
c. SLR <70º  
   hamstring stretch (perform stretch with LS neutral posture and hip maximally flexed moving knee into extension, discontinue stretch if increase in pain below the knee)

d. Thomas test failed  
   psoas stretch in side-lying
e. prone knee flexion <110º  
   quad stretch in prone
f. supine hip rotation <30º IR or ER  
   IR/ER in supine
g. ankle dorsiflexion <10º  
   gastroc & soleus stretches

STRENGTH & STABILIZATION SCREENS
Stabilization/strength tests: local TA and segmental LM, Sahrmann level 1, bridging w single leg extension 15 sec hold x 2, standing, stand to sit, seated bow-demonstrate range w control to pass

CARDIOVASCULAR
a. goal of 5 x 30 min (2 ½hr/wk) @ 60-75%MHR  
   identify tolerated form of aerobic exercise (walk/bike/elliptical/etc); log in ex diary

Appendix IIc/CORE Exercises Phase II (Examples/Options – not limited to but including)
1. 2 x 10 repetitions
2. Progress length of time POE (prone on elbows) or w press-up
3. Superman or swimmers
4. Stabilization ex. on exercise ball – only after pass level I abdominals
5. Lunges: straight and lateral
6. QL/Oblique strengthening in side plank (knees bent initially)
7. Bridging progression to knee extensions and increasing hold time to 10 seconds
8. Dying bug
9. Squats; one legged stand/balance
Appendix IIId/Additional Pain Control Interventions
1. Use if lower extremity pain has not subsided
2. Addition of manual or gravitational traction
3. More aggressive shift correction
4. Protective spine positioning
5. Neural mobility
6. Manual therapy: gapping/opening techniques, joint mobilization of joints isolated from L4-S1 (i.e. thoracic), or cautious use of grade I-II mobilization for local pain control
7. Physical modalities

Appendix IIIa/Discharge Tests
1. Required to pass all tests before discharge (if before 12th visit)
2. All neuro screens
3. All stabilization tests
4. Lumbosacral AROM measures
5. Identify chosen aerobic exercise type
6. Subject encouraged to continue HEP and maintain exercise log for review at 12 week study follow up