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Intrinsic Therapeutics

A PROSPECTIVE, RANDOMIZED, MULTICENTER STUDY TO DEMONSTRATE THE SUPERIORITY OF THE BARRICAID® TO DISCECTOMY FOR PRIMARY LUMBAR DISC HERNIATION

Protocol Number: EUBARD-CP-001

May 10, 2011

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SIGNATURE PAGE

The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to Good Clinical Practice and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (EC).

It is agreed that all participants in this study will provide written informed consent to study procedures as agreed by the Institutional Review Board or Independent Ethics Committee.

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1 PROTOCOL SUMMARY

Title:	A Prospective, Randomized, Multicenter Study to Demonstrate the Superiority of the Barricaid to Discectomy for Primary Lumbar Disc Herniation
Device:	Barricaid device (Polyester Mesh, ePTFE Coated Polyester Sutures, Platinum Iridium Markers and Ti-6AI-4V Alloy Anchor) Barricaid Delivery Tool
Indication:	The Barricaid is indicated for patients with radiculopathy (with or without back pain), a positive Straight Leg Raise (L45, L5S1) or femoral stretch test (L12, L23, L34), and a posterior or posterolateral herniation at one level between L1 and S1 with radiographic confirmation of neural compression using MRI who are found to have an annular defect (post discectomy) which measures between 4mm and 6mm tall and between 6mm and 10mm wide, have a minimum posterior disc height of 5mm, and have failed at least 6 weeks of conservative treatment
Study Objective:	The purpose of this prospective, randomized, multicenter study is to demonstrate the superiority of the Barricaid when used in conjunction with limited discectomy (as described by Spengler[1]), to limited discectomy alone, with regard to preventing reherniation and the recurrence of pain or dysfunction.

[1] Spengler, D. Lumbar Discectomy – Results with Limited Disc Excision and Selective Foraminotomy. Spine. Vol 7. No. 6, pgs 604 – 607, 1982

Study Endpoints:	This study has two co-primary endpoints. Success of the study will be analyzed at 24-months, and will be based on the Barricaid population achieving statistical superiority over the randomized non-implanted limited discectomy population. The following two co-primary endpoints will be analyzed: 1. A composite of safety and effectiveness. To be considered a success, a patient will have achieved success in **each** of the following components: • 15 point (out of 100 points) improvement in Oswestry compared to pre-op • 20 point (on a 100 point scale) improvement in VAS Leg (based on the primary leg complaint; if both legs have a minimum of 40/100 pre-operatively, the average leg score will be used) • Maintenance of average disc height (75% or greater of preoperative disc height) compared to pre-op • No deterioration of neurological status at the index level • Device integrity and lack of implant migration (radiographic, implanted patients only) • No spontaneous fusion • No reherniation at the index level (on either side) • No secondary surgical interventions at the index level 2. Reherniation: To be considered a success, a patient will have no evidence of recurrent herniation at the index level at any time up to and including the 24-month follow-up. Recurrent herniation may be confirmed surgically, or radiographically as determined by an independent review (unless surgically confirmed that the suspected herniation is not a herniation, e.g. scar tissue or residual nucleus material).
Study Design and Sample Size:	The purpose of this 24-month, prospective, randomized, multicenter study is to demonstrate the superiority of the Barricaid when used in conjunction with limited discectomy (as described by Spengler1), to limited discectomy alone, with regard to preventing reherniation and the recurrence of pain or dysfunction. This study will enroll a minimum of 400 patients and maximum of 800 patients through a Bayesian statistical approach. Patients will be enrolled at select European (approximately 15-20) sites. Patients that are scheduled for an L1-S1 discectomy and who meet the pre-operative eligibility criteria will be considered for study participation. Patients that meet all intraoperative criteria will be randomized to the Barricaid or Control. Randomization will be based on a 1:1 (Barricaid:Control) ratio. All patients randomized will be followed for at least 24 months.
Preoperative Inclusion Criteria:	<u>Subjects who meet the following criteria are eligible for study participation:</u> • Age 21 to 75 years old and skeletally mature (male or female). • Patients with posterior or posterolateral disc herniations at one level between L1 and

	S1 with radiographic confirmation of neural compression using MRI. [Note: Intraoperatively, only patients with an anular defect (post discectomy) between 4mm and 6mm tall and 6mm and 10mm wide shall qualify.] • At least six (6) weeks of failed, conservative treatment prior to surgery, including physical therapy, use of anti-inflammatory medications at maximum specified dosage and/or administration of epidural/facet injections. • Minimum posterior disc height of 5mm at the index level. • Radiculopathy (with or without back pain) with a positive Straight Leg Raise (0 – 60 degrees)[22] (L45, L5S1) or Femoral Stretch Test (L12, L23, L34) • Oswestry Questionnaire score of at least 40/100 at baseline. • VAS leg pain (one or both legs) of at least 40/100 at baseline. • Psychosocially, mentally and physically able to fully comply with the clinical protocol and willing to adhere to follow-up schedule and requirements.
Preoperative Exclusion Criteria:	<u>Subjects who meet any of the following criteria are not eligible for study participation:</u> • Spondylolisthesis Grade II or higher (25% slip or greater). • Subject requires spinal surgery other than a discectomy (with or without laminotomy) to treat leg/back pain (scar tissue and osteophyte removal is allowed). • Subject has back or non-radicular leg pain of unknown etiology. • Prior surgery at the index lumbar vertebral level. • Subject requiring a spine DEXA (i.e., patients with SCORE of ≥ 6) with a T Score less than -2.0 at the index level. For patients with a herniation at L5/S1, the average T score of L1-L4 shall be used. • Subject has clinically compromised vertebral bodies in the lumbosacral region due to any traumatic, neoplastic, metabolic, or infectious pathology. • Subject has sustained pathologic fractures of the vertebra or multiple fractures of the vertebra or hip. • Subject has scoliosis of greater than ten (10) degrees (both angular and rotational). • Any metabolic bone disease. • Subject has an active infection either systemic or local. • Subject has cauda equina syndrome or neurogenic bowel/bladder dysfunction. • Subject has severe arterial insufficiency of the legs or other peripheral vascular disease. (Screening on physical examination for patients with diminution or absence of dorsalis pedis or posterior tibialis pulses. If diminished or absent by palpation, then an arterial ultrasound is required with vascular plethysmography. If the absolute arterial pressure is below 50mm of Hg at the calf or ankle level, then the patient is to be excluded.) • Subject has significant peripheral neuropathy, patient defined as a patient with Type I or Type II diabetes or similar systemic metabolic condition causing decreased sensation in a stocking-like or non-radicular and non-dermatomal distribution in the lower extremities. • Subject has insulin-dependent diabetes mellitus. • Subject is morbidly obese (defined as a body mass index >40, or weighs more than 100 lbs over ideal body weight). • Subject has been diagnosed with active hepatitis, AIDS, or HIV. • Subject has been diagnosed with rheumatoid arthritis or other autoimmune disease.

	• Subject has a known allergy to titanium, polyethylene or polyester materials. • Any subject that cannot have a baseline MRI taken. • Subject is pregnant or interested in becoming pregnant in the next three (3) years. • Subject has active tuberculosis or has had tuberculosis in the past three (3) years. • Subject has a history of active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there have been no signs or symptoms of the malignancy for at least two (2) years. • Subject is immunologically suppressed, received steroids >1 month over the past year. • Currently taking anticoagulants, other than aspirin, unless the patient can be taken off the anticoagulant for surgery. • Subject has a current chemical/alcohol dependency or significant psychosocial disturbance. • Subject has a life expectancy of less than three (3) years. • Subject is currently involved in active spinal litigation. • Subject is currently involved in another investigational study. • Subject is incarcerated. • Any contraindication for MRI or CT scan (e.g. claustrophobia, contrast allergy).
Intraoperative Inclusion Criteria:	• Only patients with an anular defect (post discectomy) between 4mm and 6 mm tall and 6 mm and 10 mm wide shall qualify
Screening Visit *(within 30 days of surgery)*	• Determine eligibility • Signed Informed Consent • Medical/Surgical History • Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Adverse Events (occurring after Informed Consent is Signed) • Flexion/Extension, Neutral Lateral, Neutral AP X-Rays (within 60 days of surgery) • Low dose CT at index level & MRI (must be within 3 months of surgery)
Procedure Visit	• Confirmation of patients intra-operative eligibility • Randomization (Barricaid or Control) • Adverse Events • Post operative Bracing (if applicable) • Peri-operative Neutral AP and Neutral Lateral X-Rays • Length of Hospital Stay
6 week follow up visit **(-/+ 14 day window)**	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status • Pain Medications • Neutral AP and Neutral Lateral X-Rays • Adverse Events
3 month	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status

assessment **(-/+ 14 day window)**	• Pain Medications • Neutral AP and Neutral Lateral X-Rays • Adverse Events
6 month assessment **(-/+ 30 day window)**	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status • Pain Medications • Neutral AP and Neutral Lateral X-Rays • Adverse Events
12 month assessment **(-/+ 2 month window)**	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status • Pain Medications • Neutral AP, Neutral Lateral, and Flexion/Extension X-Rays • Low dose CT at index level only & MRI • Adverse Events
24 month assessment **(-/+ 2 month window)**	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status • Pain Medications • Neutral AP, Neutral Lateral, and Flexion/Extension X-Rays • Low dose CT at index level only & MRI • Adverse Events
Annual thereafter assessment **(-/+ 2 month window)**	• Pain Score Questionnaires (VAS Back, VAS Leg, Oswestry, SF-36) • Physical & Neurological Exams • Subject Work Status • Pain Medications • Neutral AP, Neutral Lateral, and Flexion/Extension X-Rays • Low dose CT at index level only & MRI • Adverse Events
Study Sponsor:	Intrinsic Therapeutics, Inc 30 Commerce Way Woburn, MA 01801 USA +1-781-932-0222

2 INVESTIGATIONAL PLAN

2.1 PURPOSE

The purpose of this prospective, randomized, multicenter study is to demonstrate the superiority of the Barricaid® when used as an adjunct to a primary lumbar limited discectomy (as described by Spengler[1]), to limited discectomy alone, with regard to preventing reherniation and the recurrence of pain or dysfunction. Patients, ages 21 – 75, will have, in part, a positive straight leg raise (or positive femoral stretch, as appropriate), MRI confirmation of a disc herniation, and minimum Oswestry and VAS leg scores of 40 out of 100 to qualify for this study. Additional patient criteria can be found in the inclusion/exclusion criteria section.

Superiority of the Barricaid relative to limited discectomy alone will be based on a comparison of overall success rates of the Barricaid and a concurrent group (randomized) of control patients treated by primary lumbar limited discectomy at select European (approximately 15-20) sites.

This study has two co-primary endpoints. Success of the study will be based on the Barricaid population achieving statistical superiority over the concurrently randomized non-implanted limited discectomy population. The following two endpoints will be analyzed:

1. A composite of safety and effectiveness. To be considered a success, a patient will have achieved success in each of the following components:

    - 15 point (out of 100 points) improvement in Oswestry compared to pre-op
    - 20 point (on a 100 point scale) improvement in VAS Leg (based on the primary leg complaint; if both legs have a minimum of 40/100 pre-operatively, the average leg score will be used)
    - Maintenance of average disc height (75% or greater of preoperative disc height) compared to pre-op
    - No deterioration of neurological status at the index level
    - Device integrity and lack of implant migration (radiographic, implanted patients only)
    - No spontaneous fusion
    - No reherniation at the index level (on either side)
    - No secondary surgical interventions at the index level

2. Reherniation: To be considered a success, a patient will have no evidence of recurrent herniation at the index level at any time up to and including the 24-month follow-up. Recurrent

herniation may be confirmed surgically, or radiographically as determined by an independent review (unless surgically confirmed that the suspected herniation is not a herniation, e.g. scar tissue or residual nucleus material).

The Barricaid will be determined to be superior to limited discectomy alone with regard to safety and effectiveness if the rates of overall success are statistically superior for the Barricaid group compared to the control group. In addition, safety will be documented based on a comparison between the two groups of the type and rate of occurrence of adverse events.

2.2 INTRODUCTION

2.2.1 BACKGROUND

A. Disease/Condition

Lumbar discectomy has become the most common spinal procedure in the US, with nearly 300,000 procedures performed each year. The epidemic problem of low-back pain, which leads to 15 million physician visits per year, has created a tremendous financial burden on society exceeding $50 billion annually.[2,3,4,5] Low-back pain causes nearly 80% of injured workers to miss at least 8 weeks of work following a back injury.[6] In persons younger than 45 years old, low-back pain is the most frequent cause of activity limitation.[7] Although only 4% of patients with low-back pain have an acute disc herniation[4,8], a disproportionate 30% of US annual costs for the treatment of low-back pain are spent on this relatively small percentage of patients.[9]

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[2] Bruske-Hohlfeld I, Merritt JL, Onofrio BM, et al: Incidence of lumbar disc surgery. A population-based study in Olmsted County, Minnesota, 1950-1979. Spine 15:31-35, 1990

[3] Dixon A: Progress and problems in back pain research. Rheum Rehabil 12:165-175, 1973

[4] Frymoyer JW, Cats-Baril WL: An overview of the incidences and costs of low back pain. Orthop Clin North Am 22: 263-271, 1991

[5] Hart LG, Deyo RA, Cherkin DC: Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey. Spine 20:11-19, 1995

[6] Mayer TG, Gatchel RJ, Mayer H, et al: A prospective two-year study of functional restoration in industrial low back injury. An objective assessment procedure. JAMA 258:1763-1767, 1987

[7] Kelsey JL, Pastides H, Bisbee GE Jr: Musculo-skeletal Disorders: Their Frequency of Occurrence and Their Impact on the Population of the United States. New York: Prodist, 1978

[8] Kinkade, Scott: Evalulation and Treatment of Acute Low Back Pain. American Family Physician Volume 75, Number 8, 2007

[9] Shvartzman L, Weingarten E, Sherry H, et al: Cost-effectiveness analysis of extended conservative therapy versus surgical intervention in the management of herniated lumbar intervertebral disc. Spine 17:176-82, 1992

The incidence of lumbar disc herniation peaks in patients between 24 and 45 years of age with surgery occurring most often in patients in the 30- to 39-year-old range.[10] There is a male predominance in lumbar disc surgery ranging from 1.3:1 to 2:1 because discs in men undergo higher mechanical stress as well as inadequate nutrition due to longer nutrient diffusion pathways.[11,12] Other risk factors for herniated lumbar discs include smoking, presence of narrower lumbar vertebral canal, sedentary occupations, prolonged motor vehicle driving, and operating vibrating machinery.[13,14]

Most surgeons initially manage patients with low-back pain and radicular symptoms with a trial of analgesic medications and physical therapy for four weeks before pursuing the option of costly radiographic studies and discussing surgical intervention because 90 to 95% of patients recover without surgery.[15] This patient management approach, including the recommendation of 4 to 6 weeks of conservative patient management for patients with low back pain and radiculopathy, is endorsed by the American Academy of Family Physicians[16]. Their practice guidelines are provided in the flowchart below along with their recommendation (#4) regarding patients with back pain and radiculopathy.

---

[10] Spangfort EV: The lumbar disc herniation. A computer-aided analysis of 2,504 operations. Acta Orthop Scand Suppl 142: 1-95, 1972

[11] Damkot DK, Pope MH, Lord J, et al: The relationship between work history, work environment, and low-back pain in men. Spine 9:395-399, 1984

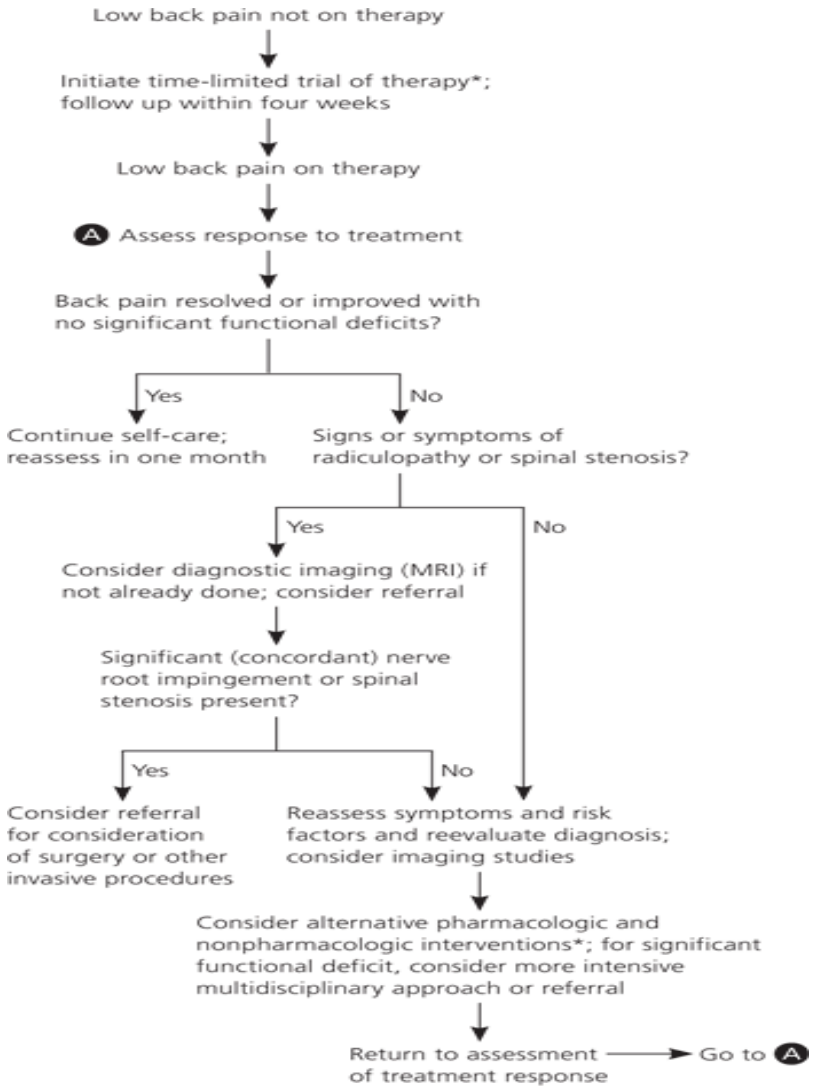
[12] Nachemson A, Lewin T, Maroudas A, et al: In vitro diffusion of dye through the end-plates and annulus fibrosus of human lumbar inter-vertebral discs. Acta Orthop Scand 41:589-607, 1970

[13] Bruske-Hohlfeld I, Merritt JL, Onofrio BM, et al: Incidence of lumbar disc surgery. A population-based study in Olmsted County, Minnesota, 1950-1979. Spine 15:31-35, 1990

[14] Heliovaara M, Vanharanta H, Korpi J, et al: Herniated lumbar disc syndrome and vertebral canals. Spine 11:433-435, 1986

[15] Fast A: Low back disorders: conservative management. Arch Phys Med Rehabil 69:880-891, 1988

[16] Horsley, L Practice GuidelinesACP guidelines for the diagnosis and treatment of low back pain. American Family Physician, Vol. 77 No. 11, June 1, 2008.



MRI = magnetic resonance imaging.

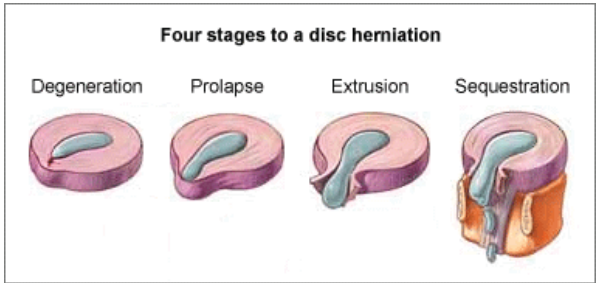
**—See Table 2 for more information.*

"Recommendation 4: Clinicians should evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with MRI (preferred) or CT only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy) (strong recommendation, moderate-quality evidence).

The natural history of lumbar disc herniation with radiculopathy in most patients is for improvement *within the first 4 weeks* with noninvasive management. There is no compelling evidence that routine imaging affects treatment decisions or improves outcomes[17] For prolapsed lumbar disc with persistent radicular symptoms despite noninvasive therapy, *discectomy* or epidural steroids are potential treatment options. Surgery is also a treatment option for persistent symptoms associated with spinal stenosis."

B. Anatomic Factors and Etiology

Lumbar intervertebral disc herniation typically occurs as a result of anular degeneration leading to a weakening of this fibrous disc capsule. This process manifests as fissuring and tearing of the wall of the anulus. This rupture or herniation allows the nuclear material (nucleus pulposus) to migrate from its natural position within the disc. Herniation has been classically defined into four categories based on the relationship of nuclear material with that of its normal position (within an intact anular wall). The following four pictures are provided to pictorially classify disc herniations.



The four stages to a herniated disc[18] include:

1. Disc Degeneration - chemical changes associated with aging causes discs to weaken, but without a herniation.

[17] Modic MT, Obuchowski NA, Ross JS, Brant-Zawadzki MN, Grooff PN, Mazanec DJ, et al. Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome. Radiology. 2005;237:597-604.

[18] LaJolla Spine Institute: Lumbar Disc Herniation http://www.lajollaspine.com/sddh_lumb_over.shtml, 2008

2. Prolapse- the form or position of the disc changes with some slight impingement into the spinal canal. Also called a bulge or protrusion.

3. Extrusion - the gel-like nucleus pulposus breaks through the tire-like wall (anulus fibrosus) but remains within the disc.

4. Sequestration or Sequestered Disc - the nucleus pulposus breaks through the anulus fibrosus and lies outside the disc in the spinal canal (HNP).

The relationship of the location of the herniation to the dura and nerve roots plays a role in determining the type of neural compromise and the clinical pain pattern. However, the extent of the neurological effect is often not directly related to the size, herniation type or location of the nuclear material. For example, large, free fragments often cause no neurological deficit. Pain resulting from a given herniation type and location also varies considerably. Small, contained herniations may create severe pain; while large extrusions can be painless. There is no wide agreement concerning the factors that determine pain production. Some have suggested that pain may be more related to biochemical factors than to mechanical compression.

The patient with lumbar disc herniation may also have concurrent abnormal pathology such as spondylolisthesis or spinal stenosis. The great majority of lumbar disc herniations occur at the L4-L5 and the L5-S1 levels, but the upper lumbar discs are also subject to herniation. Although herniation can occur at nearly any location along the disc periphery, by far the most common location is along the posterior anulus. Resorption of extruded nucleus can account for disappearance or lessening of pain although the underlying anular deficit remains present.

C. Clinical Manifestations of Lumbar Disc Herniation

The following table[7] provides a breakdown of symptoms that patients have when presenting to their primary care provider with acute lower back pain.

Table 1. Differential Diagnosis of Low Back Pain

Condition (prevalence)*	*Signs and symptoms*
Mechanical low back pain (97%)	
Lumbar strain or sprain (≥ 70%)	Diffuse pain in lumbar muscles; some radiation to buttocks
Degenerative disk or facet process (10%)	Localized lumbar pain; similar findings to lumbar strain
Herniated disk (4%)	Leg pain often worse than back pain; pain radiating below knee
Osteoporotic compression fracture (4%)	Spine tenderness; often history of trauma
Spinal stenosis (3%)	Pain better when spine is flexed or when seated, aggravated by walking downhill more than uphill; symptoms often bilateral
Spondylolisthesis (2%)	Pain with activity, usually better with rest; usually detected with imaging; controversial as cause of significant pain
Nonmechanical spinal conditions (1%)	
Neoplasia (0.7%)	Spine tenderness; weight loss
Inflammatory arthritis (0.3%)	Morning stiffness, improves with exercise
Infection (0.01%)	Spine tenderness; constitutional symptoms
Nonspinal/visceral disease (2%)	
Pelvic organs—prostatitis, pelvic inflammatory disease, endometriosis	Lower abdominal symptoms common
Renal organs—nephrolithiasis, pyelonephritis	Usually involves abdominal symptoms; abnormal urinalysis
Aortic aneurysm	Epigastric pain; pulsatile abdominal mass
Gastrointestinal system—pancreatitis, cholecystitis, peptic ulcer	Epigastric pain; nausea, vomiting
Shingles	Unilateral, dermatomal pain; distinctive rash

**—Estimated percentage of patients with this condition among all adult patients with low back pain in primary care.*

Information from references 3 and 7 through 13.

The patient with a primary complaint of severe leg pain, significant motor loss and poor functional level represents the most obvious combination of symptoms describing lumbar disc herniation. However, patients with mixed pain patterns (e.g. 50% leg pain and 50% back pain), mild motor loss and mild pain are often encountered. Because of the wide range of symptom severity and the possible alternate sources of the symptoms the differential diagnosis and early treatment course of suspected lumbar disc herniation can be problematic. Some of the traditional indicators of lumbar disc herniation can also be manifested by patient behavior, and not necessarily by damage to the disc. For example, a commonly used examination technique, the “straight leg raising test” involves a subjective response (reaction to pain) on the part of the patient. In the absence of other information (such as a foot flexion test and/or sitting leg raising test) an examiner may conclude that a hernia is present when none exists. In spite of the increased use of objective criteria, such as MRI or CT, to identify the presence of a herniated disc, most clinicians will not immediately conclude that surgery is indicated. The majority of clinicians will propose a course of conservative management (including bed rest and pain medication) for a period of at least four to six weeks before

recommending surgery[19,20,21,22,23]. There are emergency exceptions to this typical course of patient management, but such exceptions infrequently arise.

D. Conservative Treatment for Sciatica Resulting from Disc Herniation

Traditional treatment protocols for sciatica vary widely from conservative to somewhat aggressive surgical procedures. None of the current approaches attempts to close the defect in the anulus at the site of the discectomy. The following discussion provides an overview of these therapies.

The primary conservative strategies used in the treatment of sciatica involve activity restriction and the prescription of non-steroidal anti-inflammatory drugs. The most conservative therapy is a reduction of daily time spent in walking, standing, sitting or other positions that place an increased load on the lower back. For patients with severe sciatica accompanied by motor or sensory deficit bed rest of four to six weeks is commonly prescribed. Continuous bed rest is, however, undesirable because it may increase the possibility of developing deep vein thrombosis. In many cases, the patient can be ambulatory and even continue to work if he or she is not required to stand for long periods of time and this conservative approach often temporarily alleviates the episodic chronic pain of sciatica.

Other non-operative approaches to the treatment of sciatica resulting from lumbar disc herniation include the use of transcutaneous electrical nerve stimulation, manipulation, traction and the prescription of steroids and pain medications. Some physicians advocate the undertaking of a physiotherapy program to strengthen the lower back support muscles once the pain has been controlled. While up to 90% of low back pain patients benefit from these conservative treatments, the underlying degenerative process is not reversed. It is common clinical practice to consider

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[19] Butterman, G. Treatment of Lumbar Disc Herniation: Epidural Steroid Injection Compared with Discectomy - A Prospective, Randomized Study. The Journal of Bone and Joint Surgery (American) 86:670-679 (2004)

[20] Carragee, E.: Surgical Treatment of Lumbar Disk Disorders JAMA. Vol. 296, No. 20, pp 2485-2487, 2006.

[21] Peul, Wilco, et.al. Timing of surgery for sciatica: subgroup analysis alongside a randomized trial European Spine Journal, http://www.lumc.nl/rep/5038/att/812180307081046/905080251391046.pdf, January 2009

[22] Weinstein, et. Al.: Surgical vs Nonoperative Treatment for Lumbar Disk Herniation, The Spine Patient Outcomes Research Trial (SPORT), Observational Cohort. JAMA, Vol. 296, No. 20, pp 2451-2459. 2006.

[23] Vroomen, P. et.al. Predicting the outcome of sciatica at short-term follow-up. Br J Gen Pract. 2002 Feb;52(475):119-23.

surgical discectomy after four to six weeks of unsuccessful conservative (non surgical) patient care in patients that have continued pain, loss of function and/or neurological deficits with radiographic confirmation of a disc herniation (using MRI) at the clinically significant level and a positive straight leg raise or femoral stretch test.[18,19,21,22].

E. Alternate Surgical Procedures

Over time, a wide range of surgical procedures has been employed to treat the herniated lumbar disc. The proponents of the various technical approaches differ in their beliefs concerning the type of incision, the amount of nuclear material that should be removed and the requirement for stabilization (fusion). Most studies reported in the literature describe the results at a single institution, employing a specific technique. Very few reports of controlled studies are available. Although many authors have attempted to establish sub-categories of patients who are more or less likely to benefit from a given procedure it is apparent that there are no widely recognized criteria that can be used to determine what type of procedure should be preferentially performed on a patient with a given clinical history or combination of symptoms.

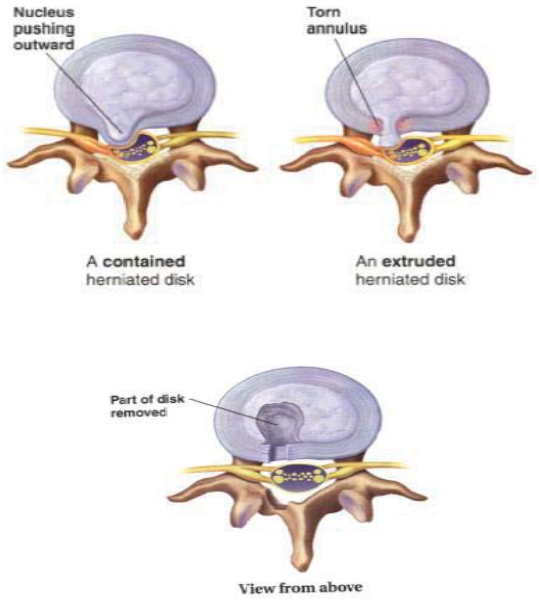

Figure 1: Discectomy Technique

Two principal variations of the discectomy technique (see Figure 1) have evolved. Each procedure is designed to excise some portion of the nuclear material. In some cases the surgeon will attempt a complete removal of the disc nucleus. The premise underlying this approach is that the anular wall has been irreparably weakened; and thus, anything less than total removal of the nucleus will ultimately result in a recurrence of the hernia. In an alternate approach, the surgeon will remove only a fragment of nuclear material that is evident outside of the disc capsule, separated within the disc capsule or causing an anular bulge. Proponents of this limited discectomy procedure believe that it is important to retain as much nuclear material as possible to maintain disc height and avoid the onset of new, mechanical low back pain. There is no agreement that either approach results in a superior outcome with respect to either relief from pain or reduction of the risk of recurrence.

A publication in the Spine Journal by Watters et al[24] presented the results of a meta analysis of published clinical studies on the subject of spinal discectomy with a focus on comparing/contrasting the clinical results of aggressive vs. minimal discectomy literature. The tables below provide a summary of both the short term and long term incidence of back/leg pain and reherniation rates as described in this article. This publication endorsed both sides of the clinical argument regarding conservative and aggressive discectomy. That is, conservative discectomy has a higher incidence of reherniation, and aggressive discectomy has a higher incidence of persistent or recurrent back/leg pain.

Table 1: Conservative Discectomy: Short and Long Term Outcomes

Conservative Discectomy	**Short-term (<2yr) Persistence Back or Leg Pain/Fair to Poor Outcome**	**Long-Term (>2yr) Persistence Back or Leg Pain/Fair to Poor Outcome**	**Recurrent Herniation**
Range	8 - 11%	7 – 16%	5 – 18%
Cumulative Total	9% (15/167)	11.5% (98/850)	8.7% (152/1752)

[24] Watters, W. et.al. An evidence-based review of the literature on the consequences of conservative versus aggressive discectomy for the treatment of primary disc herniation with radiculopathy. Spine Journal 2008.

Table 2: Aggressive Discectomy: Short and Long Term Outcomes

Aggressive Discectomy	Short-term (<2yr) Persistence Back or Leg Pain/Fair to Poor Outcome	Long-Term (>2yr) Persistence Back or Leg Pain/Fair to Poor Outcome	Recurrent Herniation
Range	9 - 24%	19 – 36%	2 – 10%
Cumulative Total	11.1% (187/1690)	28% (164/584)	3.3% (65/1938)

Other operative techniques have been developed with the objective of reducing the mass of nuclear material and thereby reducing pressure associated with the herniated anulus. These include:

- Dissolution of nuclear material by injecting biochemical substances, and
- Vaporization of nuclear material with laser energy

These procedures are performed by a limited number of physicians and there is no evidence that outcomes with respect to freedom from recurrence are any different from the outcomes reported from the more commonly performed surgical interventions. In fact, chemonucleolysis has been largely abandoned[25]. The long-term benefit of these procedures has yet to be established.

The Barricaid was developed in an effort to minimize the risk of recurrence of sciatica, back pain and disc herniation following a limited lumbar discectomy. The device is designed for implantation as an extension of the limited discectomy procedure using the same principle employed in the repair of abdominal hernias. The literature suggests that a substantial portion of recurrent disc herniations (and related sciatica) occur at the site of the original hernia intervention[26,27]. Thus, it is expected that placement of the Barricaid may offer significant benefits in the treatment of the herniated

[25] Gibson, J.N., et.al.: Surgical Interventions for Lumbar Disc Prolapse – Update Cochran Review. Vol. 32 No 16 pgs 1735 – 1747 2007.

[26] Suk, Kyung-Soo, et.al. Recurrent Lumbar Disc Herniation. Spine Vol. 26, No. 6, pp 672-676.

[27] Fu, Tsai-Sheng et.al. Long0term Results of Disc Excision for Recurrent Lumbar Disc Herniation With or Without Posterolateral Fusion. Spine Vol. 30, No. 24, pp 2830 – 2834.

lumbar disc. The following citations summarize selected publications and presentations relating to the recurrence rates of sciatic symptoms and surgical discectomy.

Balderston et al.[28] reported retrospectively on 43 patients from a single center that underwent discectomy with curettage of the nucleus and compared the outcomes with the outcomes of 40 patients from two other centers who were treated with simple fragment excision. Except for the amount of nuclear material removed, the surgical techniques were the same and the patient populations were equivalent. At a minimum of two-year follow-up there were no differences in the level of post-operative pain (1.2 vs. 0.6 on a 10 point pain scale), the incidence of reherniation (11.6% vs. 12.5%) or the incidence of further lumbar surgery (11.6% vs. 15%).

Weber[29] reported the results of a controlled prospective single-center study in which 126 patients presenting with sciatica were assigned to either conservative therapy or discectomy and followed for ten years. All discectomy procedures involved removal of the nucleus. Of the 66 patients assigned to the conservative therapy group, 17 (25.8%) required surgery within the first year. Of the remaining 49 patients, 16 (40%) reported “good” results at one year compared to 39 of 50 (78%) patients in the surgery group reporting a “good” result. At the four year and ten year follow-up there was no difference between the two groups with respect to the percentage reporting a “good” outcome.

Fritsch et al.[30] have reported summary data for a number of studies in which reintervention rates following lumbar discectomy were recorded. Although the specific type of procedure and the follow-up period varied, the revision rates ranged from 5% to 33%. In the authors’ own series of 1500 patients he noted a revision rate of 10.8%. With an average follow-up of 11.5 years, 34 of 136 (25%) patients with revision surgery required at least one additional revision. The author concludes that laminectomy should be avoided in primary disc surgery due to a higher likelihood of recurrence.

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[28] Balderston,R., Gilyard, G., Jones, A. A., et al.:The treatment of lumbar disc herniation: Simple fragment excision versus disc space curettage. Journal of Spinal Disorders: 4 (1): 22-25.

[29] Weber, H.: Lumbar disc herniation – A controlled, prospective study with ten years of observation. Spine 8 (2): 131-140, 1983.

[30] Fritsch, E., Heisel, J., Rupp, S.: The failed back surgery syndrome – Reasons, intraoperative findings, and long-term results: A report of 182 operative treatments. Spine 21 (5): 626-633, 1996.

These authors and others acknowledge that the recurrence rates for symptoms of sciatica and reherniation are a function of the patient population seen by the operator. The estimates of the incidence of "poor" outcomes range as high as 30%, but these observations are based on inconsistent, and often, subjective criteria. The rate of necessary reinterventions after primary discectomy has been reported to be as high as 20%; but the population of those studied is not homogeneous. It is clear that some subgroups fare much better than others with respect to the prospect for an uncomplicated post-operative course.

Two publications by Carragee et. al. best clarify the patient and procedural differences that affect the risk of poor outcomes following primary discectomy. Both studies are single center, prospective studies performed at Stanford Univ. School of Medicine.

The first study[31] clearly indicated that anular defect size was associated with the risk of recurrent sciatica symptoms. Patients with very small "fissure" defects had a low risk of recurrence (<2%), patients with "massive" defects had a high risk of recurrence (27.3%) while patients with intact anulus and no nuclear fragment identified at surgery had the highest risk of recurrence (37.5%). The mean risk of recurrence across the entire study population of 180 patients was 11.7%. This study indicates that anular defect size in discectomy patients spans a spectrum from none to fissure to massive. It also indicates that patients with fissure defects have a very low risk of recurrence and likely would not benefit from a device to alleviate pain and dysfunction that may occur in part as a result of such recurrence, but that all other groups suffer from a significant risk of recurrence and hence may benefit from such a device.

The second study[32] indicated that the amount of nucleus removed at the time of surgery in patients with "massive" defects affected clinical outcome. In this smaller comparative study, patients who had very little nucleus removed as part of a Spengler limited discectomy suffered from an 18%

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[31] Carragee, E., Han, M., et al.: Clinical outcomes after lumbar discectomy for sciatica: The effect of fragment type and anular competence. Journal of Bone and Joint Surgery 85: 102-108: 2003.

[32] Carragee, E., Spinnickie AO., et al.: A Prospective Controlled Study of Limited Versus Subtotal Posterior Discectomy: Short-term Outcomes in Patients with Herniated Lumbar Intervertebral Discs and Large Posterior Anular Defect. Spine 31:653-657, 2006.

reherniation rate while patients who had a more aggressive resection of the nucleus had only a 9% reherniation rate. This indicates that more aggressive resection leads to a reduction in reherniation risk. However, patients who had a more aggressive resection also had a longer return to work, worse back pain and more pain medication use at 12 months, and a lower satisfaction level at 2 years than patients with a limited resection. This study clearly shows that surgeons can reduce a patient's reherniation risk through aggressive resection, but that this will worsen long-term patient outcomes, particularly in terms of new back pain.

2.2.2 SUMMARY OF BACKGROUND

Published literature to date indicates that the optimal patient population for a study of a device to aid in preventing reherniation and the recurrence of pain or dysfunction following primary lumbar discectomy would include patients with the following pre-operative characteristics: positive straight leg raise (or femoral stretch test, as appropriate), leg pain greater than 40/100 on a visual analog scale (VAS), radiographic confirmation of a herniation at the affected level, and failed non-operative treatment for at least 6 weeks. It also indicates that patients with "fissure" defects will likely not benefit from a device to aid in preventing pain and dysfunction that may occur in part as a result of recurrence when a Spengler limited discectomy is used, and that these patients should be excluded intra-operatively. Finally, a Spengler limited discectomy should be used on all patients (control and implant) to minimize procedural technique variability on outcome.

2.3 DEVICE DESIGN AND DESCRIPTION

Intended Use: The Barricaid is intended as an adjunct to a lumbar, limited discectomy (as described by Spengler) as an aid in preventing reherniation and the recurrence of pain or dysfunction.

Indication for Use: The Barricaid is indicated for patients with radiculopathy (with or without back pain), a positive Straight Leg Raise (L45, L5S1) or femoral stretch test (L12, L23, L34), and a posterior or posterolateral herniation at one level between L1 and S1 with radiographic confirmation of neural compression using MRI who are found to have an annular defect (post discectomy) which measures between 4mm and 6mm tall and between 6mm and 10mm wide, have a minimum posterior disc height of 5mm, and have failed at least 6 weeks of conservative treatment.

Device Description: The Barricaid consists of two components – an occlusion component and an anchor component (See Figure 1). The occlusion component serves to block movement of the nucleus out of the intervertebral (or "disc") space. The anchor component is used to anchor the occlusion component to one of the adjacent vertebral bodies.

Figure 2 shows a picture of the Barricaid and its material composition. Figure 3 shows the Barricaid attached to the Barricaid Delivery Tool.

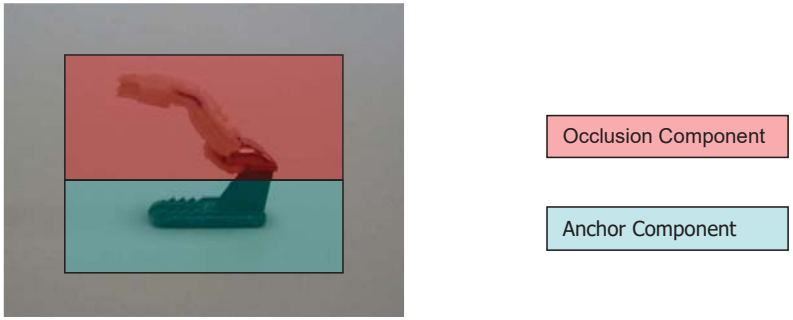

Figure 1. Barricaid

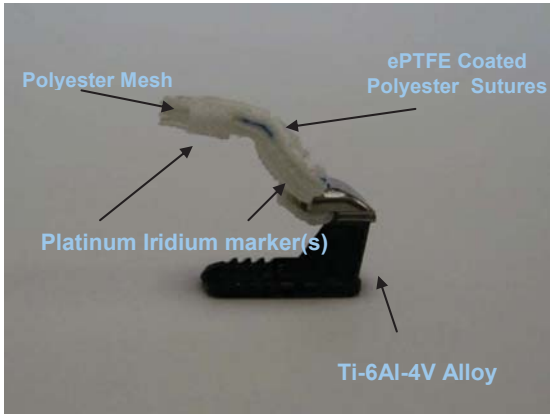

Figure 2. Barricaid – Material Composition

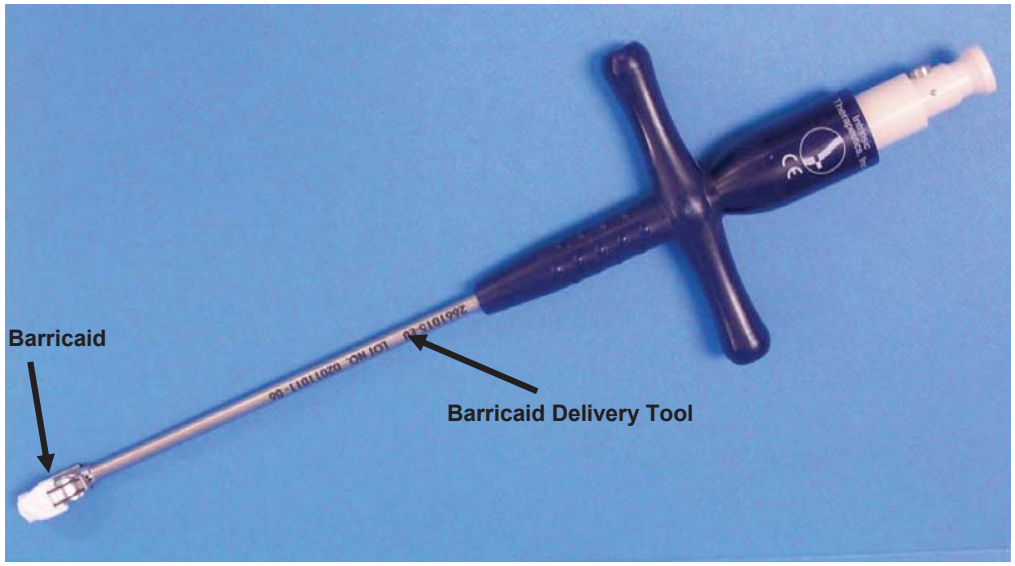

Figure 3: Barricaid pre-loaded on the Delivery Tool

The Barricaid is composed of a Ti-6Al-4V Anchor that prevents migration of the mesh. Migration is prevented short term by the mechanical interlock between the anchor and the vertebral body. Long term migration is prevented by the osseointegration of the anchor with vertebral bone.

The Barricaid occlusion component is composed of several layers of PET mesh sewn together with PTFE coated PET suture. The occlusion component also has Platinum Iridium (radiopaque) marker(s) for radiographic confirmation of mesh position. The occlusion component is attached to the anchor component using the same suture material.

All materials have undergone the appropriate ISO 10993 biocompatibility tests. All tests have confirmed that the Barricaid is biocompatible for long term implantation with bone and soft tissue contact.

2.4 SUBJECT POPULATION

This prospective, randomized controlled clinical study will be conducted under controlled conditions for subjects undergoing a single level, limited discectomy (as described by Spengler1) between L1-S1. The following inclusion and exclusion criteria will be applied to patient selection.

2.4.1 INCLUSION CRITERIA

Any subject meeting all of the following criteria will be considered acceptable for inclusion in this trial.

1. Age 21 to 75 years old and skeletally mature (male or female).
2. Patients with posterior or posterolateral disc herniations at one level between L1 and S1 with radiographic confirmation of neural compression using MRI. [Note: Intraoperatively, only patients with an anular defect (post discectomy) between 4mm and 6mm tall and 6mm and 10mm wide shall qualify.]
3. At least six (6) weeks of failed, conservative treatment prior to surgery, including physical therapy, use of anti-inflammatory medications at maximum specified dosage and/or administration of epidural/facet injections.;
4. Minimum posterior disc height of 5mm at the index level.
5. Radiculopathy (with or without back pain) with a positive Straight Leg Raise (0 – 60 degrees)[22] (L45, L5S1) or Femoral Stretch Test (L12, L23, L34)
6. Oswestry Questionnaire score of at least 40/100 at baseline.
7. VAS leg pain (one or both legs) of at least 40/100 at baseline.
8. Psychosocially, mentally and physically able to fully comply with the clinical protocol and willing to adhere to follow-up schedule and requirements.

2.4.2 EXCLUSION CRITERIA

Any subject meeting any one of the following criteria will be excluded from enrollment into the trial:

1. Spondylolisthesis Grade II or higher (25% slip or greater).
2. Subject requires spinal surgery other than a discectomy (with or without laminotomy) to treat leg/back pain (scar tissue and osteophyte removal is allowed).
3. Subject has back or non-radicular leg pain of unknown etiology.
4. Prior surgery at the index lumbar vertebral level.
5. Subject requiring a spine DEXA (i.e., patients with SCORE of ≥ 6) with a T Score less than -2.0 at the index level. For patients with a herniation at L5/S1, the average T score of L1-L4 shall be used.
6. Subject has clinically compromised vertebral bodies in the lumbosacral region due to any traumatic, neoplastic, metabolic, or infectious pathology.

7. Subject has sustained pathologic fractures of the vertebra or multiple fractures of the vertebra or hip.
8. Subject has scoliosis of greater than ten (10) degrees (both angular and rotational).
9. Any metabolic bone disease.
10. Subject has an active infection either systemic or local.
11. Subject has cauda equina syndrome or neurogenic bowel/bladder dysfunction.
12. Subject has severe arterial insufficiency of the legs or other peripheral vascular disease. (Screening on physical examination for patients with diminution or absence of dorsalis pedis or posterior tibialis pulses. If diminished or absent by palpation, then an arterial ultrasound is required with vascular plethysmography. If the absolute arterial pressure is below 50mm of Hg at the calf or ankle level, then the patient is to be excluded.)
13. Subject has significant peripheral neuropathy, patient defined as a patient with Type I or Type II diabetes or similar systemic metabolic condition causing decreased sensation in a stocking-like or non-radicular and non-dermatomal distribution in the lower extremities.
14. Subject has insulin-dependent diabetes mellitus.
15. Subject is morbidly obese (defined as a body mass index >40, or weighs more than 100 lbs over ideal body weight).
16. Subject has been diagnosed with active hepatitis, AIDS, or HIV.
17. Subject has been diagnosed with rheumatoid arthritis or other autoimmune disease.
18. Subject has a known allergy to titanium, polyethylene or polyester materials.
19. Any subject that cannot have a baseline MRI taken.
20. Subject is pregnant or interested in becoming pregnant in the next three (3) years.
21. Subject has active tuberculosis or has had tuberculosis in the past three (3) years.
22. Subject has a history of active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there have been no signs or symptoms of the malignancy for at least two (2) years.
23. Subject is immunologically suppressed, received steroids >1 month over the past year.
24. Currently taking anticoagulants, other than aspirin, unless the patient can be taken off the anticoagulant for surgery.
25. Subject has a current chemical/alcohol dependency or significant psychosocial disturbance.
26. Subject has a life expectancy of less than three (3) years.
27. Subject is currently involved in active spinal litigation.
28. Subject is currently involved in another investigational study.
29. Subject is incarcerated.

30. Any contraindication for MRI or CT scan (e.g. claustrophobia, contrast allergy).

2.5 INVESTIGATIONAL PROCEDURES

2.5.1 INVESTIGATOR TRAINING

No investigation study site will participate in this trial without investigators that have training according to the Sponsor's training program and familiarity with the surgical technique for implantation of the Barricaid. This training will inform the investigators that only a limited discectomy (as described by Spengler[1]) may be performed on any study patient.

2.5.2 SCREENING AND PRE-OPERATIVE ASSESSMENT

2.5.2.1 Screening and Consent

Subjects will be provided with an informed consent (Appendix 1) and will be given ample opportunity to review the consent and ask questions. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any one of the exclusion criteria will be excluded from the trial. Subjects will be assigned a study patient identification number ("Patient ID") after being consented. (Note: Subjects may become screen failures at any point up until randomization occurs, at which point the patient will be considered enrolled. Pre-operative data on screening failures, including intra-operative screening failures, will be collected and reported on, including a summary of the reasons for patient exclusion.) No further study follow up will be required on subjects that are not randomized.

Subjects will be cleared for surgery per hospital procedures.

2.5.2.2 Radiographic Assessment

In order to confirm a diagnosis of disc herniation, preoperative radiographic studies must be performed. Within **3 months** prior to the surgery date, an **MRI with both T1 and T2 weighted axial and sagittal images** to assess the integrity of the anulus must be performed. The MRI will allow the investigator to identify the extent of disc herniation (refer to Appendix 2 – Radiographic Protocol).

Also within 3 months prior to the surgery date, a low dose CT at the index level must be taken to document the preexisting state of the vertebral bodies.

In addition, **Neutral AP, Lateral** and **Flexion-Extension X-rays** must be performed within 60 days of surgery to determine a baseline for disc height at the involved level (refer to Appendix 2 – Radiographic Protocol which also includes information regarding the central lab that will be performing all of the radiographic analyses).

Other radiographic studies (to confirm the diagnosis) such as plain film (i.e., oblique views) or myelography may be done at the surgeon's preference.

2.5.2.3 Medical History

Within 30 days prior to the surgery date demographic information will be collected, a detailed medical history will be obtained to include documented descriptions of prior treatments for the subject's back and leg pain, and a physical examination (including height and weight). Current pain medications and other drug therapies will also be recorded.

2.5.2.4 Pregnancy Screening

A pregnancy test will be carried out on all female patients of childbearing potential to ensure patients are not enrolled into the study who are pregnant. This pregnancy test will be carried out within 30 days prior to the surgery date.

2.5.2.5 Clinical Assessment

The subject will undergo the following pain, function and neurological assessments within 30 days prior to the surgery date:

Pain/Function Disability Assessment: Pre-operatively the subject will complete the Oswestry Low Back Pain and Disability Questionnaire[33,34]. The questionnaire is a combined pain and function index. It will be used to assess the subject's back pain and how that pain affects the subject's ability to manage in everyday life.

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[33] Roland M, Fairbank J: The Roland-Morris disability questionnaire and the Oswestry disability questionnaire. Spine 25(24):3115-3124, 2000.

[34] Fairbank JCT, Pynsent PB: The Oswestry disability index. Spine 25(22): 2940-2953, 2000.

The questionnaire is divided into ten sections designed to assess limitations of various activities of daily living. Each section contains six statements and each statement describes a greater degree of difficulty in that activity than the preceding statement. The subject marks the one statement in each section, which describes his/her limitations most accurately. Each section is scored on a 0-5 scale, 5 representing the greatest disability. The scores for all sections are added together, giving a possible score of 50. The total is doubled and expressed as a percentage. If a subject marks two statements, the highest scoring statement is recorded as a true indication of his disability. If a section is not completed because it is inapplicable, the final score is adjusted to obtain a percentage. If one section is missed (or not applicable) the score is calculated as follows: (Example: 24 (total scored)/45 (total possible score) X100 = 53% disability)[34].

The subject must score ≥ 40 points of 100 (or 40% if only 9 of 10 questions are answered) on the baseline Oswestry in order to be included in trial.

Back and Radicular Leg Pain: Preoperatively all subjects will assess their back and/or radicular leg pain in one or both legs using a visual analogue scale (VAS) from 0-100 mm with 100 being considered most painful. The subject must score ≥ 40 of 100 (40%) on the baseline on either Leg VAS score in order to be included in the trial.

SF-36v2™ Health Survey: Preoperatively all subjects will complete an SF-36v2™ Health Survey as an outcome measure to assess quality of life.

2.5.2.6 Neurological Assessment

Preoperatively, and within 30 days prior to surgery, the subject will be assessed for sensory, reflex, muscle strength (motor), straight leg raising, and femoral stretch criteria as follows:

Sensory: Decreased sensation will be assessed by evaluating the sensation response (e.g., to pin prick, light touch or vibration) for the involved dermatomal levels (L1, L2, L3, L4, L5 and S1) in each leg. The examination method chosen to make these assessments will be left to the discretion of the investigator. The same evaluation (e.g. pin prick, light touch, or vibration) that is used by the examiner at the pre-operative visit should be used at each subsequent follow up visit.

Reflex: Reflexes of both legs will be evaluated by assessing patellar (knee jerk) and Achilles (ankle jerk) deep tendon reflexes. The investigator will be asked to indicate whether the knee and ankle

reflex response for each leg is normal, decreased, absent or increased. The investigator will be evaluating a subject's response during stimuli to deep muscle stretch induced by a reflex hammer. The subject must be adequately relaxed and the muscle to be tested must be in optimal tension.

Muscle Strength: Muscle strength of both legs will be assessed bilaterally at the following muscle sites: hip flexors (iliopsoas musculature), knee extensors (quadriceps), ankle dorsiflexors (tibialis anterior), ankle plantar flexors (gastrocnemius) and long toe extensors (extensor halluces longus) using the following clinical scale. The worst assessment (no evidence of contractility) will be assigned the lowest clinical score 0 out of 5 (0/5) while full range of motion against gravity, full resistance will be assigned the highest clinical score 5 out of 5 (5/5). The following scale will be used to assess muscle strength:

DESCRIPTION	CLINICAL SCORE
No evidence of contractility	0/5
Slight contractility, no movement	1/5
Full range of motion, gravity eliminated (passive movement)	2/5
Full range of motion with gravity	3/5
Full range of motion against gravity, some resistance	4/5
Full range of motion against gravity, full resistance	5/5

Straight Leg Raising: The ability of the subject to undergo passive straight leg raising maneuvers while in the supine position will be assessed for both legs. The results will be recorded as a positive or negative straight leg raise (SLR) for each leg. Upon passive straight leg raising, when a subject experiences a reproduction of radicular pain (sciatic leg pain) radiating down the leg, below the knee, a positive SLR will be recorded for that leg. The SLR will be considered positive when the reproduction of sciatic pain occurs at an angle between 0 – 60 degrees, inclusive. A negative SLR will be recorded when no reproduction of radicular pain (sciatic leg pain) occurs > 60 degrees upon passive SLR.

Femoral Stretch: The ability of the subject to undergo passive femoral stretch maneuvers while lying on one side will be assessed for both legs. The results will be recorded as a positive or negative femoral stretch for each leg. If the subject experiences pain in the anterior and anteromedial portion of the thigh upon passive movement of the extended leg backwards, which extends the hip joint and pulls on the femoral nerve, a positive femoral stretch will be recorded. A negative femoral stretch will be recorded when no reproduction of pain in the anterior and anteromedial portion of the thigh occurs upon passive femoral stretch. The femoral stretch test is only required for those subjects with L12, L23, or L34 disc herniations.

2.5.3 DAY OF SURGERY

2.5.3.1 Surgical Method

The subjects will be prepared for surgery according to the individual hospital or investigator's protocol. The surgeon will perform a conservative or limited (Spengler1 technique) discectomy. This technique will remove any nucleus that has migrated within the anular defect or beyond the anular wall (including sequestered fragments). Surgeons will be specifically trained to remove loose fragments of nucleus from within the disc in patients with extrusions or protrusions, per Spengler's published technique. Upon completion of the discectomy and measurement of the defect, the patient will be randomized if not excluded due to defect size. All patients that are randomized to Barricaid but that cannot have the Barricaid successfully implanted will be considered treatment failures. Patients who intraoperatively fail the defect size requirement will not be randomized, but will still have all data collected and reported on up to and including the day of surgery. This report will also include the reason for patient exclusion (i.e., excluded intra-operatively due to the defect size limitation). Patients excluded intra-operatively prior to randomization will not be considered enrolled.

During surgery, the amount of nucleus removed will be measured. This measurement will be made by placing the removed nucleus in an empty graduated syringe with at least 0.2cc gradations. Once all nucleus is placed in the syringe, the syringe plunger will be inserted and depressed until all air is removed from the syringe. The measurement will be taken to the nearest 0.1cc and recorded on Surgical Procedure Visit Case Report Form. There is no minimum or maximum amount of nucleus volume that can be removed for placement of the device; however, the surgeon will perform a

limited (Spengler technique) discectomy with the parameters for nucleus removal listed in the paragraph above.

All randomized subjects will have an AP and neutral lateral X-Ray perioperatively. All patients that fail intraoperative inclusion criteria will have all data collected on Surgical Procedure Visit Case Report Form. All data (baseline and surgery) on these excluded patients will be reported as part of the overall clinical dataset.

2.5.4 PERIOPERATIVE AND POSTOPERATIVE MANAGEMENT

Parameters such as duration of surgery, blood loss, length of hospital stay and complications will be recorded. **Note:** All intra-operation complications e.g. excessive blood loss, hematoma, vascular injury, etc. should be classed and reported as Adverse Events.

Immediately following surgery, the subject will be transported to the surgical recovery area and monitored according to the hospital/investigator protocol. Along with monitoring vital signs and the surgical site, the recovery room staff will also evaluate the subject's motor and sensory function. When the subject has met the hospital/investigator protocol criteria, the subject will be discharged to the nursing unit.

2.5.4.1 Immediate Postoperative Care

Immediate postoperative care will follow the hospital/investigator protocol for this type of surgical procedure. This procedure will include monitoring the subject's vital signs, neurological function and surgical site. All pain medication and antibiotics to be given prophylactically will be provided as instructed by the investigator. If the subject's neurological status changes, if there is any abnormality of the patient's vital signs, or if any other postoperative complication should arise, the investigator will be notified immediately. Subjects will be discharged according to the hospital/investigator protocol.

2.5.4.2 Immobilization/Weight Bearing

Postoperatively, ambulation will be allowed on the first postoperative day in accordance with hospital procedures.

2.5.4.3 Subject Discharge Instructions

Discharge will be conducted according to hospital procedures for discectomy patients. The subject discharge instructions will be given to each subject prior to leaving the hospital. These instructions will be consistent with the investigator's protocol. If patient bracing is recommended by the surgeon, the reason for bracing shall be documented on CRF 5.

2.5.4.4 Follow-up Assessments

All subjects will be assessed postoperatively at the following time intervals:

- 6 weeks (window equals ± 2 weeks)
- 3 months (window equals ± 2 weeks)
- 6 months (window equals ± 1 month)
- 12 months (window equals ± 2 months)
- 24 months (window equals ± 2 months)
- Annually thereafter until the last subject reaches the 24-month evaluation or the study is concluded. (window equals ± 2 months)

Each follow-up visit time point will be determined based on the date of surgery. Subject evaluations will consist of clinical and radiographic exams according to the following schedule (Table 1).

TABLE 1: Clinical and Radiographic Assessments

EVALUATION	RADIOGRAPHIC*	CLINICAL	CASE REPORT FORMS* (to be completed)
Pre-operative	Multiplanar Low dose CT at the index level with 2D Reconstructions, MRI with both T1 and T2 weighted axial and sagittal images, AP, Neutral Lateral, and Flexion-Extension X-rays*	Oswestry, Back and Leg Pain VAS, Neurological Assessments and SF-36v2™	• CRF 1 • CRF 2 • CRF 3 • CRF 4
Surgical	Peri-operative AP and	Neurological	• CRF 5

Information	Neutral Lateral X-rays	Assessment	
6 Weeks, 3 Months and 6 Months	AP and Neutral Lateral X-rays	Oswestry, Back and Leg Pain VAS, Neurological Assessments, and SF-36v2™	• CRF 6 • CRF 7
12 and 24 Months, and Annual Long-term Follow-up	AP, Neutral Lateral and Flexion-Extension X-rays Multiplanar low dose CT at index level and MRI	Oswestry, Back and Leg Pain, Neurological Assessments and SF-36v2™	• CRF 6 • CRF 7

* Radiographic studies need not be repeated at the pre-op visit if they were obtained within 60 days of the surgery date for x-rays, within 3-months of surgery date for MRI and CT if no major change in patient condition has occurred.
Refer to the Radiographic Protocol (Appendix 2), which outlines the effectiveness requirements for the x-rays required.

2.5.4.5 Follow-up Clinical Exam

Current pain medication intake will be recorded and the subject will undergo the following pain, function and neurological assessments at each follow-up visit:

Pain/Function Disability Assessment: At each required follow-up visit the subject will complete the Oswestry Low Back Pain and Disability Questionnaire [25,26]. The questionnaire is a combined pain and function index. It will be used to assess the subject's back pain and how that pain affects the subject's ability to manage in everyday life.

Back and Radicular Leg Pain: At each follow-up visit, all subjects will assess their back and leg pain in both legs using a visual analogue scale (VAS) from 0-100 mm with 100 mm being considered most painful.

SF-36v2™ Health Survey: At each required follow up visit, all subjects will complete a SF-36v2™ Health Survey as an outcome measure to assess quality of life.

Neurological Assessment: At each required follow-up visit the subject will be assessed for sensory, reflex, muscle strength (motor), straight leg raising and femoral stretch criteria (if required) as previously described.

2.5.4.6 Radiographic Exam

At each required follow-up visit all subjects will undergo radiographic evaluation as follows:

TABLE 2: Summary of Radiographic Evaluation

Radiograph*	Screening	Peri-operative	6 weeks, and 3 and 6 months	12 and 24 months	Annually Thereafter
MRI with both T1 and T2 weighted axial and sagittal images	X			X	X
Multiplanar Low dose CT at index level with 2D Coronal Reconstructions	X			X	X
Neutral AP	X	X	X	X	X
Neutral Lateral	X	X	X	X	X
Flexion/Extension X-rays	X			X	X

*Refer to the Radiographic Protocol (Appendix 2), which outlines the effectiveness requirements for the x-rays indicated.
Note: The window periods for these follow-up visits are previously defined under the heading of Follow-up Assessments.

An independent radiographic analysis will evaluate all pre-operative and post-operative radiographs to assess the subject's radiographic status.

2.5.4.7 Pre-Operative Assessment:

The specific radiographic pre-operative evaluation parameters include (index level only, unless otherwise noted):

Quantitative Measures

1. Disc Angle
2. Angular Motion (index and adjacent)
3. Translational Motion (index and adjacent)
4. Disc Height (index and adjacent)
5. Spondylolisthesis

6. Modic Change
7. Endplate Changes / Reactions (MRI-based)
8. Bone Resorption: Lesions in the Superior Vertebral Body
9. Bone Resorption: Predominant Lesion Type in the Superior Vertebral Body
10. Bone Resorption: Lesions in the Inferior Vertebral Body
11. Bone Resorption: Predominant Lesion Type in the Inferior Vertebral Body

Qualitative Assessments

12. Heterotopic Ossification
13. Osteophyte Formation (index and adjacent)
14. Anular Tears / Fissures
15. Disc Signal Intensity
16. Endplate Sclerosis (index and adjacent)
17. Modic Change
18. Bone Resorption: Lesions in the Superior Vertebral Body
19. Bone Resorption: Predominant Lesion Type in the Superior Vertebral Body
20. Bone Resorption: Lesions in the Inferior Vertebral Body
21. Bone Resorption: Predominant Lesion Type in the Inferior Vertebral Body
22. Additional Radiographic Observations

2.5.4.8 Post-Operative Assessment:

The specific radiographic post-operative evaluation parameters include the following (treated disc only, unless otherwise noted):

Quantitative Measures

1. Disc Angle
2. Angular Motion (treated and adjacent)
3. Translational Motion (treated and adjacent)
4. Disc Height & Change in Disc Ht (treated and adjacent)
5. Spondylolisthesis
6. Change in Spondylolisthesis

Qualitative Assessments

7. Heterotopic Ossification
8. Osteophyte Formation (treatment and adjacent)
9. Spontaneous Fusion (derived from a combination of quantitative and qualitative assessments)
10. Device Condition
11. Device Migration

12. Device Subsidence
13. Reherniation
14. Anular Tears / Fissures
15. Disc Signal Intensity
16. Modic Change
17. Endplate Sclerosis (treatment and adjacent)
18. Endplate Changes / Reactions (MRI-based)
19. Bone Resorption: Lesions in the Superior Vertebral Body
20. Bone Resorption: Predominant Lesion Type in the Superior Vertebral Body
21. Bone Resorption: Lesions in the Inferior Vertebral Body
22. Bone Resorption: Predominant Lesion Type in the Inferior Vertebral Body
23. Additional Radiographic Observations

2.6 SUCCESS CRITERIA

All subjects will be evaluated at every time point for each of the clinical and safety evaluations. Success of each individual subject and the study will be determined at the 24-month evaluation time point. This study has two co-primary endpoints. Success of the study will be based on the Barricaid population achieving statistical superiority over the concurrently randomized non-implanted limited discectomy population. The following two endpoints will be analyzed:

1. A composite of safety and effectiveness. To be considered a success, a patient will have achieved success in each of the following components:

- 15 point (out of 100 points) improvement in Oswestry compared to pre-op
- 20 point (on a 100 point scale) improvement in VAS Leg (based on the primary leg complaint; if both legs have a minimum of 40/100 pre-operatively, the average leg score will be used)
- Maintenance of average disc height (75% or greater of preoperative disc height) compared to pre-op
- No deterioration of neurological status at the index level
- Device integrity and lack of implant migration (radiographic, implanted patients only)
- No spontaneous fusion
- No reherniation at the index level (on either side)
- No secondary surgical interventions at the index level

2. Reherniation: To be considered a success, a patient will have no evidence of recurrent herniation at the index level at any time up to and including the 24-month follow-up. Recurrent herniation may be confirmed surgically, or radiographically as determined by an independent review (unless surgically confirmed that the suspected herniation is not a herniation, e.g. scar tissue or residual nucleus material).

2.6.1 Individual Subject Success

Individual subjects will be regarded as overall successes only if they are successes with respect to each of the following primary effectiveness and primary safety endpoints:

Primary Effectiveness Endpoints

Pain/Function/Disability: Subjects who exhibit a reduction of at least 15 points in their Oswestry Low Back Pain Disability Questionnaire score compared to their preoperative Oswestry score will be

considered a success. Beurskens et al.[35] has reported a change of 4 to 6 points of the 100 points for the Oswestry to represent a clinically significant improvement.

Pain: A 20 point improvement (out of 100) in VAS Leg[36] (based on the primary leg complaint; if both legs have a minimum of 40/100 pre-operatively the average leg score will used).

Radiographic: Any subject will be considered a success if disc height is 75% or greater when compared with preoperative disc heights.

Primary Safety Endpoints

No Reherniations: Subjects who have had no reherniations at the index level (on either side) prior to or at the 24-month follow-up will be considered a success. This will be documented radiographically.

Maintain Device Integrity (Barricaid group only): Subjects whose implant has not fractured or disassembled as identified by an independent read of x-rays will be considered a success.

Posterior migration (Barricaid group only): Subjects who do not have migration of the Barricaid will be considered a success. Migration is defined as presence of AP or lateral motion of the anchor ≥ 2 mm relative to its initial position, and/or motion of the radio-opaque marker(s) beyond the margin of the disc space, associated with extrusion of the occlusion component through the anulus. Initial position will be defined as the position on the 6-week x-ray, assuming that a qualitative review by an independent radiologist confirms that no migration has occurred between the intraoperative time point and six weeks. If migration is noted on this qualitative review, and the intraoperative images are of a quality that can be used for objective measurements, these intraoperative images will be used as the quantitative baseline.

Spontaneous Fusion: Subjects that do not have spontaneous fusions will be considered a success.

[35] Beurskens AJHM, de Vet HCW, Koke AJA: Responsiveness of functional status in low back pain: a comparison of different instruments. Pain 65:71-76, 1996.

[36] Grilo, R.M. Clinically relevant VAS pain score change in patients with acute rheumatic conditions. Joint Bone Spine 74 (2007) 358-361

Removal/Revision/Supplemental Fixation: Subjects who have the Barricaid who have not had the Barricaid removed or revised will be considered a success. Any secondary surgical intervention at the index level due to reherniation of the disc will be considered a failure in either study treatment group. Any re-operation at the index level (including supplemental fixation added to the index level) will be considered a failure in either study treatment group.

Neurological Status: Subjects who have either maintained or improved in their neurological status as it relates to the subject's index level will be considered a success. Neurological status success will be based upon Straight Leg Raising (L4/5 and L5/S1) or Femoral Stretch Test (L1/2, L2/3, L3/4 only), motor examination, sensory examination, and reflex examination. Mixed neurological outcomes will be adjudicated by the Data Safety Monitoring Board as improved, maintained, or deteriorated in comparison to the baseline visit.

2.6.2 Overall Study Success

Overall study success will be demonstrated if both the primary effectiveness and safety objectives of the clinical trial are achieved.

2.6.3 Overall Study Safety and Effectiveness:

The Barricaid will be determined to be superior to limited discectomy alone with regard to safety and effectiveness if the Barricaid group is superior when compared to the limited discectomy (as described by Spengler) non-implanted control population.

2.6.4 Overall Study Secondary Safety and Effectiveness Endpoint and Analysis:

Although the main goal of this trial is to compare the Barricaid and control populations with regard to the primary endpoint of overall safety and effectiveness at 24 months, individual outcome endpoints will be evaluated and compared between the Barricaid and control group. A gatekeeping strategy will be used to test the secondary endpoints for a claim of superiority:

1. VAS Back Pain Improvement. Rates of subject success in treatment and control will be compared at 24 months. A subject is a success if there is at least a 20 point improvement on the VAS Back at 24 months relative to baseline.
2. Oswestry Improvement. Rates of subject success in treatment and control will be compared at 24 months. A subject is a success if there is at least a 15 point improvement in the ODI at the 24 month visit relative to baseline.
3. Reoperation: A subject will be deemed a success if they have not had a second operation at the index level by the 24 month visit.Disc Height Maintenance. Rates of subject success in

treatment and control will be compared at 24 months. A subject is a success if there is at least 75% of the pre-op disc height preserved at the 24 month visit.

4. VAS Leg Pain Improvement: Rates of subject success in treatment and control will be compared at 24 months. A subject is a success if there is at least a 20 point improvement on the VAS leg pain in the ipsilateral leg at 24 months relative to baseline.

Secondary endpoints will be analyzed for superiority and non-inferiority. In addition, data analyses will also be performed on the following:

1. Composite endpoint success. The rate of success in the primary composite endpoint will be compared at each follow up, up to and including the 12 month follow up.
2. Maintenance or improvement in neurological symptoms. Analysis will be performed at each follow up relative to baseline.
3. The rate and percent improvement in VAS ipsilateral Leg pain (individual subject success). A successful subject will have at least a 20 point improvement in ipsilateral leg pain relative to baseline. The rate of subject success will be analyzed at each follow up.
4. The rate and percent improvement in the Oswestry Disability Index (ODI) (individual subject success). A successful subject will have at least a 15 point improvement relative to baseline. The rate of subject success will be analyzed at each follow up.
5. Rate of individual subject success in terms of disc height maintenance. A successful subject will maintain at least 75% of their pre-operative disc height. The rate of subject success will be analyzed at each follow up.
6. The rate and percent improvement in VAS Back Pain (individual subject success). A successful subject will have at least a 20 point improvement relative to baseline. The rate of subject success will be analyzed at each follow up.
7. Reoperations at the index level. The total number of reoperations up to and including the 24 month follow up will be analyzed. Separately, analyses will also be performed on the total number of reoperations performed specifically for recurrent disc herniation and those performed for symptoms unassociated with recurrent disc herniations.
8. Rate of ipsilateral recurrent disc herniations (at original defect, i.e, same side, same level)
9. Rate of secondary recurrent herniation (but not at original defect, i.e, contralateral herniations at same level)
10. Percent improvement in VAS leg pain in the ipsilateral leg. Analysis will be performed at each follow up relative to baseline.
11. Percent improvement in VAS back pain. Analysis will be performed at each follow up relative to baseline.
12. Mean VAS Back Pain. Analysis will be performed at each follow up.
13. Mean VAS Leg pain in the ipsilateral leg. Analysis will be performed at each follow up.
14. Mean Oswestry Disability Index. Analysis will be performed at each follow up.
15. Quality of Life analysis judged by SF-36. The body pain and physical function scores will be analyzed at each follow up relative to baseline.
16. Adverse Events- the total number of adverse events up to and including the 24 month follow-up will be compared between treatment and control, as well as the number of intra-operative and post-operative adverse events, as well as the adverse event rates by severity. Individual adverse event rates will also be compared.
17. Use of post operative pain medication to manage back and/or leg pain will be analyzed at each follow up.
18. Economic cost as judged by direct medical expenses post operatively by 1 year and 2 years.

19. Rate of subjects returning to work without restriction will be analyzed at each follow up time point.
20. The time from surgery to return to work

For a more detailed analysis, refer to the current Statistical Analysis Plan (SAP).

2.7 SAFETY

2.7.1 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will review on an at least quarterly basis accumulating data from the ongoing clinical trial. This board will consist of experts in the field of general, neurological, orthopedic and/or spine surgery. The purpose of the DSMB will be to advise Intrinsic Therapeutics regarding the continued safety of current participants and those yet to be recruited. The DSMB process (including their ability to stop an ongoing study due to safety concerns) is documented in Intrinsic Therapeutics Clinical Work Instruction – Data Safety Monitoring Board and a study specific Manual of Operations.

2.7.2 STOPPING RULES

Enrollment in the study will be suspended (i.e., no surgeries to occur) if any of the stopping rules are met. The DSMB shall then review the relevant data, and recommend: a)enrollment in the study may either resume, b) be further suspended, or c) possibly terminated based on the DSMB's review. Any Sponsor action with respect to resumption of a DSMB requested study suspension will be in accordance with regulation. (Note that at any time, the DSMB may recommend suspension of enrollment based on safety concerns not detailed in these stopping rules.) The study stopping rules can be found in the table below:

Event	Proposed Study Stopping Criteria (Barricaid patient population)	Literature References
1. Reoperation Rate of Device- or Procedure-	At least three observed occurrences in the Barricaid group, **and** the observed	• Bose et al. (2004): The reoperation rate was reported to be around 24% for patients with degenerative disc disease receiving pedicle screw

Event	Proposed Study Stopping Criteria (Barricaid patient population)	Literature References
Related Reoperations (For Revision, Removal, Supplemental Fixation, or Reherniation)	percentage of subjects experiencing re-operation in the Barricaid group is either >10 percentage points higher than the control group or is >25% (absolutely)	fixation using the Silhouette Fixation System (Zimmer Spine) and ISOLA (Depuy Acromed). [37] • Christensen et al. (2002): The reoperation rate was 28% for the Cotrel–Dubousset supplemented fusion (instrumented group) of patients with severe chronic low back pain resulting from localized lumbar or lumbosacral segmental instability caused by isthmic spondylolisthesis Grades 1 and 2, primary degeneration, secondary degeneration after decompressive surgery, or accelerating degeneration after decompressive surgery [38] • Dantas et al. (2007) reported a reoperation rate of 6.6%, as well as one surgical debridement for infection, in patient undergoing PLF using pedicle screws for spondylolisthesis.[39]
2. Device Removal Rate	At least three observed occurrences, and the percentage of subjects experiencing device removal is >15%	• 36.4% of patients in the X-STOP pivotal study using the unwelded implant experienced a device removal and 7% of patients who received the welded X-STOP had a device removal [40] • Christensen et al. (2002): Removal rate was 14% in the instrumented group [2]
3. Implant Integrity	At least three observed occurrences, and the percentage of subjects experiencing loss of implant integrity (including device breakage, fracture or	• Jutte & Castelein (2002): 12.1% of patients who underwent fusion procedures supplemented by transpedicular screws connected to Isola rods (AcroMed) experienced breakage. Indications for surgery included symptomatic spondylolisthesis, postdiscectomy syndrome, spinal canal stenosis, disc degeneration, and pseudarthrosis after previous surgery. [41]

[37] Bose B et al. (2004). Stand-Alone Interbody Fusion Versus Instrumented Interbody Fusion: A Clinical Comparison. *Neurosurgery Quarterly* 14(3): 168-173.
[38] Christensen FB et al. (2002). Long-Term Functional Outcome of Pedicle Screw Instrumentation as a Support for Posterolateral Spinal Fusion: Randomized Clinical Study With a 5-Year Follow-up. *Spine* 27(12): 1269-77.
[39] Dantas (2007) et al. Comparison between posterior lumbar fusion with pedicle screws and posterior lumbar interbody fusion with pedicle screws in adult spondylolisthesis. Arq Neuropsiquiatr 65(3-8): 764-770.
[40] X-STOP FDA Clinical Summary Review Memorandum (accessed at http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4064b1_02_clinical%20memo.pdf).
[41] Jutte PC & Castelein RM. (2002). Complications of pedicle screws in lumbar and lumbosacral fusions in 105 consecutive primary operations. *Eur Spine J* 11(6): 594-98.

Event	Proposed Study Stopping Criteria (Barricaid patient population)	Literature References
	device loosening) is >15%	• Dantas (2007): 7% of subjects undergoing pedicle screw fusion for spondylolisthesis experienced screw breakage.
4. Neurological Adverse Events (See note 3, below.)	At least three observed occurrences in the Barricaid group, and the percentage of Barricaid subjects experiencing serious device- or procedure-related (possibly, probably or definitely) neurological adverse events as defined below is 10 percentage points greater than the control group or is > 15% (absolutely)	• Dantas et al. (2007): 2 patients experienced nerve root compression requiring surgical repositioning, one CSF leak (9.9% total). • Jutte & Castelein (2002): 8.6% of patients experienced a neurologic complication [5]
5. Spontaneous Fusion (as defined in the radiographic protocol)	At least three observed occurrences in the Barricaid group, and the percentage of Barricaid subjects experiencing unintended fusion is 10 percentage points higher than the control group or is > 15% (absolutely)	• 3% of ProDisc-C patients in the IDE study experienced spontaneous fusion [42]
6. Infections (See note 4, below.)	At least three observed occurrences in the Barricaid group, and percentage of Barricaid subjects experiencing a deep wound infection is > 10%	Jutte & Castelein (2002): 4.7% of patients experienced deep infections [5]

[42] ProDisc-C SSE (accessed at http://www.fda.gov/cdrh/pdf7/p070001b.pdf).

1. Device breakage is any fracture or tearing of any component of the device. This may include fracture of the anchor or tearing of the mesh.

2. Device loosening is any loosening at the anchor-bone interface (as defined by motion of the anchor on flexion-extension of at least 1 mm, with radiolucent halo around 80% of more of the bone-apposing surface).

3. Device- or procedure-related Neurological Adverse Event is defined as any of the following conditions resulting from the device or procedure:

    - Severe motor deficit (loss of 1 or more motor grades)
    - Severe nerve root deficit (loss of 1 or more motor grades, dense sensory deficit or the combination)
    - Severe sensory deficit (dense sensory loss in a nerve root distribution)
    - Severe radiculitis (nerve root irritation that does not respond to oral agents)
    - Cauda Equina syndrome

4. Deep wound infection is defined as infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following:
    - Purulent drainage from the deep incision, but not from the organ/space component of the surgical site.

    - A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured and the patient has at least one of the following signs or symptoms: fever (>38º), or localized pain or tenderness. A culture negative finding does not meet this criterion.

    - An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

    - Diagnosis of a deep SSI by a surgeon or attending physician.

Each of the above criteria will be reviewed by the DSMB at regular intervals, at least quarterly

2.8 SUBJECT WITHDRAWAL

A subject is considered enrolled in the study after randomization and must be followed whether or not the patient received the assigned treatment. Patients who are determined to be ineligible prior to randomization (failure to meet the pre-operative or intra-operative eligibility criteria) will be considered intra-operative screen failures (not enrolled), and will not require additional study follow up visits. The reason for the screening failure will be clearly noted on the applicable CRF.

It is recognized that the subject's participation in this trial is entirely voluntary, and that any subject may refuse to participate or may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his or her discretion, may withdraw a subject from this trial to pursue other treatment modalities or if the subject cannot continue in the trial for any medical reason(s).

Every effort should be made to contact subjects who fail to return for the visits required under the protocol. This contact must be documented in the subject's chart. This includes, but is not limited to telephone calls and certified letters.

When a subject withdraws early or is dropped from the study, regardless of the reason, the Investigator shall notify the Sponsor within five (5) business days, all required evaluations should be performed at their final visit, and an End of Follow-up Form (CRF – 11) shall be completed.

Although a subject may have been withdrawn from this study, for purposes of obtaining safety data (and, if necessary, to determine the success/failure of those subjects who were withdrawn prior to this determination being clearly made), the investigator is required to make an attempt to obtain follow-up assessments at 12 and 24 months post surgery. The investigators will be asked to obtain information on radiographic and clinical status, as defined by the protocol, as well as adverse events and complications for these subjects, with the exception of those subjects withdrawn due to pregnancy, who will not receive the radiographic examination.

Other Conditions for Withdrawal:

1. A subject who becomes pregnant or suspects pregnancy during the trial will be withdrawn from participation in the trial. These subjects will be evaluated for safety and effectiveness at 12 and 24 months post surgery. The Statistical Analysis Plan defines how these patients will be utilized in the calculation of success rates.

2. Any subject who develops a significant intercurrent medical illness during the trial should be withdrawn. This type of illness is defined as any illness that would hinder the subject's ability to follow-up with the investigator at the protocol required time points. These subjects will be evaluated for safety and effectiveness at 12 and 24 months post surgery. The Statistical Analysis Plan defines how these patients will be utilized in the calculation of success rates.

Early Study Termination by the Sponsor

Investigators and subjects should understand that the study may be discontinued at any time without their consent and that the Sponsor may terminate their participation.

2.9 TRIAL RANDOMIZATION

Randomization will be accomplished via a "lottery" system. Patients will be randomized (1:1) intraoperatively after the surgeon has completed the limited discectomy (as described by Spengler). Intraoperative randomization is being performed so as to minimize surgical technique bias. All patients randomized to the treatment group and subsequently cannot have the Barricaid implanted will be considered a treatment failure and will be fully followed per the protocol.

A randomization log will be generated prior to study initiation. This log will be generated and maintained independently by a statistical consultant. An Interactive Web Based Response System (IWRS) will be used as the software platform for randomization. The clinical sites will be given their randomization either via personal computer log in or by phone during surgery.

2.10 ADVERSE EVENTS (AE)

All clinical events, including both observed or volunteered problems, complaints, symptoms, physical signs or disease which either occur during the study, having been absent at baseline, or, if present at baseline, appear to worsen during the study are to be recorded as adverse events in the subject's medical record and on the appropriate case report form using the following criteria.

2.10.1 DEFINITIONS

2.10.1.1 Adverse Event

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device [ISO 14155].

2.10.1.2 Associated with the Use of an Investigational Product

Due to the temporal proximity of the AE to investigational product administration, there is a reasonable possibility that the product may have caused the AE or may have contributed to the severity or duration of an event caused by other means.

TABLE 4: AE Relationship Assessment

AE Relationship	Description
Unknown	The relationship between the adverse event and the device (or procedure) cannot be determined based upon available data.
Not-Related	A temporal relationship to investigational product implantation or it's ongoing use, which makes a causal relationship clearly and incontrovertibly due to extraneous causes, such as other drugs, products, chemicals, underlying diseases, environment, etc. Not-related to the investigational product administration.
Possibly-Related	Occurring within a reasonable period of time relative to investigational product administration or its ongoing use which makes causal relationship possible, but plausible explanations may also be provided by other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Possibly-related to investigational product administration.

Probably-Related	Occurring within a reasonable period of time relative to investigational product administration or its ongoing use, which makes a causal relationship probable where the relationship cannot be attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Probably-related to the investigational product administration.
Definitely -Related	Occurring within a reasonable period of time relative to investigational product administration or can be directly related to the ongoing use of an investigational product, which makes a causal relationship definite where the relationship cannot be attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Definitely-related to the investigational product administration.

2.10.1.3 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device [ISO14155]

2.10.1.4 Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem, or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [21 CRF Part 812.3(s)]

2.10.1.5 Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (SAE). [ISO 14155]

2.10.1.6 Procedure Related Event

Any undesirable clinical occurrence in a subject that occurs during a medical procedure required for the investigation. This type of adverse event may or may not be directly related to the investigational device.

2.10.1.7 "Other" Adverse Events

Any event that may occur during an investigation that is none of the above but can reasonably be expected to involve the investigational device and/or medical procedure(s) being performed.

Note: Pain, neurological and function symptoms should be considered adverse events when a subject's complaint for any of these symptoms results in an unscheduled visit with the subject requiring treatment outside the standard of care.

2.10.1.8 Definitions of Adverse Event Severity

Mild: Awareness of signs or symptoms, but easily tolerated; minor irritant requiring medication or a medical evaluation; signs and symptoms are transient, resolved during the procedure.

Moderate: Discomfort/deficit significant enough to cause interference with usual activities; persists after procedure or requires treatment, but does not extend hospitalization or intensive care for the subject.

Severe: Refers to the grade or intensity of an event, which can be intense or extreme discomfort. Symptom causes intense discomfort and may be such that the subject cannot perform daily activities. May result in treatment of the symptom.

2.10.1.9 Serious Adverse Event (SAE)

Per ISO 14155, An adverse event that:

- Led to death,
- Led to serious deterioration in the health of the subject that either resulted in
    - A life-threatening illness or injury,
    - A permanent impairment of a body structure or body function, or
    - Requires inpatient hospitalization or prolongation of existing hospitalization,
    - Medical or surgical intervention to prevent a life threatening illness or injury or permanent impairment to a body structure or body function
- Led to foetal distress, foetal death, or a congenital anomaly or birth defect

2.10.1.10 Subsequent Surgical Interventions

Subsequent surgical interventions will be categorized as follows:

- Revision (only applies to Barricaid group): a procedure that adjusts or in any way modifies the Barricaid (e.g., adjustment of implant position).

- Removal (only applies to the Barricaid group): a procedure where all of the Barricaid is removed without replacement (since the Barricaid should never be replaced per the surgical technique manual).

- Supplemental Fixation: a procedure in which additional instrumentation not under study in the protocol is implanted at the involved level (e.g., supplemental placement of a rod/screw system or a plate/screw system) with or without fusion. In the case of a Barricaid patient, the Barricaid must be left in place to be considered a supplemental fixation.

- Reoperation at the index level: any surgical procedure at the involved level that does not remove or adjust the position of the Barricaid or does not involve the addition of supplemental fixation. This category may include surgeries done to treat reherniations if they do not fit into one of the other three categories.

- Other lumbar spinal procedure: a lumbar spinal procedure at a level other than the index level.

Subjects who require revision or removal of the Barricaid, re-operation, or supplemental fixation will remain in the study for the complete 24-month period.

2.10.2 ANTICIPATED ADVERSE EVENTS

The following adverse events are considered anticipated for study purposes. The AEs are assigned numbers to correlate with AE reporting on the associated CRF:

Group 10-20 – Neurologic

11. Nerve or spinal root injury (e.g., motor deficit, Ileus, Impotence, Numbness, Reflex changes, Cauda equina syndrome, partial or complete paralysis, Foot drop, Incontinence)
12. Dural tear or CSF leak
13. Nerve root or spinal cord impingement
14. Herniated nucleus pulposus at index level
15. Herniated nucleus pulposus at different level
16. Musculoskeletal spasms of the back or leg
17. Arachnoiditis
18. Cerebro-vascular accident
19. Clinically significant neurological deterioration compared to baseline
20. Prolonged operation
21. Excessive Blood loss requiring infusion
29. Other Neurologic, specify in AE Form

Group 30 – Wound

31. Hematoma
32. Bleeding
33. Thrombophlebitis
34. Infection—superficial
35. Infection—deep

39. Other Wound, specify in AE Form

Group 40 – Vascular

41. Pulmonary embolism
42. Deep venous thrombosis (DVT)
43. Vascular injury; bleeding and/or thrombosis
44. Anemia
45. Aneurysm
46. Stroke

49. Other Vascular, specify in AE Form

Group 50-79 - Post-surgical Complications

50. Discitis
51. Reaction to foreign body (allergic or implant-generated wear debris
52. Adverse reaction to anesthesia or surgery required drugs.
53. New or worsening pain resulting in an unscheduled visit or surgery at the operated level
54. New or worsening leg pain compared to baseline noted at a scheduled follow up visit
55. New or worsening back pain compared to baseline noted at a scheduled follow up visit
56. Vertebral Fracture – including body or posterior elements at index level
57. Vertebral Fracture
58. Necrosis of Bone or resorption
59. Device migration
60. Device Subsidence
61. Device loosening or dislocation
62. Device fracture/breakage
63. Spontaneous fusion
64. Heterotopic ossification
65. Facet degeneration
66. Adjacent segment degeneration
67. Increased Spondylolisthesis
68. Soft tissue damage
69. Increased Scoliosis

70. Misplaced screws in pedicle
71. Loss of bowel and bladder control
72. Diarrhea
73. Foramenal or lateral recess stenosis
74. Central stenosis
75. Cauda Equina Syndrome
76. Insomnia
77. Infection-UTI
79. Other Post-surgical complications, specify in AE Form

Group 90 – Other

90. Myocardial infarction
91. Death
92. Pain at different location from baseline
93. Narcotic addiction
94. Headache
95. Insomnia
96. Fever
97. Wrong site operation
98. Failure to achieve desired results (e.g., residual nucleus pulposus reoperation)
99. All other, specify in AE Form

2.10.3 ASSESSING AND RECORDING ADVERSE EVENTS

All AEs, including the following, must be assessed and recorded in the subject's medical record and then transcribed onto the appropriate case report form at each visit.

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- Medical condition which occurs during the study, having been absent at baseline
- Medical condition present at baseline, which appears to worsen during the study
- Anything determined to be clinically significant by the Investigator

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study product. Subjects should also be instructed to call the Investigator to report any problems between visits.

Each AE recorded must be described as follows:

1. Describe **the event** by stating the underlying cause (the diagnosis), coexisting disease, or other. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when possible. To the extent possible, the event to be recorded and reported is the event *diagnosis* as opposed to the event *symptoms*. Details and symptomology associated with the event may be reported in the narrative section of the Adverse Event case report form. Please refer to the following examples:

    - Fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as an infection only.

    - Blood loss or blood transfusion associated with an intraoperative vascular injury is to be reported as a vascular injury only.

    - Pain on urination in the presence of a clinically diagnosed urinary tract infection is to be reported as a urinary tract infection only.

2. Note **duration** by entering the date of onset and date of resolution. If the event is present at the final study visit, the continuing box must be marked.

3. Note the **grade** or **intensity** of the event as mild, moderate or severe.

4. Note if it is an **unanticipated adverse device effect** or not.

5. Note the **action taken** as none, medication, procedure, medication and procedure, or other. Any prescribed medication must be noted in the subject's medical records and then transcribed onto the appropriate case report form.

6. Note **the relationship to the Test Article** (Barricaid) as not-related, unknown, possibly-related, probably-related or definitely-related (see 5.1.2 above).

Any subject withdrawn from the study due to an AE will be followed until the outcome of the event is determined. The Investigator will prepare a complete written summary of the event and its outcome, in addition to recording the event on the appropriate case report form.

All other AEs will be followed through to the end of this study. Any unresolved AE at a subject's final study visit must be marked continuing on the appropriate case report form. Any AE that is related to the study product and continuing at the end of the study will be followed by the Investigator until the event has resolved or is determined to be irreversible.

2.10.4 REPORTING ADVERSE EVENTS

In addition to any applicable EC reporting requirements, the Investigator must submit written reports of all AEs to the Sponsor using electronic CRF 9, according to the following timeline requirements:

- The Investigator shall notify, via phone, fax, electronic mail, or electronic CRF 9 to the Sponsor of all Serious Adverse Events, including all patient deaths, within 24 hours of the time the Investigator learns of the event. All serious adverse events (SAE; see section 2.10.1.8 and/or electronic CRF 9 for definition), must be reported via the electronic CRF 9 detailing the event to the Sponsor within 5 working days, regardless of their relatedness to the device or procedure.

- The Investigator shall notify, via phone, fax, electronic mail, or electronic CRF 9 to the Sponsor of all Unanticipated Adverse Device Effects, within 24 hours of the time the Investigator learns of the event. All unanticipated adverse device effects (UADE; see section 2.10.1.4 and/or electronic CRF 9 for definition) must be reported via the electronic CRF 9 detailing the event to the Sponsor within 5 working days.

- All other adverse events must be reported to the Sponsor in a timely manner.

- The Investigator Shall notify the reviewing EC of all unanticipated adverse device effects occurring in the study as soon as possible, but no later than 10 working days after they first learn of the effect, as applicable.

Table 5- Investigator Reports

Report	Submit To:	Description/Time Constraints
Serious Adverse Event	Intrinsic Therapeutics	Notify within 24 hours Written report within 5 working days
	IRB/EC	Per IRB/EC requirements, as applicable
	Competent Authority (if applicable)	Per CA Requirements, as applicable
Unanticipated Adverse Device Effect	Intrinsic Therapeutics	Notify within 24 hours Written report within 5 working days
	IRB/EC	Within 10 working days, as applicable
Subject Death During Investigation	Intrinsic Therapeutics	Notify within 24 hours Written report within 5 working days
	IRB/EC	Per IRB/EC requirements, as applicable
Subject Withdrawal	Intrinsic Therapeutics	Within 5 working days
	IRB/EC	Per IRB/EC requirements, as applicable
Withdrawal of IRB/EC Approval	Intrinsic Therapeutics	Within 5 working days
Annual Progress Report	Intrinsic Therapeutics IRB/EC	Submitted annually, as applicable
Deviations from Investigational Plan*	Intrinsic Therapeutics IRB/EC	Within 5 working days
Protocol Deviations	Intrinsic Therapeutics	Within 5 working days
	IRB/EC	Per IRB/EC requirements, as applicable
Informed Consent Not Obtained	Intrinsic Therapeutics	Notify within 24 hours Written report within 5 working days
	IRB/EC	Per IRB/EC requirements, as applicable
Final Study Report	Intrinsic Therapeutics	Within 3 months after completion or termination of the study.

Report	Submit To:	Description/Time Constraints
	IRB/EC	

* Please refer to section 2.14.2 of the Protocol for the conditions under which this notification applies.

2.11 COLLECTION OF ECONOMIC DATA

The cost and intensity of service for the index treatment and control hospitalizations, as well as any additional spine or study related hospitalizations during the study will be tracked. These data are being collected to meet the requirements of the Centers for Medicare and Medicaid (CMS) for making coverage and reimbursement determinations for new devices.

The data to be collected include copies of the subjects' hospital bills, including the Explanation of Benefits (EOB) documentation from third party payers.

In the event that a hospital/institution is not able to provide the required bill and EOB to the sponsor, the hospital/institution will provide written documentation as to the reason why the information is not available and that written documentation must be provided to the sponsor.

The following personal health information from the bill will be collected, where applicable:

- Patient's hospital identification number
- Patient's birthdate
- Hospital's provider identification number
- Patient's hospital admission date
- Patient's hospital discharge date
- Patient's surgery date
- Total charges for the hospitalization

2.12 EXPLANT PROCEDURE

In the event that a Barricaid must be removed, the Surgical Technique Manual defines the method of extraction of the implant. The handling of a removed Barricaid is defined in the Explant Protocol.

2.13 ETHICAL AND REGULATORY REQUIREMENTS

2.13.1 CODE OF CONDUCT

The Investigator will ensure that the clinical study is conducted in accordance with good clinical practice (GCP) and all regulatory and institutional requirements, including those for subject privacy, informed consent, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval and record retention, the Food and Drug Administration (FDA) Guidelines for the conduct of clinical trials, and the CPMP/ICH/135/95.

2.13.2 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

The Investigator must obtain appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval before the study can be initiated. A copy of the written approval from the IEC/IRB and a copy of the approved informed consent form should be sent to the Sponsor. A list of the IEC/IRB members (including their Institution affiliations, gender makeup, and occupations); or a statement from the IEC/IRB specifying that the membership comply with applicable regulations is to be provided to the sponsor.

If the Investigator advertises for subjects, whether in a professional or consumer publication, radio, television or community notices, all advertising must receive prior approval by the Sponsor and the IEC/IRB.

Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the deviation is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by the Sponsor for submission to the IEC/IRB for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's medical record.

The Investigator must immediately forward to the IEC/IRB any written safety reports or updates from the Sponsor.

The Investigator must keep the IEC/IRB informed of the progress of the study at least annually. If the IEC/IRB withdraws their approval, the Investigator must notify the sponsor within five (5) business days.

2.13.3 INFORMED CONSENT

The Investigator must observe the requirements of the appropriate regulatory body by obtaining written informed consent. The Sponsor will supply a sample informed consent form (Appendix 1). Whether or not the sample informed consent form is used or adapted, the site will submit the proposed informed consent form to the Sponsor for review PRIOR to submission to the IEC/IRB. The informed consent form must be approved by the institution's IEC/IRB. Copies of the informed consent form used in the study must contain the IEC/IRB-approval stamp (if applicable) and version date.

Subjects will be informed of new information learned during the study, which may affect the subject's decision to continue participation in the study.

The study informed consent form must be obtained prior to the initiation of any study procedures. The subject (or the subject's legally authorized representative) must be allowed sufficient time to thoroughly read (or have explained to them), the informed consent form. Surrogate consents are not allowed. The Investigator should answer any questions that the subject/representative might have. If the subject agrees to participate in the study, the subject/representative must sign both copies of the informed consent form. The witness and the Investigator must also sign both copies of the informed consent form. One copy of the informed consent form should be given to the subject/representative. The study staff should adequately and accurately document the sequence of actions in the consenting process as well as the date of the subject's signature on the informed consent form in the subject's medical chart to document that informed consent was obtained prior to initiating any study procedures.

An Informed Consent Log will be completed to document the existence of the signed informed consent form. The log will contain: Subject ID, date informed consent form signed, and the version signed. The monitor will initial and date the log once the executed informed consent form has been reviewed. Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

2.13.4 SOURCE DOCUMENTATION REQUIREMENTS

Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the trial data submitted for review to the regulatory agencies. Source documentation will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, pharmacy records, device accountability records, telephone follow up records and medical consultations (as applicable).

2.13.5 SUBJECT CONFIDENTIALITY

The Sponsor will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IEC/IRB, however to the extent possible, the subject's identity will not be disclosed.

2.14 DATA MANAGEMENT AND REPORTING

The Sponsor's Clinical Data Management Department is responsible for ensuring that the planning, management and completion of the data management component of the study is conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs) and Good Clinical Practices, along with the study specific Data Management Plan (DMP).

The purpose of the DMP is to describe the data management activities, responsibilities and

timelines for the study. The DMP outlines how the Case Report Form (CRF) data collected from the sites will be entered, transmitted, reviewed, coded, cleaned and analyzed. In addition, the DMP defines how radiographic imaging data is entered, transmitted, reviewed, coded, and analyzed.

2.14.1 CASE REPORT FORMS

Electronic data capture (EDC) will be used for this study. Data will be collected and documented on provided source worksheets which follow the electronic case report forms (eCRF). Only authorized study site personnel will complete the source worksheets and eCRFs. Electronic CRFs must be reviewed and approved by an investigator listed in the Investigator's Statement and Agreement.

Since there is a potential for errors, inaccuracies, and misinterpretation in transcribing data from source documents into the EDC system, originals or photocopies of all relevant worksheets, records and reports, and copies of test results must be available at all times for inspection and comparison to the EDC data by the study monitor.

Sample CRFs to be used with this clinical trial are provided in Appendix 3.

2.14.2 PROTOCOL DEVIATIONS

In addition to any relevant EC reporting requirements, all protocol deviations must be reported to the Sponsor by the Investigator using electronic CRF 10, regardless of who identified the deviation.

In the following events, both the EC and the Sponsor must be notified within 24 hours of the event, with written notice provided within five (5) business days:

- emergency deviation to protect the life or physical well-being of the patient,
- use of an investigational device without obtaining written informed consent from the patient

In the case of all other deviations, notify the Sponsor by completing the electronic CRF within five (5) business days of becoming aware of the deviation.

The Sponsor shall conduct an evaluation of all reported protocol deviations and recommend a corrective action for the site, as necessary.

2.14.3 FINAL REPORT

Following completion of this trial, final reports will be issued as required.

2.15 RETENTION OF RECORDS BY THE INVESTIGATOR

The Investigator will retain records for a period of 2 years after the investigation is discontinued and, if required, the appropriate regulatory agency is notified.

2.16 MONITORING

The Investigator must allow regular inspection of all study records including CRFs, source documents and regulatory documents during the study by the monitor or a representative of the Sponsor. This measure is to ensure that the study is carried out and documented in accordance with federal regulations and the terms of this protocol. The Investigator also agrees to allow inspections by staff members of the FDA or other regulatory agencies before, during, or after the study has concluded, if such inspections are requested.

Monitoring will be accomplished in accordance with the Study Monitoring Plan.

2.17 STUDY RISKS

The risks associated with the surgical procedure are identical to that of a standard lumbar discectomy up to the point of completing the discectomy. This is based on the fact that no experimental instrumentation is introduced to the patient until after the discectomy is completed. An extensive literature review was conducted to identify risks associated with lumbar discectomy and their relative rates of occurrence. In addition, the results of ongoing prospective European studies with the Barricaid are included in this evaluation. A full risk analysis is documented in the Investigator's Brochure. This risk analysis supports the conclusion that the risks associated with the

Barricaid and its surgical technique/instruments have been mitigated to a sufficient level, and that the benefits of preventing reherniation and disc collapse far outweigh the potential risks of implanting the Barricaid.

2.18 BIBLIOGRAPHY

Balderston,R., Gilyard, G., Jones, A. A., et al.:The treatment of lumbar disc herniation: Simple fragment excision versus disc space curettage. Journal of Spinal Disorders: 4 (1): 22-25.

Beurskens AJHM, de Vet HCW, Koke AJA: Responsiveness of functional status in low back pain: a comparison of different instruments. Pain 65:71-76, 1996.

Bruske-Hohlfeld I, Merritt JL, Onofrio BM, et al: Incidence of lumbar disc surgery. A population-based study in Olmsted County, Minnesota, 1950-1979. Spine 15:31-35, 1990

Butterman, G. Treatment of Lumbar Disc Herniation: Epidural Steroid Injection Compared with Discectomy – A Prospective, Randomized Study. The Journal of Bone and Joint Surgery (American*)* 86:670-679 (2004)

Carragee, E.: Surgical Treatment of Lumbar Disk Disorders JAMA. Vol. 296, No. 20, pp 2485-2487, 2006.

Carragee, E., Han, M., et al.: Clinical outcomes after lumbar discectomy for sciatica: The effect of fragment type and anular competence. Journal of Bone and Joint Surgery 85: 102-108: 2003.

Carragee, E., Spinnickie AO., et al.: A Prospective Controlled Study of Limited Versus Subtotal Posterior Discectomy: Short-term Outcomes in Patients with Hernitated Lumbar Intervertebral Discs and Large Posterior Anular Defect. Spine 31:653-657, 2006.

Damkot DK, Pope MH, Lord J, et al: The relationship between work history, work environment, and low-back pain in men. Spine 9:395-399, 1984

Dixon A: Progress and problems in back pain research. Rheum Rehabil 12:165-175, 1973

Fairbank JCT, Pynsent PB: The Oswestry disability index. Spine 25(22): 2940-2953, 2000.

Fast A: Low back disorders: conservative management. Arch Phys Med Rehabil 69:880-891, 1988

Fritsch, E., Heisel, J., Rupp, S.: The failed back surgery syndrome – Reasons, intraoperative findings, and long-term results: A report of 182 operative treatments. Spine 21 (5): 626-633, 1996.

Frymoyer JW, Cats-Baril WL: An overview of the incidences and costs of low back pain. Orthop Clin North Am 22: 263-271, 1991

Fu, Tsai-Sheng et.al. Long0term Results of Disc Excision for Recurrent Lumbar Disc Herniation With or Without Posterolateral Fusion. Spine Vol. 30, No. 24, pp 2830 – 2834

Gibson, J.N., et.al.: Surgical Interventions for Lumbar Disc Prolapse – Update Cochran Review. Vol. 32 No 16 pgs 1735 – 1747 2007.

Grilo, R.M. Clinically relevant VAS pain score change in patients with acute rheumatic conditions. Joint Bone Spine 74 (2007) 358-361

Hart LG, Deyo RA, Cherkin DC: Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey. Spine 20:11-19, 1995

Heliovaara M, Vanharanta H, Korpi J, et al: Herniated lumbar disc syndrome and vertebral canals. Spine 11:433-435, 1986

Horsley, L Practice GuidelinesACP guidelines for the diagnosis and treatment of low back pain. American Family Physician, Vol. 77 No. 11, June 1, 2008.

Kelsey JL, Pastides H, Bisbee GE Jr: Musculo-skeletal Disorders: Their Frequency of Occurrence and Their Impact on the Population of the United States. New York: Prodist, 1978

Kinkade, Scott: Evalulation and Treatment of Acute Low Back Pain. American Family Physician Volume 75, Number 8, 2007

LaJolla Spine Institute: Lumbar Disc Herniation
http://www.lajollaspine.com/sddh_lumb_over.shtml, 2008

Mayer TG, Gatchel RJ, Mayer H, et al: A prospective two-year study of functional restoration in industrial low back injury. An objective assessment procedure. JAMA 258:1763-1767, 1987

Nachemson A, Lewin T, Maroudas A, et al: In vitro diffusion of dye through the end-plates and annulus fibrosus of human lumbar inter-vertebral discs. Acta Orthop Scand 41:589-607, 1970

Peul, Wilco, et.al. Timing of surgery for sciatica: subgroup analysis alongside a randomized trial European Spine Journal,
http://www.lumc.nl/rep/5038/att/812180307081046/905080251391046.pdf, January 2009

Roland M, Fairbank J: The Roland-Morris disability questionnaire and the Oswestry disability questionnaire. Spine 25(24):3115-3124, 2000.

Shvartzman L, Weingarten E, Sherry H, et al: Cost-effectiveness analysis of extended conservative therapy versus surgical intervention in the management of herniated lumbar intervertebral disc. Spine 17:176-82, 1992

Spangfort EV: The lumbar disc herniation. A computer-aided analysis of 2,504 operations. Acta Orthop Scand Suppl 142: 1-95, 1972

Spengler, D. Lumbar Discectomy: Results with Limited Disc Excision and Selective Foraminotomy. Spine Vol. 7, No. 6, pp 604-7.

Suk, Kyung-Soo, et.al. Recurrent Lumbar Disc Herniation. Spine Vol. 26, No. 6, pp 672-676.

Watters, W. et.al. An evidence-based review of the literature on the consequences of conservative versus aggressive discectomy for the treatment of primary disc herniation with radiculopathy. Spine Journal 2008.

Weber, H.: Lumbar disc herniation – A controlled, prospective study with ten years of observation. Spine 8 (2): 131-140, 1983.

Weinstein, et. Al.: Surgical vs Nonoperative Treatment for Lumbar Disk Herniation, The Spine Patient Outcomes Research Trial (SPORT), Observational Cohort. JAMA, Vol. 296, No. 20, pp 2451-2459. 2006.

APPENDIX 1

SAMPLE INFORMED CONSENT

APPENDIX 2

RADIOGRAPHIC EVALUATION PROTOCOL

APPENDIX 3

CASE REPORT FORMS

APPENDIX 4

INSTRUCTIONS FOR USE

CLINICAL PROTOCOL CHANGE HISTORY

From Version	To Version	New Version Date	Change Page No.	Description of Changes
NA	A	5/18/2010	NA	Initial Release
A	B	10/6/2010	Throughout	Changes were made to the Protocol Synopsis, Clarifications and updates of Imaging Requirements, Neurological Assessment Requirements, Radiographic Assessment Requirements, Adverse Event Reporting Examples, Investigator Reporting Requirements, Protocol Deviation Reporting, Study Risks, and various general and administrative changes.
B	C	10/15/2010	36-38; 52	Added in two additional anticipated adverse events; Added endplate sclerosis at adjacent levels and removing listhesis at adjacent levels, as well as general and administrative changes.
C	D	5/10/2011	Throughout	Clarified number of clinical sites; Adverse Event capture, Procedure visit X-Rays, Trial Randomization Software (IWRS), Separated Severe and Serious Adverse Event definitions, update and clarification to the collection of economic data, clarified ODI scoring, Clarified anticipated adverse events, clarified adverse event definitions (e.g residual disc hernation), and various general and administrative changes.