SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Reherniation reduction device
Device Trade Name:	Barricaid® Anular Closure Device (ACD)
Device Product Code:	QES
Applicant's Name and Address:	Intrinsic Therapeutics 30 Commerce Way Woburn, MA 01801
Date(s) of Panel Recommendation:	December 12, 2017
Premarket Approval Application: (PMA Number)	P160050
Date of FDA Notice of Approval:	February 8, 2019

II. INDICATIONS FOR USE

The Barricaid® ACD is indicated for reducing the incidence of reherniation and reoperation in skeletally mature patients with radiculopathy (with or without back pain) attributed to a posterior or posterolateral herniation, and confirmed by history, physical examination and imaging studies which demonstrate neural compression using MRI to treat a large anular defect (between 4-6 mm tall and between 6-10 mm wide) following a primary discectomy procedure (excision of herniated intervertebral disc) at a single level between L4 and S1.

III. CONTRAINDICATIONS

The Barricaid® ACD should not be implanted in patients with active systemic infection or infection at the site of implantation.

The Barricaid® ACD should not be implanted in patients with prior surgery at the index level other than intradiscal electro-thermal annuloplasty (IDET), percutaneous nucleoplasty, microdiscectomy, hemilaminectomy, or laminotomy.

The Barricaid® ACD should not be implanted in patients with allergies/hypersensitivity to the device's components (polyethylene terephthalate [PET], polytetra-fluoroethylene, titanium, platinum, iridium).

The Barricaid® ACD should not be implanted in patients with osteoporosis or osteopenia defined as DEXA bone mineral density T-score less than or equal to -2.0.

The Barricaid® ACD should not be implanted in patients who require spinal surgery other than a discectomy (with or without laminotomy) to treat leg/back pain (scar tissue and osteophyte removal is allowed).

The Barricaid® ACD should not be implanted in patients with back or non-radicular leg pain of unknown etiology, scoliosis >10º (rotational or angular), spondylolisthesis >Grade 1, or clinically compromised vertebral bodies in the lumbosacral region due to any traumatic, neoplastic, metabolic, or infectious pathology.

The Barricaid® ACD should not be implanted in patients with a preoperative posterior disc height <5 mm or with anular defects outside of these size ranges: between 4-6 mm tall and between 6-10 mm wide.

The Barricaid® ACD should not be implanted in patients with insulin-dependent diabetes, peripheral neuropathy, arterial insufficiency, or a BMI > 40.

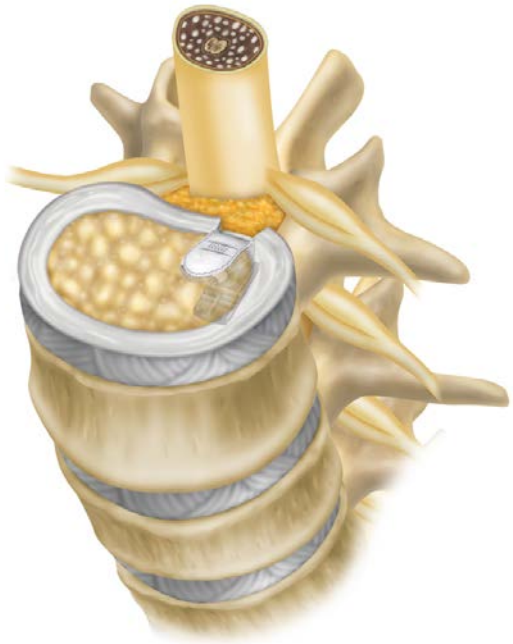
IV. WARNINGS AND PRECAUTIONS

Please refer to the Barricaid® ACD Instructions for Use for warnings and precautions.

V. DEVICE DESCRIPTION

The Barricaid® ACD, also referred to as "Barricaid," is implanted at the time of a lumbar discectomy, after the discectomy is complete. The Barricaid is a permanent implant that has two major subcomponents: a flexible woven polymer fabric component is intended to close the anular defect, and a bone anchor to affix the flexible polymer component in place.

The Barricaid serves as an adjunct to the discectomy procedure and is intended to act as a barrier to block the anular defect that is identified as part of the discectomy. The Barricaid is provided to the user preloaded onto a single use disposable delivery tool.



The flexible polymer component is formed from a flexible woven fabric comprising multiple layers of counter-angulated fibers made from a non-degrading polymer (PET, or polyethylene terephthalate) with a history of cleared use as a permanently implantable material.[1] The individual layers are sequentially sewn together using PTFE (polytetra-fluoroethylene)-coated PET suture. The flexible polymer component contains a platinum-iridium (Pt-Ir) radiopaque marker for observation of flexible polymer component position on intra- and/or post-operative radiographs. The Barricaid anchor component is made from a standard orthopedic titanium alloy (Ti-6Al-4V ELI). The titanium alloy is in compliance with ASTM F136-11 Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications.

The Barricaid is offered in two sizes to accommodate a range of anular defect sizes, each providing a barrier for closure of the anular defect. The device is available with 8mm and 10mm flexible polymer component widths, while the flexible polymer component length (15mm) and base anchor is identical for the two different flexible polymer component sizes.

The device is tapped into the vertebral body enabling the titanium bone anchor to secure one end of the flexible polymer component into the vertebral body. The anchor component is intended to help position the flexible polymer component within the anular defect.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

For the patients with radicular leg pain caused by herniated lumbar discs, non-surgical alternatives include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, oral and epidural steroids, rest, exercise, and physical therapy. Surgical alternatives vary, depending upon the severity of the disc herniation, the contribution of back pain, and the presence of instability, among other factors, and most commonly include discectomy procedures. Rarely performed index surgical interventions include fusion procedures (e.g., interbody cages, pedicle screw systems) and bone graft, or a lumbar disc arthroplasty.[2,3] Literature also includes reports of reduction in reherniation rates after discectomy by completely removing the nucleus with an aggressive nucleotomy.[4] Each alternative has its own advantages and disadvantages. A patient should discuss these alternatives with his or her physician to select the option that best meets their clinical condition and lifestyle.

VII. MARKETING HISTORY

The Barricaid has been marketed outside of the United States since 2009. The Barricaid is marketed in the following countries: Germany, Austria, Greece, Netherlands, Italy, Switzerland, Belgium, Turkey, Israel, South Korea, Russia, South Africa, Chile, Costa Rica, Poland, Hungary, Slovenia, Bulgaria, Saudi Arabia and Australia. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A list of potential adverse effects (e.g., complications) associated with use of the Barricaid is presented below. This listing was derived from results of the Barricaid clinical trial and published clinical literature for clinical experiences within the same patient population. It includes (1) those adverse effects potentially associated with lumbar spine surgery; (2) those potentially associated with lumbar discectomies; (3) those potentially associated with implantation of the Barricaid device. In some instances, additional surgery may be required to correct adverse effects.

1. Risks associated with lumbar spine surgery include: anesthetic medication reactions; blood loss, blood vessel damage, phlebitis or hematoma; blood transfusion which may cause circulatory collapse, blood incompatibility, kidney damage, hepatitis or infection with HIV; operative site infection; myocardial infarction or circulatory problems; deep vein thrombosis, pulmonary embolism or thrombus formation in other vessels; stroke; fever or infection; pneumonia; injury to muscle, soft tissue or nerves; formation of scar tissue; wound swelling, drainage, dehiscence, necrosis or delayed healing; discomfort and rehabilitation associated with recovery from surgery; inability to perform certain tasks, such as lifting or exercise; surgical site pain or discomfort; and death.

2. In addition to the risks listed above, risks associated with lumbar discectomies include: vertebral bone resorption (endplate lesions); problems from anesthesia;

spinal fluid leaks; new or worsened back or leg pain; loss of bladder and/or bowel functions; reherniation of nucleus into the epidural space, which could cause impingement or damage to neural elements, and nerve complications; damage to nerve roots or the spinal cord causing partial or complete sensory or motor loss (paralysis); dural tears (tears in the tissue surrounding and protecting the spinal cord); instruments used during surgery may break or malfunction which may cause damage to the operative site or adjacent structures; fracture, damage or remodeling of adjacent anatomy, including bony structures or soft tissues during or after surgery, unintended or spontaneous fusion; loss of disc height; foraminal stenosis; canal stenosis; facet hypertrophy; loss of appropriate spine curvature; osteomyelitis, epidural abscess, meningitis, spinal instability and surgery at the incorrect location or level.

3. In addition to the risks listed above, risks associated with implantation of the Barricaid device and associated instruments include: Expulsion of some or all of the device into the epidural space, which may cause impingement or damage to neural elements; subsidence of some or all of the device into the vertebral body; migration or dislodgement of the implant from the original position so that it becomes ineffective or causes damage to adjacent bone or soft tissues including nerves; separation of the flexible fabric component from the bone anchor component; loosening of the bone anchor component from the bone; decrease in bone density due to stress shielding; fracture of bony structures; fracture of the device; implant material sensitivity, or allergic reaction to a foreign body; discomfort, or abnormal sensations due to the presence of the device; nerve root irritation and/or damage from insertion and/or removal of device and associated instruments; excessive scar tissue formation; reoperation for removal of the device; increased vertebral bone resorption (increased frequency and size of endplate lesions); implant malposition or incorrect orientation; production of wear debris or other factors which may damage surrounding bone.

For the specific adverse events that occurred in the Barricaid clinical study, please see Section 10.5 below. For detailed information on endplate lesions, see Section X.E.9.

IX. SUMMARY OF NONCLINICAL STUDIES

A number of non-clinical studies were conducted by the sponsor including:

- Monotonic Anchor Push-Out Testing
- Cyclic Anchor Push-Out Testing
- Cyclic Nucleus Pressure Testing
- Flexible polymer Component Migration Testing
- Flexible polymer Component Detachment Testing

There were limitations to the non-clinical studies conducted, therefore limited conclusions could be drawn based on the studies performed. Due to these limitations in the non-clinical testing above, clinical data were provided to address the risk of flexible

polymer component and anchor migration, flexible polymer component detachment and ability to retain the disc nucleus that would typically be characterized by this testing.

A cadaveric usability study was performed to evaluate the implantation and removal of the device by independent surgeons.

A. Animal Studies

1. Rabbit Particulate Study

This study was designed to assess the local and systemic effect of PET particulate, with particular focus on the presence of activated macrophages and other parameters as deemed appropriate by the project pathologist. The study also assessed systemic tissues for architecture, presence of PET particulate (test material), as well as signs of foreign body giant cell/granulomas, inflammatory reactions.

Study samples (study slides) from twenty (20) rabbits implanted with the test article, polyethylene terephthalate (PET) particles, along the membranous covering and neural structures of the spinal canal at L5-L6 or left untreated after epidural exposure alone (sham control) and sacrificed at 3 or 6 months were received for microscopic evaluation.

Findings related to treatment with PET were limited to localized foreign body inflammation, and while PET particles were still present at 6 months, the inflammatory and fibrous tissue response appeared to be appropriate and non-adverse, and there was no evidence of systemic toxicity or PET particulate (test material).

2. Baboon Study

This study was designed to evaluate radiological and histopathological response of Barricaid following long-term implantation in a worst-case animal (baboon) model. A worst-case animal model was used to evaluate device migration and expulsion, the device's ability to withstand physiologic loading, wear debris generation, and risks associated with device implantation.

Nine (9) mature male baboons were implanted with the test device, Barricaid, at two operative levels of the lower lumbar spine (L4-L5 and L5-L6) and received a nucleotomy (operative control) at the L3-L4 level. Three (3) animals were sacrificed at each of three timepoints - 3 months, 6 months and 12 months. Histopathology, microradiographs, MRI and CT imaging were performed. Study samples (images, tissue and study slides) were received for microscopic evaluation.

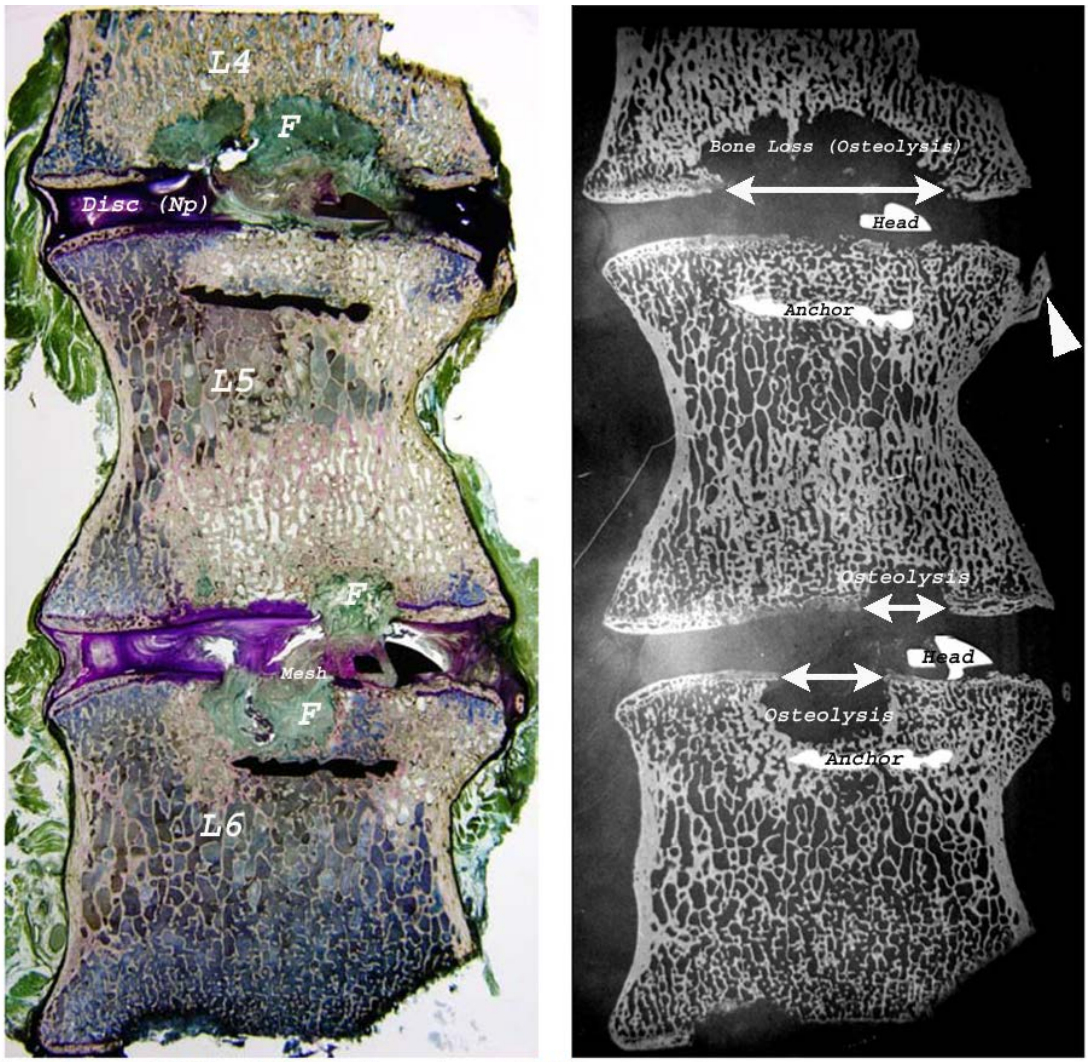


Figure 9.1 Twelve Month Baboon Study Results
Example of undecalcified sagittal histologic (left) and corresponding microradiographic (right) images from the Baboon Implantation Study at 12 months. (Note that results from the animal study may not directly correlate with clinical outcomes.) The histologic tissue image is stained with Villanueva's Osteochrome Bone Stain. Note that the purple-stained tissue is the remnant intervertebral disc (nucleus pulposus) and cartilage lining the vertebral endplate following partial nucleotomy (discectomy). Please note that the device appears in white and is labeled as "anchor" and "head" on microradiograph in the image on the right, and appears black in the corresponding location in the histologic sample on the left. The upper device (L4-L5) shows superior endplate disruption (white arrow) with the mesh (opaque whitish-brown material) subsidence into a bone loss or resorption cavity (osteolysis) with green-stained fibrous connective tissue (replacement fibrosis = F). Osteophyte formation is shown with the white arrowhead. The lower device (L5-L6) shows both superior and inferior endplate disruption (white arrow), mesh subsidence inferiorly, and bone resorption cavities with fibrosis

The limitations to the baboon study were related to the sizing mismatch for the implant and instruments due to the differences between the baboon and the human disc. The potential of oversized implant may have contributed to the development or enlargement of the lesions seen in the baboon study. Furthermore, the loading environment was altered due to a different surgical approach. An anterolateral

approach (as compared to the posterior approach used in humans), and the convex curvature of baboon endplates may promote focal loading on the flexible polymer component that is different than in humans. Lastly, imaging was performed only at post-sacrifice so it was not possible to determine longitudinal progression of bony changes. Altogether, with the over-sized device and different anatomy, there may be differences in the outcomes of the baboon study compared to clinical outcomes in humans despite the similar appearance of lesions within the vertebral body.

Osteolysis, fibrosis, endplate disruption and flexible polymer component subsidence were observed. Reactive changes in response to the flexible polymer component were observed in the form of reactive sclerosis on CT and bone marrow edema on MRI. Imaging was only performed after sacrifice. Endplate lesions at 12 months did not appear to stabilize or diminish when compared to 3 or 6-month images from other animals sacrificed at these earlier timepoints.

There was no evidence of device extrusion, fracture or separation nor was there wear debris locally or systemically. There was no evidence of systemic toxicity. However, the following risks were found to be associated with Barricaid device implantation in the baboon 1-year study:

- Vertebral endplate disruption
- Device (flexible polymer component) subsidence beyond the endplates
- Inflammation
- Fibrosis
- Osteolysis
- Osteophyte formation

Due to these results, detailed radiographic assessments as well as extensive analyses were performed on the clinical data collected and provided. The lesions were observed, measured and considered in the clinical study as potential safety risks and are discussed in further detail in Section X.E below.

B. Additional Studies

Table 9-1. Summary of Additional Studies on Barricaid

Test	Method and Results
Sterilization, Packaging and Shelf Life	The Barricaid is sterilized under controlled conditions via gamma irradiation. The minimum dose has been validated, and routine applied doses are established by dose mapping, according to ISO 11137. A protocol for substantiation of 25 kGy was utilized to verify that a minimum sterilization dose of 25 kGy will provide a Sterility Assurance Level (SAL) of 10^{-6}, or no more than one non-sterile unit for each one million units sterilized. Shelf life and packaging validation studies, including simulated distribution and subsequent package integrity, as well as real-time aging and subsequent seal strength testing, were conducted to validate package integrity and support shelf life claim of 3 years.
Biocompatibility	The Barricaid device, based on its intended use, is classified as a permanent implant (>30 days) in contact with tissue/bone. To thoroughly evaluate the safety of the device, the FDA Blue Book Memo G95-1 and the most recent FDA-recognized ISO 10993-1 standard were considered to determine the recommended testing. The sponsor provided testing or rationales to support all the required biocompatibility endpoints. Please see the above, Section IX.A for the animal studies conducted to satisfy the recommended implantation study.
MRI Compatibility	Non-clinical testing demonstrated that the Intrinsic Therapeutics Barricaid device is MR Conditional. A patient with this device can be scanned safely in an MR system immediately after placement under the following conditions: ● Static magnetic field of 1.5-Tesla and 3-Tesla, only ● Maximum spatial gradient magnetic field of 3000 Gauss/cm or less ● Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2-W/kg for 15 minutes of scanning in the Normal Operating Mode of operation for the MR system Under the scan conditions defined, the Intrinsic Therapeutics Barricaid device is expected to produce a maximum temperature rise of 1.6˚C after 15-minutes of continuous scanning. In non-clinical testing, the image artifact caused by the Intrinsic Therapeutics Barricaid device extends approximately 15 mm from this implant when imaged using a gradient echo pulse sequence and a 3-Tesla MR system.

1. Retrieval Analysis

An independent laboratory, Exponent Inc. (Philadelphia, PA), performed analysis of retrieved Barricaid devices and associated tissues. All analyses were conducted using ASTM F561 Standard Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids as a guide. This includes Stage I, II analyses for 22 of 26 explanted devices, and histological analysis for 12 of 26 explanted devices. Of the 4 missing devices, 3 were discarded at the site and one was returned to the patient per attorney request and in compliance with local regulation.

Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy (ATR-FTIR) of the cleaned flexible polymer component found similar spectra between the exemplar (as-manufactured) and explanted flexible polymer component indicating a lack of material degradation.

Histological analyses of 12 explanted devices:
A chronic foreign-body type granulomatous inflammatory response was observed in 7 out of 12 explant patients, when the foreign material (PET flexible polymer component) exited the immunoprivileged disc space (i.e., subsidence or migration of the PET flexible polymer component). This inflammation was associated the polymer fibers or particles and fibrous encapsulation, which was not unexpected as a foreign body response. The chronic inflammation severity was highest in explants from patients implanted with the device for at least 3 years. There was no indication of infection and no large colonies of polymorphonuclear leukocytes (neutrophils) observed in any of the twelve patients. In explant analyses of tissues which contained bone from subjects with flexible polymer component subsidence or migration, osteolysis was noted in four (4) out of five (5) subjects. Bone loss (osteolysis) is an additional potential safety concern with flexible polymer component subsidence or migration.

Herniated or migrated nucleus pulposus tissue, as well as PET polymeric particles, were associated with the inflammatory response. Nucleus pulposus was present on some of the histopathologic slides in the 7 cases above in which histiocytic inflammation was observed; chronic granulomatous inflammation (with foreign-body multinucleated giant cell macrophages) was associated with PET polymeric particles.

The retrieval analysis further supported concerns seen within the baboon study regarding the formation of lesions and related osteolysis due to the device. While there are concerns resulting from the retrieval analyses, particularly with the continued inflammation at late timepoints, these data were captured from patients who had the device removed and were already considered failures of the study composite endpoint. Additional concern for low level inflammation or lesion progression will be addressed in the post-approval studies.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to determine whether there was a reasonable assurance of safety and effectiveness of the Barricaid to reduce the incidence of reherniation, and reoperation for patients who require a lumbar discectomy in response to radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by radiographic confirmation of neural compression using MRI, and a large anular defect post discectomy for a primary surgery, at one level between L1 and S1. Data from this clinical study, which was conducted in Germany, Switzerland, Austria, the Netherlands, Belgium and France, were the basis of the PMA. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between December 2010 and October 2014. The database for this PMA reflected data collected through June 4, 2018 and included 554 subjects who were randomized intra-operatively following discectomy.

The Barricaid study was a prospective, multi-center, randomized controlled clinical trial comparing the Barricaid procedure to discectomy alone. The trial was conducted under Good Clinical Practice (GCP), was ISO 14155 compliant and was conducted under all applicable local and federal regulations.

A prospective superiority analysis was performed to determine the safety and effectiveness of the Barricaid device. Subjects included in this trial were considered at higher risk for reherniation due to the presence of anular defects at least 6mm wide after limited discectomy.[5] The overall success criteria defined prospectively was at 24 months, based on improvement documented in the Oswestry Disability Index (ODI), VAS Leg pain, disc height maintenance, lack of reherniations at the index level, no posterior device migration, no device fracture or disassembly, maintenance or improvement in the neurological score, no spontaneous fusion, and no reoperation of any kind at the index level including removal or revision of the Barricaid or supplemental fixation. Intrinsic Therapeutics performed this clinical study with an *a priori* statistical analysis plan that enabled the generation of valid scientific evidence to claim superiority per the Statistical Analysis Plan ("SAP").

All adverse events (device-related or not) were monitored over the course of the study and radiographic assessments were performed by an independent core laboratory. Overall success was initially determined with data collected during the initial 24 months of follow-up. All serious adverse events, other adverse events, and protocol deviations reported by the clinical investigators were independently adjudicated (for adverse event group, severity and relatedness to the device and/or procedure) by a Data Safety Monitoring Board ("DSMB") composed of three independent, US-Board certified spine surgeons and one independent US board-certified musculoskeletal radiologist.

In order to address concerns expressed by the Agency and the FDA's Orthopedic and Rehabilitation Devices Panel regarding continued development and longer-term impact of bone lesions, additional longer-term data from the original RCT cohort was provided by the company. Each enrolled subject will be followed until he/she reaches 60 months. Data handling and analyses were performed by third-party statisticians.

1. Clinical Inclusion and Exclusion Criteria

The inclusion/exclusion criteria were:

Enrollment in the study was limited to patients who met the following inclusion criteria:	Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:
• 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 qualified.] • 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)[6] (L4-5, L5-S1) or Femoral Stretch Test (L1-2, L2-3, L3-4). • 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. Intraoperative Inclusion Criteria • Only patients with an anular defect (post discectomy) between 4mm and 6 mm tall and 6 mm and 10 mm wide qualified.	• Spondylolisthesis Grade II or higher (25% slip or greater). • Subject required spinal surgery other than a discectomy (with or without laminotomy) to treat leg/back pain (scar tissue and osteophyte removal is allowed). • Subject had back or non-radicular leg pain of unknown etiology. • Prior surgery at the index lumbar vertebral level. • Subject requiring a spine Dual-Energy X-Ray Absorptiometry ("DEXA") (i.e., subjects 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 was used. • Subject had clinically compromised vertebral bodies in the lumbosacral region due to any traumatic, neoplastic, metabolic, or infectious pathology. • Subject had 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 had an active infection either systemic or local. • Subject had cauda equina syndrome or neurogenic bowel/bladder dysfunction. • Subject had severe arterial insufficiency of the legs or other peripheral vascular disease. (Screening on physical examination for subjects with diminution or absence of dorsalis pedis or posterior tibialis pulses. If diminished or absent by palpation, then an arterial ultrasound was required with vascular plethysmography. If the absolute arterial pressure was below 50mm of Hg at the

	calf or ankle level, then the subject was excluded.) • Subject had significant peripheral neuropathy; subjects 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 had insulin-dependent diabetes mellitus. • Subject was morbidly obese (defined as a body mass index >40 or weighed more than 100 lbs. over ideal body weight). • Subject with active hepatitis, AIDS, or HIV. • Subject with rheumatoid arthritis or other autoimmune disease. • Subject with a known allergy to titanium, polyethylene or polyester materials. • Any subject that could not have a baseline MRI taken. • Subject was pregnant or interested in becoming pregnant in the next three (3) years. • Subject had active tuberculosis or tuberculosis in the past three (3) years. • Subject with a history of active malignancy: a subject with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she had been treated with curative intent and there were no signs or symptoms of the malignancy for at least two (2) years. • Subject was immunologically suppressed and/or having received steroids >1 month over the past year. • Subject was currently taking anticoagulants, other than aspirin, unless the subject could be taken off the anticoagulant for surgery. • Subject with a current chemical/alcohol dependency or significant psychosocial disturbance. • Subject with a life expectancy of less than three (3) years. • Subject involved in active spinal litigation. • Subject involved in another investigational study. • Subject was incarcerated. • Any contraindication for MRI or CT scan (e.g. claustrophobia, contrast allergy).

2. Follow-Up Schedule

All patients were scheduled to return for follow-up examinations in the schedule shown with the windows listed below in Table 10-1. The measurements taken preoperatively and postoperatively are also listed in this table. Adverse events and complications were recorded at all visits.

Table 10-1: Follow-Up Schedule

Measurement	Baseline	Surgery	Discharge	6 Weeks (± 2W)	3 Months (± 2W)	6 Months (± 1M)	12 Months (± 2M)	24 Months (± 2M)	36 Months (± 2M)	Annually Thereafter* (± 2M)
ODI	X			X	X	X	X	X	X	X
VAS (Back and Leg)	X			X	X	X	X	X	X	X
SF-36v2™	X			X	X	X	X	X	X	X
Neurological Assessment	X			X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
MRI with both T1 and T2 weighted axial and sagittal images	X						X	X	X	X
Multiplanar Low dose CT at index level with 2D Coronal Reconstructions	X						X	X	X	X
Neutral AP X- rays	X		X	X	X	X	X	X	X	X
Neutral Lateral X- rays	X		X	X	X	X	X	X	X	X
Flexion/Extension X-rays	X						X	X	X	X

*The current protocol states this will be continued out to 60 months.

3. Clinical Endpoints

Per the original protocol, success of each individual subject and the study was determined at the 24-month evaluation time point. This study had two co-primary endpoints. Success of the study is based on the Barricaid population achieving statistical superiority over the concurrently randomized, non-implanted discectomy population for each of the two endpoints independently.

a. Reherniation: To be considered a success, a subject 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). This includes all reherniations, including both symptomatic and asymptomatic reherniations.

b. A composite of safety and effectiveness. To be considered a success, a subject will have achieved success in each of the following components at 24 months:

- 15-point (out of 100 points) improvement in Oswestry Disability Index (ODI) 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: Maintenance of device condition and lack of implant migrations (radiographic, implanted subjects only)
- No spontaneous fusion
- No reherniation at the index level (on either side)
- No secondary surgical interventions (SSI) at the index level

While this original composite endpoint was complex, this was a novel device for which evaluation of other endpoints was considered necessary to provide surgeons and subjects a more complete understanding of how the Barricaid performed clinically. Intrinsic Therapeutics collected a number of other endpoints and evaluations. Safety concerns regarding the device also necessitated a longer-term follow-up and assessment compared to the 24-month primary success criteria originally planned by the sponsor. These outcomes are presented in the Safety and Effectiveness sections below.

Intrinsic Therapeutics also collected the following additional endpoints, the most notable to surgeons and patients is the recurrence of symptomatic herniation. Symptomatic reherniation was defined as radiographically or surgically confirmed herniation of the index level that were associated with any of the following criteria:

- reoperation of the index level,
- an unscheduled visit,
- adverse event with treatment for index level herniation,
- adverse event for pain or neurological issue associated with the index level within a 2-month window, or
- VAS leg ≥40/100, ODI ≥40/100, and a positive straight leg raise (L4-5 or L5-S1) or femoral stretch test (L1-L4).

These criteria were designed after study initiation and approved by the DSMB, thereby creating a broad net which captured any index level reherniation that could be associated with concordant adverse symptoms, in an effort to avoid the bias created by under-reporting of events by sites.

In addition to the endpoints described above, other secondary endpoints and assessments included the following:

- Visual Analog Scale - Back Pain and Contralateral Leg Pain (mean score, mean improvement from baseline, incidence of 20 point improvement)
- Quality of Life - SF36 Mental and Physical Component Scores (mean scores, mean improvement from baseline)
- Adverse Event Rates
- Quantitative x-ray measures: Translational and Angular Range of Motion during Flexion-Extension, Sagittal Disc Angle, Spondylolisthesis (mean values, change from baseline)
- Endplate Lesion Number, Dimensions (mean size, change from prior timepoint)
- Endplate Lesion Features: Location, Proximity to Device
- Device Subsidence (prevalence)

4. DSMB Safety Oversight

The DSMB reviewed accumulating data from the ongoing clinical trial on a quarterly basis. This board consisted of experts in the field of neurological or orthopedic spine surgery and musculoskeletal radiology, with a statistician providing input as needed. The purpose of the DSMB was to advise Intrinsic Therapeutics regarding the continued safety of all study participants. The DSMB process included review, adjudication, and grouping of adverse events, serious adverse events, and protocol deviations, as well as monitoring study progress and compliance. The DSMB maintained the ability to stop the study due to pre-defined safety concerns.

B. Accountability of PMA Cohort

Subject accounting and compliance is provided in Table 10-2. Both theoretical and actual follow-up are provided for each follow-up interval through 60 months, for both randomized arms of the trial. Note that there is an allowable "window" within which the various follow-up visits may occur. The determination of whether a subject is theoretically due was based upon the exact anniversary of the surgical procedure.

Shown, for each scheduled follow-up visit, are the theoretical follow-up, defined as the number of subjects for whom data would be available at each time point if all subjects returned for follow-up on the exact anniversary of their Barricaid or Control procedure. "Not yet overdue" includes subjects whose surgical anniversary has occurred; however, clinical data has not yet been collected (i.e., ODI and/or VAS is currently unavailable) but the subject is still in the protocol specified follow-up window. Such subjects may yet be observed and so follow-up compliance estimates account for this by removing such subjects from the denominator as well as from the numerator when determining compliance ratios.

From "theoretical due" we subtract cumulative deaths and cumulative "secondary surgical intervention failures" (i.e., reoperations, revisions, removals, and supplemental fixation) – as well as those not yet overdue – to calculate the number of subjects *expected* for a follow-up visit. This would reflect the total number of subjects. Adding the expected follow-up to the number of secondary surgical interventions provides the total number of subjects serving as the denominator for composite clinical success (CCS) outcomes per the Clinical Protocol Definition (CPD).

There are two compliance estimates provided in this table. The first is follow-up compliance for clinical visit outcomes including ODI and VAS. This is determined by dividing the number of subjects with clinical visit data (among expected due) divided by total expected due as defined above. As can be seen in Table 10-2, these rates are 94% (228/243) and 91% (211/233) for Barricaid and Controls, respectively. Most importantly, Table 10-1 summarizes follow-up compliance for the primary CCS endpoint. Primary endpoint compliance rates were high at 91% (246/272) and 94% (260/278) for Barricaid and the Control group respectively. When interpreting these results in comparison to the sample sizes based on the analysis data sets presented in the analysis tables, it should be noted that all analysis tables utilized all available data so sample sizes were not restricted to subjects who were theoretically and not yet overdue. Consequently, the samples sizes with observed data are slightly higher.

Table 10-2: Subject Accounting and Follow-up Compliance Table Efficacy Evaluable Modified Intent to Treat (mITT) Barricaid (I) and Control Subjects (C)

	Mo. 24		Mo. 36		Mo. 48		Mo. 60	
	I	C	I	C	I	C	I	C
(1) Theoretical follow-up	272	278	272	278	260	267	184	187
(2) Cumulative deaths	1	0	1	0	1	0	1	1
(3a) Cumulative SSI + No implantation	28	45	32	51	40	55	43	57
(3b) Cumulative Reherniation	118	179	135	194	144	203	150	204
(4) Not Yet Overdue	0	0	0	0	5	7	3	5
(5) Deaths+SSI failures among theoretically due	29	45	33	51	41	53	37	36
(6) Expected due for clinic visit [(6) = (1) - (4) - (5)]	243	233	239	227	214	207	144	146
(7) SSI failures among theoretically due	28	45	32	51	40	53	36	35
(8) Expected due+SSI fails among theoretically Due [(8) = (6) + (7)]	271	278	271	278	254	260	180	181
All Evaluated Accounting (Actual [B]) Among Expected Due Procedures								
	Mo. 24		Mo. 36		Mo. 48		Mo. 60	
(9) Procedures with any clinical data in interval (Chg VAS or ODI)	228	211	185	166	162	144	103	107
(10) Visit Compliance (%)	94%	91%	77%	73%	76%	70%	72%	73%
(11) Change in ODI	228	211	185	166	162	144	103	107
(12) Change in VAS Leg	227	211	184	166	161	144	103	107
(13) Neuro evaluations	252	251	203	207	187	177	131	123
(14) Radiography (Avg Disc HT)	213	197	156	143	129	104	73	78
(15) CCS-CPD	246	260	219	248	208	224	145	158
(16) Actual [B] % Follow-up for CCS-CPD	91%	94%	81%	89%	82%	86%	81%	87%
Within Window Accounting (Actual [A]) Among Expected Due Procedures								
	I	C	I	C	I	C	I	C
(17) Procedures with any clinical data in interval (Chg VAS or ODI)	203	188	156	129	139	108	69	79
(18) Visit Compliance (%)	84%	81%	65%	57%	65%	52%	48%	54%
(19) Change in ODI	203	188	156	129	139	108	69	79
(20) Change in VAS Leg	202	188	155	129	138	108	69	79
(21) Neuro evaluations	222	223	173	165	160	138	88	92
(22) Radiography (Avg Disc HT)	192	178	130	114	108	84	50	59
(23) CCS-CPD	212	223	158	162	147	134	81	92
(24) Actual [A] % Follow-up for CCS-CPD	78%	80%	58%	58%	58%	52%	45%	51%

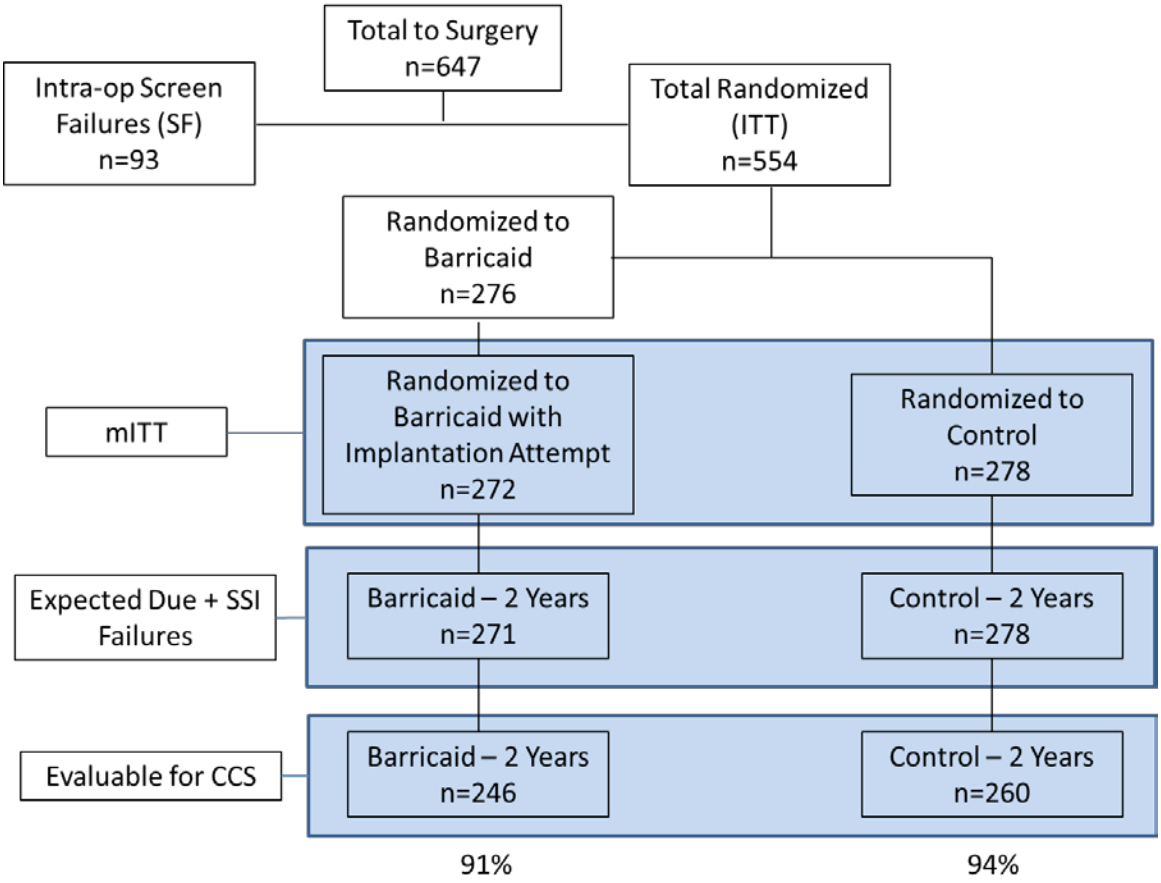


Figure 10.1:Subject Accounting Tree Relating to Evaluable Subjects for CCS Calculation at 2 years

C. Study Population Demographics and Baseline Parameters

Analyses in the PMA demonstrated the demographics of the OUS study population are similar to typical lumbar herniation US population published in literature. Demographic data and preoperative evaluations for the randomized subjects treated in the study are included in Table 10-3 and Table 10-4. There were no statistically significant differences in demographics, baseline characteristics, or preoperative evaluations when comparing the randomized treatment groups.

Table 10-3: Summary of Baseline and Demographic Continuous Variables

	Barricaid (n=272)			Control (n=278)			Nominal* t-test p-value
	Mean	**SD**	**Med**	**Mean**	**SD**	**Med**	
Baseline Demographics							
Age, years	42.9	10.9	43.0	44.0	10.4	43.0	0.235
Height, cm	175.8	9.4	176.0	175.5	9.1	175.0	0.687
Weight, kg	81.4	15.3	81.3	81.3	14.9	80.0	0.939
BMI, kg/m^2	26.3	4.1	25.5	26.3	4.1	25.8	0.809
Baseline Clinical Scores							
VAS Leg	80.8	15.1	84.0	80.8	14.6	83.0	0.970
VAS Back	56.6	30.0	66.0	55.7	31.4	66.0	0.743
ODI	59.0	12.4	58.0	58.2	13.7	56.0	0.476

BMI=body mass index, Med=median, ODI=Oswestry disability index, SD=standard deviation, VAS=visual analog scale

* "Nominal" means the statistic was not adjusted for multiple comparisons

Table 10-4: Summary of Baseline and Demographic Categorical Variables

	Barricaid			Control			Nominal Chi-squared p-value
	N	**n**	**%**	**N**	**n**	**%**	
Gender, %							
Female	272	116	42.6%	278	107	38.5%	0.321
Male	272	156	57.4%	278	171	61.5%	0.321
Smoker %*							
Current	272	121	44.5%	278	123	44.2%	0.955
History	176	52	29.5%	186	52	28.0%	0.739
Current or History	272	173	63.6%	278	175	62.9%	0.874
Race, %							
Caucasian	272	270	99.3%	278	273	98.2%	0.266
Non-Caucasian	272	2	0.7%	278	5	1.8%	0.266

* With regards to smoking status, the question "Have you ever smoked?" is only asked of subjects who answered "no" to "Do you currently smoke?"

D. Surgical Level and Approach Data

Surgical level, anular defect characteristics and surgical approach data are summarized below in Table 10-5. Barricaid devices were implanted into the inferior vertebral body of the disc in 61.4% of cases (164/267). Similarly, exploratory analyses concluded that device orientation had no significant impact on clinical outcomes.

Table 10-5: Summary of surgical level and approach data

	Overall			Barricaid			Control			Significance	
	N	n	%	N	n	%	N	n	%	Δ	Nominal Chi-squared p-value
Index Level, %											0.077
L2/3	550	3	0.5%	272	2	0.7%	278	1	0.4%	0.3%	
L3/4	550	13	2.4%	272	8	2.9%	278	5	1.8%	1.1%	
L4/5	550	225	40.9%	272	124	45.6%	278	101	36.3%	9.3%	
L5/S1	550	309	56.2%	272	138	50.7%	278	171	61.5%	-10.8%	
Anulus Defect Type, %											0.356
Bulge/Weakness	550	165	30.0%	272	80	29.4%	278	85	30.6%	-1.2%	
Fissure	550	101	18.4%	272	46	16.9%	278	55	19.8%	-2.9%	
Full Thickness	550	282	51.3%	272	146	53.7%	278	136	48.9%	4.8%	
None	550	2	0.4%	272	0	0.0%	278	2	0.7%	-0.7%	
Geometry, %											0.056
Box	550	341	62.0%	272	182	66.9%	278	159	57.2%	9.7%	
Cruciate	550	29	5.3%	272	11	4.0%	278	18	6.5%	-2.5%	
Puncture/Slit	550	155	28.2%	272	65	23.9%	278	90	32.4%	-8.5%	
None	550	25	4.5%	272	14	5.1%	278	11	4.0%	1.1%	
Surgical Approach, %											0.343
Created New	550	205	37.3%	272	96	35.3%	278	109	39.2%	-3.9%	
Through Existing	550	345	62.7%	272	176	64.7%	278	169	60.8%	3.9%	
Defect Width											0.288
6 mm	550	93	16.9%	272	49	18.0%	278	44	15.8%	2.2%	
7 mm	550	120	21.8%	272	65	23.9%	278	55	19.8%	4.1%	
8 mm	550	173	31.5%	272	88	32.4%	278	85	30.6%	1.8%	
9 mm	550	82	14.9%	272	37	13.6%	278	45	16.2%	-2.6%	
10 mm	550	82	14.9%	272	33	12.1%	278	49	17.6%	-5.5%	
Defect Height											0.934
4 mm	550	169	30.7%	272	83	30.5%	278	86	30.9%	-0.4%	
5 mm	550	271	49.3%	272	136	50.0%	278	135	48.6%	1.4%	
6 mm	550	110	20.0%	272	53	19.5%	278	57	20.5%	-1.0%	

Surgeons were trained in definitions of “Defect Type (bulge/weakness, Fissure, Full thickness defect (through hole), or None)” and “Defect Geometry (Puncture/Slit, Cruciate, Box, or None)” during the site initiation visit, prior to enrollment of the first subject at that site.

Surgeon investigators were trained to measure the size (height and width separately) of the anular defect per the instructions in the surgical technique manual. Specifically, surgeons

were trained to insert incrementally larger Defect Measurement Tools (provided in 1-mm increments) into the anular defect until a size is reached that passes with light resistance while the next-larger tool does not pass. Surgeons were trained to measure the height and width separately and to not rotate the tool within the defect (e.g., from width to height, or vice-versa).

E. Safety Results

1. Adverse Event Summary

The analysis of safety was based on the As-Treated (AT) cohort of 550 subjects (267 Barricaid subjects and 283 Control subjects) available for evaluation. All Adverse Event (AE) data presented includes all events observed at the time of data lock, which includes all patients having reached three years and additional subjects reaching four (4) and five (5) years as documented in the subject accounting table. Prior to analysis, the DSMB adjudicated all AEs for relatedness and severity. In addition, the DSMB grouped each site-reported AE into DSMB-defined categories intended to be as clinically meaningful as possible (Table 10).

When making an assessment of safety, an AE was considered as: any undesired clinical response or complication experienced by a subject. All operative and postoperative AEs, whether device-related or not, were recorded on the AE Case Report Forms. Safety outcomes were determined by evaluating the type, frequency, seriousness, and relationship to device of AEs for all subjects. AEs were categorized as device-related or procedure-related.

AE Device/Procedure-Relatedness:

- 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 its 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.

Serious AEs:

- Serious: 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 fetal distress, fetal death, or a congenital anomaly or birth defect

Table 10-6: AE Definitions used by DSMB

Adverse Event	Definition
Benign soft tissue masses/tumors	lipoma, subcutaneous nodules, liver lesion, benign mass/tumor - non-lumbar
Cancer	Includes cases of lung lymph node metastasis, brain tumor (non-malignant), CEA increase, and cholangiocarcinoma
Cardiac and Vascular • Bleeding - index procedure • Other	 • Blood loss requiring intervention due to index study procedure, epidural hemorrhage, • The Cardiac and Vascular total also includes the following subcategories which are not listed in detail: transient ischemic attack (TIA)/stroke, pulmonary embolism, aneurysm of the aorta, hypertension, heart surgery, mesenteric ischemia, varicose veins, chest pain/angina, myocardial infarction, cardiac/heart failure, cardiac arrhythmia, circulation problems
Death	Includes case of death due to metatstatic cancer of unknown primary
Dermatologic	Includes any condition of the skin such as: fungal infection, herpes zoster, and skin rash. If condition is around surgical site, AE coded to wound issue.

Adverse Event	Definition
Device Deficiency	
• Anchor (whole device) migration	• Includes anchor (whole device) migration out of the vertebral body.
• Mesh Migration	• Includes migration of the occlusion component into the epidural space (extradiscal), normal occlusion component movement within the disc space (intradiscal)
• Mesh Subsidence	• Includes occlusion component subsidence into a vertebral body with or without occlusion component detachment
• Mesh Detachment	• Includes clear detachment of the occlusion component from the anchor into the epidural space (extradiscal) or within the disc space (intradiscal)
•Anchor Fracture	• Includes fracture of the titanium anchor component of the device
•Other	• Includes difficulty upon implantation
Disc Herniation	
• Herniation - Index Level	• Includes post-operative herniation at the index level (both ipsi- and contralateral)
• Residual herniation - Index Level	• Includes residual herniation at index level
• Disc Herniation - Adjacent Level	• Includes disc herniations at a level adjacent to the index level
• Disc Herniation - Non-Adjacent Level	• Includes disc herniations at a level not adjacent to the index level including lumbar, thoracic and cervical levels
Endocrine	Includes thyroid disorders, diabetes
Eyes/Ears/Nose/Throat (EENT)	Any condition of the eyes, ears, nose, throat or mouth including: sinusitis, tinnitis, hearing loss, dental procedures/disorder, eye injury/disorder/surgery, tracheitis
Gastrointestinal	Includes nausea, vomiting, gastroenteritis, diarrhea, abdominal pain, esophageal reflux, gastric bypass/banding, gastric ulcer, appendicitis, fatty liver degeneration, hernia, diverticulitis, intestinal polyps, gastrointestinal bleeding, cholecystectomy, and ileus
Genitourinary	Includes erectile dysfunction, retrograde ejaculation, urinary retention/incontinence, urinary tract infection, sterilization/vasectomy, testicular infection, prostatic hypertrophy, nephrolithiasis, sexual dysfunction, epididymitis
OB/GYN	Pregnancy, elective abortion, temporary loss of menstruation, ovarian cysts, breast biopsy, hysterectomy
Infectious Disease	Includes systemic or local viral, bacterial or fungal infections not associated with the index or secondary lumbar procedures, sepsis
Immunological	Includes allergic reaction to medications, Grave's Disease and rheumatoid arthritis
Metabolic/Hematologic/Electrolytes	Includes hypothermia, anemia, edema, lipedema, and electrolyte disorders

Adverse Event	Definition
Musculoskeletal - Lumbar	
• Spinal Instability	• Abnormal movement between spinal segments
• Scoliosis	• Abnormal curvature of the lumbar spine
• Radiographic Finding	• Includes post-operative osteophyte formation. Does not include necrosis of bone or resorption.
• Facet Syndrome	• Includes post-operative symptomatic lumbar facet joint degeneration/disorder
• Other	• Includes pseudarthrosis (after secondary surgery), reoperation, and osteochondrosis
Musculoskeletal - Non-Lumbar	Includes non-radicular hip, knee, foot and ankle pain or injury; SI joint pain and discomfort; cervical, thoracic, sacral and coccygeal spinal pain, injury or disorders; upper extremity including, shoulder, elbow, wrist and hand pain or injury; arthritis, tendonitis, bursitis, and restless leg syndrome
Neurological - Lumbar and Lower Extremity	
• Nerve or Spinal Root Injury: Index Surgery	• Includes nerve or spinal root injury during the index surgery
• Nerve Root or Spinal cord Impingement	• Includes numbness or lumboischialgia due to nerve root or spinal cord impingement. Does not include trauma during index surgery
• Musculoskeletal Spasms of the Back or Legs	• Includes cramping or spasms in the back and/or legs
• Neurological Deterioration	• Includes clinically significant neurological deterioration from baseline and prior visit such as: new paraesthesia, absent reflexes, weakness, decreased motor strength, and sensory deficits
• Other	• Includes post-lumbar puncture and polyneuropathy of unknown origins
Neurological - Non- Lumbar/Lower Extremity	Includes peripheral nerve entrapment such as: carpal tunnel syndrome, cubital syndrome; peripheral neuropathy, loss of bowel and bladder control, cervical radiculopathy, multiple sclerosis, Bell's Palsy, facial myoclonus, psychological paraplegia, and headache/migraine
Pain - Lumbar and Lower Extremity	
• Lower Extremity Pain Only	• Pain in the upper and/or lower leg
• Lumbar Pain Only	• Includes low back pain or non-specified back pain. Does not include thoracic pain (coded to Musculoskeletal - Non-Lumbar/Lower Extremity)
• Lumbar and Lower Extremity Pain	•Pain in the upper and/or lower leg(s) and back pain
• Lumbar and/or Lower Extremity Pain: non-specific	•Non-specific pain as reported by the site in the back and/or legs.
Psychological	Includes depression, and anxiety and burnout

Adverse Event	Definition
Respiratory/Pulmonary	Includes COPD, pneumothorax, sleep apnea, bronchitis, pneumonia, influenza, and upper respiratory tract infection
Trauma	Includes fall, vehicle accident, sporting accident, work injury, animal bite, and assault
Wound Issue- Index or Secondary Surgery at Index Level	
• Dural Injury/Tear or CSF Leak	• Any tear of the dura or cerebrospinal fluid leak caused by or occurring during the index procedure or secondary surgery at index procedure
• Wound Infection	• Any wound infection, with the wound being identified as the surgical site for any index procedure or secondary surgery at index procedure. All other infections get coded with specific body systems. This includes both deep and superficial infections.
• Hematoma	• Includes seroma, hematoma associated with the index procedure or secondary surgery at index procedure
• Delayed Wound Healing	• Any delayed wound healing not associated with infection
•Deep	•Includes wound seromas
• Dehiscence	• Rupture along the incision from any index procedure or secondary surgery at index procedure
Necrosis of Bone or Resorption	Includes endplate lesions at the index level as identified by the investigator as a radiographic finding on control and treated patients.

Please note that "Necrosis of Bone or Resorption" was the category listed on the Case Report Forms (CRFs). This was the only category available for which the physician was able to report the presence of endplate lesions (EPLs) as an AE; however, it does not necessarily mean that the physician observed necrosis, or that treatment was prescribed.

The key safety outcomes are presented in Table 10-7 through Table 10-9.

A summary of the total number of adverse events, adverse events related to the device or procedure, serious adverse events, and serious adverse events that were related to the device or procedure is shown below in Table 10-7.

Table 10-7: Comparisons of Summary Adverse Event Rates between Barricaid and Control Discectomy – AT Analysis Sets

	Barricaid (N=267)			Control (N=283)			
	Events	**Subjs**	**%**	**Events**	**Subjs**	**%**	**Nominal p-value†**
All Adverse Events							
Any Adverse event (per patient)	680	227	85.0%	635	231	81.6%	0.305
Device Related Adverse Events							
Any device related* AE	362	182	68.2%	9	6	[redacted]	
Any device related (Definite / Probable) AE	96	82	30.7%	3	2		
Any device related (Possible / Unknown) AE	266	149	55.8%	6	4		
Procedure Related Adverse Events							
Any procedure related* AE	394	189	70.8%	356	183	64.7%	0.145
Any procedure related (Definite / Probable) AE	160	115	43.1%	145	103	36.4%	0.117
Any procedure related (Possible / Unknown) AE	290	153	57.3%	214	140	49.5%	0.073
Device or Procedure Related Adverse Events							
Any device or procedure related* AE	395	189	70.8%	356	183	64.7%	0.145
Any device or procedure (Definite/Probable) AE	168	119	44.6%	145	103	36.4%	0.056
Any device or procedure (Possible/Unknown) AE	227	132	49.4%	211	140	49.5%	1.000
All Serious Adverse Events (SAE)							
Any Serious AE	209	113	42.3%	219	126	44.5%	0.607
SAE - Device Related							
SAE - Dev. Related*	77	49	18.4%	3	2	[redacted]	
SAE - Dev. Related (Definite / Probable)	18	16	6.0%	2	1		
SAE - Dev. Related (Possible / Unknown)	59	40	15.0%	1	1		
SAE - Procedure Related							
SAE - Proc. Related*	82	51	19.1%	115	72	25.4%	0.082
SAE - Proc. Related (Definite / Probable)	41	31	11.6%	80	58	20.5%	0.005
SAE - Proc. Related (Possible / Unknown)	41	28	10.5%	35	26	9.2%	0.668
SAE - Device or Procedure Related							
SAE - Dev. or Proc. Related*	83	51	19.1%	115	72	25.4%	0.082
SAE - Dev. or Proc. Related (Definite / Probable)	43	32	12.0%	80	58	20.5%	0.008
SAE - Dev. or Proc. Related (Possible / Unknown)	63	41	15.4%	36	27	9.5%	0.051
Death							
Death	1	1	0.4%	1	1	0.4%	0.999

†Fisher's Exact
*Definite, Probable, Possible, Unknown

Table 10-7 shows the comparison of complication rates between the Barricaid and Control AT discectomy cohorts. Device-related events could potentially be reported in the Control AT population because it includes subjects who were randomized to Barricaid but not successfully implanted (n=5) as well as Control subjects who were later treated with a Barricaid implant due to a reherniation failure (n=5). Overall, the impact of these events in interpreting the safety data is limited as evidenced by the rare occurrences of device- related Serious Adverse Events (SAEs) in the Control AT population (3 events in 2 subjects).

There was one statistically significant difference with regards to SAEs that were definitely or probably device-related or procedure-related (12% vs. 20.5%, nominal p=0.008). Please note that "nominal" means that the p-value was not adjusted for multiple comparisons. This statistical difference was in the direction of fewer events, primarily reherniations, in the Barricaid group. This outcome is important since it balances SAEs related to Barricaid (consisting mainly of device failures such as migration) with the procedure-related SAEs (consisting mainly of reherniation-related SAE's). Despite the presence of a device, the combined device- or procedure-related SAE rate was still higher in the Control discectomy group, thereby suggesting discectomy plus Barricaid has a greater safety profile compared to discectomy alone.

Specific adverse events are listed in alphabetical order according to adverse event groups in Table 10-8. The data shows the comparison of percentages with adverse event groups and types between the Barricaid and Control cohorts for specific adverse event groups and types.

There was a statistically significant difference with disc herniation events which were significantly lower in the Barricaid group (21% vs. 32.5%, nominal p=0.003). It is important to note these were AEs documented by the clinical site, rather than the core radiographic lab, therefore less uniform in reporting.

Table 10-8: Counts and Percentages of Subjects with Specific Adverse Events (Group and Type) in Barricaid and Control Discectomy – AT Population

	Barricaid (N = 267)			Control (N = 283)			Significance	
	Events	Subjs	%	Events	Subjs	%	Dif	p-value†
BENIGN SOFT TISSUE MASSES/TUMORS	3	3	1.1%	2	2	0.7%	0.4%	0.678
CANCER	8	7	2.6%	5	4	1.4%	1.2%	0.371
CARDIAC AND VASCULAR	26	23	8.6%	25	24	8.5%	0.1%	1.000
bleeding	2	2	0.7%	0	0	0.0%	0.7%	0.235
other	24	21	7.9%	25	24	8.5%	-0.6%	0.877
DEATH	1	1	0.4%	1	1	0.4%	0.0%	1.000
DERMATOLOGIC	3	3	1.1%	4	4	1.4%	-0.3%	1.000
DEVICE DEFICIENCY	35	34	12.7%	1	1			
anchor (whole device) migration	5	5	1.9%	0	0			
occlusion component	29	29	10.9%	1	1			
other	1	1	0.4%	0	0			
DISC HERNIATION	71	56	21.0%	120	92	32.5%	-11.5%	0.003
herniation - index level	40	36	13.5%	101	83	29.3%	-15.8%	<.001
residual herniation - index level	2	2	0.7%	0	0	0.0%	0.7%	0.235
disc herniation - adjacent level	19	17	6.4%	15	14	4.9%	1.4%	0.580
disc herniation - non-adjacent level	10	9	3.4%	4	4	1.4%	2.0%	0.164
ENDOCRINE	8	8	3.0%	4	4	1.4%	1.6%	0.250
EYES/EARS/NOSE/THROAT (EENT)	11	11	4.1%	22	22	7.8%	-3.7%	0.075
GASTROINTESTINAL	28	21	7.9%	36	31	11.0%	-3.1%	0.245
GENITOURINARY	18	18	6.7%	17	16	5.7%	1.1%	0.601
OB/GYN	11	10	3.7%	8	8	2.8%	0.9%	0.635
INFECTIOUS DISEASE	7	5	1.9%	4	4	1.4%	0.5%	0.746
IMMUNOLOGICAL	3	3	1.1%	7	7	2.5%	-1.3%	0.341
METABOL./HEMATO./ELECTROLYTES	4	4	1.5%	8	8	2.8%	-1.3%	0.385
MUSCULOSKELETAL - LUMBAR	19	17	6.4%	14	11	3.9%	2.5%	0.244
spinal instability	2	2	0.7%	0	0	0.0%	0.7%	0.235
scoliosis	0	0	0.0%	3	3	1.1%	-1.1%	0.249
radiographic finding	5	5	1.9%	0	0	0.0%	1.9%	0.026
facet syndrome	10	9	3.4%	8	6	2.1%	1.3%	0.438
other	2	2	0.7%	3	3	1.1%	-0.3%	1.000
MUSCULOSKELETAL - NON-LUMBAR	89	66	24.7%	85	64	22.6%	2.1%	0.616
NEURO - LUMBAR AND LOWER EXTREMITY	44	37	13.9%	33	30	10.6%	3.3%	0.297
nerve or spinal root injury: index surgery	2	2	0.7%	4	4	1.4%	-0.7%	0.687
nerve root or spinal cord impingement	4	4	1.5%	2	1	0.4%	1.1%	0.204
muskuloskeletal spasms of the back or legs	9	9	3.4%	1	1	0.4%	3.0%	0.009
neurological deterioration	28	23	8.6%	26	24	8.5%	0.1%	1.000
other	1	1	0.4%	0	0	0.0%	0.4%	0.485
NEURO - NON-LUMBAR/LOWER EXTREMITY	21	18	6.7%	15	11	3.9%	2.9%	0.181
PAIN - LUMBAR AND LOWER EXTREMITY	146	100	37.5%	142	109	38.5%	-1.1%	0.861
lower extremity only	43	38	14.2%	53	46	16.3%	-2.0%	0.554
lumbar	72	62	23.2%	72	64	22.6%	0.6%	0.919
lumbar and lower extremity	29	25	9.4%	17	14	4.9%	4.4%	0.047
non-specific	2	2	0.7%	0	0	0.0%	0.7%	0.235
PSYCHOLOGICAL	15	15	5.6%	15	15	5.3%	0.3%	1.000
RESPIRATORY/PULMONARY	6	6	2.2%	14	14	4.9%	-2.7%	0.112
TRAUMA	23	22	8.2%	24	22	7.8%	0.5%	0.876
WOUND ISSUE- SSI AT INDEX LEVEL	26	22	8.2%	24	21	7.4%	0.8%	0.753
dural injury/tear or csf leak	19	18	6.7%	14	14	4.9%	1.8%	0.467
infection	2	2	0.7%	5	4	1.4%	-0.7%	0.687
hematoma	3	3	1.1%	2	2	0.7%	0.4%	0.678
delayed wound healing	1	1	0.4%	0	0	0.0%	0.4%	0.485
dehiscence	0	0	0.0%	1	1	0.4%	-0.4%	1.000
deep	1	1	0.4%	2	2	0.7%	-0.3%	1.000
NECROSIS OF BONE OR RESORPTION	54	52	19.5%	5	5	1.8%	17.7%	<.001

†Fisher's Exact.

Table 10-9 provides the actual counts of specific events by time of onset. While most device deficiency adverse events were distributed throughout the 24-month timepoint (24/35), roughly a third of these device deficiencies occurred at 24 months (12), with fewer events (11/35) occurring after 24 months, though the subjects with complete five year follow-up remains incomplete. The proportion of subjects with other clinically relevant adverse event categories such as lumbar and lower extremity pain (nominal p=0.861), lumbar or lower extremity neurological events (nominal p=0.181), musculoskeletal lumbar events (nominal p=0.244), and wound issues (nominal p=0.753) were not statistically different between Barricaid and Control and do not suggest any increased safety risk associated with the implant. As an example, lumbar and lower extremity pain adverse events were similar in overall number (146 Barricaid vs. 142 Control) and tracked similarly at each annual timepoint (e.g. 67 Barricaid vs. 71 Control at year 1, 93 Barricaid vs. 97 Control at year 2).

Table 10-9: Counts of Specific Adverse Events (Groups, Types) by Time of Occurrence – Barricaid and Control Discectomy AT Analysis Sets

	Immed PostOp		1 mo		3 mo		6 mo		12 mo		24 mo		36 mo		48 mo		60 mo		60+ mo		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
BENIGN SOFT TISSUE MASSES/TUMORS	0	0	0	1	2	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	3	2
CANCER	0	0	0	0	0	0	0	0	2	0	2	0	1	0	2	2	0	3	1	0	8	5
CARDIAC AND VASCULAR	3	3	1	4	2	2	2	3	2	0	3	2	5	3	6	6	2	1	0	1	26	25
bleeding	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
other	1	3	1	4	2	2	2	3	2	0	3	2	5	3	6	6	2	1	0	1	24	25
DEATH	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	1
DERMATOLOGIC	0	1	1	1	0	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	3	4
DEVICE DEFICIENCY	1	0	0	0	3	0	2	0	5	0	13	1	10	0	0	0	0	0	1	0	35	1
anchor (whole device) migration	0	0	0	0	2	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	5	0
occlusion component	0	0	0	0	1	0	1	0	4	0	12	1	10	0	0	0	0	0	1	0	29	1
other	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
DISC HERNIATION	1	0	3	11	2	11	4	8	12	17	20	32	10	20	14	11	3	8	2	2	71	120
herniation - index level	0	0	2	11	1	11	3	8	5	13	13	28	7	17	6	10	1	3	2	0	40	101
residual herniation - index level	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
disc herniation - adjacent level	0	0	0	0	0	0	0	0	4	3	6	3	2	2	5	1	2	4	0	2	19	15
disc herniation - non-adjacent level	0	0	0	0	1	0	1	0	3	1	1	1	1	1	3	0	0	1	0	0	10	4
ENDOCRINE	0	0	1	0	1	0	0	0	0	1	1	0	1	1	3	1	1	1	0	0	8	4
EYES/EARS/NOSE/THROAT (EENT)	0	0	0	3	2	2	0	2	4	3	3	7	1	0	0	3	1	2	0	0	11	22
GASTROINTESTINAL	3	3	2	4	2	2	1	2	4	5	5	4	6	7	2	3	2	6	1	0	28	36
GENITOURINARY	1	0	0	1	3	0	1	2	3	2	4	3	2	2	1	5	3	1	0	1	18	17
OB/GYN	0	1	0	0	1	1	2	0	1	2	1	0	2	1	1	3	3	0	0	0	11	8
INFECTIOUS DISEASE	0	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	1	1	2	0	7	4
IMMUNOLOGICAL	1	1	0	0	0	1	0	0	1	1	0	0	0	3	1	1	0	0	0	0	3	7
METABOL./HEMATO./ELECTROLYTES	0	3	0	1	0	0	0	2	0	1	3	0	0	1	0	0	1	0	0	0	4	8
MUSCULOSKELETAL - LUMBAR	0	0	1	0	1	1	5	1	1	2	2	2	2	2	2	3	3	3	2	0	19	14
spinal instability	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	2	0
scoliosis	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0	3
radiographic finding	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	2	0	1	0	5	0
facet syndrome	0	0	1	0	1	1	5	0	0	1	1	2	0	1	1	0	1	3	0	0	10	8
other	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	0	0	1	0	2	3
MUSCULOSKELETAL - NON-LUMBAR	1	1	3	2	6	8	14	14	8	14	14	9	22	14	9	12	10	9	2	2	89	85
NEURO - LUMBAR AND LOWER EXTREMITY	3	6	4	1	6	9	5	7	5	2	8	2	6	1	4	3	3	0	0	2	44	33
nerve or spinal root injury: index surgery	2	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4
nerve root or spinal cord impingement	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	2	1	0	0	0	4	2
muskuloskeletal spasms of the back or legs	0	0	2	0	2	1	1	0	1	0	1	0	1	0	1	0	0	0	0	0	9	1
neurological deterioration	1	2	2	1	4	8	4	7	4	2	6	2	2	1	3	1	2	0	0	2	28	26
other	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
NEURO - NON-LUMBAR/LOWER	1	2	2	1	2	1	3	1	1	2	5	2	4	4	2	2	1	0	0	0	21	15
PAIN - LUMBAR AND LOWER EXTREMITY	1	0	7	12	29	14	17	22	13	23	26	26	18	23	14	11	14	10	7	1	146	142
lower extremity only	0	0	3	8	9	7	7	8	4	8	8	10	2	4	3	4	5	4	2	0	43	53
lumbar	1	0	2	3	14	6	8	12	8	11	12	14	12	18	7	5	4	3	4	0	72	72
lumbar and lower extremity	0	0	1	1	6	1	2	2	1	4	6	2	4	1	4	2	5	3	0	1	29	17
non-specific	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0
PSYCHOLOGICAL	0	0	0	1	1	1	2	0	1	1	3	4	2	1	5	4	1	3	0	0	15	15
RESPIRATORY/PULMONARY	0	0	0	1	1	1	0	1	0	3	2	5	1	2	1	1	1	0	0	0	6	14
TRAUMA	0	2	0	0	1	2	2	1	0	7	12	5	4	2	3	2	1	3	0	0	23	24
WOUND ISSUE- SSI AT INDEX LEVEL	14	9	6	5	0	2	0	3	3	0	0	2	0	1	1	2	1	0	1	0	26	24
dural injury/tear or csf leak	12	7	1	0	0	1	0	2	3	0	0	1	0	1	1	2	1	0	1	0	19	14
infection	0	0	2	3	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	5
hematoma	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2
delayed wound healing	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
dehiscence	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
deep	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
NECROSIS OF BONE OR RESORPTION	0	0	0	0	0	0	0	0	9	0	27	3	10	1	3	0	4	0	1	1	54	5

2. Device- and Procedure-Related Adverse Events

The device- and procedure-related adverse events by Group are presented in Table 10-10. There were two statistically significant differences. First, is the disc herniation AEs (14.2% vs. 29.3%, nominal p<.001) related to the device or procedure. These outcomes mirror the Barricaid intended use, which is to reduce the incidence of reherniation. The

subject table demonstrates Barricaid significantly decreases the incidence of disc herniations, as reported by physician AEs, considered to be related to the device or procedure. This complements the reherniation analyses presented in Section 10.6.4.1 that also demonstrate Barricaid reduces the occurrence of both symptomatic and asymptomatic reherniation. The significant difference in procedure or device related reherniation AEs outweighed the number of AEs related to the device deficiencies. Device deficiency adverse events were reported in 12.7% of Barricaid subjects, with the majority (29/34) exhibiting a deficiency related to the polymer component of the implant. As discussed in further detail in 10.5.7, approximately half of observed device deficiencies were asymptomatic.

The second significant difference was site-reported bone resorption or necrosis, which were likely the clinical observation of EPLs, with a greater number of site-reported events in the Barricaid group compared to Control (19.5% vs. 1.8%, nominal $p<.001$). The presence, observation and consideration of EPLs will be discussed in more detail in Section 10.6.8.

Table 10-10: Counts of Specific Procedure- and Device-Related Adverse Events (Group and Type) – Barricaid and Control Discectomy AT Analysis Sets

	Barricaid (N = 267)			Control (N = 283)			Significance	
	Events	Subjs	%	Events	Subjs	%	Dif	p-value
CARDIAC AND VASCULAR	4	4	1.5%	8	8	2.8%	-1.3%	0.385
bleeding	2	2	0.7%	0	0	0.0%	0.7%	0.235
other	2	2	0.7%	8	8	2.8%	-2.1%	0.108
DERMATOLOGIC	0	0	0.0%	1	1	0.4%	-0.4%	1.000
DEVICE DEFICIENCY	35	34	12.7%	1	1			
anchor (whole device) migration	5	5	1.9%	0	0			
occlusion component	29	29	10.9%	1	1			
other	1	1	0.4%	0	0			
DISC HERNIATION	44	38	14.2%	103	83	29.3%	-15.1%	<.001
herniation - index level	40	36	13.5%	101	83	29.3%	-15.8%	<.001
residual herniation - index level	2	2	0.7%	0	0	0.0%	0.7%	0.235
disc herniation - adjacent level	2	2	0.7%	1	1	0.4%	0.4%	0.614
disc herniation - non-adjacent level	0	0	0.0%	1	1	0.4%	-0.4%	1.000
ENDOCRINE	1	1	0.4%	0	0	0.0%	0.4%	0.485
EYES/EARS/NOSE/THROAT (EENT)	0	0	0.0%	1	1	0.4%	-0.4%	1.000
GASTROINTESTINAL	3	3	1.1%	6	5	1.8%	-0.6%	0.725
GENITOURINARY	2	2	0.7%	3	2	0.7%	0.0%	1.000
IMMUNOLOGICAL	0	0	0.0%	1	1	0.4%	-0.4%	1.000
METABOL./HEMATO./ELECTROLYTES	0	0	0.0%	3	3	1.1%	-1.1%	0.249
MUSCULOSKELETAL - LUMBAR	17	15	5.6%	13	10	3.5%	2.1%	0.307
spinal instability	2	2	0.7%	0	0	0.0%	0.7%	0.235
scoliosis	0	0	0.0%	2	2	0.7%	-0.7%	0.500
radiographic finding	4	4	1.5%	0	0	0.0%	1.5%	0.055
facet syndrome	9	8	3.0%	8	6	2.1%	0.9%	0.594
other	2	2	0.7%	3	3	1.1%	-0.3%	1.000
MUSCULOSKELETAL - NON-LUMBAR	25	23	8.6%	21	21	7.4%	1.2%	0.640
NEURO - LUMBAR AND LOWER EXTREMITY	41	34	12.7%	30	27	9.5%	3.2%	0.277
nerve or spinal root injury: index surgery	2	2	0.7%	4	4	1.4%	-0.7%	0.687
nerve root or spinal cord impingement	4	4	1.5%	2	1	0.4%	1.1%	0.204
muskuloskeletal spasms of the back or legs	9	9	3.4%	1	1	0.4%	3.0%	0.009
neurological deterioration	26	21	7.9%	23	21	7.4%	0.4%	0.874
NEURO - NON-LUMBAR/LOWER	5	5	1.9%	2	2	0.7%	1.2%	0.273
PAIN - LUMBAR AND LOWER EXTREMITY	137	96	36.0%	129	102	36.0%	-0.1%	1.000
lower extremity only	42	38	14.2%	47	42	14.8%	-0.6%	0.904
lumbar	65	57	21.3%	65	60	21.2%	0.1%	1.000
lumbar and lower extremity	29	25	9.4%	17	14	4.9%	4.4%	0.047
non-specific	1	1	0.4%	0	0	0.0%	0.4%	0.485
PSYCHOLOGICAL	0	0	0.0%	4	4	1.4%	-1.4%	0.124
RESPIRATORY/PULMONARY	0	0	0.0%	1	1	0.4%	-0.4%	1.000
TRAUMA	1	1	0.4%	1	1	0.4%	0.0%	1.000
WOUND ISSUE- SSI AT INDEX LEVEL	26	22	8.2%	23	20	7.1%	1.2%	0.633
dural injury/tear or csf leak	19	18	6.7%	14	14	4.9%	1.8%	0.467
infection	2	2	0.7%	4	3	1.1%	-0.3%	1.000
hematoma	3	3	1.1%	2	2	0.7%	0.4%	0.678
delayed wound healing	1	1	0.4%	0	0	0.0%	0.4%	0.485
dehiscence	0	0	0.0%	1	1	0.4%	-0.4%	1.000
deep	1	1	0.4%	2	2	0.7%	-0.3%	1.000
NECROSIS OF BONE OR RESORPTION	54	52	19.5%	5	5	1.8%	17.7%	<.001

***Definite/Probable/Possible/Unknown**

†Fisher's Exact.

3. Serious Adverse Events (SAE)

Table 10-11 presents the counts and percentages of Serious AEs (SAEs) by Group and Type between the Barricaid and Control cohorts. There was a statistically significant difference in the disc herniation SAEs (12.0% vs 20.5%, nominal p=0.008). These outcomes support Barricaid's intended use, which is to reduce the incidence of reherniation. The subject table demonstrates Barricaid significantly decreased the incidence of disc herniation considered to be an SAE. Overall, this benefit in reducing SAEs related to reherniations outweighs the SAEs related to device deficiencies such that overall, Barricaid subjects exhibit a lower rate of device or procedure related SAEs. The other categories of SAEs were statistically similar between treatment arms.

Table 10-11: Counts and Percentages of Subjects with Serious Adverse Events (Group, Type) in Barricaid and Control Discectomy – AT Population

	Barricaid (N = 267)			Control (N = 283)			Significance	
	Events	Subjs	%	Events	Subjs	%	Dif	p-value†
BENIGN SOFT TISSUE MASSES/TUMORS	2	2	0.7%	2	2	0.7%	0.0%	1.000
CANCER	5	5	1.9%	4	3	1.1%	0.8%	0.493
CARDIAC AND VASCULAR	19	17	6.4%	9	9	3.2%	3.2%	0.107
other	19	17	6.4%	9	9	3.2%	3.2%	0.107
DEATH	1	1	0.4%	1	1	0.4%	0.0%	1.000
DEVICE DEFICIENCY	12	12	4.5%	0	0			
anchor (whole device) migration	4	4	1.5%	0	0			
occlusion component	8	8	3.0%	0	0			
DISC HERNIATION	39	32	12.0%	73	58	20.5%	-8.5%	0.008
herniation - index level	25	22	8.2%	67	55	19.4%	-11.2%	<.001
residual herniation - index level	2	2	0.7%	0	0	0.0%	0.7%	0.235
disc herniation - adjacent level	5	4	1.5%	5	5	1.8%	-0.3%	1.000
disc herniation - non-adjacent level	7	6	2.2%	1	1	0.4%	1.9%	0.062
ENDOCRINE	4	4	1.5%	1	1	0.4%	1.1%	0.204
EYES/EARS/NOSE/THROAT (EENT)	3	3	1.1%	9	9	3.2%	-2.1%	0.144
GASTROINTESTINAL	16	11	4.1%	17	17	6.0%	-1.9%	0.338
GENITOURINARY	8	8	3.0%	8	8	2.8%	0.2%	1.000
OB/GYN	8	7	2.6%	6	6	2.1%	0.5%	0.783
INFECTIOUS DISEASE	4	3	1.1%	4	4	1.4%	-0.3%	1.000
IMMUNOLOGICAL	1	1	0.4%	1	1	0.4%	0.0%	1.000
METABOL./HEMATO./ELECTROLYTES	0	0	0.0%	1	1	0.4%	-0.4%	1.000
MUSCULOSKELETAL - LUMBAR	7	6	2.2%	4	4	1.4%	0.8%	0.535
spinal instability	1	1	0.4%	0	0	0.0%	0.4%	0.485
facet syndrome	4	3	1.1%	2	2	0.7%	0.4%	0.678
other	2	2	0.7%	2	2	0.7%	0.0%	1.000
MUSCULOSKELETAL - NON-LUMBAR	24	20	7.5%	20	16	5.7%	1.8%	0.395
NEURO - LUMBAR AND LOWER EXTREMITY	2	2	0.7%	4	4	1.4%	-0.7%	0.687
nerve or spinal root injury: index surgery	0	0	0.0%	1	1	0.4%	-0.4%	1.000
nerve root or spinal cord impingement	1	1	0.4%	0	0	0.0%	0.4%	0.485
muskuloskeletal spasms of the back or legs	1	1	0.4%	1	1	0.4%	0.0%	1.000
neurological deterioration	0	0	0.0%	2	2	0.7%	-0.7%	0.500
NEURO - NON-LUMBAR/LOWER EXTREMITY	8	8	3.0%	8	6	2.1%	0.9%	0.594
PAIN - LUMBAR AND LOWER EXTREMITY	26	21	7.9%	20	14	4.9%	2.9%	0.167
lower extremity only	9	9	3.4%	5	4	1.4%	2.0%	0.164
lumbar	9	9	3.4%	7	6	2.1%	1.3%	0.438
lumbar and lower extremity	8	7	2.6%	8	5	1.8%	0.9%	0.567
PSYCHOLOGICAL	4	4	1.5%	5	5	1.8%	-0.3%	1.000
RESPIRATORY/PULMONARY	2	2	0.7%	6	6	2.1%	-1.4%	0.287
TRAUMA	11	10	3.7%	7	7	2.5%	1.3%	0.464
WOUND ISSUE- SSI AT INDEX LEVEL	3	3	1.1%	9	7	2.5%	-1.3%	0.341
dural injury/tear or csf leak	1	1	0.4%	2	2	0.7%	-0.3%	1.000
infection	1	1	0.4%	3	2	0.7%	-0.3%	1.000
hematoma	0	0	0.0%	1	1	0.4%	-0.4%	1.000
delayed wound healing	1	1	0.4%	0	0	0.0%	0.4%	0.485
dehiscence	0	0	0.0%	1	1	0.4%	-0.4%	1.000
deep	0	0	0.0%	2	2	0.7%	-0.7%	0.500

†Fisher's Exact.

4. Device- or Procedure-Related Serious Adverse Events (SAEs)

Serious Device- or Procedure-Related Adverse Events in the Barricaid group (51/267, 19.1%) compared with 72 subjects in the Control group (72/283, 25.41%). Results are presented in Table 10-12. There were 83 device- or procedure-related SAEs in the Barricaid group and 115 in the Control group. The majority of reherniations were at the index level in both arms. In the Barricaid group, device deficiency events were limited to anchor migration (4 subjects, 1.5%) and flexible polymer component migration (8 subjects, 3.0%). In both groups, pain related to the lumbar spine and lower extremities was evenly distributed among lower extremity, lumbar spine, and a combination thereof. There were 3 events of infection in the Control group compared to 1 event in the Barricaid group.

Table 10-12: Device- or Procedure-Related SAEs (Groups, Types) in the Barricaid Clinical Trial - AT Population

	Barricaid (N = 267)			Control (N = 283)			Significance	
	Events	Subjs	%	Events	Subjs	%	Dif	p-value
CARDIAC AND VASCULAR	1	1	0.4%	3	3	1.1%	-0.7%	0.624
other	1	1	0.4%	3	3	1.1%	-0.7%	0.624
DEVICE DEFICIENCY	12	12	4.5%	0	0			
anchor (whole device) migration	4	4	1.5%	0	0			
occlusion component	8	8	3.0%	0	0			
DISC HERNIATION	28	24	9.0%	68	55	19.4%	-10.4%	<.001
herniation - index level	25	22	8.2%	67	55	19.4%	-11.2%	<.001
residual herniation - index level	2	2	0.7%	0	0	0.0%	0.7%	0.235
disc herniation - adjacent level	1	1	0.4%	0	0	0.0%	0.4%	0.485
disc herniation - non-adjacent level	0	0	0.0%	1	1	0.4%	-0.4%	1.000
GASTROINTESTINAL	0	0	0.0%	1	1	0.4%	-0.4%	1.000
GENITOURINARY	0	0	0.0%	1	1	0.4%	-0.4%	1.000
METABOL./HEMATO./ELECTROLYTES	0	0	0.0%	1	1	0.4%	-0.4%	1.000
MUSCULOSKELETAL - LUMBAR	7	6	2.2%	4	4	1.4%	0.8%	0.535
spinal instability	1	1	0.4%	0	0	0.0%	0.4%	0.485
facet syndrome	4	3	1.1%	2	2	0.7%	0.4%	0.678
other	2	2	0.7%	2	2	0.7%	0.0%	1.000
MUSCULOSKELETAL - NON-LUMBAR	3	3	1.1%	2	2	0.7%	0.4%	0.678
NEURO - LUMBAR AND LOWER	2	2	0.7%	3	3	1.1%	-0.3%	1.000
nerve or spinal root injury: index surgery	0	0	0.0%	1	1	0.4%	-0.4%	1.000
nerve root or spinal cord impingement	1	1	0.4%	0	0	0.0%	0.4%	0.485
muskuloskeletal spasms of the back or legs	1	1	0.4%	1	1	0.4%	0.0%	1.000
neurological deterioration	0	0	0.0%	1	1	0.4%	-0.4%	1.000
NEURO - NON-LUMBAR/LOWER	1	1	0.4%	0	0	0.0%	0.4%	0.485
PAIN - LUMBAR AND LOWER EXTREMITY	26	21	7.9%	20	14	4.9%	2.9%	0.167
lower extremity only	9	9	3.4%	5	4	1.4%	2.0%	0.164
lumbar	9	9	3.4%	7	6	2.1%	1.3%	0.438
lumbar and lower extremity	8	7	2.6%	8	5	1.8%	0.9%	0.567
PSYCHOLOGICAL	0	0	0.0%	3	3	1.1%	-1.1%	0.249
WOUND ISSUE- SSI AT INDEX LEVEL	3	3	1.1%	9	7	2.5%	-1.3%	0.341
dural injury/tear or csf leak	1	1	0.4%	2	2	0.7%	-0.3%	1.000
infection	1	1	0.4%	3	2	0.7%	-0.3%	1.000
hematoma	0	0	0.0%	1	1	0.4%	-0.4%	1.000
delayed wound healing	1	1	0.4%	0	0	0.0%	0.4%	0.485
dehiscence	0	0	0.0%	1	1	0.4%	-0.4%	1.000
deep	0	0	0.0%	2	2	0.7%	-0.7%	0.500

***Definite/Probable/Possible/Unknown.**
†Fisher's Exact.

The cumulative proportion of subjects exhibiting a device or procedure related SAE is shown in the table below through survival analysis. The Barricaid population exhibits a lower rate of related SAEs through the entire 5-year time course (nominal p=0.0367).

Table 10-13: Time-course cumulative distribution of proportion of subjects with a device or procedure related SAE

	Barricaid				Control				Significance	
	Failures		95% CI		Failures		95% CI		Failure	Log-rank
Years	n	%	LB	UB	n	%	LB	UB	Delta	Nominal p-value
1	25	9.5%	6.5%	13.7%	46	16.7%	12.8%	21.6%	-7.2%	
2	32	12.2%	8.8%	16.9%	55	20.1%	15.8%	25.4%	-7.9%	
3	40	15.6%	11.7%	20.6%	63	23.4%	18.8%	29.0%	-7.8%	0.0367
4	46	18.4%	14.1%	23.8%	68	25.8%	20.9%	31.6%	-7.4%	
5	49	20.6%	15.9%	26.6%	70	27.2%	22.1%	33.3%	-6.6%	

5. Index Level Secondary Surgical Intervention

The index-level secondary surgical interventions are shown cumulatively as the proportion of subjects who had a secondary surgical intervention in using survival analysis.

Table 10-14: Time-course cumulative distribution of proportion of subjects with a secondary surgical intervention at Index level

	Barricaid				Control				Significance	
	Failures		95% CI		Failures		95% CI		Failure	Log-rank
Years	n	%	LB	UB	n	%	LB	UB	Delta	Nominal p-value
1	17	6.47%	4.07%	10.20%	35	12.85%	9.40%	17.44%	-6.38%	
2	23	8.81%	5.94%	12.96%	44	16.36%	12.44%	21.36%	-7.55%	
3	27	10.48%	7.30%	14.91%	51	19.30%	15.02%	24.62%	-8.83%	0.0300
4	35	14.22%	10.40%	19.28%	55	21.33%	16.77%	26.92%	-7.11%	
5	38	16.15%	11.94%	21.65%	57	22.69%	17.89%	28.54%	-6.54%	

The Barricaid group had a lower proportion of subjects with a secondary surgical intervention at all time points. The difference in rate of secondary surgical intervention is statistically significant at all timepoints in favor of the Barricaid group (nominal $p<0.05$). This observation of greater numbers of secondary surgical interventions in the Control group compared to the Barricaid group was expected due to the greater rate of symptomatic reherniations in the control group that required a reoperation. These results demonstrate that augmenting the discectomy with Barricaid significantly reduces the need for a secondary surgical procedure after the primary surgery compared to discectomy alone with the available data through 60 months following treatment, despite the addition of an implant to a procedure that typically does not include one. However, it can be seen that the initial reduction in secondary surgical interventions within the first year accounts for the difference between Barricaid and control groups. The data shows that this difference is maintained over time but is not increased.

Table 10-15: Time Course of Secondary Surgical Interventions by Type: Barricaid

Barricaid Secondary Surgical Interventions (n=51 events)										
Intervention Type	**Event Time Course (Months)**								**Total (events)**	**Reasons**
	0 – 1.5	**1.5 – 3**	**3 – 6**	**6 – 12**	**12 – 24**	**24 – 36**	**36 – 48**	**48 - 60**		
Removal	2	-	1	5	-	1	4	1	14	Herniation-Index Level (5) Device Deficiency (4) Lumbar Pain (3) Lower Extremity and Lumbar Pain (1) Residual Herniation (1)
Revision	-	-	-	1	5	2	2	1	11	Device Deficiency (5) Herniation-Index Level (3) Lower Extremity and Lumbar Pain (3)
Reoperation	3	1	1	4	2	2	2	1	16	Herniation-Index Level (9) Residual Herniation (2) Lower Extremity and Lumbar Pain (2) Lower Extremity Pain (1) Dural Tear (1) Neurological (1 non-lumbar or lower extremity related)
Supplemental Fixation	-	-	-	2	1	3	2	2	10	Lower Extremity and Lumbar Pain (2) Spinal Instability (2) Lower Extremity Pain (1) Lumbar Pain (1) Herniation-Index Level (1) Facet Syndrome (1) Device Deficiency (1) Musculoskeletal-lumbar-Other (1)
Subtotals	5	1	2	12	8	8	10	5	51	

Table 10-16: Time Course of Secondary Surgical Interventions by Type: Control

Control Secondary Surgical Interventions (n=81 events)										
Intervention Type	**Event Time Course (months)**								**Total (events)**	**Reasons**
	0 – 1.5	**1.5 – 3**	**3 – 6**	**6 – 12**	**12 – 24**	**24 – 36**	**36 – 48**	**48 - 60**		
Removal	-	-	-	-	-	-	-	-	-	-
Revision	-	-	-	-	-	-	-	-	-	-
Reoperation	10	4	12	6	10	10	5	1	58	Herniation-Index Level (48) Wound Infection (4) Lumbar Pain (1) Lower Extremity Pain (1) Deep Wound Infection (1) Wound Dehiscence (1) Hematoma (1) Cardiac and Vascular -Other (1)
Supplemental Fixation	2	0	1	6	5	4	2	3	23	Herniation-Index Level (11) Lumbar Pain (5) Lower Extremity Pain (3) Lower Extremity and Lumbar Pain (2) Musculoskeletal-lumbar-Other (2)
Subtotals	12	4	13	12	15	14	7	4	81	

a. Multiple Secondary Surgeries

Many subjects underwent multiple secondary surgical interventions. 39 subjects in the Barricaid arm had reoperations at any time through Day 1885 (60 months + 60 days) and 10 went on to have a further 12 subsequent reoperations for a total of 51 index level secondary surgical interventions. Reoperations included additional discectomies with and without fusion, fusions, pedicle fixations, wound revisions, decompressions and Barricaid removals. Two subjects had a third reoperation, and none had a fourth.

In summary there were 57 Control subjects with 81 index level secondary surgical interventions. 57 subjects in the control arm had reoperations and 18 went on to have a total of 24 further reoperations. These reoperations included additional discectomies with and without fusion, fusions, pedicle fixations, wound revisions and hematomas. Four subjects went on to have a third reoperation, and two had a fourth reoperation. These figures show that the Barricaid group demonstrated fewer reoperations and subsequent reoperations in comparison to Control. It is also notable that in the control group, there is a higher likelihood of any SSI to be a subsequent discectomy, while a failure of the Barricaid is more likely to result in additional hardware and supplemental fixation.

Table 10-17: Multiple Secondary Surgeries by Types

		1st	2nd	3rd	4th
Barricaid	All Secondary Surgical Interventions	39	10	2	0
	Discectomy +/- Removal	18	0	0	0
	Supplemental Fixation +/- Removal +/- Discectomy	12	9	1	0
	Other: Removal (5) Other decompression (3) Partial Removal (1) Wound (1) Dural tear repair (1)	9	1	1	0
Control	All Secondary Surgical Interventions	57	18	4	2
	Discectomy	38	7	1	0
	Discectomy + Barricaid	5	0	0	0
	Supplemental Fixation +/- Discectomy	6	9	1	1
	Other: Wound (6) Other decompression (3) Hematoma (3) Remove posterior instrumentation (1)	8	2	2	1

b. Secondary Surgical Intervention Surgical Time

Mean surgical times for all re-operations were calculated and can be found in Table 10-18. Surgical times are comparable between treatment groups (nominal p>0.15) for given surgery types.

Table 10-18. Operative Time of Secondary Surgical Intervention

	Barricaid			Control			Nominal p-value*
	n	Mean	SD	n	Mean	SD	
Fusion	22	135.3	79.5	17	125.8	63.1	0.6888
Non-Fusion	29	68.8	37.3	63	56.6	39.3	0.1642

* Unpaired t-test

c. Secondary Surgical Intervention Complications

Adverse Events that occurred intra-operatively during secondary surgical intervention or within 30 days of the secondary surgery were assessed. There was no difference in complication rate (24% Barricaid vs. 26% Control, nominal p=0.7456), no difference in distribution of number of complications (nominal p=0.769), and no difference in distribution of complication types (nominal p=0.336). A summary of the counts and types of intra- and perioperative complications can be found in Table 10-19 and Table 10-20.

Table 10-19. Distribution of Number of Intra/Perioperative Complications

# of Complications	Barricaid (n=51)		Control (n=81)	
	No.	%	No.	%
0	40	78.4%	66	81.5%
1	10	19.6%	11	13.6%
2	1	2.0%	3	3.7%
4	0	0.0%	1	1.2%

Table 10-20. Distribution of Complication Types

	Barricaid (n=12)		Control (n=21)	
	No.	%	No.	%
Dural Tear	5	41.7%	7	33.3%
Lumbar/lower extremity pain	3	25.0%	2	9.5%
Other complications	4	33.3%	12	57.1%

d. Clinical Outcomes Following Secondary Surgical Intervention

Latest clinical results from subjects with secondary surgical intervention were similar in each cohort regardless of surgery type as shown in Table 10-21 and Table 10-22. Barricaid subjects treated with interbody fusion exhibited significantly lower mean VAS Leg Pain scores and ODI scores (nominal p=0.0324 and nominal p=0.0434, respectively). These results demonstrate similar or better clinical outcomes following secondary surgical intervention in the Barricaid group when compared to the Control group.

Table 10-21. Clinical Outcomes at Latest Follow-Up for Subjects with Interbody Fusion

	Barricaid (n=19)	Control (n=14)	Nominal p-value
VAS Leg, Mean (SD)	32.7 (29.3)	54.5 (25.2)	0.0324
VAS Back, Mean (SD)	47.8 (31.2)	63.4 (24.7)	0.1325
ODI, Mean (SD)	32.0 (17.4)	45.3 (18.6)	0.0434
No neuro deterioration, % (n)	100.0% (19)	85.7% (12)	0.172*

*t-test for clinical scores. Fisher's Exact Test for Neurological Improvement/Maintenance.

Table 10-22. Clinical Outcomes at Latest Follow-Up for Subjects without Interbody Fusion

	Barricaid (n=22)	Control (n=43)	Nominal p-value
VAS Leg, Mean (SD)	18.9 (25.2)	23.1 (29.6)	0.5715
VAS Back, Mean (SD)	26.4 (27.8)	24.6 (24.3)	0.7856
ODI, Mean (SD)	20.1 (15.8)	19.2 (17.7)	0.8401
No neuro deterioration, % (n)	95.5% (21)	93.0% (40)	1.000*

*t-test for clinical scores. Fisher's Exact Test for Neurological Improvement/Maintenance.

These were investigated to also consider the potential for the presence of endplate lesions to hinder a subsequent fusion or lead to subsidence of an interbody cage device. The patient narratives and clinical history of individual subjects who underwent secondary surgical interventions were reviewed and did not yield any complications specifically relating to the presence of endplate lesions.

6. Overall Conclusions from Review of Adverse Events

Barricaid subjects had more "Device Deficiency" adverse events. However, this was expected since the Control group did not have a device. Importantly, the "Disc Herniation" counts were significantly higher in the Control group, which led to significantly more SAEs and secondary surgical interventions.

7. Device Integrity

Device integrity was included to assess mechanical failure of the device. To be considered a success, the device had to maintain device condition and not have experienced device migration. Many of the device integrity observations were free from clinical consequence (i.e., had successful clinical outcome scores, and were free of secondary surgical intervention and symptomatic reherniation within 60 months). In these instances, failure of the device to maintain the intended position does impact the ability to achieve the intended effect (i.e., do not result in a different rate of reherniations in the Barricaid group as compared to the control). However, there are instances of migration or dissociation of the device that are associated with additional AEs.

Per the radiographic protocol, device condition is graded in the investigational group as "Intact, Fractured or Disassembled" in accordance with the following definitions:

Intact: No evidence of device fracture or disassembly
Fractured: Evidence of mechanical fracture of the anchor component of the implant
Disassembled: Evidence of separation of the flexible polymer component of the implant from the anchor component

In addition, device migration is graded in the investigational group in accordance with the following definitions:

0. Absent: No anterior-posterior or lateral motion of the anchor ≥ 2mm relative to its initial position and no motion of the flexible polymer component through the anulus relative to the first available post-operative visit with adequate image quality.
1. Present

a. Type – Anchor Only: Evidence of anterior-posterior or lateral motion of the anchor ≥ 2mm relative to the first available post-operative visit with adequate image quality and no evidence of motion of the flexible polymer component through the anulus.

b. Type – Flexible Polymer Component Only: Evidence of posterior migration of the flexible polymer component through the anulus relative to the first available post-operative visit with adequate image quality and no evidence of anterior-posterior or lateral motion of the anchor ≥ 2mm relative to its initial position.

c. Type –Anchor & Flexible Polymer Component: Evidence of anterior-posterior or lateral motion of the anchor ≥ 2mm relative to its initial position and evidence of posterior migration of the flexible polymer component through the anulus relative to the first available post-operative visit with adequate image quality.

Table 10-23: Overall Rate and Type of Device Integrity Observation (Through 60 Months)

Device Integrity Observation	Total Subjects with Device Integrity Observation (% of Barricaid AT*)	Subjects with Symptomatic Device Integrity Observation (% of Barricaid AT*)	Subjects with Device Integrity Observation and Reoperated (% of Barricaid AT*)
Anchor-related	7 (2.6%)	4 (1.5%)	4 (1.5%)
Fracture and Migration	2 (0.7%)	1 (0.4)	1 (0.4%)
Migration only	5 (1.9%)	3 (1.1%)	3 (1.1%)
Flexible polymer component only	44 (16.5%)	23 (8.6%)	13 (4.9%)
Migration only	32 (12.0%)	16 (6.0%)	8 (3.0%)†
Detachment only	5 (1.9%)	2 (0.7%)	2 (0.7%)
Detachment and migration	7 (2.6%)	5 (1.9%)	3 (1.1%)
Total	**51 (19.1%)**	**27 (10.1%)**	**17 (6.4%)†**

* Simple rate estimate based on percentage of Barricaid AT population (n=267).
† n=1 occurred prior to device integrity observation.

Device integrity failures can be seen in Table 10-24 below.

Table 10-24: Qualitative Assessment Timecourse of Device Integrity Failure Onset by the Independent Radiographic Core Lab

	Week 6		Month 3*		Month 6		Month 12		Month 24†		Month 36		Month 48		Month 60		Total	
	N=223		N=248		N=239		N=248		N=229		N=161		N=136		N=75		N=267	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
All Integrity	1	0.4	2	0.8	0	0.0	11	4.4	18	7.9	6	3.7	10	7.4	3	4.0	51	19.1
Condition Only	0	0.0	0	0.0	0	0.0	1	0.4	3	1.3	0	0.0	1	0.7	1	1.3	6	2.2
Migration Only	1	0.4	2	0.8	0	0.0	7	2.8	11	4.8	5	3.1	9	6.6	2	2.7	37	13.9
Condition and Migration	0	0.0	0	0.0	0	0.0	3	1.2	4	1.7	1	0.6	0	0.0	0	0.0	8	3.0

*One migration only observation was noted in imaging obtained from an unscheduled visit within the 3M window.
†One condition and migration observation was noted in imaging obtain from an unscheduled visit at 18M and binned into the 24M reporting.

Device condition failures can be seen in Table 10-25 below.

Table 10-25: Qualitative Assessment Timecourse of Device Condition Failure Onset by the Independent Radiographic Core Lab

	Week 6		Month 3		Month 6		Month 12		Month 24		Month 36		Month 48		Month 60		Total	
	N=263		N=262		N=256		N=260		N=249		N=181		N=157		N=96		N=267	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Fractured	0	0.0	0	0.0	0	0.0	1	0.4	1*	0.4	0	0	0	0	0	0	2	0.7
Disassembled	0	0.0	0	0.0	1	0.4	2	0.8	6	2.4	1	0.6	1	0.6	1	1.0	12	4.5

* One fracture was noted in imaging obtained at an unscheduled visit (M18)

Device migrations can be seen in Table 10-26 below.

Table 10-26: Qualitative Assessment Timecourse of Device Migration Onset by the Independent Radiographic Core Lab*

	Week 6		Month 3		Month 6		Month 12		Month 24		Month 36		Month 48		Month 60		Total	
	N=259		N=254		N=249		N=249		N=242		N=191		N=219		N=118		N=267	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Anchor component only	0	0.0	1	0.4	0	0.0	0	0.0	2	0.8	0	0	2	0.9	0	0	5	1.1
Polymer component only	0	0.0	0	0.0	1	0.4	9	3.6	14	5.8	6	3.1	7	3.2	2	1.7	39	14.6
Anchor & polymer component	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0	2	0.7

*Two migrations of the anchor component were noted in imaging obtained at unscheduled visits (M3 and M18).

While there was a 19.1% occurrence of Device Integrity issues, after a subject level analysis there were successful clinical outcomes (i.e. ODI improvement, no neurological deterioration, no device/procedure related SAEs, no index level secondary surgical interventions, and no symptomatic reherniation) in 35.7% of subjects with Device Condition failures with follow-up through 60 months, and 43.5% of subjects with migration through Month 60. However, there were still a greater portion of subjects who experienced negative clinical outcomes primarily due to reherniation when there were device failures. Of the 51 observed device integrity failures, 27 were symptomatic and 17 required reoperations. All subjects with symptomatic device integrity failures had an associated reherniation.

8. Neurological Outcomes

Subjects who have either maintained or improved in their neurological status as it relates to the subject's index level are considered a success. Neurological status success is based upon Straight Leg Raising (SLR) (L4-5 and L5-S1) or Femoral Stretch Test (L1-2, L2-3, L3-4 only), motor examination, sensory examination, and reflex examination.

Table 10-27: Overall assessment of neurological outcomes (success) (motor, sensory, reflex, SLR/FST)

	Barricaid			Control			Significance			
	N	n	%	N	n	%	Dif.*	95% CI †	Chi-sq ‡	Exact §
Week 6	266	248	93.2%	271	255	94.1%	-0.9%	(-5.0%, 3.3%)	0.681	0.725
Month 3	267	256	95.9%	263	254	96.6%	-0.7%	(-3.9%, 2.5%)	0.673	0.820
Month 6	259	251	96.9%	261	249	95.4%	1.5%	(-1.8%, 4.8%)	0.371	0.495
Month 12	261	251	96.2%	260	252	96.9%	-0.8%	(-3.9%, 2.4%)	0.637	0.811
Month 24	252	247	98.0%	251	239	95.2%	2.8%	(-0.4%, 5.9%)	0.083	0.090
Month 36	203	199	98.0%	207	198	95.7%	2.4%	(-1.0%, 5.7%)	0.170	0.259
Month 48	187	184	98.4%	177	172	97.2%	1.2%	(-1.8%, 4.3%)	0.427	0.492
Month 60	135	132	97.8%	127	122	96.1%	1.7%	(-2.5%, 5.9%)	0.420	0.490

Notes:
* Difference in proportions (calculated as I minus C).
† 95% CI (asymptotic).
‡ Nominal Chi-square p-value; § Nominal Fisher's exact test p-value.

Source: Tables Neurological2.sas
Analyzed: 19JUL2018

The overall assessment of all neurological outcomes is presented in Table 10-27. The overall assessment of neurologic function indicates that there are similar rates of maintenance or improvement of neurologic function in both groups at all timepoints. The results demonstrate no acute or longer term neurological deterioration (particularly in terms of motor function) after implantation of the Barricaid.

9. Endplate Lesions

Due to concerns seen in the preclinical baboon study as well as initial clinical experience, there was concern regarding the development of lesions or voids in the bone within the vertebral body adjacent to the Barricaid device, referred to as endplate lesions (EPLs). These disruptions in the vertebral body endplates and loss of surrounding bone were observed in both the Barricaid and control groups, both pre-operatively and post-operatively, based on CT assessments performed by the radiographic core lab. EPLs consist of any defect such as chipping, scalloping or erosions that are not inherent to the natural shape of a vertebral endplate as seen in the figures below. There are many ways that physicians, scientists and researchers describe radiographic observations of bony changes and bone loss, with no consensus in the literature.[7] Since the specific etiology for these observations that are more common in the Barricaid group has not been described previously, there has not yet been conclusive terminology used to describe them.

CT is a highly sensitive imaging modality for observing these endplate lesions in comparison to the x-rays and MRIs that are typically collected for this subject population, which potentially explains why these endplate lesions have not been widely reported following discectomy.

While there were observations of endplate lesions such as Schmorl's nodes, which were present both before and after surgery in both groups that confounded the imaging analysis, there was an increased prevalence of new developing disruptions to the endplate and loss of surrounding bone that were present in the Barricaid group, many of which appeared to be in close proximity to the device and were described by the FDA musculoskeletal radiologist as "lytic." FDA had concern that development of endplate lesions with unknown etiology in the Barricaid group would grow to a point where they pose a safety risk to the patient is supported by the histologic samples seen in the baboon study as well as the inflammatory responses and necrotic bone seen in the retrieval analysis of peri-prosthetic tissue. This concern was expressed to and supported by the FDA Orthopedic and Rehabilitation Devices Panel convened on December 12, 2017 in the form of a vote regarding safety, specifically due to concern for long term clinical outcomes while these lesions were still progressing. To address this, additional longer-term data were provided to support the absence of negative clinical sequelae after a time when the lesions, specifically in the Barricaid group, have been determined to be stable.

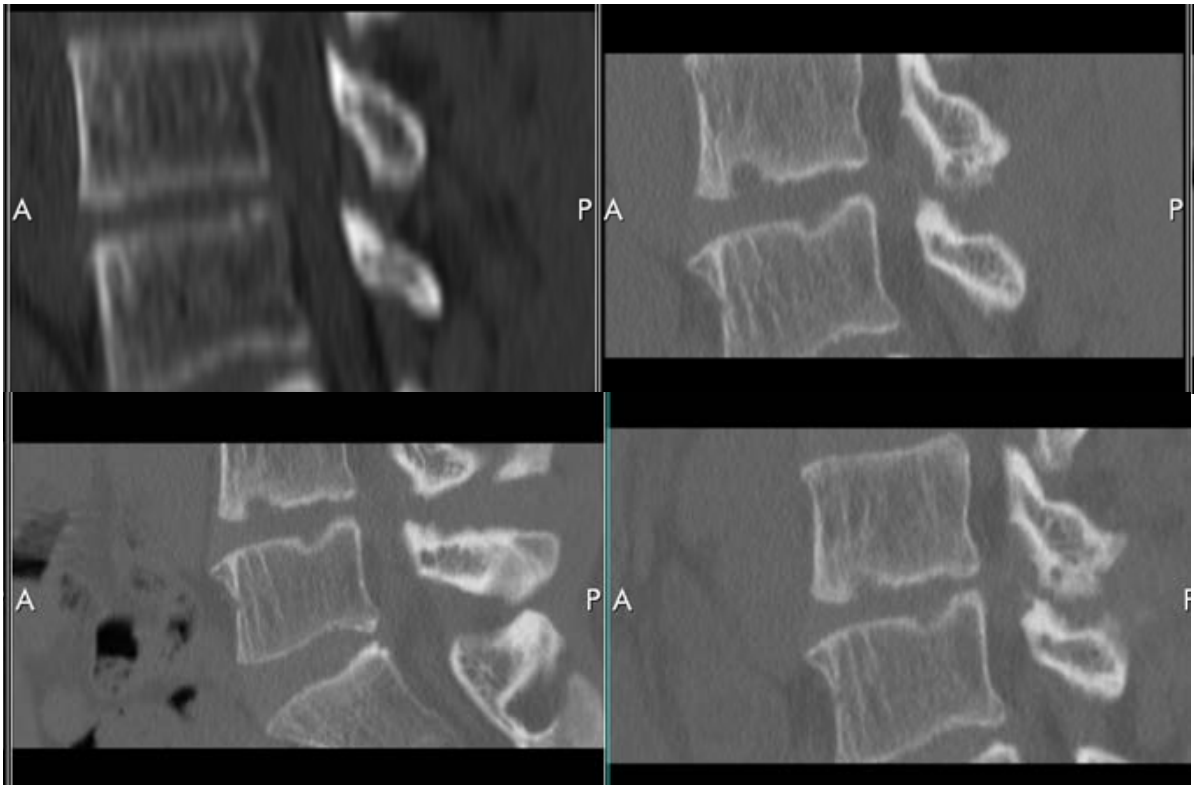


Figure 10.2. Example EPL Time Course (Control Subject) – Top left shows the preoperative image, compared to one year (top right), two year (bottom left) and five year (bottom right)

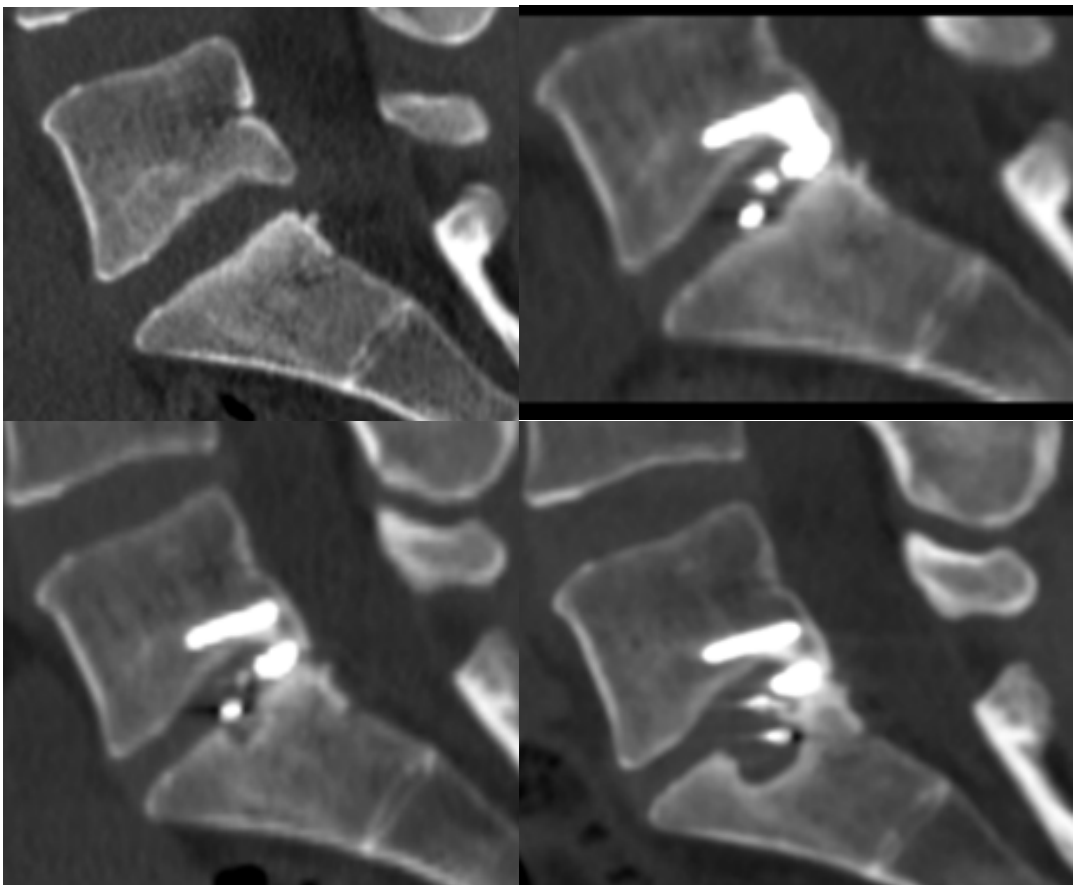


Figure 10.3 Example EPL Time Course (Barricaid Subject) – Top left shows the preoperative image, compared to one year (top right), two year (bottom left) and five year (bottom right)

The qualitative analysis of the images resulted in multiple interpretations and categorizations, so a quantitative approach was taken to examine these potential safety concerns of these developing lesions. Overall, the prevalence of EPLs in Barricaid subjects was higher and tended to be larger in size relative to Control. As of the date of database closure, June 4, 2018, the As-Treated analysis set includes 499 EPLs observed in 238 of 267 (89.1%) Barricaid As-Treated subjects and 195 EPLs observed in 116 of 283 (41.0%) Control As-Treated subjects. While both groups displayed EPLs, there was a focus on those that opposed the flexible polymer component; that is, were proximate to the flexible polymer component of the Barricaid device as they were considered directly related to the Barricaid device with loss of surrounding bone and thought to correspond to the "lytic" characteristics seen in imaging by the FDA musculoskeletal radiologist. Subsequently the EPLs that were proximate to the polymer component were used as a surrogate to define this group, and FDA and Sponsor decided together to focus on the quantitative aspects of EPL growth. There were 203 of 499 (40.7%) EPLs in 147 of 267 (55%) Barricaid subjects that were proximate to the flexible polymer component at any time point. Note also that there were 63 and 55 EPLs in the Barricaid and Control, respectively, that were present at baseline.

At the Month 36 time-point, the median EPL size was 49 mm^2 in the Barricaid and 42 mm^2 in the Control, while the third quartiles were 84 mm^2 Barricaid and 72 mm^2 Control.

Note that the maximum EPL areas were approximately the same at 308 mm^2 in both groups. The maximum EPL volume represents about 8% of vertebral body volume and hence has been judged not to present a fracture risk based on clinical experience in spinal tumors, though concern remains for any growing or localized bone resorption (fracture of bone fragment rather than complete vertebral body collapse) that is intended to be addressed in the post-approval studies. Additionally, it can be seen that those EPLs that were determined to be "proximate to the flexible polymer component" were of larger size, as exemplified in Table 10-28 below.

Table 10-28: Median Endplate Lesion Size (mm^2)

	Barricaid			**Barricaid (Proximate to Polymer Component)**			**Control**		
	N	Med	Max	N	Med	Max	N	Med	Max
Baseline	63	27	255	21	33	255	55	34	324
Month 12	264	40	328	135	70	328	110	34	306
Month 24	366	42	325	177	73	325	128	29	398
Month 36	321	49	308	146	80	308	112	42	308
Month 48	267	57	358	128	105	352	95	36	217
Month 60	158	56	391	69	106	391	73	30	277

In terms of growth rates of the EPLs, these were largest initially, at 0 to 12 months, being a median of 67mm^2 in the Barricaid and 19mm^2 in the Control. At 12-24 months the median growth rates were 30mm^2 in the Barricaid and 4mm^2 in the Control. The growth rates further decreased at 48 to 60 months to 11mm^2 in the Barricaid and 1mm^2 in the Control. Additional attention should be paid to the EPLs proximate to the polymer component and those determined to be further subsided into the lesion. Their growth rates are more striking, and likely represent those EPLs directly related to the device, rather than those attributable to the discectomy alone or natural occurrence. These had large growth rates early, that eventually slowed, which compared to a much slower EPL growth in the control group. Note that EPL size was correlated in an *inverse* manner with both growth rate and changes in growth rate. Thus, the analysis of EPL dynamics in Barricaid suggests that EPLs may be self-limiting in size; however, remaining concern of low level extended growth will be addressed in the post-approval studies.

Table 10-29: Median Endplate Lesion Growth Rates Per Subject (mm^2/year)

	Barricaid				Barricaid (Proximate to Polymer Component)				Barricaid (Proximate to Polymer Component with Subsidence)				Control			
	N	Med	Q3	Max	N	Med	Q3	Max	N	Med	Q3	Max	N	Med	Q3	Max
Months 0-12	177	67	99	367	119	80	113	367	85	84	122	367	71	19	51	267
Months 12-24	204	30	62	207	134	37	69	207	90	42	72	207	87	4	24	311
Months 24-36	160	17	49	265	104	18	53	265	72	25	54	265	65	11	29	204
Months 36-48	118	14	41	239	79	19	43	125	56	16	47	125	51	4	17	143
Months 48-60	65	11	34	270	41	14	45	270	31	14	45	270	40	1	18	220

Extensive analyses were performed to understand if the EPLs were stabilizing over time, and once stabilized, if they were a risk to the subject. A stability analysis of EPLs using all available size data showed that greater than 90% of EPLs had stabilized in both groups in the complete data through year 3 and partial data through year 5 (data locked on June 4, 2018). This assessment was based on the measurement uncertainty, growth rate, changes in growth rate, and absolute size of the lesions. The proportion of subjects in the Barricaid group with only stable EPLs was 89%, with a worst-case proportion (considering all missing data as unstable) of 70%. Having demonstrated the stabilization of lesion growth and reached a "worst case" size, the clinical outcome measures were evaluated for safety and efficacy with the assumption that the lesions would not progress significantly further in size.

The study analyses compared Barricaid subjects with EPLs and with EPLs that were proximate to the flexible polymer component, to the Control group for the primary safety and effectiveness outcomes and this resulted in no significant findings. No negative clinical correlations were observed in Barricaid subjects with EPLs based on subject reported clinical outcomes, no reoperations were performed for EPLs, and no serious adverse events were reported that were specifically linked to EPLs. Thus, the Barricaid group did not demonstrate any significant safety issues, such as reoperations or adverse events related to the EPLs. In addition, the sponsor has presented data to assess for trends associated with subjects with "any unstable EPL", "stable EPLs" and "No EPL" for the month 36 outcomes of composite success (CCS-CPD), alternate composite success (CCS-mCPD), reherniation, symptomatic reherniation, ODI success, VAS leg pain success and VAS back pain success. There were no significant findings against the unstable EPL group. Data also appear to show absence of a correlation between EPLs and device integrity findings and absence of an impact of the EPLs on outcomes after reoperation. However, EPLs are being further studied in a long-term post-approval study follow-up of the PMA study subjects. An additional concern being studied is the possible effect of lesions in subjects developing osteopenia or osteoporosis. In conclusion, there is evidence to support that the observed EPLs are not associated with adverse clinical outcomes and that remaining concerns can be addressed in the post-approval studies.

F. Effectiveness Results

1. Primary Endpoint Success

When considering the originally proposed co-primary endpoints, both endpoints demonstrated superiority of the Barricaid group when compared to the Control group (Table 10-30). The pre-specified analysis of effectiveness defined in the protocol was based on the mITT cohort comprising all 550 subjects in whom the intended procedure was attempted (272 Barricaid subjects, 278 Control subjects).

Table 10-30: Co-Primary Endpoint Success at 24 Months (mITT Analysis Data Set)

	Barricaid			Control			Δ	Chi-squared p-value	Posterior Probability of Success
	N	n	%	N	n	%			
First Co-Primary Endpoint: No Reherniation	240	122	50.8	256	77	30.1	20.8	<0.001	>0. 9999
Second Co-Primary Endpoint: Composite Success	245	68	27.8	259	47	18.1	9.6	0.010	0.9980

The first co-primary endpoint required a subject to have no evidence of recurrent herniation at the index level at any time up to and including the 24-month follow-up. The purpose of this primary endpoint was to evaluate the Barricaid's purpose, function and principal benefit: retention of nucleus material. Barricaid was superior to Control (posterior probability >0.9999), with the Control group exhibiting a success rate that was 20.8 percentage points lower than Barricaid (Table 10-30).

The second co-primary endpoint was developed as a composite of both safety and effectiveness components. These endpoints included no reherniation, no secondary surgical interventions, disc height maintenance, no spontaneous fusion, no device integrity failures, neurological success, ODI and VAS success. For a subject to be counted as a success, all eight measures must be satisfied for that subject. The rate of subject success was then compared between the Barricaid and Control groups. The data demonstrate that, with regard to the composite co-primary endpoint, the Barricaid was better by a statistically significant superiority margin compared to Control discectomy (27.8% vs. 18.1%, posterior probability=0.9980), a 9.7-point improvement.

Due to the complex nature of the new type of device there were limitations to the prospectively defined primary endpoint, including the components included as well as the time point for which the components should be evaluated. For this reason, focus was placed more on the individual endpoints collected in this study. These endpoints were evaluated over time at a potentially worst-case scenario regarding progression of the lesions, specifically with 3-year data, along with partial data for 4 and 5 years to provide a more complete picture.

2. Missing Data and Sensitivity Analysis

At the 24-month follow-up visit, in the mITT cohort there were 32 Barricaid subjects and 22 Control subjects with missing data for the first co-primary endpoint. This tipping-point analysis is designed to understand study success while assuming the extreme scenario where all missing data for Barricaid are considered failures, and all missing data for Control are considered successes. As demonstrated in Table 10-31, the result of superiority is relatively insensitive to the effects of missing data, as the posterior probability of superiority does not drop below the *a priori* defined threshold of 0.95.

Table 10-31: Sensitivity Analysis to Assess Missing Data for the First Co-Primary Endpoint: Reherniation

	Number and Percentage Achieving Month 24 No Reherniation Success						Posterior Probability of Superiority
	Barricaid			Control			
	N	n	%	N	n	%	
Missing Data Excluded (complete cases)	240	122	**50.8%**	256	77	**30.1%**	**1.0000**
All Missing Data = Failures	272	122	**44.9%**	278	77	**27.7%**	**1.0000**
All Missing Data = Successes	272	154	**56.6%**	278	95	**34.2%**	**1.0000**
"Best Case" for Barricaid	272	154	**56.6%**	278	77	**27.7%**	**1.0000**
"Worst Case" for Barricaid	272	122	**44.9%**	278	95	**34.2%**	**0.9948**

At the 24-month follow-up visit, in the mITT cohort there were 27 Barricaid subjects and 19 Control subjects without data for the second co-primary endpoint. As demonstrated in Table 10-32, the result of superiority is relatively insensitive to the effects of missing data, as only in the "worst case" for Barricaid (in which all missing Barricaid subjects are considered failures while all missing Control subjects are considered successes) does the posterior probability of superiority drop below the *a priori* defined threshold of 0.95.

Table 10-32: Sensitivity Analysis to Assess Missing Data for the Second Co-Primary Endpoint: Composite Success

	Number and Percentage Achieving Month 24 Composite Success						Posterior Probability of Superiority
	Barricaid			Control			
	N	n	%	N	n	%	
Missing Data Excluded (complete cases)	245	68	**27.8%**	259	47	**18.1%**	**0.9948**
All Missing Data = Failures	272	68	**25.0%**	278	47	**16.9%**	**0.9901**
All Missing Data = Successes	272	95	**34.9%**	278	66	**23.7%**	**0.9980**
"Best Case" for Barricaid	272	95	**34.9%**	278	47	**16.9%**	**1.0000**
"Worst Case" for Barricaid	272	68	**25.0%**	278	66	**23.7%**	**0.6344**

3. Impact of Discectomy

Pain scores (VAS) and ODI were recorded at fixed follow-up intervals, and thus these data do not explicitly capture events which occurred between annual follow-up visits; Patient Reported Outcome scores do not accurately reflect pain and disability experienced prior and concomitant to secondary surgical intervention. As expected, both cohorts exhibited similar trends of improving mean scores resulting from discectomy decompression, with no statistical or clinically meaningful difference between the two groups. These low rates of post-operative pain and disability are attributable to the

successful outcomes of discectomy decompression. ODI and VAS scores for subjects with reoperations are censored at subsequent timepoints (i.e., following the secondary surgical intervention) since these outcomes following secondary surgical intervention would confound the Barricaid and Control data.

a. VAS – Ipsilateral Leg Pain

VAS observed in the ipsilateral side was considered the most relevant symptomatic pain measure, as this is generally considered directly attributable to an observed herniation. Both cohorts exhibited similar trends of VAS Ipsilateral Leg success proportions through 36 months. The same trend continued to 60 months. The VAS – Ipsilateral Leg Pain success proportions, defined by a decrease in VAS of at least 20mm in a 100mm scale, for Barricaid and Control treated subjects are presented in Table 10-33.

Table 10-33: Clinical Significance of Primary Clinical Outcomes Relative to Baseline - Barricaid and Control Analysis Set – Ipsi-lateral Leg Pain Scores (≥20mm change on 100mm VAS)

	Barricaid			**Control**			**Significance**			
	N	**n**	**%**	**N**	**n**	**%**	**Dif.***	**95% CI †**	**Chi-sq ‡**	**Exact §**
Week 6	258	242	93.8%	261	232	88.9%	4.9%	(0.1%, 9.7%)	0.047	0.060
Month 3	255	241	94.5%	253	235	92.9%	1.6%	(-2.6%, 5.8%)	0.451	0.471
Month 6	247	236	95.5%	241	229	95.0%	0.5%	(-3.2%, 4.3%)	0.784	0.833
Month 12	240	230	95.8%	230	218	94.8%	1.1%	(-2.8%, 4.9%)	0.590	0.665
Month 24	227	215	94.7%	211	203	96.2%	-1.5%	(-5.4%, 2.4%)	0.454	0.499
Month 36	184	172	93.5%	166	156	94.0%	-0.5%	(-5.6%, 4.6%)	0.848	0.999
Month 48	161	148	91.9%	144	134	93.1%	-1.1%	(-7.0%, 4.8%)	0.709	0.829
Month 60	107	102	95.3%	110	102	92.7%	2.6%	(-3.7%, 8.9%)	0.420	0.570

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
* Difference in proportions (calculated as I minus C).
† 95% CI (asymptotic).
‡ Nominal Chi-square p-value; § Nominal Fisher's exact test p-value.

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

b. Oswestry Disability Index

The ODI success proportions, defined by a decrease in ODI of at least 15 points, for Barricaid and Control treated subjects are presented in Table 10-34. Both cohorts exhibited similar trends of ODI success proportions through 36 months. The same trend continued to 60 months.

Table 10-34: Barricaid and Control Analysis Set – Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in Oswestry Disability Score of at least 15 Points

	Barricaid			Control			Significance			
	N	**n**	**%**	**N**	**n**	**%**	**Dif.***	**95% CI †**	**Chi-sq ‡**	**Exact §**
Week 6	259	221	85.3%	261	223	85.4%	-0.1%	(-6.2%, 6.0%)	0.971	0.999
Month 3	255	230	90.2%	253	228	90.1%	0.1%	(-5.1%, 5.3%)	0.977	0.999
Month 6	248	230	92.7%	241	224	92.9%	-0.2%	(-4.8%, 4.4%)	0.930	0.999
Month 12	240	227	94.6%	230	219	95.2%	-0.6%	(-4.6%, 3.3%)	0.755	0.835
Month 24	228	213	93.4%	211	200	94.8%	-1.4%	(-5.8%, 3.0%)	0.545	0.686
Month 36	185	176	95.1%	166	158	95.2%	0.0%	(-4.5%, 4.5%)	0.984	0.999
Month 48	162	154	95.1%	144	139	96.5%	-1.5%	(-5.9%, 3.0%)	0.526	0.582
Month 60	107	102	95.3%	110	104	94.5%	0.8%	(-5.0%, 6.6%)	0.793	0.999

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
* Difference in proportions (calculated as I minus C).
† 95% CI (asymptotic).
‡ Nominal Chi-square p-value; § Nominal Fisher's exact test p-value.

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

4. Impact of Barricaid

a. All Reherniations

Index level reherniations are shown cumulatively as the proportion of subjects who had a reherniation, symptomatic or asymptomatic, in Table 10-35 using survival analysis. This endpoint was considered to demonstrate the ability for the device to reduce the number of reherniations observed either clinically or only radiographically. Specifically, this potentially includes asymptomatic reherniations that would have otherwise gone unobserved if not for the imaging regimen in this study. While not as clinically relevant, this endpoint observes the ability physically retain nucleus material regardless if the expulsed material results in clinical sequelae.

Table 10-35: Time-course cumulative distribution of proportion of subjects with an index level reherniation

	Barricaid				Control				Significance	
	Failures		95% CI		Failures		95% CI		Failure	Log-rank
Years	n	%	LB	UB	n	%	LB	UB	Delta	Nominal p-value
1	31	12.3%	8.8%	17.0%	81	31.1%	25.8%	37.1%	-18.8%	
2	104	41.9%	36.1%	48.3%	170	65.8%	59.9%	71.5%	-23.8%	
3	130	53.9%	47.7%	60.4%	188	73.5%	67.9%	78.9%	-19.6%	<0.0001
4	141	60.5%	54.0%	67.0%	199	79.5%	74.0%	84.5%	-19.0%	
5	147	66.5%	59.3%	73.5%	203	82.6%	77.0%	87.6%	-16.1%	

The results demonstrate a lower rate of reherniations regardless of symptoms in the Barricaid group by a statistically significant margin through 60 months. At 36 months, the cumulative reherniation rates for Barricaid and Control are 53.9% vs. 73.5% respectively (log-rank nominal p<0.001 over entire 5 year time course), whereby the Barricaid group had a lower rate by a statistically significant margin.

b. Symptomatic Reherniations

While symptomatic reherniations were not initially included in the *a priori* primary endpoint, it is noted that while reduction of all reherniations is important to demonstrate effectiveness of the device, the measure of symptomatic reherniations helps measure the clinical effectiveness of the device. While this was not originally a collected endpoint, criteria were created to categorize reherniations. See Section X.A.3 for the definition of symptomatic reherniation.

Index level symptomatic reherniations are shown cumulatively as the proportion of subjects who had a symptomatic reherniation in Table 10-36 using survival analysis. The results demonstrate a lower rate of symptomatic reherniations in the Barricaid group by a statistically lower margin through 60 months (nominal p=0.0002). At 36 months, the cumulative rates of symptomatic reherniations in Barricaid and Control subjects were 14.2% vs. 29.8%, respectively, whereby the Barricaid group had a lower rate by a statistically significant margin (nominal p<0.0001).

Table 10-36: Time-course cumulative distribution of proportion of subjects with an index level symptomatic reherniation

Years	Barricaid				Control				Significance	
	Failures		95% CI		Failures		95% CI		Failure Delta	Nominal Log-rank p-value
	n	%	LB	UB	n	%	LB	UB		
1	19	7.5%	4.9%	11.5%	46	17.6%	13.5%	22.8%	-10.1%	
2	25	10.0%	6.8%	14.4%	61	23.6%	18.9%	29.3%	-13.7%	
3	34	14.2%	10.4%	19.4%	74	29.8%	24.5%	36.0%	-15.6%	0.0002
4	39	17.2%	12.8%	22.9%	76	31.0%	25.6%	37.4%	-13.9%	
5	43	21.8%	16.1%	29.1%	78	32.8%	27.0%	39.5%	-11.0%	

A statistically superior and clinically meaningful treatment differential with respect to symptomatic reherniation rates between Barricaid and Control groups was demonstrated at 12 months and was maintained through 5 years, demonstrating long-term efficacy of the Barricaid device (nominal p=0.0002). These data provide the most important contribution to the benefit/risk profile, since symptomatic reherniations result in increased pain, functional loss, and increased hospital visits or additional surgeries.

5. Post-Hoc Exploratory Analysis: Alternate Composite Endpoint

The Sponsor developed (post hoc) a composite endpoint to try to capture symptomatic composite elements and be more similar and consistent with past spinal PMAs. This post-hoc alternate endpoint is referred to as the Alternate Composite Endpoint, and was designed with the following individual components for which each patient much achieve success in order to be considered a success overall:

1. No Symptomatic Reherniation (see Section 10.1.3 for definition)
2. 15- point improvement in Oswestry Disability Index (ODI) compared to baseline
3. Maintenance or improvement of neurological status at the index level
4. No secondary surgical interventions at the index level
5. No implant- (i.e., device migrations, or device condition issue) or procedure-related serious adverse events

Most notably, "all reherniations" was replaced by only "symptomatic reherniations" in an effort to be more clinically relevant. Specifically, the removed components disc height, spontaneous fusion and asymptomatic reherniation are radiographic observations not necessarily tied to a clinical outcome independently. Conversely, if a reherniation or loss in disc height is clinically relevant, the alternate endpoint is thought to be sensitive enough to detect the negative clinical outcome through a lower ODI score and/or neurological deterioration. While VAS-leg may be more appropriate in determining herniation-free symptoms, this study showed similar results between ODI and VAS-leg, so there is likely little impact using ODI instead of VAS-leg. The device integrity element was also removed as the sponsor felt that all relevant device failures would be captured as a device or procedure related AE. This specifically eliminates instances when the polymer component migrates or rotates outside of the disc space or detaches but is not associated with a specific AE.

The Barricaid group is superior when compared to the non-implanted Control population on the composite endpoint, as described above. The patient focused endpoint results are presented in Table 10-37.

Table 10-37: Alternate Composite Endpoint: Composite Clinical Success (CCS) –Modified Clinical Protocol Definition (mCPD) at 24 months – mITT Analysis Set

Barricaid			Control			Nominal Chi-squared p-value
N	n	%	N	n	%	
253	192	75.9	255	163	63.9	0.003

By focusing on symptomatic reherniations and including device- and procedure-related SAEs, the CCS-mCPD calculation provides a different insight into Barricaid clinical performance. While exploratory in nature and designed to be an adjunct to the *a priori* co-primary endpoints, the Alternate Composite Endpoint demonstrate higher (i.e., better) clinical performance compared to Control discectomy by a statistically significant margin (75.9% vs. 63.0%, nominal p=0.003).

6. Secondary Effectiveness Analysis

Additional clinical outcome measurements were utilized to determine the effect of the Barricaid compared to Control. Scores from the Visual Analog Scale (VAS) Back Pain, VAS Contralateral Leg Pain, and the SF-36 were analyzed. Success proportions were defined as ≥ 20mm VAS improvement and maintenance or improvement in SF-36.

a. VAS – Back Pain

Table 10-38: Clinical Significance of Primary Clinical Outcomes Relative to Baseline - Barricaid and Control Analysis Set – Back Pain Scores (≥20mm change on 100mm VAS)

	Barricaid			Control			Significance			
	N	n	%	N	n	%	Dif.*	95% CI †	Chi-sq ‡	Exact §
Week 6	258	166	64.3%	261	171	65.5%	-1.2%	(-9.4%, 7.0%)	0.779	0.783
Month 3	255	168	65.9%	253	167	66.0%	-0.1%	(-8.4%, 8.1%)	0.976	0.999
Month 6	248	166	66.9%	241	151	62.7%	4.3%	(-4.2%, 12.7%)	0.322	0.344
Month 12	240	164	68.3%	230	150	65.2%	3.1%	(-5.4%, 11.6%)	0.473	0.494
Month 24	228	154	67.5%	211	137	64.9%	2.6%	(-6.2%, 11.5%)	0.563	0.614
Month 36	184	125	67.9%	166	109	65.7%	2.3%	(-7.6%, 12.2%)	0.652	0.733
Month 48	162	107	66.0%	144	91	63.2%	2.9%	(-7.9%, 13.6%)	0.602	0.633
Month 60	107	69	64.5%	110	73	66.4%	-1.9%	(-14.5%, 10.8%)	0.771	0.777

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
* Difference in proportions (calculated as I minus C).
† 95% CI (asymptotic).
‡ Nominal Chi-square p-value; § Nominal Fisher's exact test p-value.

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

The VAS – Back Pain success proportions, based on 20mm improvement from baseline, for Barricaid and Control treated subjects are presented in Table 10-38 for subjects that had a baseline score of at least 40mm. Both cohorts exhibited similar trends of VAS – Back Pain success through 24 months. The same trend continued to 60 months.

b. VAS – Contralateral Leg Pain

Table 10-39: Clinical Significance of Primary Clinical Outcomes Relative to Baseline - Barricaid and Control Analysis Set – Contralateral Leg Pain Scores (≥20mm change on 100mm VAS)

	Barricaid			Control			Significance			
	N	n	%	N	n	%	Dif.*	95% CI †	Chi-sq ‡	Exact §
Week 6	244	229	93.9%	247	220	89.1%	4.8%	(-0.1%, 9.7%)	0.058	0.075
Month 3	241	230	95.4%	239	223	93.3%	2.1%	(-2.0%, 6.3%)	0.311	0.329
Month 6	234	227	97.0%	227	215	94.7%	2.3%	(-1.3%, 5.9%)	0.215	0.247
Month 12	229	223	97.4%	216	205	94.9%	2.5%	(-1.1%, 6.1%)	0.174	0.218
Month 24	217	205	94.5%	199	191	96.0%	-1.5%	(-5.6%, 2.6%)	0.472	0.501
Month 36	175	165	94.3%	156	146	93.6%	0.7%	(-4.5%, 5.9%)	0.791	0.821
Month 48	155	142	91.6%	138	128	92.8%	-1.1%	(-7.3%, 5.0%)	0.717	0.829
Month 60	103	98	95.1%	107	99	92.5%	2.6%	(-3.9%, 9.1%)	0.431	0.570

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
* Difference in proportions (calculated as I minus C).
† 95% CI (asymptotic).
‡ Nominal Chi-square p-value; § Nominal Fisher's exact test p-value.

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

The VAS – Contralateral Leg Pain scores (value) demonstrate that, with respect to VAS – Contralateral Leg Pain outcomes, both cohorts exhibited similar trends of pain scores reflecting minimal pain through 24 months. The same trend continued to 60 months. These trends are expected since this measurement is specific to the leg without pain.

c. SF-36v2™ Health Survey

The SF-36v2® Health Survey asks 36 questions to measure functional health and well-being from the subject's point of view. The survey is meaningful to subjects, clinicians, researchers and administrators across the health care spectrum and has various applications. These include:

- Measuring health improvement or decline
- Predicting medical expenses
- Assessing treatment effectiveness
- Comparing disease burden across populations

The SF-36v2® Health Survey results demonstrate that with respect to the change in SF-36 physical component score (PCS) outcomes relative to baseline, both cohorts exhibited similar trends of improving scores. With regard to the mental component

score (MCS), Barricaid subjects exhibited a greater improvement at 36 months that was statistically different (+13.5 vs. +10.2, nominal p=0.015). Significant differences in favor of greater MCS improvement in Barricaid were also observed at 3 and 6 Months with trends towards statistical significance observed at 6 weeks, 12 months, and 48 months.

Table 10-40: SF-36 PCS Change Over Time

	Barricaid						Control						Significance		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p †	p_{NP}‡	ES §
Week 6	259	11.0	9.2	10.5	-20.4	33.2	259	10.8	8.4	9.6	-12.4	39.1	0.771	0.789	0.03
Month 3	254	16.5	10.1	16.7	-15.0	38.1	252	16.2	9.6	15.6	-13.4	36.3	0.764	0.530	0.03
Month 6	247	18.0	10.1	19.0	-15.1	40.3	241	18.4	10.0	19.5	-6.6	39.3	0.699	0.871	-0.04
Month 12	240	20.1	10.1	20.9	-17.2	39.9	230	19.8	9.8	20.2	-8.9	42.9	0.684	0.457	0.04
Month 24	228	20.6	10.5	21.8	-9.9	39.2	211	19.9	9.6	20.5	-4.1	41.4	0.455	0.203	0.07
Month 36	185	21.2	9.9	22.5	-8.2	40.6	166	20.1	10.5	20.8	-6.9	43.0	0.338	0.265	0.10
Month 48	162	20.4	11.0	21.1	-10.6	45.1	144	20.0	10.9	20.8	-6.1	42.4	0.754	0.727	0.04
Month 60	107	20.5	11.4	22.7	-13.8	40.1	110	20.1	11.2	21.7	-9.0	40.7	0.796	0.618	0.04

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
† Two-sample pooled t-test nominal p-value (parametric).
‡ Two-sample Wilcoxon rank sum nominal p-value (non-parametric).
§ Standardized effect size (calculated as group difference in means divided by pooled within group SD).

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

Table 10-41: SF-36 MCS Change Over Time

	Barricaid						Control						Significance		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p †	p_{NP}‡	ES §
Week 6	259	7.8	13.6	7.1	-37.7	40.1	259	5.6	11.9	4.9	-22.0	39.3	0.053	0.029	0.17
Month 3	254	11.1	13.5	10.3	-33.7	41.8	252	8.5	12.6	7.9	-29.3	41.4	0.026	0.015	0.20
Month 6	247	12.0	13.3	11.8	-27.9	40.3	241	8.9	13.1	7.8	-28.5	43.8	0.012	0.009	0.23
Month 12	240	12.0	13.8	11.3	-26.5	43.0	230	9.7	13.1	7.9	-20.8	43.0	0.056	0.045	0.18
Month 24	228	11.8	13.9	11.6	-26.4	43.5	211	9.9	13.2	8.7	-23.8	44.7	0.154	0.154	0.14
Month 36	185	13.5	12.7	12.5	-15.0	42.0	166	10.2	13.1	9.0	-24.9	40.9	0.015	0.025	0.26
Month 48	162	11.9	14.3	11.8	-21.7	46.7	144	8.8	14.0	9.0	-35.1	35.9	0.060	0.103	0.22
Month 60	107	11.3	14.0	10.5	-24.0	37.4	110	9.8	13.5	8.3	-28.2	35.2	0.417	0.418	0.11

Notes:
Subjects censored at Index level secondary surgical interventions
(Reoperations, Revisions, Removals, and Supplemental Fixations).
† Two-sample pooled t-test nominal p-value (parametric).
‡ Two-sample Wilcoxon rank sum nominal p-value (non-parametric).
§ Standardized effect size (calculated as group difference in means divided by pooled within group SD).

Source: Tables Clinical Follow-up.sas
Analyzed: 17JUL2018

7. Disc Height Maintenance and Spontaneous Fusion

No statistically significant differences in disc height maintenance, defined as maintaining at least 75% of the pre-operative disc height, or spontaneous fusion were observed between the Barricaid and Control subjects. Disc height loss post-discectomy is consistent with reports in the literature and considered to be attributable to the natural history of the degenerative process and limited discectomy; however, it was important to note that the Barricaid device did not appear to contribute to an increased rate of disc height loss. Spontaneous fusions were evaluated by the radiographic core lab and were rarely observed. At 36 months, a total of three subjects were observed with a spontaneous fusion.

8. Radiographic Assessments

Radiographic measurements were performed in both groups to determine quantitative and qualitative measurements using X-rays (flexion/extension, neutral lateral) at the regular timepoints along with annual CT scans and MRIs. This radiographic protocol required all data to be read by an independent core radiographic laboratory. The radiographic protocol allowed analysis of reherniations as well as a detailed characterization of device integrity and disc morphology to better understand device performance over time. The assessments also included assessment of heterotopic ossification (HO) and osteophyte formation, among other imaging analyses. Most importantly the radiographic protocol allowed for the monitoring of the EPLs discussed in Section 10.5.2 above.

Table 10-42: Qualitative Assessment of Posterior Ossification - Barricaid and Control mITT Analysis Sets - First 12 Months

	Preoperative				Week 6				Month 3				Month 6				Month 12			
	Barricaid		Control		Barricaid		Control		Barricaid		Control		Barricaid		Control		Barricaid		Control	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Absent	208	78	210	76	236	90	224	85	231	88	222	85	221	86	216	84	181	70	166	65
Present	51	19	61	22	23	9	37	14	26	10	34	13	30	12	37	14	63	25	83	32
Marked	5	2	5	2	3	1	4	2	4	2	4	2	4	2	4	2	12	5	6	2
Bridging	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	1	0
Indeterminate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
NA	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	3	0

Table 10-43: Qualitative Assessment of Posterior Ossificaiton - Barricaid and Control mITT Analysis Sets – 24 to 60 Months

	Month 24				Month 36				Month 48				Month 60			
	Barricaid		Control		Barricaid		Control		Barricaid		Control		Barricaid		Control	
	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%
Absent	155	63	146	59	100	54	100	53	62	39	85	59	40	42	50	52
Present	73	30	88	35	63	34	74	39	75	47	48	33	42	44	43	44
Marked	12	5	13	5	21	11	10	5	16	10	8	6	6	6	3	3
Bridging	6	2	1	0	2	1	4	2	6	4	4	3	7	7	1	1
Indeterminate	1	0	2	0	1	0	2	0	2	0	1	0	2	0	0	0
NA	2	0	1	0	1	0	2	0	2	0	3	0	3	0	1	0

At 24 months, posterior ossification is observed in a numerically larger portion of the Control group (29.7% vs. 35.5%, nominal p=0.18). For the Barricaid treatment group, most of the changes occur in the 6 months to 12 months window. In the Control treatment group, the same changes occur in the 6 months to 12 months window; however, there is a continued trend in both groups towards the presence of posterior ossification in the 12 months to 24 months window as well.

G. Subgroup Analyses

A number of subgroup analyses on outcomes including the following groups: endplate lesions, reherniation, Barricaid anchor and/or polymer component subsidence, polymer component detachment, gender, hospital stay, comorbidities, blinding, learning curve, device generation, device size, subjects with radiculopathy only vs. radiculopathy and back pain, spondylolisthesis, demographics (gender, BMI, age, race), conservative care, intraoperative variables (spinal level, device orientation, amount of nucleus material removed, defect size, pre-existing or iatrogenic defect, Carragee herniation type), baseline outcomes (ODI, VAS,

disc height), completer vs. non-completer, previous lumbar spine surgery, and medication usage. Many of these groups have low numbers in the subanalysis group or are otherwise not notable. As noted in Section X.E.9 above, focus was placed on the analysis of effects of endplate lesions and the polymer component subsided subjects. These analyses demonstrated no evidence of correlations between these factors and clinical outcomes.

H. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

I. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit marketing applications to include certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study of the Barricaid included 21 principal investigators (68 total investigators), of which none were full-time or part-time employees of the applicant and all disclosed financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) as described below:

- Financial arrangement between the applicant and the investigator, whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study: 0 investigators;
- Any significant payment of other sorts from the applicant, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria: 8 investigators (at 6 sites);
- Any proprietary interest in the Barricaid held by the investigator: 0 investigators;
- Any significant equity interest in the applicant held by the investigator: 0 investigators.

The applicant has adequately disclosed the financial interest/arrangements they have with the investigators who participated in the Barricaid trial. Eight investigators (from six sites) disclosed financial relationships with the applicant. Statistical analyses were requested by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. FDA determined the information provided did not raise questions about the reliability of the data due to any association between financial interest and the treatment effect in favor of Barricaid in the co-primary endpoints. No additional actions were taken or deemed necessary to ensure the reliability of the data (21 CFR 54.5(c)).

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on December 12, 2017, the Orthopaedic and Rehabilitation Devices Panel voted 5-9 that there is reasonable assurance the device is safe, 12-1 (1 abstention) that there is reasonable assurance that the device is effective, and 5-8 (1 abstention) that the benefits of the device do outweigh the risks in subjects who meet the criteria specified in the proposed indication. Although the protocol called for endpoint analysis at 24 months, FDA therefore requested submission of longer term data, primarily due to safety concerns related to EPL stability and device integrity observations. The 24-hour Panel Summary is located at the following link: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM589226.pdf

B. FDA's Post Panel Meeting Action

Following the Panel meeting, the applicant provided an updated clinical evaluation report to FDA that included complete follow-up through 3 years (compared to the 2-year data reviewed at panel) as well as substantial follow-up data at 4 and 5 years. The applicant worked with FDA to develop a post-approval study to address the outstanding issues highlighted by the Panel, namely, the need for longer term follow-up. The applicant has adequately addressed the outstanding issues raised by the Panel relating to continued follow-up. FDA agrees with the applicant's response and has determined that the information the applicant has submitted to address the Panel's concerns is acceptable.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The clinical study compared treatment with the Barricaid following limited discectomy to the control treatment, limited discectomy alone, in subjects with radiculopathy (with or without back pain), a posterior or posterolateral herniation, at one level between L4 and S1 as outlined above in the Indications for Use. Results of this study demonstrate that the probable benefits of the Barricaid outweigh the probable risks through 60-months follow-up.

A. Effectiveness Conclusions

Literature shows that discectomy patients with large anular defects have a significantly elevated risk of reherniation and reoperation.[5] This study confirmed that this higher risk population resulted in higher rates of symptomatic reherniation (25.4%) and reoperation (16.2%) at 2 years as compared to literature. The clinical data from this prospective, randomized, controlled superiority study demonstrate that the Barricaid device is statistically superior in *the a priori* co-primary endpoints at the prospectively identified 24-month endpoint with strong posterior probabilities of >0.999 for reherniation and 0.998 for the composite endpoint. More importantly, survival estimates show that the Barricaid group had statistically fewer reherniations (nominal $p<0.0001$, log-rank test), symptomatic reherniations (nominal $p=0.0002$, log-rank test), and secondary surgical interventions (nominal $p=0.03$, log-rank test) out to 60 months when compared to Control.

The alternate composite endpoint resulted in a success rate of 75.9% compared to 63.9% for the Control (nominal p=0.003) at two years. At three years, the treatment differential was still statistically significant with a success rate of 68.2% for Barricaid compared to 55.7% for the Control (nominal p=0.007). This study outcome demonstrates that there was a clinical or symptom-oriented impact and safety and effectiveness of the Barricaid when it is used in this high- risk patient population.

The clinically relevant, or patient-focused, composite endpoint resulted in a success rate of 75.9% compared to 63.9% for the Control (nominal p=0.003) at two years. At three years, the treatment differential was still statistically significant with a success rate of 68.2% for Barricaid compared to 55.7% for the Control (nominal p=0.007). This study outcome demonstrates the true clinical impact and safety and effectiveness of the Barricaid when it is used in this high- risk patient population.

Barricaid and Control had nearly identical ODI and VAS Ipsilateral success rates out to 60 months. This can be attributed to the surgical treatment, discectomy, which is identical between the two groups. The discectomy procedure is responsible for removing the pain generator (i.e., herniated nucleus material impinging on a nerve root). Therefore, a noticeable difference in these clinical outcomes was not expected. However, the results confirm the discectomy procedure is identical in both arms and the presence of the Barricaid does not alter the impact of the discectomy.

The data from this study demonstrate that implantation of the Barricaid after a discectomy procedure in a higher-risk patient population with a large anular defect results in long-term preservation of pain relief and functional improvement, with significantly reduced risk of device-/procedure-related SAEs, symptomatic reherniations and secondary surgical interventions within the first year, which is maintained relative to Control in subsequent years.

B. Safety Conclusions

The risks of Barricaid device are based on animal and device retrieval studies as well as data collected in the clinical trial conducted to support PMA approval as described above. The clinical data from the AT population were used in the safety analysis. Data considered were adverse events, secondary surgical interventions, imaging data, and neurologic status out to 60 months.

The main safety endpoint of the Barricaid study was no Secondary Surgical Intervention (e.g., reoperations, revisions, removals or supplemental fixations). By Month 36 there were 38 total secondary surgical interventions in the Barricaid group and 57 in the control group. Thirty-nine Barricaid subjects underwent 51 secondary surgical interventions through 60 months; 57 Control subjects underwent 81 secondary surgical interventions through 60 months; the overall secondary surgical intervention rates were 10.1% and 18.3% for the Barricaid and control groups respectively. The difference in secondary surgical interventions between Barricaid and Control persisted through 60 months. The predominant factor for this

difference in secondary surgical interventions is the greater number of reherniations in the Control group compared to the Barricaid group.

Barricaid demonstrated a similar AE profile when compared to Control. Barricaid subjects had more "Device Deficiency" adverse events as was expected since the Control group did not have a device. Most importantly, the disc reherniation counts were significantly higher in the Control group, which subsequently led to significantly more SAEs and secondary surgical interventions. When considering the most relevant AEs, there is a similar number of "Disc Herniation" AEs in the Control group as "Device Deficiency" and "Disc Herniation" AEs in the Barricaid group. Barricaid group has less when only considering "Device Deficiency" and "Disc Herniation" SAEs. Other pain and neurologic AEs and SAEs were also similar between groups. Review of device failures in the imaging were corroborated with AE data, which again was balanced by the presence of more reherniations in the Control group.

Additional review of the imaging regarding the impact and development of EPLs was followed until the growth had reached an approximate maximum; however, no negative clinical sequelae were found to be associated with the presence of the EPLs. Despite the animal data and the biologic response seen in the peri-prosthetic tissue from the retrievals, no AEs and there were no changes in efficacy results due to the presence of lesions.

Barricaid demonstrated a positive safety profile as compared to the Control when used to treat the indicated subjects, due primarily to the lower number of secondary surgical interventions from fewer symptomatic reherniations.

C. Benefit-Risk Determination

Intrinsic Therapeutics conducted a comprehensive study of lumbar discectomy, allowing for rigorous analysis of the risks and benefits of this device compared to the standard of care, discectomy alone. Overall, the risk profile is similar intra- and peri-operatively, with several key benefits favoring use of the Barricaid. The probable benefits of the Barricaid are based on data collected in the clinical trial conducted to support PMA approval as described above.

The clinical trial demonstrated several benefits of the Barricaid device used at a single lumbar level (L4-S1) over the 60-month time period studied.

- **Significantly Fewer Symptomatic Reherniations**: 20 subjects (8.1%) in the Barricaid group had a symptomatic reherniation at any time through month 12, compared to 55 subjects (21.7%) in the Control group (nominal $p<0.001$). 27 subjects (11.6%) in the Barricaid group had a symptomatic reherniation at any time through month 24, compared to 61 subjects (24.8%) in the Control group (nominal $p<0.001$). 36 subjects (16.8%) in the Barricaid group had a symptomatic reherniation at any time through month 36, compared to 74 subjects (30.7%) in the Control group, (nominal $p<0.001$). Survival estimates confirm that this benefit is sustained through five years (Log-rank nominal p-value = 0.0002). The difference between Barricaid

and Control is observed initially within the 12 month timepoint, with the difference sustained, not widened or diminished over time.

- **Significantly Fewer Secondary Surgical Interventions**: 17 subjects (6.4%) in the Barricaid group had a secondary surgical intervention through month 12, compared to 35 subjects (12.6%) in the Control group, a 51.4% reduction (nominal p=0.013). Through Month 24, 23 subjects (8.6%) in the Barricaid group received an index-level secondary surgical intervention, compared to 45 subjects (16.2%) in the Control group, a 48.9% reduction (p=0 nominal.007). Through Month 36, 27 subjects (10.1%) in the Barricaid group received an index-level secondary surgical intervention, compared to 51 subjects (18.3%) in the Control group, a 47.1% reduction (p=0 nominal.006). Survival estimates confirm that this benefit is sustained through five years (Log-rank nominal p-value = 0.03). The subsequent rate of SSIs remained similar between groups after the initial difference in rates. This mirrors the experience with symptomatic reherniations, likely due to the SSIs resulting from those reherniations.

- **Non-Interference of Effects of Discectomy:** The discectomy decompression procedure provides the primary benefit of pain relief, function improvement and neurologic improvement. Maintenance of these improvements in the Barricaid group were observed at a comparable rate to the Control group of discectomy alone, and maintained out to 60 months. The data demonstrates that the use of Barricaid does not interfere with the effects of receiving a limited discectomy.

Additional factors that were considered in determining probable risks and benefits for the Barricaid included:

- **Comparable Rate of Total AEs and SAEs:** Using all events captured in the study over all study time points, the overall rate of adverse events in subjects treated with the Barricaid (85.0%) was comparable to the control group (81.6%) (nominal p=0.305). The overall rate of SAEs in subjects treated with Barricaid (42.3%) was comparable to the Control group (44.5%) (nominal p=0.607).

- **Fewer Device- or Procedure- Related SAEs**: The Barricaid AT group had fewer device- or procedure-related SAEs through Month 36; 44 subjects (16.5%) had 68 related SAEs in the Barricaid AT group at any time through Month 36 compared to 66 subjects (23.3%) with 98 related SAEs in the Control AT group (nominal p=0.055). Survival estimates demonstrate a benefit through five years (Log-rank nominal p-value = 0.0367).

- **Device Integrity Failures:** The observed radiographic device integrity failures seen in the Barricaid group resulted in “Device Deficiency” AEs; however, the rate of AEs and SAEs related to device integrity failures did not overcome the greater rate of reherniations in the Control group. In the Barricaid group, there were 12 subjects (4.5%) who had Device Deficiency SAEs and 32 subjects (12.0%) who had Disc Herniation SAEs compared to 58 subjects (20.5%) with Disc Herniation SAEs in the

Control group. While the migration or dissociation of the device is concerning, the overall rate is balanced against the reduced number of symptomatic herniations by the Barricaid device.

- **No Difference in Secondary Surgical Intervention Difficulty and Outcomes:** Secondary surgical interventions in Barricaid subjects were associated with no more complications than those in Control subjects. No statistical difference in operative time was observed between Barricaid and Control for secondary surgical interventions with fusion/pedicle fixation or secondary surgical interventions without fusion/pedicle fixation. Pain and function outcomes for Barricaid subjects reoperated after a device integrity observation were similar to those for reoperated Control subjects, and none of these subjects experienced any permanent neurological injury. While there was an observed greater likelihood of receiving a discectomy alone as a secondary surgical intervention rather than supplemental fixation/fusion in the Control group compared to Barricaid group, both options were conducted in both groups.

- **EPL Analyses Demonstrate Stability:** EPL analyses demonstrate >90% stability in observed EPLs, based on the 3-5 year data. While the per subject analysis fell short of 90%, subsequent missing data calculations demonstrated adequate rates of stability. Stability has been demonstrated in all EPL sub-populations, including the EPLs that were proximate to the flexible polymer component.

- **EPL Presence Does Not Impact Device Function or Clinical Outcomes:** Three year results, along with partial four and five year data demonstrate successful clinical outcomes at the time of EPL stability. Barricaid effectively reduces the incidence of reherniations in all EPL populations, including those with EPLs that were proximate to the flexible polymer component with subsidence. Data demonstrate no negative clinical effect of EPLs in each Barricaid sub-population. Subjects with the largest EPLs in both Barricaid and Control groups exhibit secondary surgical interventions, experience device- and/or procedure-related SAEs, and report pain and function scores at rates similar to and consistent with their respective overall treatment arm populations. Despite the inflammatory response seen in the retrieved peri-prosthetic tissue and suggested biologic response seen in the baboon model, no correlative negative clinical sequelae were able to be linked to the development and sustained presence of the lesions.

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for implantation following limited discectomy in subjects with radiculopathy (with or without back pain), a posterior or posterolateral herniation, at one level between L4 and S1 and a large anular defect as outlined above in the Indications for Use, the probable benefits of the Barricaid outweigh the probable risks through 60-months follow-up.

D. Overall Conclusions

The nonclinical and clinical data presented in this application support the reasonable assurance of safety and effectiveness of the Barricaid when used in accordance with the indications for use. Based on the clinical trial results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results and that the clinical benefits of the use of the Barricaid in terms of reducing the incidence of reherniation and reoperation following primary limited lumbar discectomy procedures outweigh the risks associated with the device and surgical procedure through 60-months follow-up when used in the indicated population in accordance with the directions for use.

XIII. CDRH DECISION

CDRH issued an approval order on February 8, 2019. The final conditions of approval cited in the approval order are described below.

1.) Extended Follow-Up of the Barricaid® ACD Premarket Cohort for Lumbar Disc Herniation and Interaction with Other Risk Factors –

Based on the protocol summary agreed upon on February 8, 2019, the applicant will conduct an extended follow-up PAS, following the subjects from the pre-market study out to 10 years, to assess long term safety and effectiveness of the Barricaid® ACD, with a longer follow-up for a subset of subjects given certain additional risk factors. The PAS protocol is designed to examine the long-term survivorship of the Barricaid® ACD device when used in conjunction with limited discectomy. This study is also intended to monitor the natural history of endplate lesions due to interactions with the device, potential interactions with the development of osteoporosis, lesion growth and lesion stability. The study is also intended to investigate potential underlying mechanisms that may contribute to any additional growth through retrieval analysis and histological analysis of peri-prosthetic tissue. The prospective randomized multi-center OUS cohort used for the premarket application will follow all subjects annually out to 5 years with the existing clinical protocol.

All subjects will be followed at 7 and 10 years collecting the following information: patient questionnaires (VAS, ODI, SCORE), adverse event evaluation, symptomatic reherniation, femoral neck DEXA scan if required per SCORE osteoporosis screening questionnaire (subjects with SCORE of ≥ 6) and AP/lateral radiographs, lumbar MRI, low dose CT at index level to evaluate device subsidence, endplate lesions (size and growth measurements), device condition/migration, and reherniation at index level. The potential to require further extended follow-up will be determined at the 10-year follow-up based on DEXA T Scores (femoral neck) and endplate lesion size as outlined in a Post-Approval Study Protocol.

The sponsor will analyze all Barricaid® ACD devices that are explanted as per the agreed upon retrieval analysis. Histopathologic analyses will be conducted on explanted tissue

retrieved from secondary surgery at the index level as well as explanted Barricaid® ACD devices as a routine part of secondary surgery.

The hypotheses of this extended follow-up post approval study are that the Barricaid® ACD device remains safe and effective at 10 years, the Barricaid® ACD subjects do not have late or continued slow growth of lesions that lead to new or unexpected AEs or adverse clinical outcomes, and development of osteoporosis does not negatively impact the progression of lesions observed and does not lead to new or unexpected AEs or adverse clinical outcomes.

The FDA expects at least 85% follow-up at the 10-year timepoint to provide sufficient data to assess the long-term safety and effectiveness. A final report will be submitted within 6-months of the last subject visit.

2.) Histological and Retrieval Analysis of Material and Tissue From Retrieved (Explanted) Barricaid® ACD Devices in the Real World –

Based on the protocol summary agreed upon on February 8, 2019, the applicant will conduct a 5-year PAS on any explanted tissue or devices from real-world patients in the US, to investigate potential underlying mechanisms that may contribute to endplate lesion initiation and/or growth through retrieval analysis and histological analysis of retrieved implants and/or peri-prosthetic tissue. This study is also intended to evaluate causes of device failure (fracture, migration, dissociation and wear particulate).

All surgeons who are trained to use the Barricaid® ACD device will be instructed as part of their training to return partially or totally explanted devices (along with any surrounding tissue that is removed) to the sponsor for analysis. Retrieved devices and tissue samples will be collected from real world commercial use.

Clinical sites will be instructed to: collect tissue only if patient safety is not adversely affected; take physician narrative/ surgical notes regarding the condition of implant, relative location of tissue collected, etc.; take photographs of the device and any associated tissue; and immediately store device and tissue in formalin. All retrieved material and tissue will be visually inspected and photo documented. Device retrieval analysis will be conducted by an agreed upon protocol, while all tissue will be subject to histopathological examination by a qualified pathologist by an agreed upon protocol.

This evaluation is intended to generate data to further assess endplate lesion growth and/or other biological, radiographic or clinical observations. This will also evaluate device failure as it pertains to secondary surgical interventions and potential long-term survival.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

[1] E.g., Solinas Medical SMI Cardiovascular Patch (K112683); Teleflex Cottony Silky II PET suture (K021019); Spineology Rampart D Lumbar Interbody Fusion Device (K160074)

[2] Wang et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. J Neurosurg Spine. 2014 Jul;21(1):48-53. doi: 10.3171/2014.4.SPINE14271.

[3] Zigler et al. Results of the prospective, randomized, multicenter food and drug administration investigational device exemption study of the prodisc-l total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine 32(11): 1155–1162. 2007.

[4] McGirt MJ, Ambrossi GL, Datoo G, et al. Recurrent disc herniation and long-term back pain after primary lumbar discectomy: review of outcomes reported for limited versus aggressive disc removal. Neurosurgery. 2009;64(2):338-344; discussion 344-335.

[5] Miller et al. Association of annular defect width after lumbar discectomy with risk of symptom recurrence and reoperation: Systematic review and meta-analysis of comparative studies. Spine 43(5):E308-15. 2018.

[6] 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.

[7] Zehra et al. Structural vertebral endplate nomenclature and etiology: a study by the ISSLS Spinal Phenotype Focus Group. Eur Spine J 27:2–12. 2018.