ACTUAL CONDITIONS OF USE STUDY SYNOPSIS

SPONSOR	Intrinsic Therapeutics, Inc.
NAME OF PRODUCT	Barricaid® Anular Closure Device
CLASS OF MEDICAL DEVICE	Class III
STUDY TITLE	A 2 year Evaluation of Clinical Outcomes in the Treatment of Lumbar Disc Herniation with the Barricaid® Anular Closure Device for FDA Actual Conditions of Use Study
BACKGROUND	Published literature indicates that the optimal patient population for a study of a device to aid in preventing reherniation and the recurrence of pain or dysfunction following primary lumbar discectomy would include patients with radiographic confirmation of a herniation at the affected level and with a post-discectomy anular defect 6mm or wider. The Barricaid anular closure device underwent extensive testing and was proven superior to discectomy alone in a level 1 RCT. The Barricaid is an FDA approved medical device (P160050) already being marketed in the USA and obtained marketing approval in the US on XX/XX/XXXX. The device will be implanted as described in the product brochure in patients with lumbar disc herniation.
PROTOCOL #	(b)(4) [redacted]
STUDY TREATMENT	Lumbar discectomy with surgical implantation of the Barricaid anular closure device
OBJECTIVES WITH STUDY HYPOTHESES	• The primary objective of this study is to confirm that Barricaid performance is not clinically inferior in the PAS population compared to the pivotal Barricaid oUS trial population in respect to 15 point (out of 100 points) improvement in Oswestry compared to pre-op, secondary surgical interventions at the index level, symptomatic reherniations at the index level (either side), deterioration of neurological status at the index level, and implant- or procedure-related serious adverse events.
STUDY DESIGN	Prospective, multi-center, non-randomized
STUDY GROUP(S)	Single-arm, discectomy with Barricaid
PATIENT INCLUSION/EXCLUSION CRITERIA	Subjects who meet the following criteria are eligible for study participation (are indicated per the approved instructions for use): **Inclusion:** • Skeletally mature.

	• Patients with 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 (e.g., between 4-6 mm tall and between 6-12 mm wide) post discectomy, at one level between L4 and S1. • Oswestry Questionnaire score of at least 40/100 at baseline. **Exclusion:** • Structural integrity of the vertebral body appears damaged, weakened, or compromised in the region targeted for implantation. • Prohibitive anatomic anomalies or anular defect locations • Osteoporosis. • Anular defect taller than 6mm. • Posterior disc height of less than 5mm at the target level • Active systemic infection or infection at the site of implantation. • Spondylolisthesis Grade II or higher (>25%)
SAMPLE SIZE	A total of 290 patients will be enrolled from approximately 15-20 study sites.
RECRUITMENT STRATEGY	Patients presenting with primary lumbar disc herniations, scheduled for discectomy surgery, and meet all inclusion/exclusion criteria will be recruited at 15-20 study sites.
DATA COLLECTION: STUDY ENDPOINTS	A composite clinical success (CCS) endpoint designed to be appropriate for follow-up through 24 months will be used to compare clinical status of PAS 2 patients implanted with the Barricaid anular closure device relative to Barricaid patients in the oUS Study. Primary Endpoint –non-inferiority analysis comparing PAS2 to oUS Barricaid Study subjects using a composite of (i.e., subject will have to be a success on each, in order to be considered a success for the composite primary endpoint): • 15 point (out of 100 points) improvement in Oswestry compared to pre-op • No secondary surgical interventions at the index level • No symptomatic reherniations at the index level (either side) • No deterioration of neurological status at the index level

	• No implant- or procedure-related serious adverse events. Secondary Endpoint—superiority analysis comparing PAS2 to oUS Control Study subjects using a composite of (i.e., subject will have to be a success on each, in order to be considered a success for the composite secondary endpoint): (individually): • 15 point (out of 100 points) improvement in Oswestry compared to pre-op • No secondary surgical interventions at the index level • No symptomatic reherniations at the index level (either side) • No deterioration of neurological status at the index level • No implant- or procedure-related serious adverse events. Additional Endpoints to be analyzed • Estimated blood loss • Work status and time to return to work or normal (pre-operative) activities of daily living (ADL) • Type of anesthesia • Patient Satisfaction • Rehabilitation utilization (concomitant treatments) • Post-op medications / dosage • Insurance status (Workers' Comp, Commercial, Medicare, Medicaid) • Length of hospital stay • Operative time
FOLLOW-UP SCHEDULE AND PLANS TO MINIMIZE LOSS TO FOLLOW-UP	• Visit 1: Screening (≤ 30 days before surgery) • Visit 2: Surgery • Visit 3: 6 Weeks Follow Up (±2 weeks) • Visit 4: 6 Month Follow-Up (±1 month) • Visit 5: 12 Months Follow Up (±2 months) • Visit 6: 24 Months Follow Up (±2 months)
IMAGING SCHEDULE	•Visit 1: Screening • MRI • AP/Lat, Flex/Ext radiographs •Visit 3: 6 Weeks Follow Up (±2 weeks) • AP/Lat radiographs •Visit 4: 12 Months Follow Up (±2 months) • AP/Lat, Flex/Ext radiographs •Visit 5: 12 Months Follow Up (±2 months) • AP/Lat, Flex/Ext radiographs •Visit 6: 24 Months Follow Up (±2 months) • MRI

	• Lose-dose CT* • AP/Lat, Flex/Ext radiographs *if Barricaid mesh breached opposing endplate cortex at 12 month visit, as seen on lateral radiogrphs
STATISTICAL ANALYSIS PLAN	The primary effectiveness hypothesis for this study is that device performance in not clinically inferior in the PAS2 population compared to the oUS population. A non-inferiority margin of $\delta = -0.10$ will be used. The non-inferiority hypotheses may be expressed as follows: **Ho: $\pi_{PAS2} - \pi_{oUS\text{-}device} \leq -0.10$** **Ha: $\pi_{PAS2} - \pi_{oUS\text{-}device} > -0.10$** Where π_{PAS2} and $\pi_{oUS\text{-}device}$ are the probability of achieving a Month 24 CCS with 5 components (≥15 pt. improvement in Oswestry compared to pre-op, no secondary surgical interventions at the index level, no symptomatic reherniations at the index level, no deterioration of neurological status at the index level, and no implant- or procedure-related serious adverse events.) in the PAS2 and pivotal study device groups, respectively. Propensity score (PS) sub-classification will be used to address potential selection bias arising from the non-randomized comparison between the PAS2 and oUS Barricaid populations. The PS model will be developed using a published heuristic (Maislin and Rubin 2010) and evaluated using rigorous criteria (Rubin 2001; Imbens and Rubin 2015). The heuristic is designed to identify five subclasses in which the compared groups share the same multivariate distribution of a comprehensive set of baseline variables. Since patients within a subclass share the same covariate distribution, analyses within subclass may proceed as if patients were randomized to group. In this way, selection into a PS subclass is the observational equivalent of being randomized. Importantly, the "propensity score technique allows the straightforward assessment [of] whether the treatment groups overlap enough regarding baseline covariates to allow for a sensible treatment comparison" (Yue 2007). After enrollment into PAS2 is completed, a data set containing only baseline covariates and the group designation but no post baseline information will be provided to a statistician experienced with these methods, but otherwise not involved with either study. In this way, the design phase and analysis phase are kept separate, thereby reducing study bias. An important aspect of PS subclassification design is 'trimming' of patients in one group that have covariate combinations not observed in the other group. The results in the groups having non-lapping PS distributions. Since the objectives are to evaluate device

	performance in the PAS2 population, trimming will be restricted to the oUS samples if possible when identifying the optimal design. This optimal sub classification design will be shared with key stakeholders including FDA to reach consensus regarding the adequacy of the achieved within subclass covariate balance prior to unblinding the PS design statistician. The primary non-inferiority test will be conducted using a Cochran-Mantel-Haenszel chi-square statistic (Mantel 1963) stratified by PS subclass. A one-sided type I error rate of α=0.05 will be used to test the non-inferiority hypothesis. A separate PS design will be developed for comparing the PAS2 study device population to the oUS control population in terms of the same CCS defined above. When testing superiority, a one-sided type 1 error of 0.025 will be used. The hypotheses to be tested are: **Ho: $\pi_{PAS2} - \pi_{oUS\text{-}control} \leq 0$** **Ha: $\pi_{PAS2} - \pi_{oUS\text{-}control} > 0$** In addition to the above, relevant clinical data will be summarized by group and visit using descriptive statistics including mean, standard deviation, median, IQR, and range for continuous endpoints and counts and percentages for categorical endpoints. All descriptive p-values and confidence intervals used to compare between groups will account for the PS subclassification. Adverse events will be summarized by class of adverse event and by specific adverse event using counts of events and per patient incidence rates, overall, and stratified by device or procedure relatedness, severity, and time interval of occurrence.
SAMPLE SIZE CALCULATION (BASED ON TESTABLE HYPOTHESIS)	In the pivotal trial, the Month 24 success rates using the composite clinical endpoint defined above were 75.9% (192/253) and 63.9% (163/255) for the Barricaid and controls groups, respectively. It is expected that up to 20% of the oUS sample may be trimmed. Therefore, the sample size analysis for the primary non-inferiority comparison assumes that 202 oUS Barricaid patients will be included. Assuming a non-inferiority margin of δ=-0.10 and a one-sided type 1 error set to α=0.05, then 263 PAS2 patients are required for 80% power to reject the inferiority null hypothesis. This value is increased by 10% to N=290 to account for potential loss-to-follow. For the secondary endpoint of superiority relative to oUS controls, it is again assumed that up to 20% of the sample may be trimmed leaving 204 patients. The superiority test will be performed with 1-sided type 1 error rate set to α=0.025. With 263 PAS2 Barricaid patients and 204 oUS control patients, statistical power for testing superiority will also

	be 80%. This sample size analysis was based on conventional two group power analyses. However, in fact, the oUS results are approximately fixed (approximate because up to 20% of the oUS samples may be trimmed as part of the PS matching). Nonetheless, there is less variability in the sampling statistic when one sample has (approximately) fixed results. Therefore, statistical power is likely larger than 80% even when accounting for the PS stratification.
DETAILED STUDY TIMELINE	Per-patient follow-up: 24 months Recruitment period: 18-24 months Total: 42-48 months
REPORTING REQUIREMENTS (INTERIM AND FINAL REPORTS)	Annual reports will be provided to the FDA, IRB(s), and study sites. Upon completion of final 24 month data analysis, a final report will be provided to same. Additional reporting to the FDA will be provided per requirements of the CFR Title 21 Part 803.