II. Executive Summary: Relevant Summary of Safety and Effectiveness Sections

The following is information relevant to this module and is presented as the Summary of Safety and Effectiveness for the clinical studies and the PMA in general.

SUMMARY OF SAFETY AND EFFECTIVENESS

A. General Information

DEVICE GENERIC NAME:	Artificial Cervical Disc
DEVICE TRADE NAME:	BRYAN® Cervical Disc
APPLICANT'S NAME:	Medtronic Sofamor Danek 1800 Pyramid Place Memphis, TN 38132
PREMARKET APPROVAL (PMA) APPLICATION NUMBER:	P# Pending
DATE OF PANEL RECOMMENDATION:	Pending
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	Pending

B. Indications for Use

The BRYAN® Cervical Disc is indicated in skeletally mature patients with cervical degenerative disc disease (DDD) at one level from C3-C7. DDD is defined as any combination of the following: disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy. The BRYAN® device is to be implanted via an open anterior approach.

C. Contraindications

The BRYAN® Cervical Disc should not be implanted in patients with an active infection or with an allergy to titanium, polyurethane, or ethylene oxide residues.

D. Warnings and Precautions

The BRYAN® Cervical Disc should only be used by surgeons who are experienced in the surgical procedure and have undergone adequate training with this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, such as neurological complications.

E. Device Description

The BRYAN® Cervical Disc is a spinal arthroplasty system intended for use in the cervical spine to treat degenerative disc disease. The device is intended to maintain motion at the treated level.

The BRYAN® Cervical Disc prosthesis is made up of the following components: two titanium shells, two titanium retaining wires, a polyurethane nucleus, a polyurethane sheath, and two titanium seal plugs.

The polycarbonate polyurethane nucleus is designed to fit between the two titanium shells. The nucleus-contacting side of each shell has a center pin which interacts with a central hole in the nucleus to allow a normal range of motion, to provide a soft stop at the extremes of motion, and to limit the possibility of traumatic nucleus expulsion. The bone-contacting side of each shell includes a sintered titanium porous coating designed to allow for biologic ingrowth and provide long-term device stability.

The polyurethane sheath surrounds the nucleus and attaches to each shell with one retaining wire. The two wires are placed around the sheath and seated in a circumferential groove at the edge of the shell. The ends of the wire are welded to hold the sheath firmly between the wire and the shell, thus forming a closed compartment. The sheath is designed to withstand a pressure of 1 atm without tearing, rupturing, or separating from its points of attachment.

Holes are located on the apex of each shell, pass through the post, and allow for injection of sterile saline into the compartment prior to implantation. The saline functions as an initial lubricant for the prosthesis, minimizing friction and wear. The titanium seal plugs screw into the holes used for saline introduction and function to retain the saline in the compartment.

The prosthesis is held in the intervertebral disc space by the fit of the shells' outside diameter and convex outer surfaces into the precision milled concavity of the vertebral endplates. This fit is such that device expulsion or migration is restricted in the anterior/posterior and lateral directions. In addition, the rough texture of the porous coating that contacts the milled concavity has a high coefficient of friction to minimize shell movement with respect to the bone and preferentially allow movement at the low friction shell-to-nucleus interface. A stop or wing, which extends superiorly on the cephalad shell and inferiorly on the caudal shell, is intended to prevent migration into the spinal canal.

The available components are shown in the table below.

Table 1. BRYAN® Cervical Disc sizes.

Catalog Number	Size (mm)
6470314	14
6470315	15
6470316	16
6470317	17
6470318	18

No other warranties, express or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

F. Alternate Practices and Procedures

Nonoperative alternative treatments include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs. In addition, there are alternative surgical techniques which include, but are not limited to, surgical decompression, or fusion using various bone grafting techniques (e.g., Cloward bone dowels, Smith Robinson tri-cortical wedges, and Keystone grafts) sometimes used in conjunction with anterior/anterolateral spinal systems (e.g., plate and screw systems), posterior spinal systems (e.g., hook/rod, posterior wiring systems), or cage devices.

G. Marketing History

In the United States, the BRYAN® Cervical Disc device has only been used under an IDE. The device has a marketing history outside the United States that began in 2000. The device is now widely available on six continents, in countries including but not limited to major markets such as Australia, Belgium, Brazil, Korea, Mexico, and South Africa. The device has not been withdrawn from marketing for any reason.

H. Potential Adverse Effects of the Device on Health

The adverse effects, as shown in the table below, were reported from the 242 BRYAN® device patients and 221 control patients who participated in the multi-center clinical study of the BRYAN® Cervical Disc. The control treatment was a single level anterior interbody fusion procedure with allograft and plate stabilization. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

Table 2. Adverse Events in Pivotal Study.

ADVERSE EVENTS*																
	Surgery		Postoperative 1 day - <4 Weeks		6 Weeks ≥4 Wks - <9 Weeks		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos- <9 Months)		12 Months (≥9 Mos- <19 Months)		24 Months (≥19 Mos- <30 Months)		# of Patients Reporting & Total adverse events	
Complication	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	**Investig. # Patients (% of 242) Total # Events**	**Control # Patients (% of 221) Total # Events**
Anatomical/Technical Difficulty	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0) 0	1 (0.5) 1
Cancer	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2 (0.8) 2	0 (0.0) 0
Cardiovascular	0	0	1	0	0	0	1	1	0	0	0	1	2	0	4 (1.7) 4	2 (0.9) 2
Carpal Tunnel Syndrome	0	0	0	1	3	0	2	1	3	1	2	1	2	0	12 (5.0) 12	4 (1.8) 4
Death	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0 (0.0) 0	1 (0.5) 1
Dysphagia/Dysphonia	10	1	14	14	3	3	0	1	0	0	0	0	0	0	26 (10.7) 28	19 (8.6) 20
Gastrointestinal	0	2	2	0	0	1	1	1	3	1	0	1	3	0	9 (3.7) 12	6 (2.7) 6
Infection	0	0	8	2	4	1	1	0	2	1	1	2	1	4	17 (7.0) 18	10 (4.5) 10
Malpositioned Implant	1	0	0	0	0	0	0	0	1	0	0	0	0	0	2 (0.8) 2	0 (0.0) 0
Neck and/or Arm Pain	1	0	20	14	30	23	22	28	29	19	28	20	7	18	115 (47.5) 140	96 (43.4) 128
Neurological	1	0	8	5	5	9	16	8	8	10	16	12	7	5	48 (19.8) 60	46 (20.8) 50
Non-Union	0	0	0	0	0	0	0	1	0	2	0	1	0	1	0 (0.0) 0	5 (2.3) 5
Other	7	6	17	6	11	5	7	5	10	10	13	5	11	7	59 (24.4) 84	39 (17.6) 47
Other Pain	0	0	6	4	6	7	11	13	10	7	9	8	12	7	49 (20.2) 56	44 (19.9) 47
Pending Non-Union	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0 (0.0) 0	5 (2.3) 5
Respiratory	0	0	3	4	1	0	0	2	0	0	0	0	0	0	4 (1.7) 4	6 (2.7) 6
Spinal Event	1	0	1	1	2	4	6	2	1	5	6	7	6	6	21 (8.7) 23	20 (9.0) 25
Trauma	1	0	2	2	2	2	5	3	10	5	11	6	7	7	34 (14.0) 42	22 (10.0) 27
Urogenital	0	0	0	0	0	0	0	1	2	0	4	2	2	0	6 (2.5) 8	3 (1.4) 3
Vascular Intra-Op	2	1	0	2	0	0	0	0	0	0	0	0	0	0	2 (0.8) 2	3 (1.4) 3
Any Adverse Event															202 (83.5)	174 (78.7)

* Based on 24-month cohort.

The reported rates of several adverse events were greater than 10% in the investigational and/or control groups. These events included dysphagia/dysphonia, neck and/or arm pain, neurological, other, other pain, and trauma.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention classified as a revision, removal, reoperation, or supplemental fixation was 2.5% (6/242) in the investigational group and 4.1% (9/221) in the control group. The investigational group had a statistically lower rate of supplemental fixations than the control group.

Investigational patients had lower rates of serious adverse events that were classified as implant- or implant/surgical procedure-associated. Eleven (11) serious (WHO Grade 3 or 4), implant- or implant/surgical procedure-associated adverse events were reported; seven of these occurred in control patients and four occurred in investigational patients. No deaths were reported among investigational patients. One control group death was reported due to injuries sustained in a motor vehicle accident.

Potential Adverse Events:

Risks associated with the use of the BRYAN® Cervical Disc include: 1) those commonly associated with any surgery; 2) those specifically associated with cervical spinal surgery using an anterior approach; and 3) those associated with a spinal implant, as well as those pertaining to the BRYAN Cervical Disc. There is also the risk that this surgical procedure will not be effective, and may not relieve or may cause worsening of preoperative symptoms. Some of these effects may have been previously reported in the adverse events table.

1. Risks associated with any surgical procedure are those such as adverse reactions to anesthesia; pulmonary complications such as pneumonia or atelectasis; infection of the wound; systemic infection; abscess; cellulitis; wound dehiscence; swelling; wound hematoma; thrombosis; ischemia pulmonary embolism; thromboembolism; hemorrhage; thrombophlebitis; organ, nerve or muscular damage and death.
2. Risks associated with anterior interbody replacements of the cervical spine include dysphagia; dysphasia; dysphonia; otitis media; recurring aspirations; fistula; nerve deficits or damage; malunion of the mandible; tracheal, esophageal, and pharyngeal perforation; airway obstruction; external chylorrhea; hoarseness; vocal cord paralysis; warmth or tingling in the extremities; neural damage; damage to the spinal cord or nerve root; or graft in the neural canal; dural tears or leaking; loss of disc height; loss of proper curvature, correction, height or reduction of the spine; vertebral slipping; nerve root trauma; scarring, herniation or degeneration of adjacent discs; nerve damage possibly resulting in paralysis or pain, and surrounding soft tissue damage, vascular damage; spinal stenosis; and spondylolysis.
3. Risks associated with any implants in the spine are early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; loss of purchase; implant fracture; bone fracture; foreign body reactions to the implant including allergic reaction; infection; possible tissue reaction; bone absorption; tumor formation or graft rejection; bone resorption; development of new radiculopathy; myelopathy or pain; cessation of bone growth of the operated portion of the spine; decreased strength of extremities; decreased reflexes; appearance of cord or nerve root injury; pseudoarthrosis; fracture of the vertebral body. Additionally, there is the possibility of misdiagnosis or missed diagnosis with radiographic imaging of the spine when implants are present.
4. Early or late loosening or movement of the device.
5. Loss of range of motion.
6. Implant migration.
7. Breakage of any or all of the components or instruments.
8. Foreign body reaction to the implants including possible tumor formation, auto immune disease, metallosis, and/or scarring.
9. Pressure on the surrounding tissues or organs, possibly resulting in oesophagas or trachea breakdown from component parts where there is inadequate tissue coverage over the implant. Implant or graft extrusion can lead to fistular complications.

10. Loss of proper spinal curvature, correction, height, and/or reduction.
11. Infection.
12. Bone fracture or stress shielding at, above, or below the level of surgery.
13. Loss of neurological function, appearance of radiculopathy, dural tears, and/or development of pain. Neurovascular compromise including paralysis or other types of serious injury. Cerebral spinal fluid leakage.
14. Incontinence.
15. Hemorrhage and/or hematomas.
16. Discitis, arachnoiditis, and/or other types of inflammation.
17. Deep venous thrombosis, thrombophlebitis, and/or pulmonary embolus.
18. Inability to resume activities of normal daily living.
19. Death.

NOTE: Additional surgery may be necessary to correct some of the adverse effects.

I. Summary of Nonclinical Laboratory Studies

1. Mechanical Studies

The biomechanical properties of the BRYAN® Cervical Disc prosthesis were assessed in a series of preclinical experiments. When applicable, all tests were performed on the worst-case size device. Tests were performed at the component, subassembly, and device levels for a thorough evaluation. Finished devices were used in all tests, except as indicated. Summary data for the most relevant tests are provided in the following table.

Table 3. Mechanical Testing.

Tested Component	Test Description	Sample size	Methods	Results
Shell	Static and fatigue testing in shear	n = 12	Shear load applied directly to shell post. Fatigue tests continued to a runout of 10,000,000 cycles.	Met predetermined acceptance criteria.
Shell	Static and fatigue testing of the shell in bending	n = 11	Worst-case bony support at anterior edge and posterior edge only. Static tests with metallic nucleus analog, fatigue tests with polyurethane nucleus to 10,000,000-cycle runout.	Met predetermined acceptance criteria.
Shell	Friction testing in axial rotation	n = 10 n = 5	Axially rotate the porous coating of shell against prepared ovine cervical vertebrae under axial compression. Axially rotate shell against the nucleus under axial compression.	Mean breakaway bone-shell torque exceeded nucleus-shell for all samples.
Shell	Mechanical testing of the shell surface coating	n = 10 n = 5 + 5* n = 5 + 5* n = 6	ASTM F1160 Fatigue testing in shear ASTM F1044 Static testing in shear ASTM F1147 Static testing in tension ASTM F1978 Abrasion resistance	Characterization only. Met acceptance criteria. Met acceptance criteria. Met acceptance criteria.
Shell	Microstructural analysis of the shell surface coating	20 fields 30 fields 10 fields 30 fields 30 fields	ASTM F1854 Stereologic Evaluation Thickness Volume percent void Mean intercept length Pore diameter Weld width	No acceptance criteria; characterization only.
Shell	Stability in antepulsion and retropulsion	n = 10 n = 10	Apply 130 N compression, pull shells anteriorly at 0.1 mm/sec. Apply 130 N compression, pull shells posteriorly at 0.1 mm/sec.	Met predetermined acceptance criteria.

* Thickness of glue used to attach test coupon to test fixture was changed after 5 samples.

Tested Component	Test Description	Sample size	Methods	Results
Nucleus	Static and fatigue testing of the nucleus in axial compression	n = 10 n = 8	Compress device at 12 mm/sec until shells are within 0.1 mm of each other. Compress at 10 Hz, R=10 until failure or runout of 10,000,000 cycles.	Met predetermined acceptance criteria.
Nucleus	Device viscoelasticity as a function of compression fatigue test frequency	n = 1	Compress at frequencies from 0.5 Hz to 10 Hz, R=10, minimum load = -130 N, while monitoring device stiffness.	No acceptance criteria; characterization only.
Nucleus	Device temperature as a function of compression fatigue test frequency	n = 1	Compress at frequencies from 1 Hz to 20 Hz, R=10, minimum load = -285 N, while monitoring device temperature.	No acceptance criteria; characterization only.
Nucleus	Creep	n = 7	Compress at 130 N for 700 hours in saline at body temperature	Met predetermined acceptance criteria.
Nucleus	Saturation	n = 4	Soak in saline at room temperature. Monitor mass over period of 31 days.	No acceptance criteria; characterization only.
Sheath	Static tensile testing	n =10	Place device in tension to maximum physiologic displacement (2.1 mm) and check sheath seal. Repeat test to 10.0 mm.	All passed leak test at both physiologic and 10 mm displacements.
Sheath	Static torsion testing	n =10	Under 130 N compression, apply ± 12 degrees of axial rotation at 1 degree per second and check sheath seal. Repeat test at ± 90 degrees.	All passed leak test at both angular displacements.
Seal Plug	Pressurization testing	n = 6	Pressurize device seal plug (both internal and external pressure tested separately) with compressed air at 100 psi for 10 seconds. Monitor for leaks under water.	All passed high-pressure leak test.

Tested Component	Test Description	Sample size	Methods	Results
Device Assembly	Wear simulator testing	n = 6 load & motion n = 3 load only (control)	Spine simulator test under -130 N in bovine serum at 37°C, 4 Hz to 10,000,000 cycles. Flexion/extension and/or right/left lateral bending and axial rotation simultaneously at ± 4.9 and ± 3.8 degrees. Assess mass loss and particle size distribution. Pressure test device to assess sheath integrity.	No acceptance criteria for mass loss and particle characterization. All devices passed pressure test.
Device Assembly	Device temperature as a function of simulator test frequency and compressive load	n = 1	Vary frequency of wear test from 0.5 Hz to 6.0 Hz at both -130 N and -300 N.	No acceptance criteria; characterization only.
Device Assembly	Device wear	n = 4	Spine simulator test under -130 N in saline at 37°C, 4 Hz until shell-to-shell contact at the extremes of motion. Flexion/extension and/or right/left lateral bending and axial rotation simultaneously at ± 4.9 and ± 3.8 degrees.	No acceptance criteria; characterization only.
Device Assembly	Evaluation of load, lubricant, and frequency effects on device wear in the absence of a sheath	n = 16	Spine simulator test at 37°. DOE included media of either saline or bovine serum, test frequency of either 4Hz or 6 Hz, and load level of either -130 or -300 N. Flexion/extension and/or right/left lateral bending and axial rotation simultaneously at ± 4.9 and ± 3.8 degrees.	Devices were within acceptable weight loss ranges. No nucleus failures.
Device Assembly	Shear testing of the prosthesis in a cadaveric model	n = 6	Apply 130 N axial compression to single cadaveric FSUs. Simultaneously apply posterior shear to disengage the facet joints at 1.0 mm/second. Record shear load.	Shear integrity exceeded acceptance criteria. No device failures.

Tested Component	Test Description	Sample size	Methods	Results
Device Assembly	Materials characterization of: Bionate Biospan Titanium Titanium alloy	n = 6 n = 6 n = 6 10 gm 2 gm 200 cm2 2 gm 2 gm 300 cm2 600 cm2	Modulus of elasticity Ultimate tensile strength Yield strength Specific gravity Molecular weight Hardness Crystallinity Glass Transition Temperature FTIR characterization Aqueous and non-aqueous extract	Material characteristics for multiple lots of materials met specifications.

2. Animal Testing

Both goats and chimpanzees were implanted with the BRYAN® device to assess *in vivo* performance, and a particle injection study was conducted in a rabbit model to characterize the reaction to wear debris particles generated from the prosthesis. Characterization tests were also performed on the injected particles. Summary data for the most relevant studies are provided in the following table.

Test Description	Tested Component	Sample size	Methods	Results
6-month chimpanzee study	Device assembly	6 animals (previous prosthesis design)	Devices implanted, then explanted after 6 months and fusion performed.	Animals resumed normal activities.
3-month chimpanzee study	Device assembly	4 animals (2 received device in current design)	Devices implanted, then explanted after 3 months and fusion performed.	Animals resumed normal activities. No operative or post-operative complications.
Goat study	Device assembly	16 animals – 12 received BRYAN® device and 4 received ATLANTIS® plate	Devices implanted for 3, 6, or 12 months. Pathology of spinal and various tissues.	No device-related failure in BRYAN® group. No evidence of reaction to particulate.
Animal injection study	Sheath and nucleus particulate	28 animals at 2 investigational dose levels + 6 control	Particle characterization using laser scatter technique. Rabbit model tested up to 24 wks. Pathology of spinal and various tissues.	Sheath and nucleus particles tolerated at both low and high doses.

3. Biocompatibility Testing

Per the requirements of ISO 10993-1, the BRYAN® Cervical Disc prosthesis is classified as a permanent contact, tissue/bone-contacting implant. The testing strategy was based on these requirements in addition to FDA's Program Memorandum G95-1. Biocompatibility tests were undertaken on the complete device (or extract, as required) for cytotoxicity, sensitization, intracutaneous reactivity, and acute toxicity tests. Pyrogenicity tests were also performed. Data are also available for genotoxicity, implantation, chronic toxicity, and two-year carcinogenicity for the polymer components. All standard acceptance criteria were met.

The results of this testing support the biocompatibility of the device materials. In addition, there is a large amount of clinical experience with similar polyurethanes in other types of implanted medical devices. The titanium materials used in the shell, seal plug, and retaining wire are well-characterized materials with a long history of use in implanted medical devices. Therefore, this material is considered to be safe for use in the lumbar spine.

J. Summary of Clinical Study

1. Study Background

The goals of the IDE clinical study of the BRYAN® Cervical Disc System were to evaluate the safety and effectiveness of the anterior cervical spinal use of the device in the treatment of patients with cervical disc disease. The assessments of safety and effectiveness of the BRYAN® Cervical Disc were through direct clinical data comparisons between data collected from patients implanted with the BRYAN® device to an equivalent group of patients who received a surgical fusion utilizing bone graft and plate stabilization. The investigational and control treatments were randomized in a 1:1 manner.

The effectiveness of the BRYAN® device was based primarily on a patient having Neck Disability Index (NDI) pain/disability improvement. In addition, neck pain, arm pain, patient gait, general health status, patient satisfaction, and radiographic parameters were evaluated. Safety was based primarily on the nature and frequency of adverse events and second surgeries. The maintenance or

improvement in neurological status following surgery was also a safety measurement.

The primary endpoint for the clinical investigation was a composite variable termed "overall success." Overall success was comprised of NDI and neurological results. Success for these factors, as well as the patient not having a serious adverse event classified as implant- or implant/surgical procedure-associated or having a second surgery classified as a "failure", determined whether the patient was an overall success. Investigational treatment success was based on the 24-month overall success rate being statistically non-inferior to the control group rate.

2. Inclusion Criteria

The indication studied was degenerative disc disease (DDD) at a single level between C3 and C7 for any combination of disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy.

The following additional inclusion criteria had to be present:

- At least 6 weeks unsuccessful conservative treatment, except in cases of myelopathy requiring immediate treatment (e.g., acute onset of clinically significant signs);
- Requirement for surgical treatment demonstrated by CT, myelography and CT, and/or MRI;
- Skeletally mature (≥ 21 years of age);
- Preoperative Neck Disability Index score of ≥ 30 and at least one clinical sign associated with level to be treated;
- Willing to sign informed consent and comply with protocol.

3. Exclusion Criteria

Subjects were excluded if they had any of the following:

- Any of the following at the treated level:
  - Significant cervical anatomical deformity; e.g., ankylosing spondylitis, rheumatoid arthritis, etc.
  - Moderate to advanced spondylosis. Patients who demonstrate advanced degenerative changes. Such advanced changes are characterized by any one or combination of the following:
    - Bridging osteophytes;
    - Marked reduction or absence of motion;
    - Collapse of the intervertebral disc space of greater than 50% of its normal height;
  - Radiographic signs of subluxation greater than 3.5 mm;
  - Angulation of the disc space more than 11 degrees greater than adjacent segments; and
  - Significant kyphotic deformity or significant reversal of lordosis;
- Axial neck pain as the solitary symptom;
- Previous cervical spine surgery;
- Metabolic bone disease, such as osteoporosis, defined as a BMD T-score equal to or worse than -2.5. If significant radiolucence is detected, a BMD scan in the spine, wrist, and femoral neck must be obtained.
- Active systemic infection or infection at the operative site;
- Known allergy or to titanium, polyurethane, or ethylene oxide residuals;
- Concomitant conditions requiring steroid treatment;
- Diabetes mellitus requiring daily insulin management;

- Extreme obesity, as defined by NIH Clinical Guidelines Body Mass Index;
- A medical condition that may interfere with the postoperative management program, such as advanced emphysema or Alzheimer's disease;
- A medical condition that may result in patient death prior to study completion: unstable cardiac disease, active malignancy;
- Pregnant;
- Current or recent alcohol and/or drug abuser requiring intervention;
- Signs of being geographically unstable, such as recent or pending divorce, or high level of job dissatisfaction;

4. Postoperative Care

The recommended postoperative care for the first two weeks postoperative included avoidance of heavy physical activity as well as limiting extended automobile rides, lifting, bending, and twisting. The recommended postoperative regimen also included avoidance of physically demanding sports or recreational activities for up to 3 months postoperatively.

5. Clinical and Radiographic Effectiveness Parameters

Patients were evaluated preoperatively (within 2 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12, and 24 months. Patients in the investigational arm will then be followed biennially thereafter until the last subject enrolled in the study has been seen for his/her 24-month evaluation. Adverse events were evaluated over the course of the clinical trial. At each evaluation timepoint, clinical and/or radiographic outcome parameters were evaluated.

Success was determined from data collected during the initial 24 months of follow-up.

Clinical and/or radiographic outcome parameters were evaluated for treated subjects at the follow-up evaluation timepoints identified above. Clinical parameters assessed were of pain/disability, neck and arm pain, general health, patient global perceived effect, and doctor's perception of results. Additional measures included gait, patient satisfaction, and work status. The radiographic outcome parameters consisted of functional spinal unit height as well as evaluations of motion and fusion at the treated level for the investigational and control group, respectively. Implant position and adjacent level motion were also evaluated.

Pain/disability status was measured using the Neck Disability Index Questionnaire. Success was defined as a 15-point improvement in the NDI score from the preoperative baseline score.

Neurological status is based on motor function, sensory function, and reflexes. Neurological status success was defined as maintenance or improvement of the pre-op baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

6. Patient Demographics and Accountability

The study was approved for up to 35 investigational sites and up to 470 total subjects. A total of 242 investigational and 221 control patients had surgeries in the study. There were no differences between the two populations for any of the demographic parameters.

Table 5. Study Patient Demographics.

	Investigational	Control
n	242	221
men/women	110/132	113/108
mean age (range)	44.4 (25.0-78.0)	44.7 (27.0-68.0)
mean weight (lbs) (range)	173 (108-312)	180 (100-285)
worker's comp (%)	15 (6.2)	11 (5.0)
tobacco user (%)	61 (25.5)	53 (24.0)

For some subjects, complete 24-month data for all effectiveness variables were not available, however. In order to "complete" the 24-month dataset for the subjects with missing data, 24-month values were predicted from the existing 12-month data using Bayesian statistical methods.

An analysis was performed to assess the ability to pool data across sites and to compare data across the study arms. These analyses evaluated the primary clinical outcome variables as well as overall success and found no differences that would prevent pooling of the data across the sites within a given group of subjects.

7. Surgical Results and Hospitalization

In summary, investigational device patients had statistically longer operative times and higher blood losses as compared to control patients. These findings are believed to be attributed to the newness of the BRYAN device surgical technique and the use of first generation instruments. The large sample sizes which power this study also play a major role in these statistical differences. Despite the statistical findings, the actual mean differences are considered to be of marginal clinical relevance. The hospital stays were statistically similar for the two treatments.

Table 6. Surgical Results.

	Investigational	Control
mean operative time (hrs)	2.2	1.4
mean EBL (ml)	91.5	59.6
hospitalization (days)	1.1	1.0
spinal level treated		
C_{34} (%)	1.2	0.0
C_{45} (%)	5.0	7.7
C_{56} (%)	57.9	49.8
C_{67} (%)	36.0	42.5

8. Clinical and Radiographic Effectiveness Evaluation

Individual subject success (i.e. overall success) was defined in the study protocol as success in certain clinical outcome parameters. Success for these parameters included:

1. An improvement of at least 15 points from the baseline Neck Disability Index score;
2. Maintenance or improvement in neurological status;
3. No serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
4. No additional surgical procedure classified as "Failure."

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for individual outcome parameters and overall success. All success rates were based on the data from the 24-month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods. The conclusions were based on an interim analysis which was pre-defined in the protocol.

Table 7. Posterior Probabilities of Success at 24 Months.

Primary Outcome Variable	Investigational Posterior Mean (95% HPD Credible Interval)	Control Posterior Mean (95% HPD Credible Interval)
NDI	85.0% (79.7%, 89.9%)	76.2% (69.7%, 82.6%)
Neurological	92.4% (88.4%, 96.1%)	90.9% (86.4%, 95.3%)
Overall Success	80.4% (74.3%, 85.8%)	71.8% (65.0%, 78.9%)

Bayesian statistical analyses yielded a posterior probability of non-inferiority at 24 months of essentially 100%. The posterior probability of superiority was found to be 96.9%.

When a patient receives the BRYAN® Cervical Disc, the chance (posterior probability) of overall success at 24 months is 80.4%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 74.3% to 85.8%. When a patient receives the control treatment, the chance of overall success at 24 months is 71.8%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 65.0% to 78.9%.

K. Conclusion

The scientific evidence that has been presented here supports the safety and effectiveness of the BRYAN® Cervical Disc in the treatment of cervical degenerative disc disease from C3 to C7. The study demonstrated that the treatment of DDD with the BRYAN® Cervical Disc was as effective as the control treatment (fusion with bone graft and plate stabilization). The results for the primary effectiveness outcome parameters for the investigational group were non-inferior to the control group. The investigational group demonstrated superiority to the control group for NDI and overall success. The BRYAN® Cervical Disc was able to achieve

comparable or better clinical performance while maintaining motion at the involved cervical level.

L. Panel Recommendation

To be determined.

M. CDRH Decision

To be determined.

N. Approval Specifications

To be determined.