Cigna Medical Coverage Policy

Subject: Intervertebral Disc (IVD) Prostheses

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Coverage Policy

Lumbar Disc Prosthesis

Cigna covers the surgical implantation of an FDA–approved lumbar intervertebral disc (IVD) prosthesis for chronic, unremitting, discogenic low back pain and disability secondary to single-level degenerative disc disease (DDD) as medically necessary in a skeletally mature individual when ALL of the following criteria are met:

- Unremitting low back pain and significant functional impairment is refractory to at least six consecutive months of structured*, physician supervised conservative medical management, which includes ALL of the following components
  - exercise, including core stabilization exercises
  - nonsteroidal and/or steroidal medication (unless contraindicated)
  - physical therapy, including passive and active treatment modalities
  - activity/lifestyle modification
- Single-level disc degeneration has been confirmed on complex imaging studies (i.e., computerized tomography [CT] scan, magnetic resonance imaging [MRI]).
- The implant will be inserted at an FDA approved lumbar/sacral level specific to the implant being used.
*Note: Structured medical management consists of medical care that is delivered through regularly scheduled appointments, including follow-up evaluation, with licensed healthcare professionals.

Cigna does not cover the surgical implantation of a lumbar intervertebral disc prosthesis for ANY of the following because each is considered experimental, investigational or unproven:

- The planned procedure includes the combined use of a prosthesis and spinal fusion (i.e., hybrid surgery).
- Simultaneous multilevel implantation is planned.
- The implant will be inserted outside of the recommended lumbar/sacral level for the specific implant being used.
- The individual has osteopenia or osteoporosis (T-score < -1.0).
- The individual has a history of prior lumbar fusion.
- There is evidence on imaging studies of ANY of the following:
  - degenerative spondylolisthesis of Grade 2 or greater
  - infection
  - multilevel degenerative disc disease
  - nerve root compression or spinal stenosis
  - pars interarticularis defect with either spondylolysis or isthmic spondylolisthesis
  - scoliosis
  - severe facet joint arthrosis
  - spinal fracture
  - tumor
- Non FDA–approved lumbar intervertebral disc

**Cervical Disc Prosthesis**

Cigna covers surgical implantation of FDA–approved cervical intervertebral disc (IVD) prosthesis) for degenerative cervical disc disease with intractable radiculopathy and/or myelopathy as medically necessary in a skeletally mature individual when ALL of the following criteria are met:

- Unremitting neck and arm pain, resulting in disability and/or neurological deficit that are refractory to at least six weeks of standard medical and surgical management (e.g., reduced activities, exercise, analgesics, physical therapy).
- Single-level disc degeneration has been confirmed on complex imaging studies (i.e., computerized tomography [CT] scan, magnetic resonance imaging [MRI]).
- The planned implant will be used in the reconstruction of a cervical disc at C3-C7, following single-level discectomy.
- The individual is a candidate for single-level anterior cervical decompression and interbody fusion.

Cigna does not cover the surgical implantation of a cervical intervertebral disc (IVD) prosthesis for ANY of the following because each is considered experimental, investigational or unproven:

- The planned procedure includes the combined use of a prosthesis and spinal fusion (i.e., hybrid surgery)
- Simultaneous multilevel implantation is planned
- The individual had prior fusion at an adjacent cervical level
- The individual had prior surgery at the treated level
- Osteopenia, osteomalacia, or osteoporosis (T-score of -3.5, or -2.5, with vertebral crush fracture)
- Neck or arm pain of unknown etiology
- Absence of neck and/or arm pain
- Progressive neurological deficit or deterioration
- Infection, systemic or local
- Rheumatoid arthritis or other autoimmune disease
- Paget’s disease, osteomalacia or any other metabolic bone disease
• There is radiological evidence of ANY of the following:
   clinically significant cervical instability, such as kyphotic deformity or spondylolisthesis (e.g., > 3.5 mm subluxation or > 11 degrees angulation)
   significant cervical anatomical deformity or compromised vertebral bodies at the index level (e.g., ankylosing spondylitis, rheumatoid arthritis, or compromise due to current or past trauma)
   multilevel degenerative disc
   spinal metastases
• Non FDA–approved cervical disc prosthesis

General Background

Intervertebral disc prostheses are prosthetic devices used to replace a degenerated intervertebral disc for the treatment of degenerative disc disease (DDD) in the lumbar or cervical spine. When conservative treatment of DDD fails, spinal fusion is considered the standard surgical treatment, however there are associated complications. Complications are reported in approximately 10% of all cases, and include nonunion, loss of spinal curvature and loss of flexibility. In addition, spinal fusion alters the biomechanics of the spine, reducing motion of the spinal segments, and potentially leads to premature disc degeneration at adjacent levels. Replacement of the degenerated disc, (intervertebral disc replacement) has been recommended as an alternative to spinal fusion as a means of improving spinal flexibility, maintaining spinal curvature, providing an equalized weight-bearing surface, and reducing or possibly eliminating back pain.

Lumbar Intervertebral Disc Prostheses

Lumbar intervertebral disc prostheses currently in use are implanted anteriorly in the lumbar spine, the approach is the same for anterior interbody fusion. Devices that have been approved by the U.S. Food and Drug Administration (FDA) for surgical implantation within the spine for single-level disc replacement included the Charité® Artificial Disc (DePuy Spine, Inc., Raynham, MA) and the ProDisc®-L Lumbar (SYNTHES Spine, Inc., West Chester, PA). Following the initial approval of these devices various supplemental approvals have been granted for each device based on modifications to the initial device. The Charité® was initially developed in 1984 and has been modified several times, with one prior modification being called the SB Charité III. The INMOTION Lumbar Artificial Disc System (DePuy Spine, Inc., Raynham, MA) is a more recent modification of the initial Charité design, has been cleared by the FDA, and is currently available for implantation.

Charité Artificial Disc

The Charité Artificial Disc is proposed for use in the lumbar spine for the treatment of DDD device and consists of two cobalt chromium alloy endplates and a polyethylene sliding core.

U.S. Food and Drug Administration (FDA): In October 2004, the FDA granted a premarket approval (PMA) for the initial Charité Artificial Disc. This device is approved for patients who are skeletally mature with DDD at one level from L4–S1 with no more than three millimeters (mm) of spondylolisthesis at the involved level; the patient should have failed at least six months of conservative nonsurgical treatment prior to implantation of the device.

The FDA defined DDD as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies (i.e., patient selection criteria for these studies included magnetic resonance imaging [MRI] or computerized tomography [CT] in conjunction with a discogram that mapped the specific anatomic location of the DDD as well as demonstrated concordant pain reproduction).

FDA approval was based on a review of a clinical study of safety and effectiveness conducted by DePuy at six medical centers (Geisler, et al., 2004, [see below]). Upon approval of the device, the FDA required the manufacturer to conduct a post-approval study to determine the long-term safety and effectiveness of the IVD device. The FDA required the patients to be evaluated for a total of five years post-implantation and identified endpoints for determining overall success.

In addition, the FDA required annual reports regarding all subjects enrolled in the post-approval study measuring: overall success; surgical interventions at the index or adjacent levels; pain (i.e., measured at rest using visual analog scales [VAS]); quality of life using SF-36; disc height; displacement of the device; incidence
of radiolucency; correlation of range of motion with VAS scores, ODI scores, and overall success; evaluation of adjacent segment degeneration; and neurological status (FDA, 2004).

According to the FDA, the Charité device is contraindicated in patients with the following conditions:

- active systemic infection or infection localized to the site of implantation
- osteoporosis
- osteopenia
- bony lumbar stenosis
- allergy or sensitivity to implant materials
- isolated radicular compression syndromes, especially due to disc herniation
- pars defect

**Literature Review:** Early evidence supporting the use of the SB Charité III device was primarily in the form of case series, retrospective case reviews and observational studies (Griffith, et al., 1994; Cinotti, et al., 1996; LeMarie, et al., 1997; Zeegers, et al., 1999; Van Ooij, et al., 2003, 2007; DeKleuver, et al., 2003). The studies were generally small in sample size, evaluated the use of various models of the device and included heterogeneous patient populations. Throughout the early published studies the device was implanted for both single and multilevel disease. Improvements in radicular and back pain were reported; however there was concern regarding rates of implant migration and other complications, in addition to the need for reoperation. Overall, the reported clinical outcomes of these initial studies are short-term (2 to 4 years).

Randomized controlled trials that were performed as part of the investigational device exemption (IDE) studies for the Charité device (Geisler, et al., 2004; Blumenthal, et al., 2005; McAfee, et al., 2005) demonstrated promising results favoring lumbar disc replacement compared to anterior lumbar interbody fusion. Authors continued to evaluate and report on the safety and clinical utility of intervertebral disc replacement devices and subsequent studies published in peer-reviewed scientific literature continued to support safety and improved health outcomes such as reduction of pain and improved motion.

Initial FDA approval of the Charité device was based on two-year safety and effectiveness data from a multicenter, prospective, randomized investigational device exemption (IDE) study, the CHARITE IDE trial (N=304), which was conducted by the manufacturer at six medical centers (Geisler, et al., 2004). The purpose of the study was to demonstrate the non-inferiority of the Charite Artificial Disc to an interbody fusion system. Patients were followed and evaluated at three, six, 12, and 24 months using patient response questionnaires, radiographic films of the spine, Oswestry Disability Scores, (ODI) and visual analogue scale (VAS) scoring for pain reduction. At two year follow-up the study showed that patients treated with the artificial disc did no worse than patients treated with intervertebral body fusion. Rates of adverse events from the use of the artificial disc were similar to those from treatment with fusion; furthermore there was no statistically significant difference in the range of motion noted at the level of disc replacement or in the relief of the patients’ pain.

Upon approval of the device the FDA required the manufacturer to conduct a post-approval study to determine the long-term safety and effectiveness of the IVD device; the FDA identified endpoints for determining overall success, patients were required to be evaluated for a total of five years post-implantation. The FDA required annual reports regarding all subjects enrolled in the post-approval study measuring: overall success; surgical interventions at the index or adjacent levels; pain (i.e., measured at rest using visual analog scales [VAS]); quality of life using SF-36; disc height; displacement of the device; incidence of radiolucency; correlation of range of motion with VAS scores, ODI scores, and overall success; evaluation of adjacent segment degeneration; and neurological status (FDA, 2004).

After two years of the five-year mandated patient follow-up required by the FDA, McAfee and colleagues (2006) conducted an analysis of the reasons for and the success rate of revising the Charité prosthesis within this entire study population. Of the 589 patients (71 nonrandomized, 205 randomized and 313 continued access) who underwent TDR, 52 (8.8%) required secondary revisions at the index level. Within the control group of 99 BAK procedures, 10 (9.9%) required revisions. According to the authors there was no significant difference between the two groups with respect to the rate of revisions (p=0.7041). McAfee and colleagues concluded that lumbar TDR did not preclude additional surgery at the primary site with replacements being revisable to a new motion-preserving prosthesis, ALIF and/or posterior instrumentation.
Five year prospective follow-up results to the multicenter Charité IDE randomized controlled trial comparing arthroplasty to arthrodesis was published in September 2008 (Guyer, et al. 2008a). A total of 160 patients completed the five year study (27 nonrandomized training cases and 133 randomized cases [90 Charité and 43 BAK cases]). Clinical evaluations were completed preoperatively, and at six weeks, three, six, 12, 24, and 60 months after surgery utilizing ODI, VAS scores, SF-36, neurological status and work status evaluations. Results were presented on an “intent-to-treat” basis rather than “as treated”; patients who crossed over to a different treatment group were maintained in the “intended-to-treat” group. The results included an improvement in ODI scores, a decrease in VAS scores, and improvements in SF-36 scores. Device success rates favored the Charité group as well as return to work status. Mean ROM at the index level also favored the Charité group. Overall, the results of the five year study are consistent with the two year reports of noninferiority of the Charité device versus ALIF with BAK cages and iliac autograft.

Aside from the FDA-related trials which support noninferiority two to five years following implantation, safety and efficacy has been evaluated by several authors following the device approval. These studies are primarily in the form of retrospective case series with some comparative trials and few other randomized controlled trials. Evidence evaluating device revision or removal consists of case reports (Kurtz, et al., 2005) and case series (Wagner, et al., 2005; Kurtz, et al, 2007; Punt, et al., 2008) with variable outcomes such as those regarding oxidation, access-related complications (iliac vein injury, temporary retrograde ejaculation, small-bowel obstruction requiring lysis, and symptomatic, large retroperitoneal lymphocele) and reason for reoperation, which included absence of pain relief, new pathology, arthrosis or migration of the device in some cases. Some of the other published studies included evaluation of outcomes of the SB Charité III such as axial rotation and flexion measures (SariAli, et al., 2005), radiological outcomes (Putzier, et al., 2006; David, et al., 2007), effect of age and prior surgery on TDR clinical outcomes (Guyer, et al., 2008), comparison of clinical outcomes between subjects with and without prior surgery (Geisler, et al., 2008) and evaluation of range of motion outcomes (Cunningham, et al., 2008). Nonetheless, the various outcomes measured among these studies continue to lend support to safety and efficacy.

ProDisc®-L
The second IVD device that is proposed for use in the lumbar spine for the treatment of DDD is the ProDisc®-L. The ProDisc®-L Total Disc Replacement (Synthes Spine, Inc., West Chester, PA) is a weight-bearing modular implant consisting of two endplates and one polyethylene inlay. The endplates (i.e., one inferior and one superior) are manufactured from cobalt-chromium alloy, with the superior endplate available in two sizes (i.e., medium and large) and two lordotic angles (i.e., 6 and 11 degrees).

U.S. Food and Drug Administration (FDA): The ProDisc-L was approved on August 14, 2006, under the FDA’s premarket approval (PMA) process and is indicated for spinal arthroplasty in skeletally mature patients with DDD at one level of the lumbar spine from L3–S1. Other patient selection criteria include no more than a Grade 1 spondylolisthesis at the involved level and no relief from pain after at least six months of nonsurgical treatment (FDA, 2006).

In addition to the contraindications listed for the Charité disc, contraindications for the ProDisc-L include:
- involved vertebral endplate smaller than 34.5 in the medial lateral view and/or 27 in the anterior-posterior view
- Clinically compromised vertebral bodies at affected level due to current or past trauma
- Lytic spondylolisthesis or degenerative spondylolisthesis of grade >1

The FDA has also mandated a five-year post-approval study to be conducted that will evaluate the long-term safety and effectiveness of the ProDisc-L. The FDA has provided guidance on acceptable overall success parameters, and radiological parameters that will be required in the investigational arm and the control group during this post-approval study. The FDA will also require ODI, ROM with VAS scores, and evaluation of adjacent segmental degeneration. All adverse events are to be reported, including those that occur within the continued access subjects who participated in the IDE study (FDA, 2006).

Literature Review: As part of the IDE study, outcomes from a multicenter, prospective randomized controlled clinical trial of 292 patients (162 randomized, 50 nonrandomized, and 80 control subjects) were submitted to the FDA. The control group was treated for DDD at a single level between L3 to S1 using a circumferential fusion technique (i.e., interbody fusion with femoral ring allograft, posterolateral fusion with autogenous iliac crest bone graft, combined with pedicle screw instrumentation). The randomized patients received implantations of the
ProDisc-L via an anterior surgical approach, with no additional instrumentation being used to secure the device placement.

During this study, the FDA requested that the data be analyzed and reported using the following criteria:
- improvement in the ODI score ≥ 15 points at 24 months compared to the score at baseline
- maintenance or improvement of ROM defined as (24-month flexion/extension ROM, Pre-operative flexion/extension ROM) ≥ 0 (with ± 3° measurement error applied)
- a non-inferiority margin of 10%

The outcomes from this study led to the FDA’s PMA decision based on the severity and number of adverse events that were no worse than the control group, and the overall success rate of the ProDisc that was no worse than the overall success rate of the control group; a non-inferiority margin of 10% (FDA, 2006; Zigler, 2007).

Several other well-designed studies, some including patients from the FDA IDE trial, support safety and efficacy of ProDisc-L (Delamarter et al., 2003; 2005; Leivseth, et al., 2006; Bertagnoli, et al., 2005, 2006a, 2006b; Siepe, et al., 2006; Chung, et al., 2006). Delamarter et al. (2003) reported results at 18-24 months indicating fusion patients reported a decrease in pain and functional status within the first six months, which was comparable to the scores obtained from the ProDisc implant group. At 24 months follow-up, Leivseth et al. (2006) documented the rotational and translational ROM at the level of implant versus adjacent levels of the spine. The ROMs obtained from this study group were compared to ROM norms that had been published within the literature. The authors found that sagittal plane rotational ROM of lumbar segments with ProDisc implants was low compared to the norm. When the researchers compared the ROM of the treated levels to the ROM of adjacent levels, they found these measures to be low as well. Thus, the researchers concluded that prospective studies are required to show whether the ROM of instrumented and untreated segments depends on prosthesis design, patient selection, or surgical technique and whether postoperative physical therapy could restore a normal ROM at least at the untreated levels of the spine.

Bertagnoli and colleagues evaluated ProDisc arthroplasty in several studies (2005, 2006a, 2006b). In 2005 the authors reported the results of prospective data collected from 104 subjects who underwent single-level ARD for DDD. By three months post-surgery there was a decrease in ODI scores and individual pain scores. The results of this study show a 96% rate of satisfaction as reported by the patients at two years. In 2006 Bertagnoli and associates evaluated the efficacy of ProDisc arthroplasty in patients with symptomatic adjacent-segment degeneration following remote lumbar fusion (n=20). In this group of subjects at 24 month follow-up, Leivseth et al. (2006) documented the rotational and translational ROM at the level of implant versus adjacent levels of the spine. The ROMs obtained from this study group were compared to ROM norms that had been published within the literature. The authors found that sagittal plane rotational ROM of lumbar segments with ProDisc implants was low compared to the norm. When the researchers compared the ROM of the treated levels to the ROM of adjacent levels, they found these measures to be low as well. Thus, the researchers concluded that prospective studies are required to show whether the ROM of instrumented and untreated segments depends on prosthesis design, patient selection, or surgical technique and whether postoperative physical therapy could restore a normal ROM at least at the untreated levels of the spine.

Three-year clinical results of ProDisc insertion for different indications were reported by Siepe et al. in 2006 (n=92). Average follow-up was 34.2 months and was subdivided into three distinct diagnostic groups in order to compare their subjective, VAS and ODI findings. Group I (n=40) was categorized as having DDD without additional pathology and served as the control group during this study. Group 2 (n=12) had DDD with nucleus pulposus prolapse (NPP); group 3 (n=17) had previously undergone discectomy procedures, and group 4 (n=23) had DDD with modic changes. The combined group analysis showed highly significant postoperative improvement for VAS and ODI in all groups; however, postoperative differences between groups 1, 3 and 4 were not statistically significant. Group 2 appeared to achieve and maintain the best subjective and objective results, at a mean follow-up of 33.1 months. Complication rate was 19.6%, requiring revision surgery at the index level in 8.7% of the patients and another 2.2% at the non-index level. These occurrences were considerably higher for bisegmental disc replacements (n=5 of 14 operations; 35.7%) compared with monosegmental interventions (n=11 of 77; 14.3%). The researchers concluded:
- monosegmental symptomatic DDD changes can be regarded as an acceptable indication for TDR
- previous discectomy did not have a negative impact on outcomes
- patients with DDD and large, contained, soft disc herniations with predominant low back pain are candidates for TDR
- bisegmental and multisegmental implantations were associated with a considerably higher complication rate
• three-dimensional CT reconstruction of the prevertebral vessels should be obtained for all TDRs planned for levels L4–L5 and above before surgery
• patient selection must be precisely determined
• longer follow-up evaluations are needed to determine the real benefits of TDR for patients

Subsequent studies published in the peer-reviewed scientific literature have continued to evaluate safety and efficacy and consist of various retrospective, prospective and comparative trials involving small populations evaluating short-term outcomes (Chung, et al., 2008; Leahy, et al., 2008; Yaszay, et al., 2008; Siepe, et al., 2008). The focus of these studies varied and included occurrence of surgical complications, comparison of clinical outcomes using ODI scores and range of motion between single-level and tow-level replacement, the impact of prior discectomy on results of TDR clinical outcomes, and the effect of preoperative disc height on postoperative motion using ODI scores and VAS scores. Results of these studies supported that better clinical outcomes occurred in single-disc replacement compared to two level (Chung, et al., 2006); prior discectomy did not compromise TDR outcomes (Leahy, et al., 2008); preoperative and postoperative disc height did influence range of motion (Yaszay, et al., 2008) and that the level of disc replacement did influence post-operative pain outcomes with L5-S1 replacement or two level replacement resulting in a significant incidence of high pain levels.

Literature Review—Adjacent Segment Degeneration: The effect of TDR on adjacent segment degeneration has been investigated (Park et al., 2008; Zigler, et al., 2012a). Park et al. (2008) reported on the results of a retrospective case series (n=46, 32 which completed the trial) evaluating radiologic changes in the discs at the adjacent levels and facets after disc replacement using the ProDisc II device. At an average follow-up of 32.2 months using outcome measures such as VAS scores, ODI scores, and imaging examinations facet degeneration was noted in 12 out of 41 segments; and among 47 adjacent segments, facet arthrosis was noted in 6.4%. Degenerative changes in the discs and facets were minimal at adjacent segments; however the progression of facet arthrosis at the index level was 29.3%. In 2011 Park and colleagues reported a minimum five year follow-up in this same cohort noting that improvements in clinical outcomes were maintained (VAS, mean ODI, physical component scores, and sports activity scores) although outcome scores at last follow-up were lower when compared with one or two year scores. The authors noted clinical success for 25 subjects (71.4%). In a larger study Zigler et al. (2012a) compared adjacent level degeneration among subjects who underwent either circumferential lumbar fusion for single-level disc degeneration (n=75) or total disc replacement using ProDisc-L (n=161). Average follow-up was five years and clinical outcomes were measured using ODI, SF-36, and VAS. Degenerative disc disease was evaluated with radiograph confirmation by CT, MRI, discography, plain film x-ray, myelography, and/or flexion and extension radiography. Changes in adjacent level degeneration were demonstrated in 9.2% of TDR subjects and 28.6% of fusion subjects (p=0.0040). Clinical outcomes were improved at five years in both groups and were not correlated with adjacent level degeneration. Nevertheless additional studies are warranted to support longer term outcomes regarding the continued effect of TDR on the adjacent segments.

Literature Review—Comparative Device Studies: Evidence evaluating and comparing outcomes of Charité and ProDisc devices are limited to comparative trials and systematic reviews. Freeman and Davenport (2006) conducted a systematic review of the current evidence for total disc replacement using the Charité or ProDisc devices. Their search produced two randomized trials, two systematic reviews, seven prospective cohort studies, eleven retrospective cohort studies and eight case series. The level of evidence that was assigned to these studies was in accordance with the Center for Evidence Based Medicine, Oxford, UK. The authors concluded that the long-term benefits of TDR in preventing adjacent disc degeneration is unknown; the role of two- or multi-level TDR remains unproven; the role of arthroplasty adjacent to a TDR is unproven; the complications of TDR may not be known for many years; and well-designed prospective RCTs are needed.

Shim and colleagues (2007) published the results of a retrospective study evaluating and comparing radiologic outcomes of the Charité and ProDisc devices among a total of 61 patients who underwent TDR (n=57). They concluded that, while the clinical outcomes were fairly good, the facet joint of the index level and the disc at the adjacent level showed an aggravation of the degenerative process in a significant number of patients, regardless of the device used.

Literature Review—Multilevel versus Single-Level: Increased segmental instability, increased load and altered stress distribution following total disc replacement remains a concern among authors. The FDA approved disc replacement prostheses are approved for single-level replacement. Total disc replacement for
multisegmental DDD in the lumbar spine is currently considered an off-label indication for disc replacement. Studies comparing the clinical outcomes of single-level disc replacement with disc replacement performed at more than one level remain limited.

Hannibal and colleagues (2007) compared the clinical effect of single-level ProDisc (n=27) versus two-level ProDisc replacement (n=32) at a minimum of two years follow-up. The data analysis was obtained from two FDA IDE clinical trials. There was a reported decrease in the overall averages of VAS scores: 47% for single-level versus 37% for two-level replacement at two-year follow-up. Single-level showed a slight reduction in pain on the VAS compared to two-level but the difference was not statistically significant at 12 months or two years. There was also a decrease in ODI scores for both single and two-level replacement, 38% and 28% respectively at two years follow-up. Single-level disc replacement performed better, but not significantly better at either one- or two-year follow-up. Two level procedures resulted in increased operative time; blood loss and hospital stay compared to single level. One and two-level scores were not significantly different in any of the evaluation measures; there was no significant difference shown by the authors in single-level or two-level disc replacement in this cohort. The authors concluded that further long-term studies are needed to support recommendations for multilevel disc replacement.

The results of a prospective nonrandomized study evaluating the clinical results of disc replacement with ProDisc II performed at different lumbar motion segments was published by Siepe et al. (2007). Total disc replacement was performed in 218 patients for single-level, bi-level and multi-level DDD. A total of 99 patients met inclusion criteria which consisted of diagnosis limited to DDD without accompanying pathologies. Patients with transitional vertebrae were not included. Minimum follow-up was 12 months, average 25.8 months. The study groups were defined as follows: Group A (single-level L4–L5, n=22), Group B (single-level L5–S1, n=57) and Group C (bi-level L4–L5, L5–S1, n=20). Clinical outcome measures included VAS scores, ODI scores, and various clinical and radiograph parameters. All groups achieved highly significant improvements for VAS and ODI scores throughout the entire follow-up. Best results and the most pronounced postoperative VAS and ODI improvement however was reported for disc replacement performed at L4–L5 (Group- A). When comparing single-level replacement (L4–L5 scores to L5–S1), VAS and ODI for L5–S1 patients deteriorated, with a trend toward statistical significance at 24 months follow-up (p=0.07). A further decline was noted when disc replacement was performed bisegmentally. When comparing single-level to bi-level replacement, VAS and ODI scores for single-level replacement demonstrated superior results (p< 0.05). In addition, patients who had single-level replacement showed a more rapid postoperative recovery at both the three and six month follow-up. A comparison between Group A (L4–L5) and Group C (L4–L5, L5–S1) favored L4–L5 replacement for both VAS and ODI scores from the six month follow-up exam forward. Bi-level replacement showed deteriorating postoperative results for both ODI and VAS scores from six months to 12 months. At the time of last follow-up 77.2% of Group A patients returned to work, whereas for Group B 67.8% returned to work and 50% returned to work in the bi-level group. Complication rates for Group A, B and C was 18.2%, 12.3% and 30.0%, respectively. The revision surgery rate increased from 7% following L5–S1 replacement to 20% following bi-level replacement. Fluoroscopically guided spine infiltrations revealed the incidence of postoperative pain was 9.1% for Group A, 28.1% for Group B and 60.0% for Group C.

Zindrick et al (2008) published an evidence based medicine review for determining factors that may affect the outcome of lumbar disc replacement. The authors reviewed patient selection issues, surgical technique issues, and motion technology issues. In particular, when reviewing the patient selection issues, the authors reviewed studies regarding the outcomes of single versus multisegmental implantation. Ten case series without comparison groups were available; two were retrospective reviews and the remaining eight were prospective in design. The follow-up periods ranged from one year (two studies) to greater than 10 years (one study) with most studies averaging two year follow-up. Sample populations were small with the number of patients who received single-level replacement ranging from 106 to 25 and the number of patients receiving ≥ two-level replacement ranging from three to 45. Three studies reported inferior results while seven studies reported no differences. When reviewing evidence to determine how spinal level, a patient’s age, and prior surgery affect patient selection outcomes, study design and overall conclusions were similar. The available evidence for surgical technique issues and motion preservation also consisted mainly of case series with only a limited number of higher level studies. The authors concluded that overall, the existing evidence does not provide strong conclusions regarding factors that affect clinical outcomes.

DiSilvestre et al. (2009) published the outcomes of a retrospective clinical trial evaluating patients who received bisegmental disc replacement for DDD, comparing results to single level treatment using the same disc device.
A total of 32 patients with at least three year follow-up participated in the study, 16 received two level disc replacement and 16 received single level disc replacement. Radiograph, functional analysis (VAS, ODI, SF-36 scores) and patient satisfaction were evaluated following surgery. There were no signs of degenerative adjacent segment changes, and no statistically significant difference in functional outcomes at three year follow-up. It was reported that more complications occurred in the two level group (nine) than in the single level group (four).

In 2011 Delamarter et al. (2011) published the results of a prospective randomized multicenter FDA IDE trial evaluating the ProDisc-L compared to circumferential fusion for two-level DDD (n=237). Reported outcomes included patient self-assessments, physical, neurological and radiograph assessment pre-operatively and six weeks, three, six, twelve, eighteen and twenty-four months postoperatively. At final follow-up 58.8% subjects who received disc replacement were classified as statistical success compared to 47.8% in the arthrodesis group. Although ODI scores significantly improved in both groups from preoperative to postoperative, results were significantly better in the total disc group (p=0.0282). A total of 73.2% of subjects in the disc group were defined as a clinical success based on ≥ 15 point improvement in the ODIS from baseline while 59.7% of the arthrodesis group were defined as a clinical success. In addition, SF-36 scores and VAS scores were significantly better for the disc group compared to the arthrodesis group. A significant reduction in narcotic usage was also reported for the disc group (p=0.0020). In the authors opinion two-level lumbar disc replacement using the ProDisc-L device was a viable alternative to lumbar arthrodesis for the treatment of two-level disc disease.

Other Lumbar Protheses: Premarket FDA approval was not found for other lumbar intervertebral disc prostheses. However, there are several artificial disc replacement (ADR) devices that are being studied for use in the lumbar spine. Until approval can be obtained through the FDA, and clinical trials are conducted that provide guidance on specific patient selection, or patient net health outcomes, the use of these devices for the treatment of lumbar degenerative disc disease remains investigational. Some of these devices include (This list may not be all inclusive):

- Maverick (Medtronic Sofamor Danel, Memphis, TN)
- FlexiCore™ Intervertebral Disc (Stryker Spine, Allendale, NJ)
- AcroFlex® (DePuy Acromed, Raynham, MA)
- Activ-L (Aesculap, Center Valley, PA))
- Freedom Lumbar Disc (Axiomed Spine Corporation, Newton, PA)
- Kineflex Lumbar Artificial Disc (SpinalMotion, Inc.)

Lumbar Technology Assessment/Guidelines: In 2005 several organizations reviewed the available literature and published recommendations regarding safety and efficacy of lumbar artificial disc replacement (Cochrane, 2005; California Technology Assessment Forum [CTAF], 2005; Institute for Clinical Systems Improvement [ICSI], 2005). All of these reports concluded there was insufficient data to adequately assess the performance of total disc replacement and further evidence is required regarding long term clinical outcomes.

In 2007 the Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) published their evaluation of artificial lumbar disc replacement. Based on the available evidence (case series, randomized controlled trials for the Charité and ProDisc) the committee determined the evidence was insufficient to conclude whether the use of artificial lumbar discs improved net health outcomes or whether they were as beneficial as any established alternatives. The TEC assessment indicates that the effectiveness of fusion for chronic DDD is not well established, both noninferiority trials may not provide evidence of effectiveness, specific noninferiority margins are not justified, and lower than expected success rates raise additional questions for validity. The randomized trials did not prove superiority. BCBSA TEC concluded the use of artificial lumbar discs for degenerative disc disease did not meet the TEC criteria.

In 2009, the National Institute for Health and Clinical Excellence (NICE) published an update to their 2005 guidance (without change to position) on intervertebral lumbar disc prosthesis and considered the evidence on safety and efficacy adequate to support the use of the procedure under normal arrangements (NICE, 2009). NICE acknowledged that although some studies have a follow-up of 13 years, a majority of the evidence is from studies with a shorter duration of follow-up.
ECRI reported their findings on the intervertebral disc replacement prostheses in an Emerging Technology Evidence Report (ECRI, 2009a). The evidence reviewed included systematic reviews, two randomized controlled trials (one each evaluating Charité and ProDisc-L), seven comparison trials and nine case series. The evidence to address key issues for lumbar discs in general as identified by ECRI included two randomized trials. Those studies enrolled a total of 596 patients, 487 of whom provided data for 24-month follow-up. According to the report, these RCTs had several limitations that weaken the reliability of results, including failure to analyze data on an intent-to-treat basis (i.e., to account for all patients entered in the trial when analyzing outcomes data; patients who were lost to follow-up were not accounted for). The data suggest that AIDR may offer some potential advantages over spinal fusion in terms of reduced operative time, decreased length of hospital stay, and increased patient satisfaction. The short-term adverse-event rate for AIDR may be similar to that for spinal fusion. However, the rate and clinical impact of complications cannot be determined with the currently available data. The studies assessed different implants, and the safety and efficacy may differ between implants. Also, the impact, if any, of changing implant designs complicates assessment of the data. Furthermore, the safety data on lumbar AIDR are inadequate to draw conclusions about long-term safety. Long-term safety issues may be addressed more fully by the ongoing postmarket study assessing five-year safety and efficacy of the Charité Artificial Disc and ongoing trials for other implants.

A Cochrane review (Jacobs, et al., 2012) was conducted to determine how total disc replacement compared with other treatments for chronic low back pain. The review included seven randomized trials involving 1474 subjects in total, and involved the use of four discs: Charite, Maverick, Prodisc-L, Flexicore. Six of the trials compared disc replacement to lumbar fusion and one compared disc replacement to nonsurgical treatment consisting of a rehabilitation protocol with cognitive treatment and physical therapy. Follow-up was 24 months in all studies with the exception of one which was five years. The subjects who had disc replacement surgery had slightly better back pain and function outcome scores compared to those who had fusion surgery; the differences did not appear clinically significant. The studies did not demonstrate any other benefit and did not provide any insight regarding long-term risks. As a result, the review concluded the spine surgery community should be cautious with regards to adopting the technology on a large scale, long-term outcomes are lacking. Pain relief outcomes are short-term and studies evaluating adjacent segment degeneration and facet joint degeneration are lacking.

Summary Lumbar Intervertebral Disc Prostheses: Prospective randomized controlled FDA trials comparing total disc replacement to lumbar fusion support safety and efficacy with two to five years follow-up for single level disc disease. The results of these trials support these devices are noninferior to lumbar fusion. Several studies to date show positive patient outcomes, including reduction of pain and improved motion, using the Charité and the ProDisc-L intervertebral disc devices for the treatment of DDD within the spine. The effect on adjacent spinal segments is not yet determined and continues to be investigated. Furthermore, additional studies are needed to determine the number of spinal levels that can be sequentially implanted in order to obtain the best patient results, or if the differences in the design of the currently available devices result in different clinical outcomes. Data supporting long-term safety, efficacy and improvement of net health outcomes are still being obtained. At present the ProDisc®-L and INMOTION Lumbar Artificial Disc System are the only available discs being used in the U.S outside of clinical trials.

Cervical Intervertebral Disc Prostheses
Surgical decompression of the nerve root or spinal cord by anterior cervical discectomy and fusion, with or without plate fixation, using autologous or allogeneic bone is considered the standard surgical treatment for symptomatic cervical DDD when conservative measures have failed. Adjacent segment degeneration following cervical fusion is a concern however; Hilibrand et al. (1999) estimated that more than 25% of patients will develop adjacent segment disease during the first 10 years following cervical fusion and the risk of repeat operation after a prior fusion in half of all symptomatic patients. In hopes of restoring spinal motion and preventing adjacent segment disease, cervical intervertebral disc prostheses have been developed for use in patients with symptomatic cervical disc disease associated with DDD at a single level between C3 to C7. Cervical disc arthroplasty utilizes the same surgical approach as a fusion; however instead of using bone graft and anterior plate fixation during the arthroplasty, the surgeon secures a prosthetic disc into the intervertebral space. The device is designed to assist in maintaining vertebral height while decompressing the spinal cord or nerve root in the neck.

Cervical intervertebral disc prostheses that have been approved by the FDA for surgical implantation within the spine, for single-level cervical disc replacement include but are not limited to: The Prestige™ ST Cervical Disc...
(Medtronic Sofamor Danek, Memphis, TN), the PRODISC-C® Total Disc Replacement (Synthes, Inc., New York, NY), the BRYAN® Cervical Disc (Medtronic Sofamor Danek, Memphis, TN), Secure®-C Cervical Artificial Disc (Globus Medical, Audubon, PA) and PCM® Cervical Disc System (NuVasive, Inc., San Diego, CA).

**PRESTIGE™ ST Cervical Disc**
The PRESTIGE™ ST Cervical Disc consists of a two-piece articulating metal-on-metal device that is inserted into the intervertebral disc space at a single cervical level using an anterior approach. The components are affixed to the vertebral body by two bone screws through an anterior flange, and locked into place with a lock screw mechanism. This prosthesis is designed to allow the following motions ex-vivo: a minimum of 10 degrees motion off the neutral position in flexion/extension and lateral bending, unconstrained axial rotation, and two millimeters (mm) of anterior/posterior translation. (This device has been modified since its original design, and previous versions have included the Bristol/Cummins disc, the Prestige I and the Prestige II.).

**U.S. Food and Drug Administration (FDA):** In July 2007, the FDA granted a premarket approval for the PRESTIGE™ ST Cervical Disc prosthesis. According to the manufacturer and the FDA premarket approval, this device is indicated for use in a skeletally mature patient for the reconstruction of a cervical disc from C3–C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The intractable radiculopathy and/or myelopathy (i.e., herniated disc, and/or osteophyte formation) should be severe enough to produce symptomatic nerve root and/or spinal cord compression, documented by patient history (e.g., neck and/or arm pain, functional deficit, and/or neurological deficit) and radiographic studies (e.g., CT, MRI, x-rays).

According to the FDA the Prestige Cervical Disc prosthesis is contraindicated in patients with an active infection or with an allergy to stainless steel. In addition, the safety and effectiveness of this device has not been established in patients with the following conditions:

- more than one cervical level with DDD
- not skeletally mature
- clinically significant cervical instability
- prior fusion at an adjacent cervical level
- severe facet joint pathology or involved vertebral bodies
- prior surgery at treated level
- osteopenia, osteomalacia, or osteoporosis as defined by bone mineral density T-score of -3.5, or -2.5 with vertebral crush fracture
- spinal metastases
- chronic or acute renal failure or history of renal disease
- taking medications known to potentially interfere with bone/soft tissue healing (e.g., steroids)
- pregnant
- severe insulin-dependent diabetes

The safety and effectiveness of the use of this device has also not been established in patients who have not undergone six weeks of conservative treatment or had signs of progression or spinal cord/nerve root compression with continued nonoperative care.

As part of the approval, the FDA is requiring a seven-year post-approval study to evaluate long-term safety and effectiveness of the Prestige ST Cervical Disc. Data will be collected at three, five and seven years postoperatively for all patients. Outcome measures will include Neck Disability Index (NDI) scores, radiograph information and neurological status as well as detailed information regarding adverse events.

**Literature Review—PRESTIGE ST Cervical Disc:** Evidence in the peer-reviewed published scientific literature evaluating early models of the PRESTIGE cervical disc included case series with few randomized trials (Wigfield, et al., 2002; Robertson and Metcalfe, 2004; Porchet, 2004). Sample populations of these studies were small ranging from 15 to 55 subjects with follow-up that ranged from 24 to 48 months. The results of these studies supported device stability, deceased neck and arm pain, improved SF-36 quality of life scores and improved NDI scores.

Mummaneni et al. (2007) conducted a prospective, randomized controlled study under an FDA-approved IDE to assess the safety and effectiveness of the PRESTIGE ST Cervical Disc System. This study compared anterior cervical discectomy with fusion and plating to cervical discectomy with immediate arthroplasty and insertion of
the PRESTIGE ST Cervical Disc System (n=541). Subjects were randomized into an investigational group (n=276) and a control group (n=265) within 32 institutions. Patients in the investigational group received a PRESTIGE ST Cervical Disc system prosthesis, and individuals in the control group underwent interbody fusion with cortical ring allograft and supplemental fixation using cervical plating. All patients entering the study had Neck Disability Index (NDI) scores of 30 or greater and numeric pain scores greater than or equal to 20. Prior to surgery, patients received six weeks of medical management (e.g., physical therapy, a reduction in activities, and anti-inflammatory medications) unless progressive neurological worsening occurred.

Mummaneni reported that the 24-month overall follow-up rate was 80% (223 of 276) in the investigational group and 75% (198 of 265) in the control group. Patients were counted as treatment failures if data could not be obtained during this 24-month period. Secondary surgery occurred within both groups. No revisions occurred in the investigational group, while five revisions occurred within the control group. Implant removal was required in both groups (1.8%—investigational versus 3.4%—control), although not statistically significant. Reoperations were required for adjacent-segment disease in both groups, with a statistically significant lower rate occurring in the investigational group (p=0.0492) versus the control group. During the perioperative period, 17 adverse events (6.2%) occurred in the investigational group and 11 (4.2%) occurred in the control group. These events included hematoma formation, dysphagia, and dysphonia. Neck Disability Index (NDI) scores in both groups improved significantly over preoperative scores (p<0.001), with statistical significance noted at six weeks and at three months for the investigational group. Neck pain scores improved significantly throughout the study in both groups, with no statistical difference noted in arm pain improvement between the groups.

At 24 months, neurological success was 92.8% in the investigational group versus 84.3% in the control group, the incidences of employment were 75.4% and 74.7% (investigational versus control group), there were no implant failures, migrations, or subsidence found; and only one case of ectopic ossification was in the investigational group. Radiographic angulation was increased in the investigational group. Evidence of fusion in the control group was high at 12 (98.7%) and 24 (97.5%) months. Overall success for the investigational group was 77.6% at 12 months and 79.3% at 24 months. Overall success for the control group was 66.4% at 12 months and 67.8% at 24 months. The researchers determined that the outcomes proved the device was noninferior to anterior cervical discectomy with fusion (ACDF) (p<0.0001) at both 12 and 24 months. They also determined that neurological functioning outcomes were statistically superior (p=0.0040, 12 months; p=0.0053, 24 months).

Burkus et al. (2010) published five-year results of a prospective randomized multicenter RCT (32 centers, n=541), comparing cervical disk replacement using the Prestige disc (n=276), to anterior instrumented interbody fusion (n=265). The study was a continuation of 36 month data which is used in this study as a point of comparison. All surgeries were performed at a single disc space level between C3-C4 and C6-C7. All patients had neck and arm pain which continued despite nonoperative treatment for at least six weeks prior to surgery. One center did not participate in the long term follow-up study leaving 533 subjects eligible for the post-approval study. Of those patients, 271 have completed the 60-month follow-up. A total of 197 patients of the investigational group and 160 of the control group were included in the results evaluated at 36 months. Clinical outcome measures included NDI, SF-36 PCS, neck and arm pain scores, return to work status range of motion and secondary surgical procedures. The latter were classified as revision, removals, supplemental fixations or reoperations. Adjacent segment ossification was not a specific data point in the study. Reported results favored the cervical implant for the following end points which was statistically significant:

- NDI scores at 35 and 60 months
- Rates of revision (5 versus 0) and supplemental fixation (3.4% versus 0%)
- Sagittal motion retention (averaging 7.3° at 36 months and 6.5° at 60 months

Non- statistical results were identified for the following end points:

- Subsistence rates
- Neck and arm pain scores as well as SF-36 scores, which improved in both groups
- Neurological success rates which were high in both groups
- Subjects returning to work, each exceeding 70%
- Complaints of dysphagia and dysphonia were similar among both groups

The authors concluded the Prestige disc maintains improvement of clinical outcomes at five year follow-up.
PRODISC-C®:
The ProDisc-C Total Disc Replacement is composed of three components: a cobalt chromium molybdenum alloy plate that is anchored into the inferior vertebral body, an ultra-high molecular weight polyethylene insert that is attached to the alloy plate providing an inferior convex bearing surface, and a second cobalt chromium molybdenum alloy plate that anchors to the superior vertebral body and has a concave bearing surface. The device forms a ball and socket joint and allows unconstrained axial rotation.

U.S. Food and Drug Administration (FDA): In December 2007, the FDA granted a premarket approval for the ProDisc-C Total Disc Replacement prosthesis. This device is indicated for use in skeletally mature individuals for the reconstruction of the disc from C3–C7 following single-level discectomy for intractable symptomatic degenerative disc disease (SCDD). SCDD is defined as neck or arm (radicular) pain and/or functional/neurological deficit with imaging confirmation (i.e., CT, MRI, X-rays) of at least one of the following conditions: herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes) and/or loss of disc height. Candidates for this device should have failed at least six weeks of nonoperative treatment (e.g., physical therapy, medication) prior to implantation.

The FDA has reported this device is contraindicated in people with the following conditions:
- active systemic infection or infection localized to the site of implantation
- osteoporosis
- marked cervical instability on neutral resting lateral or flexion/extension radiographs
- allergy or sensitivity to implant materials
- severe spondylosis
- compromised vertebral bodies at the affected level
- individuals with SCDD at more than one level

Safety and effectiveness of this device has not been established in patients with the following conditions:
- skeletally immature patients, pediatric or adolescent children (<21 years old)
- over the age of 60
- more than one vertebral level with SCDD
- prior fusion surgery at an adjacent vertebral level
- prior surgery at the level to be treated
- patients with progressive symptoms and signs of spinal cord/nerve root compression with less than six weeks of conservative treatment
- facet joint disease or degeneration at the level to be treated
- neck or arm pain of unknown etiology
- Paget's disease, ostemalacia, or other metabolic bone disease
- pregnancy
- taking medications known to potentially interfere with bone/soft tissue healing (e.g., steroids)
- rheumatoid arthritis or other autoimmune disease
- severe diabetes mellitus requiring daily insulin treatment
- systemic disease including AIDS, HIV, and Hepatitis
- active malignancy

Similar to the Prestige ST cervical disc, the FDA is requiring a post-approval study be conducted to evaluate long-term safety and effectiveness of the ProDisc-C Total Disc Replacement. Overall success parameters have been defined by the FDA in addition to guidance for radiological parameters evaluating adverse events and adjacent segment degeneration.

Literature Review—PRODISC-C®: Nabhan and colleagues (2007) reported on the results of a prospective randomized controlled study evaluating segmental motion following artificial disc replacement with the ProDisc-C device over one year. The authors compared segmental motion and clinical results of disc replacement (n=25) to the "gold standard" anterior cervical discectomy and fusion (n=24). Eight patients were excluded due to ineligibility for roentgen stereometric analysis, leaving 41 for the RCT, one patient died during the trial period. Clinical symptoms of neck and arm pain were evaluated at baseline and at one, three, six, 12, 24 and 52 weeks after surgery. VAS was used for grading neck and arm pain. At one year there was no sign of adjacent level degeneration in either group, pain relief was comparable in both groups and mean VAS scores for neck and arm...
pain decreased significantly in both groups from preoperative. The authors reported that cervical spine motion decreased over time in both the prosthesis and fusion group although the loss was significantly higher in the fusion group at one year postoperatively. The authors noted further studies are warranted with long-term follow-up to ascertain whether or not cervical motion is preserved following disc replacement.

Murrey et al. (2008) conducted a prospective, randomized controlled study under an FDA-approved IDE study (noninferiority design) to assess safety and effectiveness of the ProDisc-C Total Disc Replacement. The study population involved 209 patients with symptomatic cervical degenerative disc disease causing intractable debilitating radiculopathy from one vertebral segment (between C3 and C7) who were unresponsive to nonoperative treatment for at least six weeks and had neck disability index scores of 15/50 (30%) or more. The study compared ProDisc-C (n=103) to a control group who received anterior cervical discectomy and fusion (n=106). Overall success was determined by four-component endpoints: NDI success (defined as a 15 point improvement from baseline value), neurological success (defined as the maintenance of improvement of each neurologic evaluation [sensory, motor, reflex functions], device success and absence of adverse events related to the device or its implantation with ratings defined as the percentage of individual patients achieving success in all four-component endpoints. The clinical status of each patient was evaluated pre and postoperatively at six weeks, three, six, 12, 18 and 24 months and included self-assessment, physical and neurological examination and radiograph evaluation.

The follow-up rate at 24 months for the entire group was 96.5% and the authors noted there were no statistically significant differences between ProDisc-C patients (98.0%) and control patients (94.8%) returning at 24-months. Both operative time and blood loss were lower for the fusion group compared to the ProDisc-C group and were statistically significant. Other statistically significant outcomes favored the disc group and included neurological success at 6 months, NDI scores at three and 24 months and device success. Other reported outcomes that favored the disc group but were not statistically significant included secondary surgical procedures, adverse event success, VAS scores and return to work.

There was no evidence of migration, subsidence, change in disc height, or visible gaps found on radiograph assessment in either group at 24 month follow-up. The fusion rate for patients who did not require a secondary surgery at 24 months was 90.2%. A total of 84.4% or ProDisc-C patients achieved a more than or equal to 4° of motion or maintained motion relative to preoperative baseline at the operative level.

Based on FDA criteria for success, 72.3% of ProDisc-C patients and 68.3% of fusion patients were successful at 24 months. The additional minimally clinically important difference (MCID) found 73.5% of ProDisc-C patients and 60.5% of fusions patients successful at 24 months. The authors concluded that the ProDisc-C is proven as safe and effective compared to standard treatment of anterior cervical discectomy and fusion.

In 2010 Delamarter et al. published the four year follow-up results of the 24-month IDE trial of ProDisc-C versus anterior cervical discectomy and fusion. In total, 63% of the subjects who underwent disc replacement were available for 48 month follow-up and 46.2% of subjects who underwent cervical fusion were available at 48 months. The measured outcomes were the same as for the initial FDA trial and included NDI scores, VAS scores for pain and satisfaction, radiographic, and neurological and physical examinations. The results remained superior for neurological success, and sustained improvement for NDI and VAS scores, and SF 36 scores. Range of motion was maintained for the disc replacement group who reached 48 month follow-up. A total of 2.9% of disc patients and 11.3% required secondary surgery at 48 month follow-up. In the authors opinion although the cervical fusion group had higher risk for secondary surgical intervention, both groups demonstrated good clinical results at 48 month follow-up. The authors noted the subjects were continuing to be followed up for seven years (Delamarter, et al., 2010).

Kelly et al. (2011) compared adjacent segment motion following disc arthroplasty using the ProDisc-C device versus ACDF in 209 patients in a prospective randomized controlled trial. Changes in motion were compared, and flexion and extension radiographs were obtained at an average 24 month follow-up. At 24 months the ACDF group had a significant decrease in ROM while the disc replacement group did not (p<0.0001, p=0.275). Linear regression analysis revealed that treatment and time from surgery were significantly associated with changes in postoperative motion, the effect of time differed between the ACDF group and the disc group (p<0.0001). In the ACDF group only, there was a significant increase in motion at the cranial and caudal adjacent segments, time from surgery was a significant predictor of postoperative ROM. ROM decreased over
time with fusion whereas disc replacement results in immediate motion sustained throughout the follow-up period.

Nabhan et al. (2011) conducted a prospective randomized controlled trial comparing segmental motion following cervical disc replacement (n=10) versus cervical fusion (n=10) and correlation to clinical outcome. Results were evaluated using the VAS and NDI scales, roentgen stereometric analysis (RSA) was performed immediately postoperative and after six weeks and 12 months. In the authors opinion the precision of RSA is high making it suitable for small study samples compared to functional X-ray. At an average of 12 months there was no change in the average segmental motion immediately cranial to the disc prosthesis; there was an increase in the average segmental motion immediately cranial to the fusion but without significant difference (p>0.05) when compared with the prosthesis. Both procedures resulted in significant reduction in arm and neck pain; statistical significance however was lacking between groups (p>0.05). The authors concluded here was no significant difference in segmental motion of the adjacent level, with either prosthesis or fusion, one year post surgery.

Zigler and colleagues (Zigler, et al, 2012) published interim five year clinical outcomes of the patient cohorts in the original noninferiority FDA IDE trial comparing cervical arthroplasty using ProDisc-C to anterior cervical discectomy and fusion (ACDF). This study is an interim report to the seven year post-approval study. The FDA IDE study involved 209 subjects from 13 sites. NDI scores, VAS neck and arm pain scores, SF-36, neurological exam, devices success, adverse events, and patient satisfaction were evaluated. At five years follow-up, 13 subjects withdrew from the study and five were deceased (n=195). An additional 52 subjects were lost to follow-up. The authors accounted for those who dropped out and were lost to follow-up by using a “last observation carried forward” sensitivity analysis, reporting that the results with this method were consistent with results obtained with the missing data. All clinical outcomes improved at both two and five years compared to baseline with a statistically significant difference in NDI scores (p=0.0001), neck and arm pain scores (p=0.0001), and SF-36 scores (p=0.0001). There were no differences between groups at two and five years for NDI scores, SF-36 scores, patient satisfaction or neurological assessments. There was no percent change between groups for neck pain intensity and frequency at two years but there was a difference at five years. Though both groups had statistically significant reduction of neck pain intensity and frequency at five years compared to baseline, the reduction was more significant in the Pro-Disc group. A between groups analysis did reveal a statistical difference between the intervention groups at five years on both neck pain intensity and frequency, at p=0.0122, and p =0.0263, respectively. The fusion group demonstrated significantly reduced ROM at the index level at two and five years compared to preoperative values; the ProDisc-C group maintained ROM at the index level compared to preoperative values. A statistical assessment was not reported. Device migration was not detected in either group. Rates of adverse events related to implants were not statistically different though Pro-Disc trended lower at 1% compared to 2.8% for fusion patients. No p value was reported. Surgical adverse events were statistically comparable between groups with an overall incidence of 12 in the ProDisc-C group versus 22 in the fusion group (p=0.09). For all subjects included in the analysis, the ProDisc-C patients were reported to have had statistically significantly less secondary spinal surgery compared to the ACDF group (2.9% versus 11.3% respectively, p =0.0292). The data reported in this interim study are promising regarding the authors’ conclusion of non inferiority however there are limitations of the study. More than 25% of subjects were lost to follow-up; 27 in the Pro-Disc group and 25 in the ACDF group and the statistical inclusion of last data point as part of the outcomes for those lost to follow-up is a concern, and introduces treatment bias favoring reduced adversity, reoperation rates, and diminishing validity of reduced symptom severity over time. Both groups had statistical improvement in nearly all areas and both groups were very satisfied with their outcomes. Additional follow-up of this cohort is needed to determine long-term outcomes supporting safety and clinical utility for this group of subjects, and results that can be generalized to a larger population.

BRYAN® Cervical Disc:
The BRYAN cervical disc is composed of a plastic (polyurethane) center with titanium endplates. It is designed as a one-piece device that allows unconstrained motion and is unique in that there is a flexible membrane that surrounds the nucleus (the inner portion of the disc) that is filled with a lubricant. This membrane is designed for two purposes: to contain any wear debris that forms and to prevent any soft tissue in-growth. The articulating surfaces of this device are polyurethane on titanium. It has beaded porous coated endplates intended for biological fixation instead of fixation using screws into the vertebrae or fixation by use of stabilizing keels.

U.S. Food and Drug Administration (FDA): In May 2009, the FDA granted a premarket approval for the BRYAN Cervical Disc. Based on the information provided from the manufacturer and the FDA premarket approval, the device is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following
single-level discectomy for intractable radiculopathy and/or myelopathy. The BRYAN® device is implanted via an open anterior approach. Patients receiving the BRYAN® Cervical Disc should have failed at least six weeks of non-operative treatment prior to implantation of the device.

Similar to other FDA approved cervical disc replacement devices, the FDA is requiring a post approval study to evaluate the safety and effectiveness of the BRYAN Cervical Disc. Data is to be collected at five, seven and 10 years (due to the polyurethane articulating surface) and include NDI, radiographic information, neurological status, heterotopic ossification, disc orientation and adjacent level disease, as well as other outcomes as measured in the IDE study. The FDA is also requiring data for explanted devices and all adverse events including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome, reported for these patients. A five-year enhanced surveillance study is also being required to more fully characterize adverse events when used in a broader population.

The FDA has indicated the device is contraindicated in patients with the following conditions:
- active systemic infection or infection at the operating site
- allergy to titanium, polyurethane, or ethylene oxide residues
- osteoporosis defined as a DEXA bone mineral density T-score equal to or worse than -2.5
- moderate to advanced spondylosis characterized by bridging osteophytes, marked reduction or absence of motion, or collapse of the intervertebral disc space of greater than 50% of its normal height
- marked cervical instability on radiographs (e.g., radiographic signs of subluxation greater than 3.5 mm or angulation of the disc space more than 11 degrees greater than adjacent segments)
- significant cervical anatomical deformity or compromised vertebral bodies at the index level (e.g., ankylosing spondylitis, rheumatoid arthritis, or compromise due to current or past trauma)
- significant kyphotic deformity or significant reversal of lordosis
- symptoms necessitating surgical treatment at more than one cervical level

In addition, the safety and effectiveness of this device has not been established in patients with the following conditions:
- axial neck pain as solitary symptom
- not skeletally mature
- prior cervical spine surgery, including prior surgery at the Index level
- facet joint pathology of involved vertebral bodies
- active malignancy
- Paget's disease, osteomalacia, or other metabolic bone disease
- chronic or acute renal failure or history of renal disease
- taking medications known to potentially interfere with bone/soft tissue healing (e.g. steroids)
- pregnant
- unstable cardiac disease
- diabetes mellitus requiring daily insulin management
- extreme obesity as defined by the NIH Clinical Guidelines Body Mass Index (i.e., DM1 SO).

The safety and effectiveness of this device has also not been established in patients who have undergone less than six weeks of conservative treatment or in those who had signs of progression or spinal cord/nerve root compression with continued nonoperative care.

**Literature Review—BRYAN® Cervical Disc:** Results from preliminary prospective trials evaluating this device supported range of motion of ≥ 2 degrees, improved activities of daily living scores and neurological improvement at follow-up periods of six months, 12 months, and 24. Nonetheless the authors acknowledged five year data was needed to evaluate long term device functionality and impact on adjacent segments (Goffin et al. (2002 [b]; (2003 [a]).

Sasso et al. (2007a, 2007b) reported a subset of data from 115 patients who participated in the FDA IDE study of the BRYAN® cervical disc. At 12 months, data from 109 patients were available; data from 71 patients were available at 24 months in the initial publication, however in the second publication 99 subjects were available for 24 month follow-up. Outcomes from these both groups were determined by comparing preoperative PCS, NDI and VAS pain scores to those recorded at each follow-up time. Sasso reported that both groups had significant improvement from baseline NDI scores and neck pain at 24 months. The disc replacement group retained an
average ROM of 7.3 degrees at 12 months and 7.0 degrees at 24 months. By 24 months, there was no statistically significant change noted over preoperative measurements. Three patients in the investigational group required ACDF due to adjacent level disease during the 24 months of follow-up. No spontaneous fusions or heterotopic ossification (HO) were noted in the BRYAN group.

Some studies evaluating the BRYAN artificial disc included a subset of subjects involved in the FDA IDE trial (Garrido, et al., 2010; Anderson, et al., 2008; Sasso, et al., 2008a, Sasso, et al., 2008 b). Other clinical trials published in the peer-reviewed scientific literature consisted of randomized controlled trials (Anderson, et al., 2008; Heller, et al., 2009), prospective comparative trials (Yang, et al., 2008), prospective case series (Heidecke, et al., 2008), and retrospective case series (Yang, et al, 2009). The type of outcomes evaluated in all of these trials varied by author group and included outcomes such as occurrence of adverse events of disc replacement compared with cervical anterior fusion, the ability of the disc to maintain motion at the implanted level, range of motion, clinical outcomes such as improvement of neck and arm pain, changes in functional activity, radiographic outcomes such as migration or subsidence, and overall quality of life improvements. Sample populations and outcome follow-up varied among trials but ranged from 15 to 98 subjects with the FDA IDE trial consisting of 463. Follow-up time ranged from 12 to 24 months; Garrido et al. (2010) reported 48 month results and Goffin et al. (2010) reported follow-up at four and six years. Although study design, sample size, outcomes measured and follow-up time varied these studies support safety and efficacy of the implanted BRYAN Disc. Results of the studies demonstrated improvements postoperatively in neck and arm pain, NDI, VAS, SF-36, cervical motion, and improved quality of life.

In 2010 the Swiss federal office of health conducted a prospective multicenter observational study to evaluate safety and efficacy various cervical discs. As part of a mandatory Health Technology Assessment registry 808 interventions with implantation of 925 discs from five different suppliers were evaluated. Data was recorded preoperatively, at three months, one year and annually thereafter and included patient self-reported measures (EQ-5D, COSS, comorbidity questionnaire) as well as surgeon reported outcome instruments which included intervention, implant and follow-up forms. Evaluation of results extending to two years was published. Disc replacement resulted in significant and clinically relevant reductions of neck pain and arm pain (using VAS scale) and decreased use of analgesics. Quality of life improved from preoperatively to postoperatively on the EQ-5D scale. The authors reported four intraoperative complications and 23 revisions during the same hospitalization for 691 monosegments, and two complications and six revisions for 117 two-level replacements. Cervical total disc arthroplasty was determined to be safe and effective for relief of pain, reduction of analgesic use and improved quality of life in the short-term (Schluessman, et al., 2010).

Some authors have reported on clinical outcomes for the Bryan disc that range intermediate to long-term (Ren, et al., 2011; Quan, et al., 2011; Yan-bin, et al., 2010; Walraevens, et al., 2010). Although not in the form of randomized controlled trials and often involving small sample populations, the reported intermediate to long-term outcomes suggest preservation of motion, reduction in adjacent level degeneration, and improvement in neurological symptoms. In 2010 Walraevens et al. published preliminary results of a prospective case series involving 89 subjects who received the Bryan disc. Eight-year results were available for 26 (radiographic assessment) out of 89 patients at the time of publication, although 82 completed four year follow-up. At four years 85% of the devices were mobile, at six years 87% were mobile, and of those available at eight years 88% were mobile. Improvements in ROM stabilized around the preoperative value at the four year time period. A total of 66% were free from heterotopic ossification at four years, at six years 62% were free and at eight years 61% were free. At all follow-ups there were no cases of anteroposterior migration >3 mm or of subsidence >2mm. Good to excellent clinical outcomes were reported for 87% at four years, and 85% and 82% respectively for six and eight year follow-up.

Zhao et al (2010) reported from a case series the radiograph and MRI results of 22 patients who underwent cervical disc replacement using the Bryan disc. Mean follow-up was five years. Range of motion on radiograph at the operated level improved at baseline from final follow-up 7.2° to 7.8°. Eight levels developed heterotopic ossification and two had lost motion. Upper adjacent segment worsened by a grade in 2 of 22 subjects and lower adjacent segment worsened by a grade for 3 of 22 patients; 22 of 24 levels showed preserved motion at five years while 8 of 24 developed heterotopic ossification and two levels lost motion. In the authors opinion by preserving motion the Bryan disc may reduce adjacent segment degeneration.

Ren at al. (2011) reported the results of a prospective case series involving 45 subjects who received 51 Bryan cervical discs, 39 received single-level replacement and six subjects received two-level replacements. Follow-
up evaluation ranged from 24 to 70 months, with an average of 35 months. The authors noted all patients had improvement in neurological symptoms. Japanese Orthopedic Association Scale (JOA) scores increased from 10.2 preoperatively to 15.4 at final follow-up. NDI scores were reduced from 43.6 to 28.4 at final follow-up and Odom’s Criteria also improved and was rated as excellent in 23 subjects, good in 11 subjects, fair in 6 subjects, poor in 5 subjects. Overall clinical success rates were 88.8%. The average ROM improved, stabilization was achieved for all discs and migration of the disc greater than 2mm was not seen.

Quan et al. (2011) reported the results of a prospective cohort of 21 subjects who underwent single- or two-level disc replacement using the Bryan cervical disc. Although initially there were 30 subjects, nine subjects were either lost to follow-up or had incomplete data and were not included. The authors reported no patient required further spinal surgery on either the arthroplasty or adjacent segment at final follow-up. Fourteen of the 21 patients were working and the remaining seven were either retired or not working due to poor health. Twelve subjects reported no occupational or recreational limitations when compared to preoperative activity levels; seven retired patients also reported no limitations. Based on Odom criteria 18 of 21 subjects had excellent outcomes. VAS scores for neck and arm pain both improved postoperatively, mobility was maintained in 21 of 27 segments and there was no significant difference in range of motion between functional prostheses and upper or lower adjacent segments. A total of 13 of 27 subjects had heterotopic ossification and those patients had slightly higher VAS scores for neck and arm pain. One case of posterior migration was reported which consolidated and did not result in additional surgery. Radiograph evidence of adjacent segment degeneration was noted in four subjects, and in three of those the prosthesis had fused. These patients did have pre-existing degenerative disc disease.

Sasso and colleagues (2011) reported 48 month follow-up data to the pivotal FDA clinical trial published by Heller et al (2009). Of the original 463 subjects who were enrolled in the FDA trial, 24 month results for 424 subjects in total have been previously reported. A condition for approval of the device from the FDA was an extension of the original trial to 10 years post-surgery. The results reported by Sasso et al. (2011) reflect a total of 319 subjects (181 arthroplasty, 138 fusions) who were available for follow-up at 48 months (68%). The measured clinical outcomes were similar to the original trial and included NDI scores, SF-36 scores, determination of neurological success, radiograph assessment and adverse events. The primary endpoint was overall success for which patients had to achieve all of the following: > 15 point improvement in NDI, neurological improvement, no serious (WHO grade-3 or 4) adverse events, and no subsequent surgery or intervention that would be classified as a treatment failure. The authors reported that at 48 months greater improvement in NDI scores, arm pain scores, SF-36 results, and overall success (p=0.004) continued to favor the experimental group. Neurological success rates at 48 months were similar to those reported at 24 month and were not significantly different. At 48 months more TDR subjects returned to work compared to the fusion group, although not significantly different. Mean cervical spine motion increased for the disc group at all time points whereas the fusion group showed a decrease of motion at 48 months. Forty-four subjects in the arthroplasty group had 63 adverse events while 36 of the subjects in the fusion group had 64 adverse events; the difference was not significant. The authors noted most of the events were unrelated to the index surgery or cervical spine. Nine patients of TDR group and ten of the fusion had secondary surgical procedures involving the index cervical spine level. One patient in each group had the device removed. Despite the limitation of a low rate of follow-up, which the authors attribute to the original design of the study (set for 24 months), the authors concluded significantly superior outcomes were sustained for cervical spinal arthroplasty with the Bryan disc compared to fusion at 48 month follow-up.

The results of two separate FDA IDE trials were combined to evaluate long term outcomes of cervical TDR (n=41) with ACDF (n=33) (Coric, et al., 2013). Sixty-three subjects were available for a minimum of 48 month follow-up, although average follow-up was six years. Both groups demonstrated significant improvement of NDI scores and VAS scores (p<0.0001) that continued through the 48 month follow-up with no significant differences between groups. ROM in the cervical group was significantly greater compared with the ACDF group. There was no statistically significant difference in overall reoperation rate or adjacent–level reoperation rate between groups. The authors concluded both treatments appeared to be safe and effective at a minimum of 48 months follow-up. The study is limited by small sample population.

A meta-analysis published by Gao and colleagues (2013) of 27 RCTs indicated as expected ACDF subjects had less range of motion at the operated level compared with TDR. The arthroplasty subjects had significantly better neurological success (p=0.000) and significantly lower neck and arm pain scores (p=0.01, p=0.02) while maintaining a comparable NDI score. Data for adverse events were not consistent, some studies supported less
adverse events in the TDR group compared with the ACDF group and some did not. Overall, outcomes were either equivalent or superior in favor of the disc replacement group.

Other FDA-approved Cervical Disc Devices

Other cervical artificial discs that have received FDA PMA approval include the Secure®-C Cervical Artificial Disc and the PCM® Cervical Disc System. The Secure-C device is an articulating intervertebral disc device that has two endplates and a central core; the endplates have multiple serrated keels and a pure titanium plasma spray coating on the bone contacting surfaces. The sliding core is composed of ultra-high molecular weight polyethylene. The PCM device is also an articulating device, is composed of two cobalt chromium molybdenum alloy endplates and an ultra-high molecular weight polyethylene spacer fixed to the caudal endplate. The contact between the spacer and cephalad component is a bone and socket articulation. The bone contacting surface of each endplate has a layer of calcium phosphate and consists of transverse ridges designed to improve postoperative bone fixation. Both devices are inserted with an anterior approach and according to FDA labeling the indications for use and contraindications for these two devices are similar to those for other devices previously approved.

According to the FDA (PMA -P110009) approval has been granted for the Mobi-C® Cervical Disc (LDR Spine USA, Inc). This device is a cervical disc prosthesis approved for use at two adjacent levels for the treatment of intractable radiculopathy with or without neck pain, or myelopathy due to abnormality localized to the level of the disc space, and at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height compared to adjacent levels. According to the manufacturer the device can be used for either one or two level disc disease. The FDA is requiring a 7-year post approval for this device, similar to other FDA approved disc prosthesis.

Literature Review—Other FDA Approved Devices:
The Secure-C, PCM, and Mobi-C cervical devices were evaluated in investigational device exemption (IDE) studies as part of the FDA PMA approval process. These studies were prospective randomized trials involving multiple centers, used ACDF as the control, and evaluated clinical outcomes extending to at least two years ([PCM-Phillips, et al, 2013]; [Mobi-C-Davis, et al., 2013]). As per the IDE protocol outcome measures and definitions of success were similar although not identical to other cervical disc IDE trials. According to the PMA for each device the IDE trials supported safety and efficacy of the devices at two year follow-up. Similar to some of the other FDA approved devices the FDA is requiring a 7 year post approval study for each device in order to evaluate the longer-term safety and effectiveness. The FDA expects at least 85% follow-up at the 7 year time period for each of these studies to provide sufficient data.

Literature Review—Adjacent Segment Disease

The effects of cervical TDR on adjacent segments are under investigation. Robertson et al. (2005) compared data from two prospective studies to document radiological changes and symptomatic adjacent-level cervical disc disease after single-level discectomy and subsequent cervical fusion or arthroplasty with the BRYAN cervical disc prosthesis. This cohort of patients included 158 with cervical fusions and 74 with BRYAN discs that were followed 24 months after their initial surgery. Radiological evidence of adjacent-level disease included new anterior osteophyte formation or enlargement of existing osteophytes, increased or new narrowing of a disc space (≥30%), and new or increasing anterior longitudinal ligament (ALL) calcification. Robertson and colleagues noted that in the fusion group, new osteophyte formation in the superior adjacent space was noted in 85% of the patients and in the inferior space in 15%; whereas, in the BRYAN group all osteophytes were new and only one was located in the inferior adjacent space. The researchers concluded that: 1) the presence of moderate or severe kyphosis if present at the symptomatic level may be a contraindication for use of the BRYAN disc; 2) radiographic findings demonstrate changes in the adjacent levels of the spine after fusion within 24 months (p=0.009), as well as adjacent-level symptomatic cervical disc herniation (p=0.018); and 3) it appears that maintaining motion after single-level cervical discectomy may delay or prevent symptomatic postoperative disc disease. It is hard to determine the degree of clinical improvement regarding decrease in pain or improved function as two types of evaluation tools were used, and the outcomes of only one was available during this study.

Yi et al. (2009) reported the results of a retrospective case series (n=72) evaluating adjacent segment degeneration following single-level arthroplasties using a Bryan Cervical Disc prosthesis. Preoperative disc degeneration was documented by x-ray and MR studies. Radiological change was evaluated and evidence of adjacent segment disease included new formation or enlargement of anterior osteophyte, new or increasing ALL
calcification or narrowing of the disc space documented on serial plain radiographs. Nine patients demonstrated evidence of adjacent segment degeneration (12.5%) at an average follow-up period of 24.2 months. The mean period of onset was 16.3 months. Four of the nine cases also showed various degrees of heterotopic ossification at the original operated segment. Upper segment degeneration was present in four cases and lower segment degeneration was present in five cases. Further studies are warranted documenting the different types of degeneration seen at levels adjacent to the artificial disc.

Nunley et al. (2012) published the results comparing clinical success rates and occurrence of adjacent segment disease in subjects following ACDF and TDA (n=182). The control group consisted of 57 subjects who received ACDF and an experimental group who received TDA (n=113). It was noted that twelve subjects did not complete follow-up. The initial trials were conducted as part of the FDA IDE trials. The identification of adjacent segment disease was not required as part of the IDE trials; subjects documented as having adverse events such as cervical radiculopathy/myelopathy, were evaluated with MRI or CT scans in addition to plain radiographs as part of the IDE protocol. Once the presence of adjacent segment disease was established, records of subsequent surgery or medical management were maintained and are reported on within this study. The follow-up period ranged from 32 to 54 months (median 42 months); 16.5% (n=28) subjects had established adjacent segment disease during the follow-up period (nine ACDF, 19 TDA). A total of seven were categorized as severe disease and underwent subsequent surgery at the adjacent level; five underwent fusion and two underwent decompression. Twenty-one who had less severe grades of disease received conservative management which included pain medications, physical therapy and at least one epidural steroid injection. The authors reported that at most recent follow-up 83.2% of the TDA group and 86% of the fusion group were free of adjacent segment disease. There was no statistical difference in the incidence of disease between the two groups. Survival analysis for the adjacent level disease-free period demonstrated a trend towards increased survival rates for subjects without osteopenia compared to those with osteopenia (82.3% ± 0.425; 54% ± 1.76%, respectively). The result was statistically significant (P=0.04). The presence of concurrent degenerative disc disease was also associated with lower disease-free survival rate compared to those without disease (55.5%± 0.12%, 74.5%± 0.6%, respectively) and was statistically significant (P=0.023). The authors concluded the development of adjacent segment degeneration was equivalent at 38 month median follow-up and that the presence of osteopenia and degenerative disc disease significantly increased risk of adjacent segment degeneration.

Ding et al (2012) published the results of a retrospective case series (n=34 patients) evaluating intermediate clinical and radiograph outcomes of the Bryan cervical disc. Follow-up ranged from 32 to 69 months, average 49.4 months. Clinical outcomes, adjacent segment degeneration, complications and reoperations were evaluated. Radiograph outcomes demonstrated the Bryan discs preserved normal range of motion at the operative level as well as the adjacent segments. Degeneration scores of the upper and lower discs increased significantly to 1.5 ± 1.4 and 1.3 ± 1.2 respectively, at 24 months following surgery (P>0.05) and at 1.7±2.3 and 1.4 ± 2.1, respectively at last follow-up (48 months). While degeneration did not affect the mid-term clinical outcome, at last follow-up degeneration was noted in 25% of the upper and 22 % of the lower segments which was either new degeneration or progression of the initial degeneration. Long term follow-up is required to determine if and when degeneration will result in symptoms.

Yang et al. (2012) published a meta-analysis of randomized controlled trials evaluating the incidence of adjacent segment degeneration following TDA using guidelines of the Cochrane Collaboration. Five RCTS met the inclusion criteria. The devices evaluated included Kineflex-C, Mobi-C, Advent Cervical Disc, Bryan Cervical Disc, and Prestige disc. There was no statistical heterogeneity among any studies. The rate of adjacent segment disease was fewer in the TDA group compared with ACDF although the difference was not statistically significant (P=0.32). Three trials reported reoperations were required; the rate of adjacent segment surgery was fewer in TDA group (3.21%) compared to the fusion groups (4.84%). The authors suggest that adjacent segment degeneration is affected by patient individuality and not only by the fusion. Due to the low number of studies included the results of the analysis should be interpreted carefully.

**Literature Review—Multilevel versus Single-Level:** Pimenta et al. (2007) compared single-level cervical disc replacement utilizing the Porous Coated Motion (PCM) Device to multilevel disc replacement in a consecutive series of 140 patients. A total of 71 patients had single-level replacement and 69 patients had multilevel replacement (53 double, 12 three-level, four four-level). A total of 19 cases were complex revision cases and 21 had adjacent segment disease following cervical fusion. Estimated blood loss, length of hospital stay and length of surgery were greater for the multilevel group. Self-assessment outcome instruments (i.e., NDI, VAS scores) demonstrated more improvement for multilevel cases. The mean improvement in the NDI for single cases was
37.6% compared to 52.6% for the multilevel cases; the difference was statistically significant (p=0.021). The mean improvement in VAS score was similar, 58.4% for single-level cases versus 65.9% for multilevel cases. The Treatment Intensity Score and Odom’s criteria were also more improved for multilevel cases when compared to single-level. Reoperation and adverse events were similar between groups. Using Kaplan–Meier analysis implant survivorship for the overall group was 94.5% at three years. The results of this study suggest a greater clinical outcome improvement for multilevel disc replacement, although the authors note further analysis is necessary.

Cheng and associates (2009) published the results of prospective randomized controlled clinical trial comparing the functional results and radiographic outcomes of fusion (n=34) and BRYAN cervical disc replacement (n=31) as treatment for two-level cervical disc disease. Evaluation was conducted using the VAS scale, SF-36 and NDI during a two-year follow-up period. Three patients were lost to follow-up. The results demonstrated significant improvement in outcome measures at 24 months, including arm pain VAS, neck pain VAS, NDI, and SF-36 physical scores. While both groups showed statistically significant improvement at two years compared to preoperative scores, the BRYAN group showed better clinical outcomes in comparison to the fusion group. The results to this study are limited by a small sample population and short term outcomes and long-term outcome data is needed to support improvement in health outcomes when used for treatment of two-level disease.

Barbagallo et al. (2009) reported the early results of a surgical technique that combined cervical fusion and disc replacement for treating multilevel DDD (n=24). Disc prostheses were implanted at either the level above or below the one receiving a cage as part of the fusion. In some cases two prostheses were implanted and in others two cages were implanted. Average follow-up was 23.8 months. In all but one patient clinical follow-up demonstrated significant improvement; radiological evaluation demonstrated functioning disc prostheses and fusion through cages. While the surgical approach seemed a safe and valid option for patients with multilevel symptomatic cervical DDD, long-term follow-up with larger patient populations are needed to support the clinical effectiveness of this approach.

In a prospective multicenter study, Huppert et al. (2011) compared clinical and radiological outcomes of cervical disc replacement using the Mobi-C disc (non FDA-approved device) between single- and multilevel subjects. A total of 231 subjects were treated with disc replacement and completed 24 month follow-up; 175 subjects received a single-level replacement and 56 received replacement of two levels or more. Measured outcomes included NDI scores, VAS scores, ROM, and satisfaction. Improvement in NDI and VAS scores for neck and arm pain were similar among groups (p=0.713, p=0.790 respectively). However in the multilevel group there was significantly more use of analgesics (p=0.029). Occurrence of heterotopic ossification was significantly lower in the single-level group. Satisfaction was comparable among subjects in both groups. Absolute range of motion improvement between pre-op and 24 months was not significantly different.

Wu and associates reported the results of a prospective case series (n=102) evaluating the differences between single and multilevel (2 or 3 levels) DDD treated with the Bryan cervical disc device. At 24 months follow-up 86 subjects completed clinical/ radiographical follow-up; 16 subjects were either lost to follow-up or had inadequate evaluations. The authors noted the multilevel group demonstrated a high rate of heterotopic ossification compared to the single level group (66.0% versus 25.0%, P<0.001) at an average follow-up of 38.3 ± 8.7 months. Most of the artificial discs remained mobile despite the heterotopic ossification (97.7%) and there were no significant differences in the mobility between single level and multilevel groups. Both groups demonstrated significant improvements postoperatively in clinical outcomes such as VAS neck and arm scores. In the authors opinion results of multilevel surgery were similar to single level surgery at three years.

As part of the FDA IDE prospective, randomized trial, Davis et al. (2013) reported on the use of the Mobi-C cervical disc. The entire study involved two experimental groups and a control group and was designed as a noninferiority trial (n=600). Within this publication the authors reported the 24 month follow-up of one arm of the study to compare clinical outcomes of two-level disc replacement (n=225) to two-level ACDF (n=105) for subjects with two-level DDD disease of the cervical spine. Measured outcomes included NDI scores, VAS scores, reoperation at the index level, complications, neurological function and radiological success. Overall study success was defined similar to other cervical disc IDE trials. Follow-up occurred at 6 weeks, 3, 6, 12 and 24 months post-operatively. Follow-up rates were 98.2% (disc group) and 94.3% (ACDF) at 24 months. Both groups had improvement in VAS neck and arm pain scores, had high patient satisfaction, and quality of life scores from baseline to postoperative. Physical component scores (PCS) scores were statistically significant
and favored the disc group (p=0.03) at all time periods. NDI scores improved from baseline to postoperative for both groups although it was significantly greater in the disc group at every time period (p<0.05). The disc group had less neurological deterioration (p<0.0001), less reoperations, less device related events, and less serious adverse events that were either possibly or definitely related to the device when compared to the ACDF group. In addition in the experimental group segmental motion was maintained at both segments. According to the authors based on all scores, the experimental group demonstrated statistical superiority at 24 months follow-up compared to two-level ACDF. Results of this trial are encouraging however additional trials evaluating outcomes beyond two years are necessary to establish long-term device durability, and safety and efficacy.

Other Cervical Prostheses: Several additional devices are under development and clinical study for possible use in the treatment of degeneration within the cervical spine. None of these devices are currently approved by the FDA. Some of these devices include (this list may not be all-inclusive):

- Cervicore™ (Stryker Spine, Summit, NJ)
- Flexicore™ Cervical Disc Replacement (SpineCore-Stryker Spine, Summit, NJ)
- Kineflex®C™ (SpineMotion, Inc., Mountain View, CA)
- DISCOVER® (Depuy Spine, Incorp. Raynum, Mass.)
- NeoDisc™ (NuVasive, San Diego, CA)

Cervical Technology Assessments/Guidelines: NICE published guidance in 2005 on prosthetic intervertebral disc replacement in the cervical spine and considered the device safe and effective for use in the National Health System (NHS). The evidence reviewed included clinical trials evaluating the BRYAN cervical disc, Prestige I and Prestige II cervical discs and consisted of two RCTs and three case series. NICE recommended patients understand that long-term uncertainties remain regarding the procedure (NICE, 2005).

An updated version to the 2007 BCBSA TEC report regarding artificial cervical disc replacement as a proposed treatment for DDD of the cervical spine was published August 2009 (BCBSA, 2009). The assessment focused on data from randomized controlled trials for the Prestige ST and ProDisc-C intervertebral disc, non-FDA approved and precursor devices were excluded. Data for the BRYAN disc which was FDA approved May 2009 was included in the index of the TEC report and did not change the conclusions of the assessment. The report indicates that although informative, the evidence is not sufficient to allow concluding whether artificial intervertebral disc arthroplasty with either device is as beneficial as anterior cervical discectomy and fusion (ACDF) because of uncertainty regarding longer-term outcomes. Furthermore, experience with ACDF and its high success rate requires a convincing rationale and supporting evidence to utilize a different procedure—noninferiority alone is insufficient. Neither trial provides adequate direct evidence over a relevant follow-up period (suggested to be 5 to 7 years) on subsequent adjacent-level DDD in control and investigational group patients. BCBSA TEC concluded artificial intervertebral disc arthroplasty did not meet TEC criteria.

The ECRI Institute reported their findings on intervertebral cervical disc replacement prostheses in an Emerging Technology Evidence Report (ECRI, 2009b). ECRI identified six randomized controlled trials that met their inclusion criteria to address key questions. Common study exclusion criteria were multilevel disease, evidence of cervical instability, previous surgery at the involved level, systemic disease, and chronic disease requiring long-term steroid use. Limitations of the evidence base included lack of long-term outcomes, difficulty estimating adverse event rates, differences in design and materials, potential conflict of interest, and moderate attrition. Based on their review of the evidence ECRI concluded that the limited data currently available suggest that cervical AIDR may be as effective as cervical fusion for relieving pain and improving function in the short-term (one to two years). While adverse events were reported in both AIDR and fusion groups in all the studies assessed, determining specific adverse event rates associated with cervical AIDR was not possible. Long-term follow-up data on larger numbers of patients are needed to assess the long-term durability of artificial cervical discs.

In September of 2012 ECRI Institute published an evidenced report evaluating cervical disc replacement that included evidence published until April 2012. Eleven publications met the inclusion criteria, six were randomized controlled trials and five consisted of case series. Improvements in outcomes such as neck pain, arm pain, disability and work status were comparable in both groups, although outcomes such as range of motion, reoperation, neurological deterioration and overall success favored the disc group. None of the studies evaluated comparisons of the effectiveness of the various discs or compared disc replacement to other methods...
of treatment, including nonsurgical, therefore no conclusions could be drawn. Evidence evaluating long-term outcomes, which was defined as greater than two years, supported similar disability scores among both groups (strength of evidence: moderate). Disc replacement subjects had better results than fusion for outcomes such as ROM, reoperation, and neurological deterioration (strength of evidence: high, moderate, low, respectively). The evidence reviewed by ECRI did not permit conclusions regarding rate of occurrence of adverse events (ECRI, 2012).

California Technology Assessment Forum (CTAF) published a technology assessment of artificial disc replacement for degenerative disc disease of the cervical spine (CTAF, 2009). According to the report the evidence evaluating the long term clinical impact of artificial cervical disc replacement is lacking, consequently whether or not the technology ultimately improves net health outcomes is not known; it is not known whether or not the technology is as beneficial as the established alternatives, and whether or not an improvement in long term clinical outcomes is attainable outside the investigational is unknown due to lack of long-term evidence. Cervical disc replacement as an alternative to anterior fusion did not meet TEC criteria.

Although it is not an official position statement, in 2010 the American Academy of Orthopaedic Surgeons (AAOS) published a technology overview of cervical disc arthroplasty. The overview was based on the findings of studies published prior to September 2009. The committee addressed four key questions regarding the technology, comparing the outcomes of patients treated with cervical IVD replacement to patients treated with ACDF. The key questions addressed what patient characteristics predicted successful outcomes in patients who underwent cervical IVD replacement compared to ACDF; do patients with herniated disc and arm pain, with or without neck pain, have equal or better outcomes when compared to ACDF, are the revision rates and/or complication rates equal or better in those who receive disc replacement compared to ACDF, and for patients which is more economical, according to hospital length of stay and return to work. Regarding patient characteristics, the data was inconclusive, most studies did not report a statistical analysis, and only one level II study reported no statistically significant difference. For clinical outcomes, five level II studies were included. There was a trend for better NDI scores and NDI success rate at early follow-up, data for long term follow-up was inconclusive. While one study reported arthroplasty had significantly higher neurologic success rates, two level II studies reported no statistically significant differences. A majority of the studies reported no statistically significant difference in either neck or arm pain scores at short term follow-up (six months to 24 months), long term data was inconclusive. The result reported by three level II studies was inconclusive regarding SF-36 scores and there were no differences in the number of patients who returned to work at 24 months. The results of four level II studies were included, three did not report secondary surgery results similarly, and therefore the results could not be compared. The results for adverse events were also inconclusive in these same studies. Patients who underwent arthroplasty returned to work in significantly fewer days although the length of hospital stay did not vary between groups.

Cochrane conducted and published a review evaluating arthroplasty versus fusion in single-level cervical degenerative disc disease (Boselie, et al., 2012). The evidence reviewed included RCTs that directly compared any type of cervical disc arthroplasty to any type of cervical fusion with outcomes extending at least one year. A total of nine RCTs (n=2400) met inclusion criteria, eight were industry sponsored; five had high methodological quality and low risk of bias. With regards to relief of arm pain at one to two years, low-quality evidence favored arthroplasty as having a small but significant difference (i.e., between 1 and 5 points on a 100 point scale). The authors noted a small study effect could not be ruled out. Moderate quality evidence demonstrated a small difference in neck related functional status and neurological outcome at one to two years, in favor of arthroplasty. A clinically relevant difference was not seen in any of the primary outcomes (arm pain, neck pain, neck related functional status, patient satisfaction, neurological outcome, global health status). Mobility was preserved after disc replacement in the short-term (1-2 years). Long term effectiveness has yet to be determined and Cochrane concluded use of the devices should be limited to clinical trials.

**Summary Cervical Intervertebral Disc Prostheses:** When measuring safety and efficacy outcomes at 24 months of follow-up, several studies consistently demonstrate single-level cervical TDR is noninferior to anterior cervical disectomy and fusion when using FDA approved devices. When used for more than single-level disc replacement in the cervical spine the evidence is insufficient to support safety, efficacy and long-term improvement in health outcomes. As part of the FDA post approval process, there are some published clinical studies that support noninferiority at five years post cervical disc insertion, for the portion of subjects who have completed evaluation at this time. The current evidence suggests that cervical disc replacement offers some advantages over cervical fusion in the short-term (one to two years), with some data supporting long-term
advantages (five years). Improvement in clinical outcomes such as neck pain, disability scores and neurological status as well as more rapid return to work has been reported. Comparison across studies is confounded by variables such as differences in device design and materials and there is limited long term data evaluating device performance, durability, revision rate, and functional clinical outcomes. The post-surgical effect on adjacent spinal segments is not yet determined and remains under investigation. In addition, the FDA mandated post-approval studies are still being conducted at this time.

Hybrid Surgery: Artificial disc replacement at one level combined with spinal fusion surgery at another level (adjacent or non-adjacent) is referred to as hybrid surgery. Biomechanical studies lend some support that combined lumbar fusion and disc replacement function similar to single level fusion; however there are few clinical trials to support improved health outcomes and patient selection criteria has not been firmly established. While some authors have investigated this method of treatment for multilevel cervical DDD (Kang, et al, 2013; Lee, et al., 2012, Cardosa, et al., 2010) the evidence in the published peer-reviewed scientific literature demonstrating the safety and efficacy of combining cervical disc replacement and cervical arthrodesis procedures at multiple adjacent or non-adjacent levels is insufficient to support safety, efficacy and improved net health outcomes. Although some of the authors offer a comparison of outcomes between subjects who underwent hybrid surgery or multilevel arthroplasty, the evidence is limited by lack of controls, small sample populations and short term outcomes. Additional research is needed to clearly establish a role for hybrid technologies.

Partial Disc Replacements
As an alternative to the complete replacement of both an injured or diseased disc, researchers are also exploring the possibility of performing a partial disc replacement, also referred to as a nucleus arthroplasty. With this procedure only the nucleus of the disc is replaced; theoretically the annulus and endplates function properly. Nucleus arthroplasty devices are in the earliest stages of development and study. Examples include, but are not limited to: NUBAC™ Disc Arthroplasty System (Pioneer Surgical Technology, Marquette, Michigan) Prosthetic Disc Nucleus PDN (Raymedica, Inc., Bloomington, MN); NeuDisc (Replication Medical, Inc., New Brunswick, NJ); and the Newcleus (Zimmer Spine, Warsaw, IN) (Bertagnoli, 2005). The devices may be classified as hydrogel, polymer/synthetic or mechanical technologies. Until approval can be obtained through the FDA, and clinical trials are conducted that provide guidance on specific patient selection, or patient net health outcomes, the use of these devices for the treatment of DDD remains investigational.

Professional Societies/Organizations
At the present time, no professional societies or organizations have published a position statement or evidence-based clinical practice guidelines regarding the use of intervertebral lumbar disc prostheses.

The International Society for the Advancement of Spine Surgery (ISASS) published a position statement December 2009 for cervical disc arthroplasty. The position of ISASS is as follows: “Total disc arthroplasty (TDA) is an acceptable, proven alternative to anterior cervical discectomy and fusion (ACDF) in the treatment of symptomatic cervical disc disease (CDD) for the indications, as described in the FDA approvals. Even at the relatively early 2 year post-operative time point, several high quality studies have shown significantly lower re-operation rates after TDA when compared to ACDF” (ISASS, 2009).

Use Outside of the US: Companies are continuing to develop new cervical and lumbar artificial disc replacements. Several of these devices are available for use in markets outside of the United States and are being used for single and multi-level disc replacement surgeries. These markets include but are not limited to countries such as Australia, Brazil, China, Europe, and the United Kingdom.

Summary
Several randomized controlled clinical trials in the published, peer-reviewed scientific literature have demonstrated safety and efficacy of the Charité and ProDisc® in a select group of individuals for single-level degenerative disc disease. While the long-term safety and efficacy of these devices continues to be monitored, clinical outcomes have shown that these devices can improve the maintenance of range of motion within the lumbar spine and provide stabilization to the intervertebral disc space. Postsurgical study results have shown that use of the disc prostheses can reduce pain while improving disability scores.

Several randomized controlled clinical trials also provide sufficient evidence supporting safety and efficacy of cervical disc replacement using the Prestige ST Cervical Disc System, ProDisc-C, or BRYAN cervical disc, for
the treatment of single level cervical degenerative disc disease presenting with intractable radiculopathy and/or myelopathy, when compared to anterior cervical disectomy and fusion. Long-term clinical outcomes are still being investigated however there is some evidence to support that at four and five years post insertion, clinical outcomes from cervical disc replacement are equivalent to fusion with some outcomes being superior.

The use of the use of these devices for multilevel disc disease is under investigation. While some studies support clinical outcomes in the short-term that are comparable to single level disc replacement or ACDF the data is limited and long term safety and durability of these devices when used for multilevel replacement has not been proven.

The safety and efficacy of partial disc(s) replacement systems (i.e., nucleus arthroplasty) cannot be determined at this time, due to the lack of FDA approval for the devices and the lack of clinical trial evidence within the published literature. In addition, evidence supporting improved health outcomes of hybrid surgery, involving both disc replacement and arthrodesis at adjacent or nonadjacent spinal levels, is limited and strong conclusions cannot be made at this time. Further large, well-designed clinical trials demonstrating these procedures are clinically safe and effective are needed.

### Coding/Billing Information

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

#### Single-Level Lumbar Disc Arthroplasty

Covered as medically necessary:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>22857</td>
<td>Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression), single interspace, lumbar</td>
</tr>
</tbody>
</table>

#### Multi-Level Lumbar Total Disc Arthroplasty

Experimental/Investigational/Unproven/Not Covered:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0163T</td>
<td>Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression), each additional interspace, lumbar (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

#### Single-Level Cervical Disc Arthroplasty

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>22856</td>
<td>Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophyectomy for nerve root or spinal cord decompression and microdissection), single interspace, cervical</td>
</tr>
</tbody>
</table>

#### Multi-Level Cervical Total Disc Arthroplasty

Experimental/Investigational/Unproven/Not Covered:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0092T</td>
<td>Total disc arthroplasty (artificial disc), anterior approach, including discectomy</td>
</tr>
</tbody>
</table>
with end plate preparation (includes osteophyteectomy for nerve root or spinal cord decompression and microdissection), each additional interspace, cervical (List separately in addition to code for primary procedure)


References


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http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?start_search=N

http://google2.fda.gov/search?q=P070001%2FS001&client=FDAgov&site=FD.Agov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&getfields=*&x=5&y=11

http://google2.fda.gov/search?q=P040006.&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&getfields=*&x=6&y=8

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm367809.htm.


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