Washington State Health Care Authority

Health Technology Assessment

HTA Final Report
Artificial Discs Replacement (ADR)

Date: September 19, 2008

Health Technology Assessment Program
676 Woodland Square Loop SE
P.O. Box 42712
Olympia, WA 98504-2712
http://www.hta.hca.wa.gov

Artificial Disc Replacement (ADR)

Provided by:

Spectrum Research, Inc.

Prepared by:

Joseph R. Dettori, PhD, MPH
Andrea C. Skelly, PhD, MPH
Robin E. Hashimoto, PhD
Erika Ecker, BA
August 26, 2008

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLES

TABLE OF CONTENTS (continued)

FIGURES

TABLE OF CONTENTS (continued)

EXECUTIVE SUMMARY

Introduction

Low back pain is a major health problem throughout the world and is the leading cause of pain and disability in adults in the United States. As much as 40% of chronic low back pain is thought by some to originate in the intervertebral disc. Chronic low back pain with degenerative disc disease (DDD) is typically managed conservatively for at least six months before surgery is considered.

Cervical radiculopathy and myelopathy are neurologic conditions characterized by dysfunction of the spinal nerve or spinal cord often as a result of degenerative disc disease or spondylosis. The average annual age-adjusted incidence of radiculopathy has been reported as 83 per 100,000, and the prevalence as high as 350 per 100,000 people. While the overall prevalence of cervical spondylotic myelopathy (CSM) is unknown, it is the most prevalent spinal cord dysfunction in people 55 years or older. It is not uncommon for both conditions to be present. It is estimated that nearly one fourth of surgical patients being treated for cervical DDD have a combination of radiculopathy and myelopathy.

Surgery is generally indicated when nonoperative conservative treatments fail to relieve symptoms attributed to lumbar DDD or relieve signs of neurological compression or prevent progression of nerve damage in the case of cervical DDD. The current surgical standard of care for lumbar DDD is lumbar fusion. The goal of this surgery is to remove the disc and fuse the vertebrae, thereby limiting the motion at the painful segment. For cervical DDD resulting in radiculopathy or myelopathy, the current surgical standard is anterior cervical discectomy and spinal fusion. The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. Spinal fusion is thought by some to promote the degeneration of the vertebrae above or below the fusion site (adjacent segment disease); however, many uncertainties remain regarding the extent to which this occurs.

Lumbar artificial disc replacement (L-ADR) is a potential alternative to spinal fusion in patients with disabling mechanical low back pain. Cervical artificial disc replacement (C-ADR) offers a possible surgical alternative to spinal fusion for patients with radiculopathy and/or myelopathy secondary to DDD. Both L-ADR and C-ADR are intended to preserve motion at the involved spinal level and therefore decrease stresses on adjacent segment structures and the risk of adjacent segment disease.

In light of the possible benefits of ADR, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short and long term, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of ADR. Thus, the objective of this technology assessment is to critically appraise and analyze research evidence on the efficacy/effectiveness and safety of ADR in the lumbar and cervical spine in patients with degenerative disc disease and to the extent possible, consider the potential financial impact. To that end, the following key questions developed by the Washington State Health Technology Assessment Program will be addressed:

- **Key Question 1:**

  What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

- **Key Question 2:**

  What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?

- **Key Question 3:**

  What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

- **Key Question 4:**

  What are the cost implications and cost effectiveness for ADR?

Note: In this technology assessment, artificial disc replacement will refer to mechanical total disc arthroplasties and not nucleus replacements, annular reconstruction techniques or other forms of intradiscal spacers.

Methods for evaluating comparative effectiveness

Spectrum Research, Inc.'s (SRI) method for technology assessment involves formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Each included study is critically appraised using SRI's Level of Evidence (LoE) system which evaluates the methodological quality based on study design as well as factor which may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Meta-analysis was conducted on the primary outcomes using a random effects model to determine risk difference (RD) when data from two or more RCTs were available and when there was no clinical or statistical heterogeneity among studies. Two analytic perspectives on the meta-analysis for effectiveness are presented: intent-to-treat (ITT) analysis and completer-only analysis.

Throughout the process, SRI sought clinical review to assure that the clinical components are accurately represented and relevant. In addition, peer-review by clinical experts, health services researchers and those with expertise in economic and outcomes evaluation provide an assessment of the systematic review methodology, analyses and report conclusions.

Summary and Implications

1. Efficacy/effectiveness of artificial disc replacement (ADR)

- Findings contained in this technology assessment reflect the use of lumbar or cervical ADR in patients who have failed conservative treatment. For the lumbar spine, conservative treatment for at least six months was required prior to study enrollment. For the cervical spine, six weeks of conservative treatment or a progression of neurological signs was an indication for ADR. Neither the type of conservative treatment nor the level of patient compliance with pre-study conservative treatment was detailed in the published studies used in this technology assessment and therefore, unknown.
- There is insufficient evidence to draw extensive efficacy/effectiveness conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the efficacy/effectiveness of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion. One study is underway that includes three surgical treatment arms for cervical radiculopathy: C-ADR versus anterior cervical discectomy without fusion versus anterior cervical discectomy with fusion (ACDF).
- With respect to the comparison of L-ADR and fusion, there is moderate evidence that the efficacy/effectiveness of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery. This evidence is based on two moderate quality randomized controlled trials conducted as FDA Investigational Device Exemption non-inferiority trials. Overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving L-ADR and 48% receiving lumbar fusion. Though the results suggest that 24 month outcomes for L-ADR are similar to lumbar fusion, it should be noted that a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question.
- There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index, and pain up to two years following surgery. The evidence is based on two moderate quality randomized controlled FDA Investigational Device Exemption non-inferiority trials. An interim analysis of approximately 65% of a third RCT was reported in an FDA Panel Executive Summary. If the results following completion of the trial are similar to the

interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase.

- There is evidence that segmental motion is maintained or improved up to three years in the L-ADR patients and up to four years in C-ADR patients compared with preoperative motion. It is unclear the true extent to which preserving segmental motion by using ADR instead of fusion influences rates of adjacent segment disease (ASD). Whether ASD is a continuation of a disease process necessitating fusion or a result of fusion continues to be disputed. Furthermore, there continues to be debate on whether the presence of ASD is clinically important given that patients with marked radiographic ASD often have no symptoms.

2. Safety of artificial disc replacement (ADR)

- There is insufficient evidence to draw extensive safety conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the safety of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion.

- There is moderate evidence that L-ADR is as safe as lumbar anterior or circumferential fusion, and that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery.
- There is insufficient data at this time to determine the longer term safety of both L-ADR and C-ADR.

3. Special or subpopulations

- There is insufficient evidence to draw conclusions regarding the safety and efficacy of L-ADR in the few special populations studied (elderly, smokers, athletes). No studies or sub-analyses were found on the use of C-ADR in special or subpopulations.

4. Economic implications

- There are inadequate data from partial economic studies reflecting short time horizons for L-ADR and no economic studies for C-ADR to truly assess the potential cost-effectiveness of ADR technology. One report and one previously done HTA suggest that the type of fusion may influence complication rates and therefore costs.

5. Additional implications

- The studies primarily reflect outcomes measured up to 24 months and therefore questions remain regarding the longer term safety and efficacy of L-ADR or C-ADR compared with fusion. This is an important matter, particularly in those receiving C-ADR where the average age is near 45 years. Since these are mechanical devices, future failure is a possibility and may influence complication rates and costs in the longer-term.

- Findings contained in this report primarily reflect use of ADR at a single level and it may not be appropriate to extrapolate the results to patients with ADR at multiple levels or for indications other than those evaluated during the FDA trials. As diffusion of these devices increases and they are used for additional indications, the safety and efficacy profiles may change.
- Studies which met the inclusion criteria for this report encompassed only two biomechanical types, an unconstrained device and a semiconstrained device. While it was deemed reasonable to pool information from trials despite difference in device design, it is probably appropriate to consider that such differences may influence longer term outcomes. There are a variety of different biomechanical designs for ADR. There is limited data which directly compare outcomes and complications for different devices in the short-term or longer term and thus, the influence of different designs is unknown.
- One study suggests that surgeons and institutions with a high volume of L-ADR cases have shorter operating time and hospital stay, and lower complication rates which may have an economic effect. No effect on clinical outcomes was reported between high and low volume surgeons or institutions.

ASSESSMENT
ARTIFICIAL DISC REPLACEMENT

Final Scope

Rationale for the Assessment

Low back pain is a major health problem throughout the world and leading cause of pain and disability in adults in the United States.[60] As much as 40% of chronic low back pain may originate in the intervertebral disc.[143] Chronic low back pain with degenerative disc disease (DDD) is typically managed conservatively for at least six months before surgery is considered. For those patients who do not experience pain relief during that time, the natural history of the disease is not well documented.

Cervical spondylotic myelopathy (CSM) is the most prevalent spinal cord dysfunction in people 55 years or older.[167] A study of 450 surgical patients being treated for DDD reported that 61% presented with radiculopathy, 16% with myelopathy, and the other 23% had a combination of the two[133]. A study of Nationwide Inpatient Sample (NIS) data collected between 1993 through 2003 shows that the number of cervical spinal fusion procedures conducted in the U.S. increased from 26 to 50 per 100,000, with symptomatic DDD representing more than four out of every five cases of cervical DDD cases in 2003.[26,167]

Surgery is generally indicated when nonoperative conservative treatments fail to relieve symptoms attributed to lumbar DDD or relieve signs of neurological compression or prevent progression of nerve damage in the case of cervical DDD. The current surgical standard for lumbar DDD is lumbar fusion. The goal of this surgery is to remove the disc and fuse the vertebrae, thereby limiting the motion at the painful segment. For cervical DDD resulting in radiculopathy or myelopathy, the current surgical standard is anterior cervical discectomy and spinal fusion. The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. Spinal fusion is thought by some to promote the degeneration of the vertebrae above or below the fusion site (adjacent segment disease); however, many uncertainties remain regarding the extent to which this occurs.

Lumbar artificial disc replacement (L-ADR) is a potential alternative to spinal fusion in patients with disabling mechanical low back pain. Cervical artificial disc replacement (C-ADR) offers a possible surgical alternative to spinal fusion for patients with radiculopathy and/or myelopathy secondary to DDD. Both L-ADR and C-ADR are intended to preserve motion at the involved spinal level and therefore decrease stresses on adjacent segment structures and the risk of adjacent segment disease.

Although such devices have been used outside of the U.S. for many years and a number of research reports have described positive outcomes, questions remain regarding a number of important issues:

1. How does the effectiveness of ADR compare with conventional surgical treatment (and if appropriate, nonsurgical treatment) with respect to patient functional outcomes and pain relief as well as other outcomes including those related to quality of life?
2. How does the safety of ADR compare with conventional surgical treatment both over the short-term and over the long-term (eg, ASD, heterotopic ossification, spontaneous fusion), given that implants are intended to remain intact for the life-time of the patient?
3. Might specific patient populations in particular benefit from ADR or have increased risks for complications from its use?
4. Do different biomechanical designs influence comparative safety and efficacy?
5. How might the substitution of ADR for fusion in a proportion of patients with the appropriate indications impact health care systems and costs?

In light of the possible benefits of ADR, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short term and longer time horizons, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of ADR.

Objective

To critically appraise and analyze research evidence on the effectiveness of and complications related to the use of ADR in the lumbar and cervical spine. If available, formal economic analyses of ADR will also be critically appraised.

Key questions

Key questions were developed by the Washington State Health Technology Assessment Program. A conference call with Spectrum Research and representatives of the HTA program provided clarification of the questions and outcomes.

- **Key Question 1:**

  What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

- **Key Question 2:**

  What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?

- **Key Question 3:**

  What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

- **Key Question 4:**

  What are the cost implications and cost effectiveness for ADR?

Note: In this technology assessment, artificial disc replacement will refer to mechanical total disc arthroplasties and not nucleus replacements, annular reconstruction techniques or other forms of intradiscal spacers.

Outcomes
The following outcomes were sought:

- Efficacy and effectiveness measures
  Primary outcomes
  - Overall clinical success
  - Disability indices (Oswestry Disability Index for lumbar, Neck Disability Index for cervical)
  - Neurological success defined as maintenance or improvement in neurological status
  - Pain or pain reduction

  Secondary outcomes
  - Quality of life (SF-36)
  - Return to previous activity or work status
  - Rate of adjacent segment disease (ASD)
  - Range of motion at the instrumented segment
- Complications and adverse events
  - Device failure (reoperation due to revision, reoperation, or removal)
  - Complications or adverse events reported in included studies and based on regulatory/FDA surveillance
- Economic measures
  - Costing data

Key considerations highlighted by clinical experts:

1) **Interventions**
   Lumbar - Indications for L-ADR include, among other factors, primary lumbar and/or leg pain in the absence of nerve root compression. This group of patients is different than those undergoing cervical ADR and results from one group should not be inferred to the other. Cervical ADR is performed in patients with radiculopathy (cervical nerve root compression) causing arm pain and possibly motor weakness, or even myelopathy (compression of the spinal cord that could affect upper extremities, lower extremities, bowel, and bladder function). Consolidating cervical and lumbar disc replacements into one assessment will defeat the purpose of an evidence-based review by too broadly defining the topic area.

   Currently L-ADR is indicated for patients who have failed conservative care for a minimum of six months. Often patients have suffered for much longer without relief from nonoperative care. As a result, some believe that comparison of arthroplasty surgery to conservative management is not appropriate in that failure of conservative care is a prerequisite for surgical intervention. For many patients enrolling in a clinical trial, nonsurgical options are not acceptable at the time of enrollment. L-ADR is a surgical procedure to help remedy a degenerative disc disease that has not responded to conservative care.

In addition to currently available devices, over 40 industry competitors are involved in the development of devices for disc replacement, annular repair and nuclear repair/replacement technologies.[9] Differences in biomechanical design and materials for future devices may influence the overall picture of safety and efficacy for these devices in both the short-term and the long-term. In addition to the use of such devices for indications listed for the devices, as is the case with many technologies, diffusion of L-ADR for new indications as well as off-label use may have a potential impact on the overall safety and efficacy as well as the costs and longer-term trends in device use.[151]

Cervical - Surgery results in mechanical alteration of specific anatomic structures. The surgeon decides to operate when three conditions are met[34]:

- Knowing that the specific anatomic structure is diseased
- Believing that the diseased structure is responsible for the clinical problem
- Judging that the condition is suitable to treatment

For patients with cervical radiculopathy or myelopathy, the anatomical structures can often be identified through physical exam and imaging studies. Tying the diseased structures to the cause of the clinical problem can often be done in these conditions. However, the evidence for the efficacy/effectiveness of various treatments for these conditions remains unclear.

For patients with neck pain without neurological compromise, the cause of pain is frequently unknown. Often physical exam and imaging studies do not uncover any specific pathology. And in those patients in whom imaging studies do reveal common degenerative disease, it is not certain that these changes are the cause of the disease. In fact, the prevalence of many degenerative changes on imaging studies has been found to be similar among those without cervical disease symptoms compared with those with symptoms.

By contrast, the symptoms are less discrete in those presenting for lumbar artificial disc replacement (L-ADR) since such patients most frequently present with back pain without neurological deficit, which may or may not be associated with a specific disc problem. There are greater diagnostic challenges in determining the cause of low back pain compared with cervical radiculopathy or myelopathy and intervention options differ. The loading characteristics of the cervical spine and lumbar spine are also different. Thus, although similar types of ADR technology may be used for both cervical and lumbar sites, there are potential differences with regard to outcomes for treating cervical DDD compared with lumbar DDD. For these reasons, consideration of C-ADR and L-ADR should be separate.

FDA approval of C-ADR devices is fairly recent (2007) and there are a number of devices with various designs that are still under development and/or currently undergoing clinical trials. It is not yet clear what biomechanical designs, if any, may provide the best outcomes over the long term.

2) Costs:

Citing data from a 2003 JP Morgan marketing analysis, Singh, et al report that by 2010, 70% of spine procedures may involve some sort of disc replacement technology.[151] The report estimates that by that time, the worldwide spine arthroplasty market may range from $1.4 to more than $3 billion and that at least 47.9% of the fusion market may be converted to motion-sparing devices. More recent market assessments suggest that the U.S. market for artificial disc replacement will grow from $55 million in 2007 to $440 million by 2013.[9] To the extent that these predictions are correct, the potential impact of these devices on the costs of medical care is likely to be significant.[151] However, evaluation of long term costs or savings is difficult given the lack of high quality evidence from which to determine patient outcomes beyond 24 months.

Evaluation of long term costs or savings is difficult given the lack of high quality evidence currently available in the peer-reviewed literature from which to determine patient outcomes, particularly beyond 24 months. While it is postulated that ADR may reduce the likelihood of adjacent segment disease, it unclear how this and other potential longer-term complications, possible need for revision and other factors may ultimately influence costs as well as patient quality of life. Post approval studies are required for some lumbar and cervical ADRs, and data from these may help us understand the longer-term outcomes and costs.

3) Patient considerations

Lumbar - Identifying the right patient with spine disease who will respond to any specific treatment remains important yet often illusive. In many clinical trials, some patients clearly benefit from a specific treatment while others do not. The key to applying any new technology to patient care is to properly recognize those patients who have the greatest probability of success. In the area of spine treatment, this concept is most important due to the complex etiology of spine disability which includes physical and psychosocial factors. This problem of identifying those likely to respond to treatment is of concern for L-ADR in that the surgical procedure is designed to treat degenerative disc disease that is thought to be the origin of the patient's pain. Certainty around the diagnosis as the cause of low back symptoms varies. If the pain arises from non-disc structures, replacing the disc is unlikely to be successful. The surgeon must be convinced that a patient's symptoms are coming from the disc before proceeding with this procedure.

Though L-ADR for degenerative disc disease has been compared with lumbar fusion, not all patients who have an indication for fusion are candidates for L-ADR. Those include patients with nerve root compression, spondylolisthesis, stenosis and osteoporosis. In fact, some estimate that the proportion of patients who have an indication for L-ADR make up only about 5% of those who have an indication for lumbar fusion.[81]

Cervical - The current indications for currently approved C-ADR devices are for patients with intractable symptomatic single-level cervical DDD who have failure of at least six weeks non-operative treatment presenting with neck or arm pain and

functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, X-ray):

- Herniated nucleus pulposus
- Spondylosis (defined by the presence of osteophytes)
- Loss of disc height

For some contraindications, such as osteoporosis, there may be some subjectivity on the part of the surgeon regarding the degree to which it is present and therefore a problem to C-ADR placement. Expansion of C-ADR use for new indications combined with off-label use may have a potential impact on the overall safety and efficacy as well as the costs and longer-term trends in device use.[151]

4) **Professional considerations:**

Lumbar - High-surgical volume is associated with better clinical outcomes across a wide range of procedures and conditions to include orthopedic procedures such as total joints.[88] It is reasonable to expect similar findings with L-ADR. In fact, one study was recently published that made 3 comparison of patients receiving L-ADR: nonrandomized cases (n = 71) versus randomized cases (n = 205); randomized cases performed by high-enrolling surgeons versus low-enrolling surgeons; and randomized cases at high-volume institutions versus low-volume institutions.[135] The investigators found that surgeons and institutions with a high volume of L-ADR cases have reduced key perioperative and postoperative negative outcomes that provide a clinical and/or economic benefit. There needs to be more work done to determine the optimum surgeon and institutional volume of L-ADR cases to achieve the best possible results.

Cervical – None identified.

1. Background

1.1 The Condition

Back pain caused by degenerative disc disease (DDD) is a major health problem throughout the world. Over 90% of spinal procedures are performed because of disc degeneration and a reported 15%-20% of patients do not recover from back pain after lumbar surgery.[13,41] DDD is the leading cause of pain and disability in adults in the United States.[60] Data indicate that at least 80% of Americans have at least one significant episode of low back pain in their lifetime, and 5% have chronic low back pain.[15,169] Approximately 2.4 million Americans are disabled by lower back pain at any given time, and half of those are chronically disabled.[120] The annual incidence rate of lower back pain is estimated to be 5%, and upwards of 13 million physician visits are for chronic lower back pain, according to the National Center for Health Statistics.[120] Lower back pain due to DDD peaks at 40 years of age and affects both men and women equally.[120] In 2001, 122,469 lumbar fusion surgeries were performed for DDD at an estimated cost of $4.8 billion.[47] In Australia, according to data from the 1995 National Health Survey[105], the incidence of back problems was estimated to be 65,938 per 100,000. A Swiss study reported that approximately 14% of the population had chronic back pain.[112] Using information from the 1990 Ontario Health Survey database[17], the overall prevalence of back and neck disorders in residents of Ontario was determined to be around 11%.

Cervical radiculopathy and myelopathy are neurologic conditions characterized by dysfunction of the spinal nerve or spinal cord often as a result of degenerative disc disease or spondylosis. Cervical spondylotic myelopathy (CSM) is the most prevalent spinal cord dysfunction in people 55 years or older.[167] The major risk factor for cervical spondylosis is aging; although trauma may contribute, there is usually no history of significant trauma. An estimated 60% of individuals older than 40 years of age have radiographic evidence of cervical DDD secondary to spondylosis.[26,155] By age 59, 70% of women and 85% of men have radiographic evidence of these changes, and by age 70, the number increases to 93% and 97%, respectively.[64] One study found that 11% of patients between 70-102 years of age experienced neck pain in a month's time.[73] Another study of 450 surgical patients being treated for DDD found that 61% presented with radiculopathy, 16% with myelopathy, and the other 23% had a combination of the two.[133]

Because aging is the primary risk factor, as the US population ages, the incidence of DDD is expected to increase. A study of Nationwide Inpatient Sample (NIS) data collected between 1993 through 2003 shows that the number of cervical spinal fusion procedures conducted in the U.S. increased from 26 to 50 per 100,000, with symptomatic DDD representing more than four out of every five cases of cervical DDD cases in 2003.[26,167]

Intervertebral discs are soft, spongy pads of tissue that separate and provide stability to the individual vertebrae of the spine, and function by absorbing shock and facilitating motion of the spine. They are composed of water, collagen, and proteoglycans. Intervertebral discs consist of an annulus fibrosus, located in the outer region of the disc that surrounds the nucleus pulposus. The annulus fibrosus consists primarily of collagen and functions to resist tensile loads; the nucleus pulposus has a higher water and proteoglycan content that makes it jelly-like in substance, and functions to prevent compression of the spine.[112,139] Cervical spondylosis has been associated with the aging process, during which discs lose moisture content and elasticity,

leading to a loss of disc height. These changes put increased stress on the articular cartilage of the vertebrae and their endplates, and osteophytic spurs may form at the endplates.[26,64,112,139,167] In addition, annular degeneration may lead to disc herniation or protrusion.[139] Narrowing of the spinal canal by osteophytic spurs, ossification of the posterior longitudinal ligament, or bulging of a large central disc can compress the cervical spinal cord resulting in myelopathy, and impinge the spinal nerve roots, causing radiculopathy. As a result of this disc deterioration, patients may experience neck, shoulder, and arm pain as well as various degrees of neurological symptoms and impairment, including unsteady gait and clumsiness.[64,167] In severe cases, stenosis of the cervical spine can result in myelopathy affecting the lower extremity and radiculopathy affecting the upper extremity.[159]

1.2 The Technology and its Comparator(s)

Lumbar artificial disc replacement (L-ADR)

The success of total joint arthroplasty of the hip and knee for patients with osteoarthritis gives some hope that a similar remedy can be developed for the spine patients. The improvements in patients undergoing total hip and knee arthroplasty are large by any measures of responsiveness commonly used in orthopedic research.[7,8,33,71,72,85,94] In a 1979 publication of the Mayo Clinic Proceedings, total hip arthroplasty was declared one of the most successful orthopedic procedures of the century as it provided relief of pain and improved function in a wide variety of hip conditions[33]. It was recognized at that time as early long term follow-up studies were being evaluated, that some problems were being observed especially with the femoral prosthesis which led to improvements that continue to this day. Similar publications have followed, ultimately leading to consensus statements by the NIH decades after initial development that hip and knee replacement surgeries are strongly supported by more than 20 years of follow-up data concluding that there is rapid and substantial improvement in patient's pain, functional status, and overall health related quality of life in about 90% of patients with 85% being satisfied with the results of surgery.[7,8]

The success of total hip and knee replacement has helped to motivate the development of spinal artificial discs. Like these procedures, ultimate success will be based on a continuous monitoring of outcomes and complications with concurrent improvements in the technology. Similarly, these previous procedures had few alternate treatment remedies apart from continued pain management through conservative care or fusion of the joint, neither of which have been a solution to these problems, leading to decades of treatment and technology improvement in total joint replacement.

Disc replacements have a relatively long history as far as spinal implants are concerned. Ulf Fernstrom is widely believed to have inserted 191 simple Swedish Ball Bearing spheres into the lumbar and cervical spine of approximately 125 patients in the early 1960's.[54] Anecdotal information suggests that after a short period of symptom relief, the prosthesis ultimately failed secondary to subsidence of the implant within the spine vertebra leading to abandonment of the technique. However, failure rates have not been found in the published literature. Since that first prototype, more complex designed prostheses have been developed to maintain height, replicate the range of motion of a healthy spinal disc, and provide stability.[101]

Around the world the market penetration and regulatory status of artificial discs has remained varied. In the United States, only the SB Charité (DePuy Spine, Inc., Raynham, MA) and the Prodisc-L (Synthes, Inc., West Chester, PA) are currently approved for clinical use. In Canada, there are four types of lumbar artificial discs available for clinical use: the SB Charité, the Prodisc-L, the Maverick (Medtronics, Memphis, TN), and the Active L (Aesculap Implant Systems, Center Valley, PA). In Europe, the SB Charité, the Prodisc-L, the Activ-L, and the Maverick have European CE (Conformité Européne) mark certification. In Australia, the SB Charité and the Prodisc-L are available for use. Other discs currently being used or tested include the MobiDisc (LDR Medical, Cedex 9, France), the Flexicore (Stryker, Allendale, NJ), the Kineflex Lumbar Disc (SpinalMotion, Inc., Mountain View, CA), the Lumbar Motion Preservation (LMP; Vertebron, Stratford, CT), the eDisc (Theken Disc, Akron, OH), the CAdisc (Ranier Technology, Cambridge, United Kingdom), Freedom Lumbar Disc (AxioMed, Garfield Heights, OH), the Percutaneous Disc Reconstruction (PDR; TranS1, Wilmington, NC), the SaluDisc (SpineMedica, Marietta, GA), the Rescue Total Disc Replacement (Biomet/EBI, Warsaw, IN), the Min T Total Disc Replacement (Biomet/EBI, Warsaw, IN), the Altia Spine Disc (Amedica, Salt Like City, UT), the Physio-L (Nexgen Spine, Inc., Whippany, NJ), the Spartacus (US Spine, Boca Raton, FL), the Dynardi Artificial Lumbar Disc (Zimmer, Inc., Warsaw, IN), and the Total Spine Motion Segment System (TSMS; Disc Motion Technologies, Boca Raton, FL).

Each artificial disc is comprised of two or three components including two endplates and an articulating mechanism with either a metal-on-metal (eg, the Maverick and Flexicore) or metal-on-polymer surface (eg, the SB Charité and the Prodisc). To secure the disc in place and provide stability within the host vertebral body, devices feature a number of designs, such as teeth-like components called spikes or fins that are driven into the vertebral bone, a porous coated surface on the endplates which promotes bony in-growth around these structures, or are secured into the recipient vertebral body with screws.[106]

Each intervertebral disc is sandwiched between two adjacent vertebrae, and is anterior to paired facet joints that link the adjacent vertebrae. The facet joints and disc make up a single motion segment which is referred to as the "tri-joint complex".[139] This motion unit in its healthy state allows for six potential motion directions: compression, distraction, flexion, extension, lateral bending, and axial rotation.[111] The ability of artificial disc prostheses to mimic these ranges of motion provides the basis for a biomechanical classification system.[51] "Unconstrained" refers to a device that provides no mechanical assistance and allows for hypermobility beyond the normal physiological range for a given motion excursion. A "semiconstrained" device allows unrestricted motion within the normal physiological range but is blocked (ie, mechanically restrained) beyond that range. "Constrained" devices provide a fixed center of rotation that does not change and prohibit natural motion by imposing mechanical restrictions within the normal range of segment motion.[51] The constrained design concept is thought to minimize anteroposterior movement at the treated facet level, potentially reducing stresses on these structures. Table 1 below provides an overview of biomechanical classification of the most frequently studied devices.

Table 1. Biomechanical classification of select lumbar total disc arthroplasty prostheses [14,56,101]

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
SB Charité III	unconstrained	mobile	CoCrMo UHMWPE	metal on polymer	2	small fins/ bone ingrowth
Prodisc-L (also called Prodisc II in European literature)	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	1	keel
Maverick	semiconstrained	fixed	CoCrMo	metal on metal	1	keel
FlexiCore	fully constrained	fixed	CoCrMo	metal on metal	1	small fins/bone ingrowth
Mobidisc	unconstrained	mobile	CoCrMo UHMWPE	metal on polymer	2	keel

COR = center of rotation.
CoCrMo = cobalt-chromium-molybdenum alloy.
UHMWPE = ultra-high molecular weight polyethylene.

Another important aspect of disc design that relates to restoration and preservation of natural motion and stability is the center of rotation (COR). In both the cervical and lumbar spine, the center of rotation is not a fixed point but rather a locus of points that tend to be posterior to the midline and caudal to the inferior endplate.[14] Some artificial discs are designed with the center of rotation fixed, either in the center of the disc or in the posterior aspect of the disc space. Alternatively, other devices create a mobile center of rotation so that the locus of points that define the normal centers of rotation can be replicated.[14]

Metals and polymers are the primary material components of disc prostheses used in total disc replacement. Polymers provide low friction surfaces for articulating bearings and shock absorption. Metals supply the necessary material properties such as high strength, ductility, hardness, corrosion resistance, formability, and biocompatibility needed for use in load-bearing. The three main metal alloys used are titanium based, cobalt based, and stainless steal based alloys.[69]

The material components may influence the wear of the ADR. Wear is the physical process caused by motion across a bearing surface, and in prostheses it can be associated with loss of joint height and subsequent failure. Typically, the softer of the two material components bearing against each other will generate the most debris, so in a metal-on-polymer disc, the polymer generates nearly all the wear debris.[69] The local and systemic response to particulate wear debris is a potential clinical concern, as wear debris may cause an inflammatory response or infection leading to pain, osteolysis, pannus formation, and prosthetic loosening.[14] Metal debris of implants has been shown to be associated with upregulation of cytokines, however, analysis of both animal studies and human explants of various disc prostheses have not demonstrated any significant inflammatory response or osteolysis.[14] These results only describe short term effects, however, and future studies evaluating long term outcomes are needed.

Artificial discs are intended for the full life span of the patient. Inclusion criteria for the FDA clinical trials for the Prodisc-L and Charité lumbar ADR were patients 18-60 years of age, and the studies were conducted in patients with a mean age of 39 (Prodisc-L) and 40 (Charité) years.[28,171] Artificial disc prostheses should be designed to last at least 40-50 years, which are conservative approximations for the average time a 35-year old patient will need a functioning disc prosthesis.[69,111]

Indications for FDA-approved use of the Charité and Prodisc-L artificial lumbar discs can be summarized as follows:

- Skeletally mature patients
- Single-level DDD from L3-S1 (Prodisc-L) or L4-S1 (Charité)
    - DDD confirmed by patient history and radiographic studies
- If spondylolisthesis (vertebral displacement towards an adjacent vertebrae) is present at the involved level, it cannot be more than grade 1 (Prodisc-L) or 3 mm (Charité)
- Failure of at least six months of nonoperative treatment

Contraindications for FDA-approved Charité and Prodisc-L artificial lumbar discs can be summarized as follows:

- Active systemic infection or infection localized to site of implantation
- Osteopenia or osteoporosis
- Bony lumbar spinal stenosis
- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Isolated radicular compression syndromes, especially due to disc herniation
- Pars defect (spondylosis)
- Involved vertebral endplate that is dimensionally smaller than 34.5 mm in the medial-lateral and/or 27mm in the anterior-posterior directions (Prodisc-L only)
- Clinically compromised vertebral bodies at the affected level due to current or past trauma (Prodisc-L only)
- Lytic spondylolisthesis or degenerative spondylolisthesis of more than grade 1 (Prodisc-L only)

A 2004 retrospective review on the prevalence of contraindications for L-ADR in 100 patients who underwent lumbar surgery found that 10% of patients had osteoporosis, 70% had lumbar stenosis, 35% had a herniated nucleus pulposis with radicular compression, 7% had spondylosis, and 44% had spondylolisthesis.[81]

Lumbar artificial disc replacement (L-ADR) is designed to preserve motion at the target spinal level. As well as possibly providing greater pain relief, this motion preservation may potentially decrease stress on and mobility of the adjacent segment structures, factors that are thought to contribute to adjacent segment disease (ASD). L-ADR can also restore pre-degenerative disc height and spinal alignment and does not require a bone graft. Other theoretical advantages include maintenance of mechanical characteristics, decreased perioperative morbidity compared with fusion, and early return to function.[14] Insertion of the prosthesis involves an anterior approach and is usually performed by a vascular or general surgeon and a spine surgeon (with orthopaedic or neurologic surgery background) working in tandem to facilitate exposure. The

procedure is technically more demanding, has a steeper learning curve, and requires greater precision than fusion surgery. Potential problems associated with L-ADR may include injury to other structures (vascular, neurologic, intestinal, or urogenital), infection, loosening/dislodgment, polyethylene or metal wear, loss of motion over time, impact/pressure on adjacent discs and facet joints, subsidence, implant failure, heterotopic ossification, and device related endplate fracture.[122,155]

Cervical artificial disc replacement (C-ADR)

Given the reported success of lumbar artificial disc devices, The Department of Medical Engineering at Frenchay Hospital, Bristol, United Kingdom, began the initial design process for a cervical device in the late 1980's. Referred to as the Bristol-Cummins artificial joint, this disc was comprised of a two-piece, stainless steel, metal-on-metal, ball-in-socket construct with anchoring screws placed anteriorly. The results of a clinical study comprised of 20 patients implanted with this disc were promising, with most patients reporting symptomatic improvement as well as showing radiographic evidence of preserved intervertebral motion. However, several complications, mainly screw breakage and pullout, occurred attributed to poor screw placement and the fact that the joint was uniform in size.[146] Later, a second generation design, the Frenchay (now called the Prestige), was developed. This disc was less bulky, had a redesigned screw locking mechanism, and allowed for more physiological motion preservation, theoretically having less effect on adjacent vertebral segments as well. Following the reported success of the Bristol discs, other artificial cervical discs began to emerge, some using a new metal-on-plastic design (ie, Bryan).[80]

Artificial discs are functional prostheses that were developed to mimic the decompressive and supportive properties of intervertebral discs. ADR is designed to preserve motion at the target spinal level by restoring the natural distance between the vertebrae. In addition to reducing pain, this preservation of motion is hypothesized to decrease stress on and increase mobility of adjacent segments, which is theorized to reduce the incidence of adjacent segment degeneration (ASD), thought to accompany spinal fusion.[26,112]

The cervical artificial discs evaluated in this report are comprised of two or three components including two endplates and an articulating mechanism with either a metal-on-metal (e.g., the Prestige) or metal-on-polymer surface (e.g., the Bryan). To secure the disc in place and provide stability within the host vertebral body, devices feature a number of designs, such as a porous coated surface on the endplates to promote bony in-growth around the structure, or can be secured into the recipient vertebral body with screws.[155] Artificial discs are composed of the same materials used in other well-established prostheses, such as those used to replace hips or knees.[112]

The C-ADR surgical procedure involves a standard anterior cervical discectomy followed by C-ADR implantation, and is performed on an in-patient basis by an orthopedic surgeon or neurosurgeon specializing in cervical spinal conditions. Following disc and osteophyte removal, the nerves are carefully decompressed, and the artificial disc is then inserted.[112] Potential problems associated with ADR may include injury to other structures (vascular, neurologic, esophageal), temporary paralysis or loss of voice, infection, loosening/dislodgment, subsidence, polyethylene or metal wear, loss of motion over time, new or worsening pain, impact/pressure on

adjacent discs and facet joints, implant failure, heterotopic ossification, subsequent revision surgery, and device-related endplate fracture.[14,112,155]

The motion of a healthy cervical spine allows for six potential motion directions: compression, distraction, flexion, extension, lateral bending, and axial rotation.[111] The ability of the artificial disc prostheses to mimic these ranges of motion provides the basis for a biomechanical classification system. There are currently two types of cervical artificial discs available: "unconstrained" and "semiconstrained." "Unconstrained" refers to a device that provides no mechanical assistance and allows for hypermobility beyond the normal physiological range for a given motion excursion. A "semiconstrained" device allows unrestricted motion within the normal physiological range but is blocked (i.e. mechanically restrained) beyond that range.[51] Table 2 provides an overview of biomechanical classifications for the most frequently studied devices.[14,26,90]

Table 2. Biomechanical classification of select cervical total disc arthroplasty prostheses

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
Prestige (Frenchay)	semiconstrained	mobile	stainless steel	metal on metal	1	dual rails/ bone ingrowth
Prodisc-C	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	1	keel/ bone ingrowth
Bryan	unconstrained	mobile	titanium alloy polyurethane	metal on polymer	2	milled cavities/ boneingrowth
CerviCore	unconstrained	NR	CoCrMo	metal on metal	NR	dual rails/ bone ingrowth
Kineflex C	unconstrained	NR	CoCrMo	metal on metal	NR	keel/ bone ingrowth
Mobi-C	unconstrained	mobile	titanium UHMWPE	metal on polymer	NR	NR
PCM	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	2	dual rails/ bone ingrowth

COR = center of rotation.
CoCrMo = cobalt-chromium-molybdenum alloy.
UHMWPE = ultra-high molecular weight polyethylene.

Another important aspect of disc design related to restoration and preservation of natural motion and stability is the center of rotation (COR). In the cervical spine, the center of rotation is not a fixed point, but instead a locus of points that tend to be posterior to the midline and caudal to the inferior endplate. Artificial discs are designed either with the center of rotation fixed in the center or in the posterior aspect of the disc, or with a mobile center of rotation so that the locus points that define normal centers of rotation can be replicated.[14]

Artificial discs should have a life expectancy of at least 50 years to accommodate the younger patient, and the materials that constitute the disc directly affect its long-term wear.[69] Disc prostheses are primarily composed of polymers and metals. Polymers provide shock absorption and low friction surfaces on articulating bearings, while metals supply the necessary material

properties such as high strength, ductility, hardness, corrosion resistance, formability, and biocompatibility needed for use in load-bearing. The primary metal alloys used are titanium based, cobalt based, and stainless steel based alloys.[69] Wear is caused by motion across a bearing surface, and in prostheses it can be associated with the formation of debris, loss of joint height, and disc failure.[14] Metal debris of implants has been shown to be associated with upregulation of cytokines, however, analysis of both animal studies and human explants of various disc prostheses have not demonstrated any significant inflammatory response or osteolysis[9]. These results only describe short term effects, however, and future studies evaluating long term outcomes are needed.

While artificial intervertebral discs have been used for almost two decades in Europe and some Asian countries, only two of the artificial discs described in Table 1 are marketed in the United States and there are no high quality long-term studies yet available. The Prestige (Frenchay) artificial disc received FDA marketing approval on July 16, 2007. The second FDA approved ADR, the Prodisc-C, was approved on December 17, 2007. Indications and contraindications for these devices are summarized below. A third product, the Bryan Cervical ADR, received an approvable decision by an FDA advisory panel on July 17, 2007, but at this time has not received final marketing approval from FDA.[6] Other discs currently being used or tested include the PCM (Porous Coated Motion) Cervical Disc System (Cervitech, Inc., Rockaway, NJ), the Mobi-C (LDR Spine, Austin, TX), the Kineflex/C Cervical Disc (SpinalMotion, Mountain View, CA), the CerviCore Artificial Cervical Disc (Stryker Spine, Kalamazoo, MI), the Secure-C Cervical Artificial Disc (Globus Medical, Audubon, PA), the Discocerv (Scient'x, Maitland, FL), the NeoDisc (NuVasive, San Diego, CA), the Discover Artificial Cervical Disc (DePuy Spine, Raynham, MA), the Cervical Motion Preservation Device (CMP; Vertebron, Stratford, CT), and the Advent Cervical Disc (Blackstone Medical, Springfield, MA).

Indications for FDA-approved Prestige and Prodisc-C artificial cervical discs can be summarized as follows[4,5]:

- Skeletally mature patients
- C3-C7
- Patients with intractable symptomatic single-level cervical DDD
    - Neck or arm pain
    - Functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, X-ray):
        - Herniated nucleus pulposus
        - Spondylosis (defined by the presence of osteophytes)
        - Loss of disc height
- Failure of at least six weeks of nonoperative treatment
- Implanted via an open anterior approach

Contraindications for FDA-approved Prestige and Prodisc-C artificial cervical discs can be summarized as follows[4,5]:

- Active systemic infection or infection localized to site of implantation
- Osteoporosis
- Cervical instability

- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Severe spondylosis characterized by bridging osteophytes or a loss of disc height >50% or an absence of motion (< 2˚), as this can result in limited range of motion and may promote bone formation

Nonoperative treatment, lumbar

In general, treatment of symptomatic DDD initially consists of non surgical approaches such as physical therapy, acupuncture, facet joint injections, epidural steroids, anti-inflammatory drugs, analgesic medication, ultrasound, and cognitive behavioral interventions.[27,108,138] Percutaneous laser discectomy and intradiscal electrothermal therapy are two examples of minimally invasive methods used to relieve pain. It is estimated that 10% to 20% of people with lumbar DDD and up to 30% with cervical DDD will be unresponsive to nonsurgical treatment.[46] Patients who do not respond to conservative treatment are then potentially referred for fusion.

Nonoperative treatment, cervical

Initially, patients with mild DDD are typically treated with conservative, noninvasive therapies in order to relieve pain and prevent permanent injury to the spinal cord and nerves. These nonoperative treatments may include the use of a cervical collar, temporary bed rest, application of heat or ice, physical therapy (muscle-strengthening exercises, aerobic training), weight control, electrical therapy, and the administration of analgesics, including anti-inflammatory medications and epidural injections.[26,112,133] However, nonoperative management typically does not reverse or permanently stop the progression of the disease.[133]

If no improvement is seen after six weeks of nonoperative treatment or if symptoms significantly worsen, patients become candidates for surgical treatment.[26]

Many patients with symptomatic DDD become eligible for surgery; the pain of 50 to 70% of patients with cervical myelopathy and 25% with cervical radiculopathy fails to resolve with nonoperative treatment.[155] Furthermore, surgical treatment is frequently a consideration for patients with cervical DDD due to the risk of neurological deterioration.[133]

Operative treatment (lumbar fusion)

Spinal fusion is currently the surgical standard for patients with symptomatic DDD of the lumbar spine who do not respond to conservative treatment. However, there are many disadvantages to the procedure as well as concerns about its long-term consequences and benefits that have prompted research on alternative surgical methods. Complications include the potential for adjacent segment degeneration (development of disc degeneration, hypertrophic facets, dynamic instability, and/or spinal stenosis in adjacent levels), pseudoarthrosis, bone graft donor site pain and infection, instrumentation prominence or failure, neural injuries, and simple failure to relieve pain. [27,57,157] Four RCTs comparing lumbar fusion to nonsurgical treatments found that nearly 15% (58/399) of patients receiving lumbar fusion experienced complications.[30,31,53,59]. The most frequent complications reported included reoperation (with rates ranging from 0%-46.1%), infection (0%-9%), device-related complications (0%-17.8%), neurologic complications (0.7%-25.8%), thrombosis (0%-4%), bleeding/vascular complications (0%-12.8%), and dural injury (0.5%-29%).[30,31,53,59] In another study, a 12% two-year incidence rate of major complications following lumbar spinal fusion was reported, with a reoperation rate of 14.6% for that

population.[58]

Because surgical fusion results in loss of movement in the spine, adjacent vertebrae experience increased mobility and stress due to motion transfer from the immobile fused vertebrae. Spinal fusion is believed by some to promote the degeneration of the vertebrae above or below the fusion site. Evidence from one study suggests that approximately 26% of patients receiving lumbar fusion may develop new lumbar adjacent segment disease (L-ASD) within the first 10 years following fusion.[62] Annualized incidence rates of symptomatic ASD from case-series ranged from 0%[38] to 3.9%[52]. Length of follow-up varied from 32 months to 215 months across studies. It is unclear whether there is a greater risk for radiographic L-ASD in fusion patients compared with nonfusion patients. L-ASD rates among fusion patients ranged from 14.2% to 44.3% compared with 7.4% to 26.0% among patients who didn't receive fusion based on four comparative studies.[70,86,92,144] From case-series, radiographic ASD rates ranged from 1%[37] to 100%[114] following lumbar fusion and again, varied based on definition. The poor quality of these studies, divergent definitions of ASD, and the lack of correlation between radiographic L-ASD and symptomatic clinical disease make definitive conclusions regarding the extent to which L-ASD occurs following fusion difficult.

Operative treatment (anterior cervical fusion)

Surgery is generally indicated when nonoperative conservative treatments fail to prevent neurologic progression. A variety of surgical approaches and procedures are available, and the optimal choice of treatment remains controversial. Surgical procedures designed to decompress the spinal cord and, in some cases, stabilize the spine have been shown to be successful, but there is a persistent percentage of patients who do not improve with surgical intervention.[134] Additionally, the potential complications of surgery for cervical DDD may depend on the various methods of surgical management.

For many years, the posterior approach to decompress the cervical spine was used. In general this procedure resulted in favorable results for soft, accessible disc fragments. However, in order to better access midline fragments and calcified spurs, the anterior approach was developed.[48] Anterior approaches include anterior cervical discectomy alone (ACD) and anterior cervical discectomy with fusion (ACDF, using autograft, allograft, bone graft substitutes).[126] ACD has usually been associated with postoperative neck pain, low fusion rates and higher rates of cervical deformity.[11,104,116] As a result, for ACDF has become the treatment of choice for many surgeons for the treatment of radiculopathy or myelopathy as a result of central or paracentral disc herniations, or osteoarthritis of the facet or uncovertebral joint.

A range of factors must be considered when deciding which surgical technique to use, and surgeons are often challenged with determining the most appropriate technique because there is limited information about whether there is a difference between surgical procedures in terms of clinical and radiographic outcomes or in postoperative complication rates. Among surgically managed patients, an anterior or posterior approach may be employed.[133] Among those managed posteriorly, laminoplasty or laminectomy with fusion are common surgical techniques. With several standards of care available for this population, a better understanding of the corresponding positive and negative outcomes with respect to clinical and patient-centered outcomes is warranted.

The current definitive standard of care is anterior cervical discectomy and spinal fusion (ACDF). The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. The spinal fusion procedure begins with a partial or complete discectomy and decompression. The remaining intervertebral space is then filled with bone graft. The graft may be an autograft taken from patient's hip bone, an allograft taken from a donor, or synthetic and composed of bone morphogenic proteins. The bone graft stabilizes the spine by filling the intervertebral space and also promotes fusion of the vertebral endplates.[112,133,139,155]

There is a general trend for patients to see continued improvement for a few years after spinal fusion, but this improvement is often followed by functional deterioration. When the anterior surgical approach is used, this deterioration is thought to be caused by adjacent segment degeneration (ASD).[133] Because surgical fusion results in loss of movement in the spine, adjacent vertebrae experience increased mobility and stress due to motion transfer from the immobile fused vertebrae. Spinal fusion is believed to promote the degeneration of the vertebrae above or below the fusion site. The incidence of ASD following cervical fusion is difficult to estimate due to the lack of comparative studies and poor quality of the few existing studies. In addition, varying definitions of ASD make definitive diagnosis difficult. For symptomatic C-ASD, the most methodologically rigorous longitudinal study found reported a 2.9% annual incidence rate of C-ASD[79], and case-series report rates of ASD between 6%-17%.[65,87,103,154,168] Radiographic evidence of ASD has been reported to occur in 41%-92% of patients following spinal fusion based on varying definitions.[65,75,87,91,154,168] Importantly, there is a lack of correlation between radiographic ASD and clinical symptoms. Studies which were able to effectively evaluate the separate effects of degeneration due to aging and degeneration which may be exacerbated following fusion were not identified. The development of symptomatic ASD can increase the need for subsequent surgery if it causes pain or disability.[155] Data from two studies suggest that while the majority of patients (74%–84%) appeared to remain free of symptomatic C-ASD at 10 years after surgical fusion, survival analysis suggests that 16%–26% of patients have new disease within the first 10 years.[79,83] By 17 years, the rate of C-ASD increased to 33% in one study.[83]

Spinal fusion surgery is also associated with complications such as pseudoarthrosis, graft or implant failure, instrument failure, continued growth of osteocytes, and neural injuries, as well as reoperation.[133,155] There is also the risk of prolonged pain, deep infection, adjacent nerve and artery damage, and increased risk of stress fracture at the bone donor site in the hip; immunological reactions to allografts may also occur.[112]

1.3 Clinical Guidelines

National Guideline Clearinghouse

No clinical guidelines related to the use of artificial discs were found when the AHRQ, NGC database was searched. Personal contact with professional organizations confirmed that evidence-based, transparently-developed clinical guidelines have not yet been formulated.

National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE), (which provides guidance on health technologies and clinical practice for the National Health Service in England and Wales) concluded in 2004 that "current evidence on the safety and efficacy of prosthetic intervertebral

disc replacement appears adequate to support the use of this procedure." NICE acknowledges that longer term data are required to compare results with spinal fusion, and further recommended that physicians should ensure patients understand the long-term uncertainties of the ADR procedure; and that clinical outcomes be audited. Since this guidance was issued, additional studies have been reported.

1.4 Previous Systematic Reviews/Technology Assessments

Lumbar

Previously conducted reviews/assessments have reached somewhat differing conclusions regarding the safety and efficacy of lumbar ADR. Table 3 provides an overview of previous assessments.

Table 3. Overview of previous technology assessments of lumbar ADR

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Ontario Medical Advisory Secretariat Health Technology Policy Assessment (2006)	2003 through 9/2005	SB Charité, Prodisc-L, Maverick	• 2 RCTs (90% f/u, 24 months); N =540; monolevel arthroplasty only • 6 case series (98% f/u, 15–136 months); N = 285	Yes- Cochrane Musculoskeletal Injuries Group Quality Assessment Tool Overall study quality was considered moderate for effectiveness and short-term complications and very low for ASD based on GRADE analysis.	One RCT was unpublished and conducted by the device manufacturer. More recent literature now available.	**Efficacy:** Based on 2 RCTs, lumbar ADR is 79% superior to spinal fusion, although data for long-term (>2 year) outcomes are not available. **Safety:** The rates of major complications were less than 13% per L-ADR implanted, although data for long-term (>2 year) outcomes are not available. **Economic:** Lumbar ADR is more costly than fusion.
Commonwealth of Australia Medical Services Advisory Committee (MSAC) Assessment Report (2006)	1966 through 2/2005	Charité, Prodisc-L, Acroflex	• 3 RCTs (69% for 1/3 reports, 6–24 months); N = 398; monolevel and/or bilevel arthroplasty • 14 case series (% f/u NR, 12–51 months); N = 579	Yes- Level of evidence as defined by the National Health and Medical Research Council; NHS Centre for Reviews and Dissemination validity criteria Overall quality of studies was moderate and presented several limitations, case series reviewed for safety considerations only.	More recent literature now available. No overall formal level of evidence scores presented.	**Efficacy:** Recommends interim funding for L-ADR in eligible patients with monolevel DDD. **Safety:** No significant differences in complication rates were found in L-ADR versus fusion. The long-term (>5 years) safety is unknown; adverse events occurred in less than 14% of patients in all case series evaluated. **Economic:** Lumbar ADR is less costly than fusion.
Federaal Kenniscentrum voor de Gezondheidszorg KCE reports vol.39A (2006)	through 2/2006	SB Charité	• 1 RCT (% f/u NR, 24 months); N =304; monolevel arthroplasty	Yes- Dutch Cochrane Center checklist used Overall study quality was rated as fair, although overall quality of evidence available is poor.		**Efficacy:** Based on only 1 available RCT, L-ADR should be considered an experimental procedure. **Safety:** Concerns remain due to based on unavailable information on rate of ASD and long-term complications. **Economic:** Considers information to be lacking.
NHS National Institute for Clinical Excellence Interventional Procedure	through 10/2002	SB Charité III	• 1 RCT (% f/u NR, 24 months); N = 304; monolevel arthroplasty only	Not reported Literature lacks good-quality long-term evidence.	More recent literature now available.	**Efficacy:** Current evidence is adequate to support ARD, although long-term efficacy is uncertain.

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Guidance 100 (2004)			• 1 nonrandomized CT (% f/u NR, time of f/u NR); N = 20 • 4 case reports (97% f/u for 1/4 studies, 12–52 months); N = 294		No formal grading of evidence quality.	**Safety:** Current evidence is adequate to support ARD, although long-term data is needed. **Economic:** not addressed
ECRI Institute (2007)	through 9/2006	Charité, Prodisc-L, Activ-L, Maverick, FlexiCore, Kineflex	• 2 RCTs (61% f/u for 1/2 reports, 6–24 months); N = 460	Yes- State of Evidence Base grading system The available quality of evidence was rated as low.	More recent literature now available.	**Efficacy:** Limited data suggests that L-ADR may offer advantages over fusion. **Safety:** The long-term (>2 years) safety of L-ADR is uncertain. **Economic:** The cost of L-ADR is comparable to that of fusion.
Institute for Clinical Systems Improvement Technology Assessment Report (1995)	1995 through 2005	Charité, Prodisc-L, Maverick	• 3 RCTs (90% f/u for 1/3 reports, 18–24 months); N = 526; monolevel arthroplasty only (in 2/3 reports) • 6 case series (75% for 3/6 reports, 12–120 months); N = 494	Yes- Evidence Grading System as described The overall study quality has many inconsistencies.	More recent literature now available.	**Efficacy:** The long-term efficacy of L-ADR is not known, and its use not supported. **Safety:** The long-term safety of L-ADR is not known. **Economic:** ARD is more expensive than fusion ($10,000–$12,000 for ARD, $4,000–$5,000 for fusion).
Hayes brief (2007)	2002 through 8/2007	Charité, Prodisc-L, Maverick, FlexiCore, LIDR	• 2 RCTs (87% f/u for 1/2 reports, 24 months); N = 540 (plus an additional 348 nonrandomized patients); monolevel arthroplasty only • 7 case series (87% for 4/7 reports, 18–158 months); N = 714	Yes- Hayes Ratings System The overall study quality prevents clear interpretation of the data.		**Efficacy: L-ADR** for DDD using Charité or Prodisc may lead to improved outcomes versus fusion for at least 2 years after surgery, only recommended as a last resort. **Safety:** The long-term safety of L-ADR remains uncertain. **Economic:** not addressed
California Technology Assessment Forum (2007)	1966 through 1/2007	Charité, Prodisc-L	• 2 RCTs (94% f/u, 24 months); N = 540; monolevel arthroplasty only (in 1/2 reports) • 11 case series (86% f/u for 3/11 reports, 12–208 months); N = 644; some case series were reported in multiple papers with overlapping patient populations	Yes- Studies graded for level of evidence (system not described) Overall quality of available evidence was moderate, noting that case series provide weak evidence.		**Efficacy: L-ADR** using Charity or Prodisc discs does not meet TA criteria for effectiveness or outcome and is not recommended. **Safety: L-ADR** using Charity or Prodisc discs does not meet TA criteria for safety and is not recommended. **Economic:** not addressed
Washington State Department of Labor and Industries HTA (2004)	through 7/2004	Charité III, Prodisc II, PDN	• 2 RCTs (100% f/u for 1/4 reports), 6–24 months); N = 393; monolevel and bilevel arthroplasty • 9 case series (78% f/u for 5/9 reports, 3–48 months); N = 403	Not reported The overall quality of the literature is poor and limited	No formal grading of the overall quality of evidence.	**Efficacy:** Data insufficient to draw conclusions, L-ADR should be considered experimental only. **Safety:** No conclusions were drawn. **Economic:** not addressed
Workers' Compensation Board of BC Review (2005)	through 10/2004	Charité III, Prodisc-L, PDN	• 1 RCT (% f/u NR, 24 months); N = 366; monolevel arthroplasty only	Yes- WCB of BC grading system.	RCT conducted by manufacturer of Charité III disc.	**Efficacy:** Efficacy cannot be determined at this time and L-ADR should be considered experimental.

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
				The overall quality of the literature is poor (?) and limited.	More recent literature now available.	**Safety:** Safety cannot be determined at this time. **Economic:** not addressed

ADR: artificial disc replacement.
ASD: adjacent segment degeneration.
GRADE: Grading of Recommendations Assessment, Development and Evaluation.
NR = not reported.
PDN = Prosthetic Disc Nucleus.
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Percent follow-ups were not given for all RCTs or case studies. Mean time of follow-up is reported here.
† N reflects numbers before loss to follow-up.
‡ Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

Cervical

Many previously conducted reviews/assessments have primarily been formulated prior to the publication of randomized trials related to cervical ADR. Consequently, they have used case-series and concluded that there is a lack of evidence for the use of C-ADR. Table 4 provides an overview of previous assessments.

Table 4. Overview of previous technology assessments of cervical ADR

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal?‡	Comments	Primary conclusions
Ontario Medical Advisory Secretariat Health Technology Policy Assessment (2006)	2003 through 9/2005	Bryan	▪ 4 case-series (59% f/u, 12–24 months) N = 229	Yes- Cochrane Musculo-skeletal Injuries Group Quality Assessment Tool Overall study quality was considered to be very poor based on GRADE analysis.	No RCT data available. RCT data became available after publication (in 2007). Complication rates were not assessed beyond a 2-year follow-up, ASD rate not reported.	**Efficacy:** Without data from RCTs, the effectiveness of C-ADR versus spinal fusion could not be determined. **Safety:** The rates of major complications ranged from 0-8.1% per C-ADR implanted, the rate of ASD is not reported. **Economic:** none.
Commonwealth of Australia Medical Services Advisory Committee (MSAC) Assessment Report (2006)	1966 through 2/2005	Prestige I/II, Bryan, Bristol/ Cummins, porous coated motion disc	▪ 1 RCT (preliminary report, 44% f/u, 24 months) N = 55 Monolevel arthroplasty ▪ 11 case-series (% f/u NR, 12–65 months) N = 578	Yes- Level of evidence as defined by the National Health and Medical Research Council; NHS Centre for Reviews and Dissemination validity criteria Quality of RCT was inadequate and presented several limitations, case-series reviewed for safety considerations only.	RCT data became available after publication (in 2007). Formal level of evidence scores not presented.	**Efficacy:** Does not recommend public funding for C-ADR in the cervical spine due to inadequate evidence of effectiveness. **Safety:** No significant differences in complication rates were found between patients treated with C-ADR versus fusion, although the long-term (>5 years) safety is unknown; adverse events occurred in less than 14% of patients in all case-series evaluated. **Economic:** Cervical ADR is more costly than fusion.
Institute for Clinical Effectiveness and Health Policy-	NR	Prestige, Bryan, Prodisc	▪ 5 RCTs (65% f/u for 1/5 reports, 6–24 months) N = 1117	Not reported There are few RCTs, some with few patients	No formal grading of evidence quality described.	**Efficacy:** There are no significant differences in C-ADR versus fusion, in studies with up to 2 year follow-up.

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal?‡	Comments	Primary conclusions
Argentina (abstract) 2007			The 5 RCTs include FDA IDE studies, one preliminary report and two small RCTs independent of FDA trials	and methodological defects.		Longer follow-up periods are necessary. **Safety:** not addressed **Economic:** not addressed
NHS National Institute for Clinical Excellence Interventional Procedure Guidance 143 (2005)	through 2/2005	Bryan, Prestige I/II	▪ 2 RCTs (16% f/u for 1/2 studies, 6–24 months) N = 68 Monolevel arthroplasty only (reported for 1/2 RCTs) ▪ 3 case-series (% f/u NR, 6–24 months) N = 168	Not reported	More recent literature now available. No formal grading of evidence quality described.	**Efficacy:** Current evidence supports the short-term efficacy of C-ADR, although can't compare C-ADR to fusion without long-term data. **Safety:** There are no major safety concerns for C-ADR, although long-term outcomes are unknown. **Economic:** not addressed
Hayes brief (2007)	1/2000 through 9/2007	Prestige	▪ 1 full RCT (78% f/u, 24 months) N = 541 Monolevel arthroplasty ▪ one preliminary RCT report (44% f/u, 24 months) N = 55 ▪ 2 case-series reports (27% f/u, 24–48 months) N = 70	Not reported The RCT was sponsored by the manufacturer and is subject to bias.	No formal grading of the overall quality of evidence described.	**Efficacy:** Results from one RCT suggest that C-ADR is at least equivalent to fusion for at least two years after surgery. **Safety:** Long-term safety has not been demonstrated, and there are no significant differences between C-ADR and fusion in results from one RCT. **Economic:** The cost of cervical ADR is similar to that of fusion.
Workers' Compensation Board (WCB) of BC Review (2005)	through 10/2004	Bryans, Prestige ST, Prodisc-C, CerviCore (FlexCore), PCM	▪ 2 RCTs (73% f/u, 12–24 months) one is an initial report, the other a meeting abstract N = 115 Monolevel arthroplasty only ▪ 13 case-series (59% f/u for 5/13 reports, 6–60 months) N = 500 (NR for 1 study)	Yes- WCB of BC grading system. The overall quality of the literature is limited.	More recent literature now available.	**Efficacy:** Efficacy cannot be determined at this time and C-ADR should be considered experimental. **Safety:** Safety cannot be determined at this time. **Economic:** not addressed

ADR: artificial disc replacement
ASD: adjacent segment degeneration
GRADE: Grading of Recommendations Assessment, Development and Evaluation
NR: not reported
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Percent follow-ups were not given for all RCTs or case studies. Mean time of follow-up is reported here.
† N reflects numbers before loss to follow-up.
‡Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

1.5 Medicare and Representative Private Insurer Coverage Policies

Variations exist in coverage policies for L-ADR for CMS and selected bell-weather payers. Table 5 provides an overview of policy decisions. There is currently no Centers for Medicare and Medicaid Services (CMS) National Coverage Determination specific to cervical spine disc replacement. It is slated as potential topic for the third quarter of 2008. Overview of payer assessments and policies for C-ADR are found in Table 6 below.

- **Medicare**
  The Centers for Medicare and Medicaid Services (CMS) will not cover lumbar ADR for patients older than 60 years of age and decisions regarding coverage of patients younger than 60 years of age are at the discretion of local CMS contractors. CMS's assessments include information from the BCBS TEC reports. An internal assessment used data from the two primary IDE randomized controlled trials for the Charite and ProDisc L as well as case series and one non-randomized study. Information on long-term outcomes was derived from case-series. A critical appraisal scheme for assessing study quality was described. The assessment deals only with lumbar ADR.

- **Aetna**
  Aetna considers FDA-approved prosthetic intervertebral discs medically necessary for spinal arthroplasty in skeletally mature person with lumbosacral degenerative disc disease at one level from L3 so S1, and who have failed at least 6 months of conservative management.

- **Blue Cross/Blue Shield**
  Coverage was not recommended.

- **Cigna**
  Cigna covers the implantation of a SB Charité or Prodisc-L lumbar intervertebral disc 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 patient when ALL of the following criteria are met:
  - The unremitting low back pain and disability described has been refractory to at least six consecutive months of standard medical and surgical management (eg, exercise, analgesics, physical therapy, spinal education).
  - Single-level disc degeneration has been confirmed on complex imaging studies (ie, computerized tomography [CT] scan, magnetic resonance imaging [MRI]).
  - The planned implant will be used in the L4-S1 region if Charité or the L3-S1 region if Prodisc-L.

- **Harvard Pilgrim**
  Harvard Pilgrim does not cover artificial disc replacement for DDD as an alternative to spinal fusion.

Table 5. Overview of payer technology assessments* and policies for L-ADR

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services (2007)	2002- 2007	Prodisc-L	▪ 2 RCTs (86% f/u, 24 months); N = 596; monolevel arthroplasty only ▪ 1 nonrandomized CT (% f/u NR, 24 months); N = 24 ▪ 19 case series (87% f/u for 5/19 reports, 1–204 months); N = 1082 ▪	▪ The Centers for Medicare and Medicaid Services (CMS) will not cover lumbar ADR for patients older than 60 years of age and decisions regarding coverage of patients younger than 60 years of age are at the discretion of local CMS contractors.	▪ No clear conclusion can be drawn as to whether L-ADR is beneficial in patients younger than 60 years old. ▪ There is not enough evidence of benefit of L-ADR for patients over 60 years old.
Aetna Clinical Policy Bulletin (2007)	2000-2007	SB Charité Prodisc-L	▪ 1 RCT (87% f/u, 24 months); N = 304; monolevel arthroplasty only ▪ 1 nonrandomized CT (% f/u NR, 24 months); N = 24 ▪ 11 case series (91% f/u for 4/11 case reports), 24–91 months); N = 588 (not reported for all case series)	▪ FDA-approved prosthetic discs are considered medically necessary for adults with monolevel DDD (L3-S1) and who have failed at least six months of conservative treatment. ▪ Considered investigational for all other indications.	▪ No rationale for policy stated ▪ Policy is in accordance with FDA recommendations ▪ CPT codes if selection criteria are met: 0090T, +0092T, 0093T, +0095T, 0096T, +0098T, +0163T, +0164T, +0165T, 22857, 22862, 22865 ▪ Other CPT codes related to the CPB: 22533, 22558, 22612, 22630
BlueCross BlueShield Techonology Evaluation Center Assessment (2007)	through 5/2007	SB Charité Prodisc-L	▪ 2 RCTs (86% f/u, 24 months); N = 546; monolevel arthroplasty only (noted for 1/2 RCTs) ▪ 1 nonrandomized CT (100% f/u, 12 months); N = 24 ▪ 6 case series (94% f/u, 24–104 months); N = 334	▪ Not recommended	▪ There is insufficient evidence from RCTs to establish effectiveness
Cigna HealthCare Coverage Position (2007) **Cigna HealthCare Coverage**	1994 through 2007	Charité Prodisc-L Maverick	▪ 2 RCTs (75% f/u for 1/2 reports, 24 months); N = 596; monolevel arthroplasty only ▪ 19 case series (95% f/u for 1/19 reports, 3–120 months, NR for 5 studies); N = 1873	▪ Single-level L-ADR using Charity or Prodisc discs is considered superior to fusion and will be covered in patients who have failed six months of conservative treatment. ▪ Charité disc can be used in the L4-S1 region. ▪ Prodisc can be used in the L3-S1 region.	▪ Evidence has shown that the use of Charité and Prodisc disc proteheses are safe and effective. ▪ Results from short-term studies show that L-ADR improves range of motion within the lumbar spine and stabilizes the invertebral disc space.

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
Position (2007) (continued)					▪ ADR is regarded as safe, although more data is needed regarding the long-term safety and rate of complications. ▪ CPT codes covered when medically necessary: 22857 ▪ CPT codes considered experimental, investigational, unproven, not covered: 0090T, 0092T, 0163T ▪ No specific HCPCS codes
Harvard Pilgrim HealthCare TA Policy (2006)	1994 through 3/2006	Charité	▪ 1 RCT (% f/u NR, 24 months); N = 304 ▪ 2 case series (% f/u NR, 120–204 months); N = 153	▪ Not covered	▪ Long-term data on safety, efficacy, and durability of the discs are needed. ▪ ADR is a more technically difficult surgery than spinal fusion.
Nordian Medicare B 2006	Through 8/2006	Charité		▪ Lumbar ADR will not be covered for patients older than 60 years of age. For patients under 60 years of age, there is no national coverage policy, and local contractors will determine coverage.	▪ No clear conclusion can be drawn as to whether L-ADR is beneficial in patients younger than 60 years old. ▪ There is not enough evidence of benefit of L-ADR for patients over 60 years old. ▪ CPT codes covered for patients over 60 years of age if procedure performed under an approved IDE/clinical trial and/or approved by the contractor: 00091T, 00092T
Washington State Payers					
Premera Blue Cross (2008)	2000-2008	Charité Prodisc-L	▪ 2 RCTs (88% f/u reported for 1/2 reports, 24 months); N = 546 ▪ 3 case series (39% f/u reported for 1/3 reports, 12-104 months); N = 216	▪ Lumbar ADR is considered investigational.	▪ ADR is appropriate for some patients in which lumbar fusion is indicated, but not in patients who need additional procedures such as laminectomy or decompression. ▪ CPT category I codes for single-level ADR: 22857, 22862, 22865 ▪ CPT category III codes for multi-level ADR: 0163T, 0164T, 0165T

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
Regence (2008)	through 2008	Charité Prodisc-L	▪ 2 RCTs (% f/u NR, length of follow-up NR); N = NR	▪ Lumbar ADR is considered investigational	▪ No clear conclusions can be drawn from RCTs about long-term health outcomes, safety, and durability
Group Health Cooperative (2007)	through 2007	Charité	▪ 1 RCT (88% f/u, 24 months); N = 304 ▪ 1 cohort analysis (% f/u NR, 24 months or longer); N = 688	▪ Not covered	▪ There is insufficient evidence to demonstrate the safety or efficacy of lumbar ADR in comparison to current standard treatments ▪ Other plans, including Medicare, do not cover cervical ADR at this time ▪ Noted that the Group Health Permanente chief of neurosurgery recommended to wait until ADR has been shown to yield better results than spinal fusion before covering this procedure

ADR: artificial disc replacement.
DDD: degenerative disc disease.
NR: not reported.
*Formal critical appraisals were not reported in any of the payer HTAs. The CMS report does provide description as does the BCBS report.
†Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Mean time of follow-up is reported here.
‡N reflects numbers as reported in the assessment before loss to follow-up.

Table 6. Overview of payer assessments and policies for C-ADR

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services (CMS) (2007)	N/A	N/A	▪N/A	There is currently no National Coverage Determination.	
Aetna Clinical Policy Bulletin (2007)	2000-2007	Prestige SP	▪1 RCT (78% f/u, 24 months) ▪N = 541 ▪Monolevel arthroplasty only ▪1 RCT compared postoperative imaging quality before and after arthroplasty at the operated and adjacent levels and between implant types in 20 patients.	▪FDA-approved prosthetic discs are considered medically necessary for adults with monolevel DDD (C3-C7) and who have failed at least six weeks of conservative treatment. ▪Considered investigational for all other indications.	▪No rationale for policy stated ▪Policy is in accordance with FDA recommendations ▪CPT codes if selection criteria are met: 0090T, +0092, 0093, +0095, 0096, +0098, +0163, +0164, +0165, 22857, 22862, 22865 ▪Other CPT codes related to the CPB: 22533, 22558, 22612, 22630
BlueCross BlueShield Technology Evaluation Center Assessment (2007)	Through 8/2007	Prestige ST	▪ 1 RCT (46% f/u, 24 months) ▪ N = 541 ▪ Monolevel arthroplasty only	▪ Not recommended	▪Cervical discs considered experimental ▪Insufficient evidence from RCTs ▪The 24-month follow-up period is insufficient to prove long-term safety and efficacy.
Cigna HealthCare Coverage Position (2007)	2002 through 2007	Prestige, Frenchay, Bryan	▪ 2 RCTs (71% f/u, 24 months) ▪ N =596 ▪ Monolevel arthroplasty only ▪ 6 case-series (48% f/u for 2/6 reports, 12–48 months) ▪ N = 617 ▪	▪ Not covered	▪Insufficient evidence from RCTs ▪There is a lack of long-term data to prove safety and efficacy.
Nordian –CMS Medicare B 2006	Through 8/2006	NR		▪ Cervical ADR is non-covered per the LCD for Artificial Disc ▪	
Washington State Payers					
Premera Blue Cross (2008)	2007-2008	Prestige ST Bryan ProDisc-C	▪ 1 RCT (52% f/u, 24 months) ▪ N = 541	▪ Cervical ADR is considered investigational	▪ 24 months f/u is not adequate to evaluate long-term results, especially

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Policy	Rationale/Comments
					ASD, durability, safety, and revisability ▪ RCT was not blinded leading to potential bias ▪ CPT category III codes: 0090T, 0092T, 0093T, 0095T, 0096T, 0098T
Regence (2008)	through 2008	Prestige	▪ 2 RCTs (% f/u NR, 24 months) ▪ N = 55 for 1/2 studies	▪ Cervical ADR is considered investigational	▪ No clear conclusions can be drawn from RCTs about long-term health outcomes, safety, and durability ▪ There are significant design and analysis flaws in one RCT
Group Health Cooperative (2007)	through 2007	Prestige	▪ 1 RCT (83% f/u, 24 months) ▪ N = 541	▪ Not covered	▪ There is insufficient evidence to demonstrate the safety or efficacy of cervical ADR in comparison to current standard treatments ▪ Other plans, including Medicare, do not cover cervical ADR at this time ▪ Noted that the Group Health Permanente chief of neurosurgery recommended to wait until ADR has been shown to yield better results than spinal fusion before covering this procedure

ADR: artificial disc replacement.
DDD: degenerative disc disease.
NR: not reported.
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Mean time of follow-up is reported here.
† N reflects numbers as reported in the assessment before loss to follow-up.
Formal critical appraisals were not reported in any of the payer HTAs.

1.6 Other Significant Evidence

Lumbar

Two other L-ADRs are currently undergoing clinical trials: the Flexicore and the Activ-L.

The FlexiCore L-ADR is currently undergoing a prospective, randomized, controlled, multicenter investigational device exemption (IDE) study to compare its effectiveness versus standard circumferential fusion for the treatment of discogenic pain due to single-level

degenerative disc disease (DDD). The cohort is made up of 401 patients randomized to FlexiCore group or fusion group with a 2:1 ratio. Inclusion criteria consist of skeletally mature patients between 18 and 60 years of age with DDD at a single level between L1 and S1. Confirmation of the diagnosis of DDD is made by MRI, CT myelography, or lateral flexion/extension films demonstrating either translational instability, angular instability, or disc height decreased by greater than 2 mm compared to adjacent disc height. Outcomes to be measured are the Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) to determine preoperative and postoperative function and pain level. To be included in the study, patients have to score at least 40 on a 0 to 100 point scale on both the ODI and VAS.

The Activ-L Artificial Disc is being investigated for the treatment of single-level degenerative disc disease of the lumbar spine that has been unresponsive to prior conservative treatment of at least six months duration. The design incorporates a center core intended to allow both translation and rotation and to more closely approximate physiological motion. The study is being conducted under an investigational device exemption (IDE) and is a prospective, randomized, single-masked, controlled, multicenter clinical trial consisting of an estimated 387 subjects. In the study, the Activ-L ADR is being compared with the Prodisc-L ADR and the Charité Artificial Disc. Between 15 and 20 investigational sites will participate in the investigation.

Cervical

The Bryan artificial disc is currently undergoing clinical trials both in the US as part of an FDA IDE, and in the Netherlands as part of the PROCON trial (referring to the pros and cons associated with each treatment). Initial results from an international trial of the Prestige II C-ADR were published in 2004, but no further peer-reviewed publications on this trial were found.[129]

The FDA Bryan C-ADR trial

A randomized controlled trial to evaluate the safety and effectiveness of the Bryan disc was initiated in May 2002.[6] Patients recruited for the trial were those with radiculopathy or myelopathy attributable to single-level cervical disc disease refractory to nonoperative interventions. Patients were randomized in a 1:1 ratio to single-level anterior cervical discectomy and fusion (ACDF) using bone graft and plate stabilization or single-level cervical arthroplasty with the Bryan cervical disc prosthesis. A total of 463 patients participated, 242 receiving the Bryan ADR and 221 receiving ACDF. The study was designed to demonstrate non-inferiority of the Bryan ADR compared with ACDF. The primary endpoint for the clinical investigation was "overall success", a composite variable that included the following:

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

Treatment success was based on the 24-month overall success rate being statistically non-infererior to the control group rate.

The secondary endpoints included:

Operative time	Blood loss	Hospital stay
Treatment levels	External orthosis	Overall neuro status
NDI score	Neck pain score	Arm pain score
SF-36 Health Survey	FSU height/implant subsidence	AP implant migration
Change in angular motion	Translation	Gait
Bending at target level	Fusion status	Patient satisfaction
Angular motion at adjacent levels – below	Summary of radiographic success	Angular motion at adjacent levels – above

Two preliminary reports have reported on subsets of patients from this FDA trial. The first report published in 2006 included 33 patients (17 receiving Bryan ADR and 16 receiving ACDF) from one site.[43] Follow-up ranged from 13 to 25 months. The authors concluded that the Bryan disc treatment group showed similar improvements in clinical parameters compared with those in the fusion group.

The second report published in 2007 included the results from 115 patients enrolled at three centers.[142] At the 2-year follow-up, the investigators report reduced arm pain (14 versus 28, P = .014), reduced neck pain (16 versus 32, P = .005), better SF-36 physical component scores (51 versus 46, P = .009), and more motion retained at the index level (P = .006) for the Bryan ADR compared with ACDF. There were six additional operations in this report, two in the C-ADR group and four in the ACDF group. There were no intraoperative complications, no vascular or neurologic complications, no spontaneous fusions, and no device failures or explantations in the Bryan group. The authors concluded that the Bryan ADR compares favorably to anterior cervical discectomy and fusion for the treatment of patients with 1-level cervical disc disease.

The initial study protocol called for an interim analysis which has been done on the first 300 patients to complete 24 month follow-up (about 65% of the entire study population) and reported in an FDA Executive Summary from a July 12, 2007 Panel Meeting.[6] This Technology Assessment presents some results with and without data from the interim analysis.

The PROCON Bryan C-ADR trial

The PROCON multicenter trial is designed to accomplish three aims[18]:

- To conduct a multicenter, randomized controlled trial comparing the clinical outcome of three different surgical options: cervical anterior discectomy without fusion, cervical anterior discectomy and fusion using a cage and, finally, C-ADR using the Bryan's disc prosthesis
- To define differences in disc degeneration of the adjacent discs between the three surgical options
- To estimate the cost-effectiveness of the three surgical options
  The study population will include 18 to 55 year old patients with radiculopathy from single-level cervical disc disease. Patients with myelopathy will be excluded. Primary outcomes will include SF-36, McGill Pain score, the NDI, and the Work Limitations Questionnaire. Follow-up will last 60 months.

The Prestige II C-ADR trial

A multicenter RCT was published in 2004 involving four centers in the United Kingdom, Australia, Belgium and Switzerland.[129] The investigators enrolled 55 patients experiencing intractable radiculopathy or myelopathy caused by herniated disc or osteophyte formation; 27 were randomized to receive the Prestige II C-ADR and 28 to receive ACDF with iliac crest autograft. Only patients with single-level disease in C4-5, C5-6 or C6-7 were included. At the time the time of publication, only 67% and 16% of the patients had reached the one and two year follow-up, respectively. During the available follow-up, the C-ADR group experienced 17 adverse events. One patient had persistent pain and a subsequent fusion. One WHO Grade 3 adverse event was recorded which was considered unrelated to the surgery (pancreatitis). Two other permanent events (Grade 2) included continuous neck pain and continuous shoulder pain without evidence of neurocompression. The ACDF group had 19 adverse events, three directly related to the surgical procedure. Two WHO Grade 3 events were recorded; both involving secondary myelopathy requiring additional adjacent segment surgery. Three additional patients with continuous neck pain were considered permanently affected and required symptomatic treatment.

2. The Evidence

2.1 Systematic Literature Review

Objectives

The primary objective of the systematic literature review was to compare physical function/disability, pain, economic measures, complications, and adverse events in patients receiving artificial disc replacement versus other forms of treatment for lumbar degenerative disc disease without neurological compromise or cervical degenerative disc disease resulting in radiculopathy or myelopathy.

Secondary outcomes assessed include quality of life, return to previous activity or work, the rate of adjacent segment disease (ASD), and range of motion at the instrumented segment. Evidence of differential efficacy or safety issues among special populations was sought within the literature on test characteristics, supplemented with evidence obtained from review articles and expert guidance.

2.2 Methods

Inclusion/exclusion

- *Population.* Studies of adults who underwent primary L-ADR for DDD without neurological compromise and primary C-ADR for DDD resulting in cervical radiculopathy or myelopathy and who had not had prior spine surgery at the instrumented level were included.
- *Intervention.* Included studies evaluated L-ADR and C-ADR using commercially available devices: FDA approved or unapproved devices in Phase III trials with ≥ 1 year of follow-up data in a peer-reviewed journal. Studies reporting on disc nucleus replacement were excluded.

- *Study design.* Eligible studies compared L-ADR and C-ADR with other treatments for lumbar and cervical DDD utilizing a randomized or cohort study design. In order to provide additional context regarding key questions 2 and 3, studies with historical/nonconcurrent controls and/or summaries of case series of greater than 10 patients were included. Formal economic analyses published in peer-reviewed journals were eligible for inclusion to help answer key question 4 as were cost data reported in other systematic reviews or technology assessments.
- *Outcomes*. Eligible studies reported on at least one of the following outcomes: physical function/disability (overall clinical success, ODI [L-ADR] or NDI [C-ADR]), pain, device failure (revision, reoperation, or removal), or complications.

Table 7 below summarizes the inclusion/exclusion criteria.

Table 7. Summary of inclusion and exclusion criteria for both L-ADR and C-ADR

Study Component	Inclusion	Exclusion
Population	• Patients undergoing primary L-ADR for DDD without neurological compromise and who have not had prior spine surgery at the instrumented level • Patients undergoing primary C-ADR for DDD resulting in radiculopathy or myelopathy and who have not had prior surgery at the instrumented level	• Patients with contraindications to receive L-ADR or C-ADR • ADR in the thoracic spine
Intervention	• L-ADR or C-ADR with commercially available device: FDA approved or unapproved devices in Phase III trials with ≥ 1 year of follow-up data in a peer-reviewed journal	• Disc nucleus replacement
Comparator	• Nonoperative treatment • Spinal fusion • Other spine surgery	
Outcomes	Studies must report on at least one of the following • Physical function/disability (overall clinical success, ODI [L-ADR] or NDI [C-ADR]) • Pain/pain reduction • Device failure (revision, reoperation or removal) • Complications (eg, migration, subsidence, neurologic injury as well as infection, vascular damage, others) The following secondary outcomes are reported if presented with studies meeting the above criteria: • Quality of life (SF-36) • Preservation of motion • Incidence of adjacent segment disease	
Study Design	• Only randomized controlled trials (RCTs) and comparative studies with concurrent controls were considered for question 1. • RCTs and comparative studies with concurrent controls were sought initially for questions 2 and 3. • In order to provide additional context regarding questions 2 and 3, studies with historical/non-	• For question 1, studies other than RCTs or comparative studies with concurrent controls were excluded • Case reports • Case-series with fewer than 10 patients

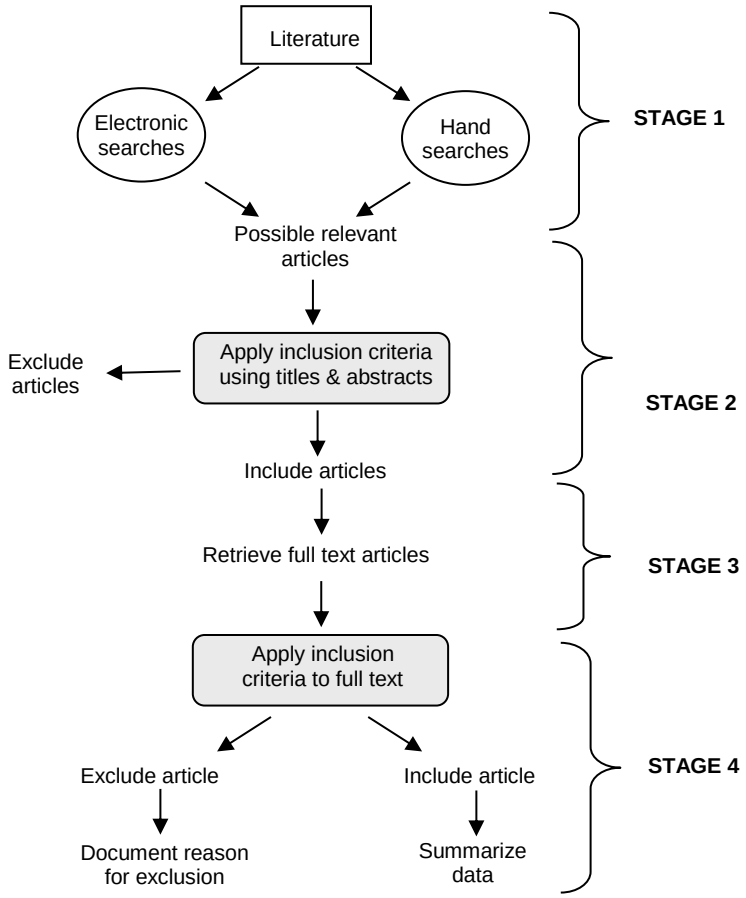
Study Component	Inclusion	Exclusion
	concurrent controls and/or summaries of case-series were obtained and very briefly summarized. • For question 4, formal economic analyses (eg, cost-utility study) were sought. • In the absence of formal economic analyses, cost data reported in other systematic reviews or technology assessments were briefly summarized.	

Publication	• Studies published in English in peer reviewed journals
	• FDA reports
	  • L-ADR: Summary of Safety and Effectiveness Data (SSED), In-depth Statistical Review, In-depth Clinical Review
	  • C-ADR: Summary of Safety and Effectiveness Data (SSED), Executive Summary of FDA panel meeting
		• Abstracts, editorials, letters
		• Duplicate publications of the same study which do not report on different outcomes
		• Single site reports from multicenter trials
		• White papers
		• Narrative reviews
		• Articles identified as preliminary reports when results are published in later versions

Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Figure 1 below. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 1. Algorithm for article selection



Electronic databases searched included PubMed, EMBASE, CINAHL, ClinicalTrials.gov, CRISP, HSTAT, *The Cochrane Library*, EconLIT, PsychINFO, MAUDE, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. Reference lists of all eligible studies were also searched. The search strategies used for PubMed and EMBASE, are shown in Appendix A. Figures 2 and 3 on the next two pages show a flow chart of the results of all searches for included primary studies for L-ADR and C-ADR, respectively. The searches went through May 9, 2008.

For L-ADR, in addition to two primary studies, searches identified one Cochrane systematic review[63] and 16 HTAs, six of which were done by insurance carriers. Two FDA Summary of Safety and Effectiveness Data (SSED) reports were obtained, one for the Charité and one for the Prodisc-L ADR. An additional FDA In-depth Statistical Review and an In-depth Clinical Review were also included for the Charité ADR. Two partial economic analyses were found in the peer-reviewed literature and included.

Searches for C-ADR identified three randomized controlled trials and nine HTAs. The technology assessments are listed in Tables 4 and 6. No systematic reviews were found. Two FDA Summary of Safety and Effectiveness Data (SSED) reports were obtained, one for the

Prestige ST and one for the Prodisc-C ADR. An additional FDA Panel Meeting Executive Summary was found for the Bryan C-ADR that included a pre-specified interim analysis of approximately two-thirds of the enrolled patients with 24 month follow-up. No economic analyses were found in the peer-reviewed literature.

Figure 2. Flow chart showing results of literature search for L-ADR

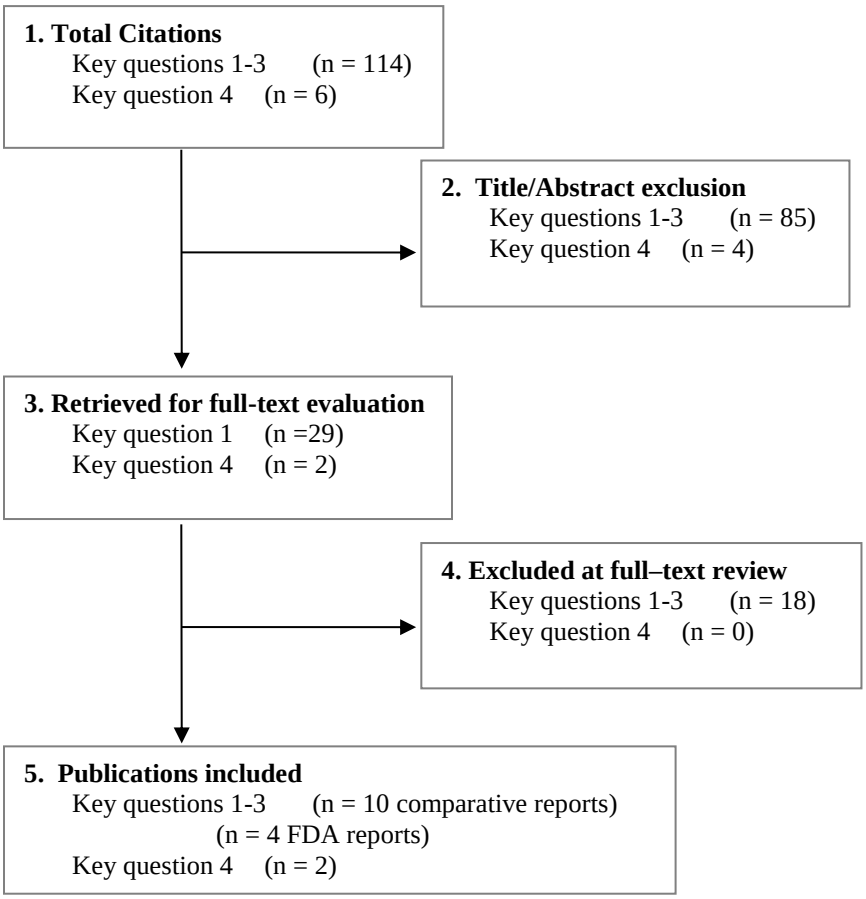
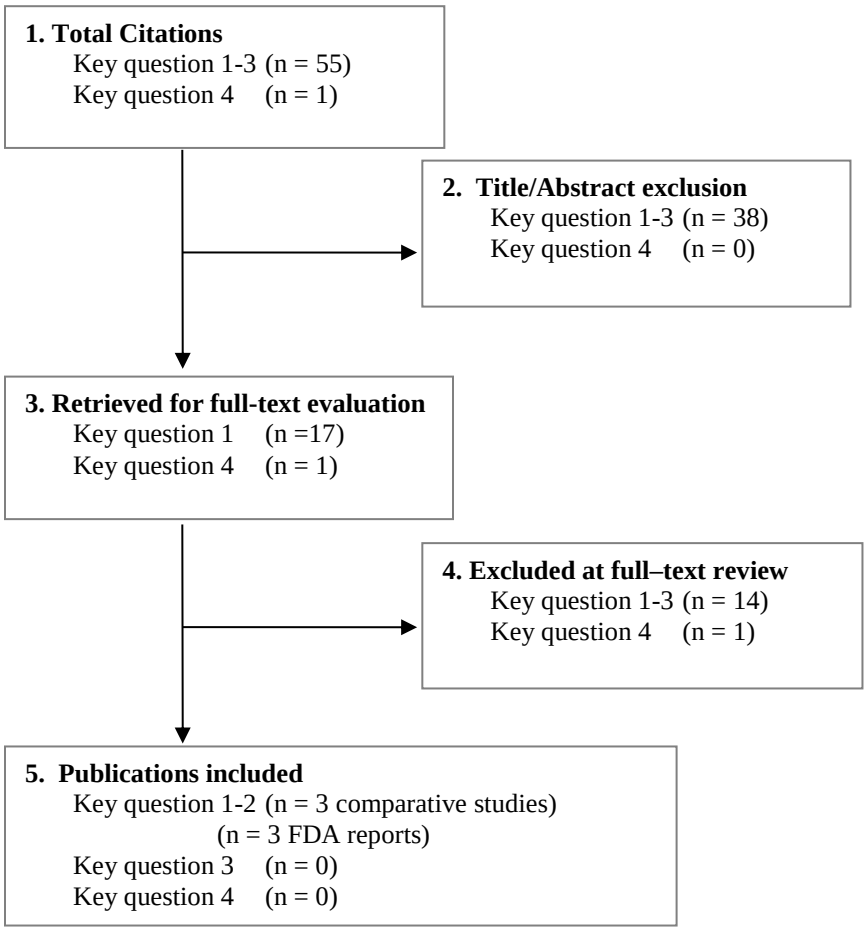


Figure 3. Flow chart showing results of literature search for C-ADR



Data extraction

Reviewers extracted the following data from the included clinical studies: study population characteristics, study type, study eligibility/exclusion criteria, study interventions, study outcomes, follow-up time, complications, and adverse events. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. When this occurred between the FDA reports and the published peer-reviewed reports, the FDA data were used since patient accounting tended to be more complete.. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

Data were abstracted from the July, 2007 FDA Panel Meeting Executive Summary regarding the Bryan cervical disc (P060023). An approval order had not been posted as of May 20, 2008 for this device. The Executive Summary provides an overview of the indications, safety and efficacy data provided by Medtronic Sofamor Danek regarding the PMA for this device. This report describes a 24 month, multicenter, prospective randomized controlled trial sponsored by Medtronic to compare the Bryan cervical disc with standard anterior fusion using a non-inferiority study design. A total of 242 patients with cervical degenerative disc disease received C-ADR and 221 received fusion between May 28, 2002 and October 8, 2008. The summary and data are based on interim data

available at the time of the report and do not represent all enrolled patients through the end of the study. The results and conclusions in the PMA are based on a pre-specified interim analysis of 300 patients with 24 month follow-up. In particular, it appears that 82 C-ADR patients and 81 ACDF controls had not yet reached 24 month follow-up. Thus, approximately 2/3 of patients receiving treatment were represented in the interim analysis. Information on loss to follow-up is not explicitly stated.

Since any given individual patient's procedure may be deemed an "overall success" at 12 months, but a failure at 24 months or alternatively a failure at 12 months but a success a 24 months, the Spectrum Research team chose to report only the outcomes at 24 months. Abstracted data are based on the presentation of the "primary analysis dataset". According to the Bryan Panel Executive Summary, intention to treat (ITT) analyses were not presented initially but were provided in a PMA amendment (not available) and considered to be "qualitatively similar" to the results obtained based on analysis of the primary dataset as presented in their Executive Summary, table 16. The data on "overall success" below are based on this table and on data in tables 14 and 15 of the Bryan Panel Executive Summary.

Table 8. Data from FDA Panel Meeting[6] on Bryan C-ADR used for Spectrum Research analysis

	ADR	ACDF
n at 24 month based on interim report	160	140
n with "overall success" at 24 months based on interim report	129 (80.6%)	99 (70.7%)
Neurological improvement – number of successes	150 (93.7%)	128 (91.4%)
Neurological improvement – number of failures	10 (6.3%)	12 (8.6%)
NDI score success – number of successes	134 (83.7%)	106 (75.7%)
n not yet observed at 24 months	82 (33.9%)	81 (36.7%)
Total N receiving treatment	242	221

Study quality assessment: Level of evidence (LoE) evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine[123], precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[16], recommendations made by the Agency for Healthcare Research and Quality (AHRQ)[160], and the system used by the *Journal of Bone and Joint Surgery*.[163]

Details of the level of evidence (LoE) methodology are found in Appendix B. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Table 9 below for therapeutic studies. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.

Table 9. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Cointerventions applied equally • F/U rate of 85% + • Adequate sample size • Intent-to-treat
II	Moderate or poor quality RCT	• Violation of one or more of the criteria for a good quality RCT
	Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Cointerventions applied equal • F/U rate of 85% + • Adequate sample size • Controlling for possible confounding†
III	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	
IV	Case-series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those potential prognostic variables that are unequally distributed between treatment groups.

There is no universally accepted, standardized approach to critical appraisal of economic evaluation studies. The criteria described in the Quality of Health Economic Studies (QHES) tool[119] provided a basis for the critical appraisal of included economic studies and was augmented with the application of epidemiologic appraisal precepts (see Appendix B). The QHES employs widely accepted criteria for appraisal, such as choice and quality of cost and outcomes measures, transparency of model and presentation, use of incremental analysis, uncertainty analysis, and discussion of limitations and funding source and was primarily used to facilitate description of primary strengths and limitations of the studies. A weighted global score can be obtained based on these measures with a possible range of scores from 0 (worst) to 100 (best), theoretically providing a common metric to compare study quality. This tool and the weighted score have not yet undergone extensive evaluation for broad use but provide a valuable starting point for critique.

Two individuals critically appraised each study independently using the QHES. Discrepancies were resolved by discussion to arrive at a final appraisal. In addition, elements of critical appraisal consistent with epidemiologic principles and evaluation of bias (e.g., selection bias) were applied.

Data analysis

Meta-analysis was conducted on the primary outcomes when data from two or more RCTs were available and when there were no clinical or statistical heterogeneity. A random effects model was used following the DerSimonian and Laird method for pooling which accounts for

heterogeneity among studies, if it is present. Dichotomous data were reported using risk difference (RD). Associated 95% confidence intervals are reported for all estimates unless otherwise noted. The data analysis was performed using the procedure "metan", within the software STATA 10. The procedure also generates the Cochran's Q statistic to test heterogeneity of the studies, from which the I^2 statistics was derived.[77,78]

Two analytic perspectives on the meta-analysis for effectiveness are presented: intent-to-treat (ITT) analysis and completer-only analysis. ITT analysis includes all randomized patients in the groups to which they were randomized without regard to the actual treatment received or to whether they withdrew from treatment. The completer-only analysis considers only those patients who completed the study up until the last follow-up. The ITT is conservative for a superiority study. However, in a non-inferiority trial, ITT tends to make the treatments appear more similar in effect than they are, when subjects receive the unintended treatment or are otherwise noncompliant. This could result in a truly inferior treatment appearing to be non-inferior.

In contrast, a completer-only analysis excludes data from patients who violate protocol or fail to follow-up. Excluding these data can bias the results in either direction. Therefore, non-inferiority studies are often analyzed using both ITT and completer-only analyses, and an intervention is considered non-inferior only if both approaches support non-inferiority. Therefore, both types of analyses were done.[152]

A non-inferiority clinical trial design is often used in FDA trials to show that a new treatment is no worse than a reference treatment. In order to accomplish this, a pre-stated margin of non-inferiority is defined for the treatment effect of a primary outcome. The new treatment will be recommended if it is similar to or better than the existing one, but not if it is worse by more than the pre-stated margin. It is acceptable to assess whether the new treatment is superior to the reference treatment using the appropriate statistical test.[124,152,168] Therefore, results of the meta-analysis for the primary outcome of clinical success were interpreted using the following steps (see Appendix D for flow sheet):

1. The results were evaluated for superiority; was the ADR superior to the comparator treatment in both the ITT and completer-only analyses?
2. If so, what effect do the missing data have on the results (sensitivity analysis)?
3. If not, check for non-inferiority; was the L-ADR non-inferior to comparator treatment in both the ITT and completer-only analyses using a-10% non-inferiority boundary as per the FDA analyses of the Blumenthal et al[28] study? Was the C-ADR non-inferior to the cervical fusion in both the ITT and completer-only analyses using a -10% non-inferiority boundary as per the FDA request for the Prestige ST and Prodisc-C studies?
4. If non-inferiority is supported, what effect does missing data have on the results (sensitivity analysis)? Does sensitivity analysis support non-inferiority using -12.5%[*] non-inferiority boundary?

[*] Blumenthal et al and Zigler et al set non-inferiority boundaries at -15% and -12.5%, respectively. The FDA required a -10% non-inferiority boundary for their analysis. The FDA -10% was used in this technology assessment based on the ITT and completer-only analysis. However, the FDA's lead was followed when it came to assessing the effect of missing data by using the non-inferiority boundary of the sponsor. In the In-depth Statistical Review of the Blumenthal et al paper, the FDA used -15%. For this review, the more conservative -12.5% established by Zigler et al was used.

The remaining outcome measures were interpreted for superiority. Ranges of means or proportions are given to summarize secondary outcomes.

2.3 Quality of literature available

Quality of studies retained, lumbar

The literature search resulted in 114 citations using the search strategy in Appendix A. There were 10 comparative reports (7 RCT reports, 3 cohort studies) and one systematic review.[63] From among these, two index RCTs were identified: one evaluating the Charité L-ADR[28] and one the Prodisc-L ADR.[171] One preliminary study was found that reported on partial data from two sites of a multicenter RCT assessing the FlexiCore L-ADR.[141] Four FDA reports were located in the grey literature: three reporting on the Charité L-ADR (one Summary of Safety and Effectiveness Data (SSED)[3], one In-depth Statistical Review[2], one Clinical Review[1]) and one SSED reporting on the Prodisc-L. All compared L-ADR with lumbar fusion. No studies were found comparing L-ADR with any other treatment. Studies retained for analysis are listed in Table 10 below.

For the Charité ADR, the index study and six companion reports[44,61,67,109,110,156] along with the three FDA reports were retained and are included. Three of the six companion studies reported on complications[61,110,156] and two on secondary outcomes.[44,109] These five studies are graded as level of evidence (LoE) II. One companion study on a subset of patients collected in the index study was a prognostic study evaluating the outcome of L-ADR in different age groups.[67] This study was graded as LoE III.

For the Prodisc-LADR, one FDA SSED and four published reports are included: the index study (LoE II), two cohort studies,[21,22,150] and a costing study.[68] The cohort studies evaluated outcome of L-ADR on subpopulations and all graded as LoE III.

For the FlexiCore L-ADR, the only publication found reported limited data from two sites of a multicenter study with only 27% of patients available for the 24 month follow-up.[141] This study was excluded from analysis in this technology assessment. Description of this ongoing study can be found in section 1.6 above.

In addition, 25 case series (LoE IV) were included to help address short and long term complication rates and secondary outcomes.

Two economic analyses, one related to Charité ADR[68] and another related to the Prodisc-L[99] were identified in the peer-reviewed literature and critically appraised. The Levin report is based on data from one of 19 centers participating in the randomized FDA study of Prodisc-L. It is unclear whether the Guyer study is linked to the FDA trial of the Charité device.

Table 10. Comparative clinical studies retained to answer key questions for L-ADR

Disc	Author	Study Type	Key Questions Addressed	Level of Evidence
Charité	**Blumenthal (2005)**	**RCT (index study)**	1 and 2	II
	FDA (2004)	SSED	1 and 2	--
	FDA (2004)	In-depth Statistical Review	1 and 2	--
	FDA (2004)	Clinical Review	1 and 2	--
	Geisler (2004)	RCT (companion study to Blumenthal)	2	II
	McAfee (2005)	RCT (companion study to Blumenthal)	1	II
	McAfee (2006)	RCT (companion study to Blumenthal)	2	II
	Tortalani (2007)	RCT (companion study to Blumenthal)	2	II
	Cunningham (2008)	RCT (companion study to Blumenthal)	1	II
	Guyer (2008)	Cohort* (companion study to Blumenthal)	3	III
	Guyer (2007)	Costing study	4	n/a†
Prodisc-L	**Zigler (2007)**	**RCT (index study)**	1 and 2	II
	FDA (2006)	SSED		--
	Bertognoli (2006)	Cohort*	3	III
	Seipe (2007)	Cohort	3	III
	Levin (2007)	Costing study	4	n/a†

SSED = Summary of Safety and Effectiveness Data.
*Study design is determined relative to the exposure being compared. For example, Bertognoli et al compared outcomes between smokers and non-smokers in those who received L-ADR only. In this case, the exposure is smoking status. As a result, the study, while part of the index RCT comparing L-ADR with fusion, is considered a cohort study for the purposes of comparing the effect of smoking status on outcomes in the L-ADR group only.
†Criteria for economic analysis critical appraisal do not provide a level of evidence rating.

Study quality assessment, lumbar

The two index trials (Blumenthal for the Charité and Zigler for the Prodisc-L) were each conducted as a randomized, multicenter, FDA regulated Investigational Device Exemption, non-inferiority clinical trial. A summary of the methodological quality for these two studies are reported in Table 12.

Table 11. Methodological quality of RCTs comparing L-ADR with lumbar fusion

Methodological principle	Blumenthal	Zigler
Study design Randomized controlled trial Cohort study Case-series	✓	✓
Statement of concealed allocation	✓	
Intention to treat		✓
Independent or blind assessment		
Cointerventions applied equally	✓	✓
Complete follow-up of $\geq$ 85%		✓
Adequate sample size	✓	✓
Controlling for possible confounding		✓
Evidence class	**II**	**II**

Critical appraisal of study methods, Charité ADR
The essential data from the 14-site multicenter FDA trial on the Charité L-ADR was published in 2005.[28] A number of methodological flaws in this study led to its classification as a moderate randomized clinical trial (LoE II). Baseline characteristics between the L-ADR and control groups were different with respect to a few potentially important variables. Compared with the L-ADR group, the control group tended to weigh more (82 kg versus 78 kg) and have lower activity level at enrollment (6% versus 17% moderate or active) suggesting that the control group may have been slightly worse than the L-ADR group prior to treatment.

The accounting of patients through the completion of the study was reported differently among the three FDA reports and the Blumenthal publication. Using the Blumenthal publication, the two-year follow-up rate was reported at 91.5% (161/176) for the L-ADR group and 89.2% (66/74) for the control group. However, the denominators for these proportions did not include deaths, failures, or early discontinuation. When all patients randomized to a treatment are considered, follow-up rates are lower, 161/205 (78.5%) for the L-ADR group and 66/99 (66.7%) for the control group. In order to determine the effect of those not available for follow-up, an intent-to-treat (ITT) analysis was reported. However, the investigators excluded from the analysis those who had not yet reached or were overdue for their 24-month visit. Excluding such randomized patients from the analysis could lead to strong bias in either direction (either in favor of or against the technology). The ITT population should consist of all patients who were randomly allocated to receive treatment.

Blinding of treatment providers and study subjects can be difficult in surgical interventions. The investigators acknowledged that blinding was not carried out in this trial for providers, patients, or assessors. Bias arising from the lack of blinding is possible.

Critical appraisal of study methods, Prodisc-L
The essential data from the17-site multicenter FDA trial on the Prodisc-L ADR were published in 2007.[171] In this study, like many surgery studies, the patient was not blinded to the treatment. Radiographic assessments were completed by an independent evaluator. There was no mention as to who completed the physical and neurological exams at follow-up or whether these evaluators were blinded to the treatment received. Investigators compared demographic characteristics between groups by way of statistical testing and found no significant differences.

The accounting of patients through the completion of the study was reported differently between the FDA report and the Zigler et al publication. The FDA report identifies 183 L-ADR and 93 control patients "enrolled", but only 162 L-ADR and 80 control patients treated. It is not clear if all enrolled patients received random assignment or not. The two-year follow-up rate was reported at 91.0% (142/156) for the L-ADR group and 89% (69/78) for the control group. Using all enrolled and treated patients, the more accurate follow-up rates for L-ADR and control groups are 88% (142/161) and 86% (69/80), respectively.

Quality of studies retained, cervical

Data from randomized controlled trials (RCTs) published in peer review journals and those available from publicly available FDA reports were used to answer questions 1 and 2. No studies addressing questions 3 and 4 were found.

The literature search resulted in 55 citations using the search strategy in Appendix A. A total of three RCT reports and three FDA reports were used in this technology assessment. For the Prestige ST C-ADR, there was one full report of the FDA randomized controlled trial published in the peer-reviewed literature[115] and its associated FDA Summary and Safety of Efficacy Data (SSED) report (P060018).[4] For the Prodisc-C, no full published reports of an RCT were found other than the FDA SSED report (P070001).[5] A summary of the July, 2007 FDA Panel Meeting Executive Summary regarding the Bryan cervical disc (P060023)[6] was located, as was one RCT evaluating the Bryan C-ADR that was not associated with the Bryan FDA trial.[121] It should be noted that the Bryan summary and data are based on interim data available at the time of the report and do not represent all enrolled patients through the end of the study. The results and conclusions in the PMA report presented in the executive summary are based on a pre-specified interim analysis of 300 patients with 24 month follow-up. In particular, it appears that 82 C-ADR patients and 81 ACDF controls had not yet reached 24 month follow-up. Thus, approximately 2/3 of patients receiving treatment were represented in the interim analysis. Information on loss to follow-up is not explicitly stated. Additional study information from this report is found in Appendix G.

In addition, 22 case-series (LoE IV) were included to help address short and long term complication rates and secondary outcomes.

Table 12. Comparative studies retained to answer key questions for C-ADR

Disc	Author	Study Type	Key Questions Addressed	Level of Evidence
Prestige ST	Mummaneni (2007)	RCT (index study)	1 and 2	II
	FDA (2007)	SSED	1 and 2	II
Prodisc-C	FDA (2007)	SSED	1 and 2	II
	Nabhan (2007)	RCT	1 and 2	*
Bryan	FDA (2007)	FDA panel summary	1 and 2	II
	Feng-Pei (2008)	RCT	1 and 2	*

SSED = Summary of Safety and Effectiveness Data

*There is not enough information in the methods section of this paper to warrant an evidence rating

Study quality assessment, cervical

The three primary clinical trials were conducted as a randomized, multicenter, FDA regulated Investigational Device Exemption (IDE), non-inferiority clinical trials. Full data from one of the trials reporting on the Prestige ST ADR has been published in the peer review literature.[115] Since only partial methods are given in the FDA SSED, no critical appraisal of those reports is undertaken. The level of evidence for randomized controlled trials in general may be level of evidence I or II depending on how well the investigators limited bias on key principles. Given that the SSEDs report on randomized controlled trials, a LoE of I or II would be considered, however since information on such methodological principles is not completely available in these reports, the more conservative level of evidence for the SSEDs is used without formal

critical appraisal. Two additional studies not associated with the FDA trial were found. One was conducted by Peng-Fei et al[121] on a small sample size using the Bryan C-ADR and the second by Nabhan used the Prodisc-C also in a small number of patients.[118] There was not enough information in the methods section of the Peng-Fei or the Nabhan articles to warrant a level of evidence rating. A summary of the methodological quality for the one published FDA trial is reported in Table 13.

Table 13. Methodological quality of studies comparing single-level C-ADR with anterior cervical discectomy and fusion

Methodological principle	Mummaneni
Study design Randomized controlled trial Cohort study Case-series	✓
Statement of concealed allocation	✓
Intention to treat	✓
Independent or blind assessment	*
Complete follow-up of ≥ 85%	†
Adequate sample size	✓
Controlling for possible confounding	✓
Evidence Level	**II**

Blank space indicates criterion is either not present or not reported by authors
*Independent radiologist used for radiographic assessment. However, no blinding for other outcomes
†Criteria met for twelve month follow-up but not 24 month.

Critical appraisal of study methods, Mummaneni et al (Prestige ST)
Data from a 32-site FDA trial conducted within the US on the Prestige ST ADR was published in 2007.[115] This trial compared the Prestige ST C-ADR (n = 276) with interbody fusion (n = 265) via cortical ring allograft spacers and an Atlantis Cervical Plate System (Medtronic Sofamor Danek) using a non-inferiority design with a non-inferiority margin of 10%. Efficacy/effectiveness was determined by the primary endpoint of overall success, defined as achieving all the following criteria: NDI increase from pre- to postoperative score of ≥15 points, maintenance or improvement in neurological status, no serious implant-associated or implantation procedure-associated adverse event or have undergone a second surgery classified as a failure. Safety was determined by assessing adverse events, complications and secondary surgeries defined as revisions, hardware removals, supplemental fixations, or reoperations. An interim analysis was performed on the first 250 patients in whom there were overall success data 24 months postoperatively.

Random assignment was described as occurring after informed consent by giving a sequential computer generated clinical trial number to the patient. What is not clear in the description of the study is whether any patient after receiving the treatment assignment withdrew from the study. It appears that allocation concealment from the surgeon prior to enrollment was sufficient. Patient characteristics between groups were similar, though the fusion group tended to be slightly less educated, to use alcohol more and to have a slightly less proportion of patients who worked preoperatively. A multivariate analysis that included these small baseline differences had no effect on the results.

One significant shortcoming of this study with respect to methodology is the low follow-up, 80% in the C-ADR group and 75% in the fusion group. This follow-up rate is due in part to the fact that not all patients enrolled had reached their 24-month follow-up at the time the analysis was performed. The authors attempt to assess the impact of the missing data by doing a sensitivity analysis; however, they perform this analysis on 12-month follow-up rather than the 24-month follow-up.

Blinding in a surgical study remains difficult to carry out. In most instances, patients cannot or should not be blinded to the surgical intervention they receive. Whenever possible, those who assess outcomes should be blinded. In this study, neurological exam was conducted as part of the overall success and safety of the intervention, and the examiner could and should have been blinded to the treatment. There is no recording of who performed the exam and whether that person was blind to the treatment. Radiographic evaluation was done by independent radiologists; a good alternative since radiographs reveals the treatment given.

Given the high rate of missing values and the lack of blinding in the evaluation of the patients, this study was determined to be level of evidence II.

Critical appraisal of study methods, Peng-Fei et al (Bryan C-ADR)
Twenty four patients with disc herniation at C5-6 were randomly assigned to receive the Bryan C-ADR or interbody fusion. The average follow-up time was 17 months (range, 10 to 35 months). Percent follow-up was not given. Outcome was assessed using the Japanese Orthopaedic Association (JOA) cervical scale, adjacent segment motion and complications.

This small study has many methodological flaws which makes it difficult to interpret. First, the main effectiveness outcome used by the investigators is the JOA. The JOA is primarily a clinician-based assessment of neurological status in four areas: (1) the ability to feed oneself using utensils (motor function of the arm); (2) the ability to walk (motor function of the legs); (3) sensation of arms, trunk and legs; (4) bladder function. Potentially important outcomes for patients were not assessed with this instrument such as pain, disability, leisure activity and sleeping. The trial is portrayed as a randomized controlled trial, but the method of allocation is unclear. The authors describe the patients as being “divided into two groups”, but do not explain how. The length of follow-up was not fixed; the patients’ results were recorded from as early as 10 months

postoperatively and as late as 35 months postoperatively. Since outcomes are, in part, time-dependent, comparisons may be confounded by length of follow-up.

Critical appraisal of study methods, Nabhan, et al (Prodisc-C)
Forty-nine patients were randomly assigned to receive either C-ADR using the Prodisc C (Synthes) or ACDF using a Solis cage (Stryker Howmedia GmbH) with titan anchoring spikes. The authors report that 25 received C-ADR and 24 had ACDF. Measures for 3, 6, 12, 24 and 52 weeks post-surgery were recorded. The focus was on roentgen stereometric analysis (RSA) of segmental motion in the medial-lateral (x) axis, proximal-distal (distraction-compression, y) axis and the anterior-posterior (sagittal, z) axis. With the exception of the three week y –axis measure, mean values for segmental motion were significantly better for C-ADR compared with ACDF (P = .0083). The only clinical outcomes reported were arm and neck pain assessed using a VAS. Although both treatment groups experienced reduction in pain, there was no statistically significant difference in pain reduction between groups. It is possible that the sample size was too small to detect a difference between groups on this outcome.

Methodological details related to study execution; follow-up, analysis and other factors which may lead to potential bias are not well-reported. Some of these areas are described below.

Although the authors report that randomization was carried out by drawing cards in sealed envelopes, there is potential for bias if these were not opaque. While randomization generally results in even distribution of confounding factors (e.g. age, smoking status), no information on the distribution of such factors was given for the treatment groups. The authors do not state that an intention-to-treat analysis was performed or whether any cross-over between treatments occurred, although they do state that 25 patients received C-ADR and 24 had ADCF.

It is not clear whether the RSA examination/positioning and interpretation, or determination of VAS for pain, were done by persons who were blinded with regard to treatment status. Because of the report's focus on RSA, eight patients were excluded from the analysis since RSA measurements were compromised by implants and bony structures. These exclusions combined with one death, lowered the follow-up rate to 82% by 12 months.

2.4 Description of study population

Lumbar

Both studies included patients with single-level symptomatic degenerative lumbar disc disease without neurological compromise who failed conservative treatment of at least six months duration. The inclusion and exclusion criteria are listed for each study in Appendix C. Operative and demographic data are presented in Table 14 below.

Study population, Charité ADR

The average age of study participants in the Blumenthal et al study[28] was 40 years, range 19 to 60 years. Fifty two percent were males. One third of the participants had previous spinal surgery, and 87% reported their pre-enrollment activity level as minimal to light. Thirty percent of the procedures were carried out at L4-L5 disc space and 70% at L5-S1 disc space. The control and L-ADR groups were similar in most baseline characteristics. The control group compared to the L-ADR group tended to have fewer males (44% versus 55%), to be slightly heavier (82 kg versus 78 kg), and to be less active at time of enrollment (6% versus 17% reporting moderate to active activity level).

Study population, Prodisc-L

In the Zigler et al study[171], the average age of study participants was 40 ± 8 years, and included equal proportion of males and females. One third of the participants had previous spinal surgery, and 94% reported their pre-enrollment activity level as none to light. Three percent of the procedures were carried out at L3-L4 disc space, 33% at L4-L5 disc space and 64% at L5-S1 disc space. The control and L-ADR groups were similar in most baseline characteristics. The control group compared to the L-ADR group tended to have fewer males (46% versus 51%), to have slightly fewer prior spinal surgeries (31% versus 35%), and to have more current smokers (30% versus 21%).

Table 14. Operative and demographic data for the two index randomized controlled trials for L-ADR

Variable	Blumenthal et al		Zigler et al	
	Charité (n = 205)	Fusion (n = 99)	Prodisc-L (n = 161)	Fusion (n =75)
Implant level				
No. L3–L4 (%)	0	0	3 (2)	3 (4)
No. L4–L5 (%)	61 (30)	32 (32)	254 (34)	22 (29)
No. L5–S1 (%)	144 (70)	67 (68)	104 (65)	50 (67)
Operative time, min; mean (SD)	110.8 (47.7)	114 (67.9)	121 (59.2)	229 (75.9)
Blood loss, ml; mean (SD)	205 (211.7)	208.9 (283.9)	204 (231.3)	465 (440.0)
Length of hospital stay, day	3.7 (1.2)	4.2 (2.0)	3.5 (1.3)	4.4 (1.5)
Patient demographics				
Gender				
No. males (%)	113 (55.1)	44 (44.4)	82 (51)	34 (45)
No. females (%)	92 (44.9)	55 (55.6)	79 (49)	41 (55)
Age, years mean (SD)	39.6 (8.16)	39.6 (9.07)	38.7 (8.0)	40.4 (8)
Race				
No. Caucasians (%)	188 (91.7)	87 (87.9)	133 (82.6)	59 (78.7)
No. African-Americans (%)	8 (3.9)	5 (5)	5 (3.1)	5 (6.7)
No. others (%)	9 (4.4)	7 (7.1)	13 (14.3)	11 (14.6)
Body mass index, kg/m2; mean (SD)	26 (4.23)	27 (4.76)	26.7 (4.2)	27.3 (4.3)
Smoking status				
No. never (%)	not recorded	not recorded	87 (54)	34 (45)
No. former (%)	not recorded	not recorded	40 (25)	17 (23)
No. current (%)	not recorded	not recorded	34 (21)	24 (32)
Prior surgical treatment				
Yes	70 (34)	33 (33)	57 (35)	23 (31)
No	135 (66)	66 (67)	104 (65)	52 (69)
Preoperative activity level				
Minimal to none	116 (56.6)	66 (66.7)	94 (58.0)	38 (50.0)
Light	54 (26.3)	27 (27.3)	59 (36.4)	33 (43.8)

Moderate, active, or sport	35 (17.1)	6 (6.0)	9 (5.6)	5 (6.2)

Cervical

The three studies included patients with single-level symptomatic degenerative lumbar disc disease without neurological compromise who failed conservative treatment of at least six weeks duration. The inclusion and exclusion criteria are listed for each study in Appendix C. Operative and demographic data are presented in Table 15 below.

Study population, Prestige ST

The average age of study participants in the Mummaneni et al study was 43 ± 8 years. Forty-six percent were males. Less than 1% had previous neck spinal surgery. Fifty-four percent of the procedures were carried out at C5-C6 disc space and 38% at C6-C7 disc space. The control and C-ADR groups had similar baseline characteristics.

Study population, Prodisc-C

In the Prodisc-C FDA report, the average age of study participants was 43 ± 8 years and included 45% males. Patients with prior neck surgery at the treatment level were excluded from the study. Fifty-seven percent of the procedures were carried out at C5-C6 disc space and 33% at C6-C7 disc space. The two groups were similar in most baseline characteristics. The control group compared to the C-ADR group was slightly heavier (180 lbs versus 171 lbs).

Study population, Bryan

The Bryan Panel study reported an average age of 44 years for study participants, range 25 to 78 years. Forty-eight percent of the patients were male. Fifty-four percent of the procedures were carried out at C5-C6 disc space and 39% at C6-C7 disc space. Baseline characteristics showed a few minor differences between the study groups. The control group had more males (51%) than the C-ADR group (45%). The mean weight of the control group was heavier than the C-ADR group (180 lbs versus 173 lbs).

Table 15. Operative and demographic data for the three FDA randomized controlled trials for C-ADR

	Mummaneni		Prodisc-C FDA SSED		Bryan FDA interim analysis*	
Variable	Prestige ST (n = 276)	Fusion (n = 265)	Prodisc-C (n = 103)	Fusion (n = 106)	Bryan (n = 242)	Fusion (n = 221)
Implant level						
No. C3–C4 (%)	7 (2.5)	10 (3.8)	3 (2.9)	1 (0.9)	3 (1.2)	0 (0)
No. C4–C5 (%)	14 (5.1)	15 (5.7)	10 (9.7)	6 (5.7)	12 (5.0)	17 (7.7)
No. C5–C6 (%)	142 (51.4)	149 (56.2)	58 (56.3)	61 (57.5)	140 (57.9)	110 (49.8)
No. C6-C7 (%)	113 (40.9)	91 (34.3)	32 (31.1)	38 (35.8)	87 (36.0)	94 (42.5)
Operative time; mean	1.6 hrs	1.4 hrs	107.2 min	98.7 min	2.2 hrs	1.4 hrs
Blood loss, ml; mean	60.1	57.5	83.5	63.5	91.5	59.6
Length of hospital stay, day	1.1	1.0	1.4	1.3	1.1	1.0
Patient demographics						
Gender						
No. males (%)	(46.4)	(46.0)	46 (44.7)	49 (46.2)	110 (45.4)	113 (51.1)
No. females (%)	(53.6)	(54.0)	57 (55.3)	57 (53.8)	132 (54.5)	108 (48.9)
Age, years; mean (SD)	43.3 (7.6)	43.9 (8.8)	42.1 (8.42)	43.5 (7.15)	44.4 (25.0-78.0)	44.7 (27.0-68.0)
Race						
No. Caucasians (%)	260 (94.2)	243 (91.7)	88 (85.4)	97 (91.5)	NR	NR
No. African-Americans (%)	6 (2.2)	13 (4.9)	4 (3.9)	1 (0.9)	NR	NR
No. others (%)	10 (3.6)	9 (3.4)	11 (10.7)	8 (7.5)	NR	NR

Body mass index, kg/m2; mean (SD)	NR	NR	26.4 (5.3)	27.3 (5.5)	NR	NR
Weight, lbs; mean (SD or range)	181.7 (39.7)	184.7 (41.5)	171 (42)	180 (47)	173 (108-312)	180 (100-285)
Smoking status						
No. never (%)	NR	NR	51 (50)	49 (46)	NR	NR
No. former (%)	NR	NR	18 (18)	20 (19)	NR	NR
No. current (%)	(34.4)†	(34.7)†	34 (33)	37 (35)	61 (25.5)†	53 (24.0)†
Prior surgical treatment						
Yes	1 (0.4)	2 (0.8)	NR	NR	NR	NR
No	275 (99.6)	263 (99.2)	NR	NR	NR	NR
Worker's compensation (%)	(11.6)	(13.2)	NR	NR	15 (6.2)	11 (5.0)
Involved in litigation (%)	(10.9)	(12.1)	NR	NR	NR	NR

*Demographic and patient characteristic data listed in the FDA Panel summary are for all those who received treatment. Data for primary outcomes in this report are based on the 300 (160 ADR and 140 ACDF) participants available for interim analyses

†Described as "tobacco user" (Bryan) or "tobacco use" (Prestige)

2.5 Description of study outcomes

Lumbar efficacy and effectiveness measures
The primary efficacy/effectiveness outcome measure is a composite clinical measure referred to as overall clinical success measured 24 months following surgery. This clinical success measure was defined using similar but not identical criteria between the two index studies. Both index studies contained the following core criteria:

- ≥ 25% improvement in the Oswestry Disability Index (ODI) at 24 months compared with preoperative score (≥ 15 point improvement from baseline ODI was also reported at the request of the FDA)
- No device failure requiring revision, reoperation or removal
- No neurological deterioration compared with preoperative status

Blumenthal et al added the criteria of no major complications, defined as major vessel injury, neurological damage, or nerve root injury. Zigler et al added one quality of life criteria and five radiographic criteria:

- Improvement in the SF-36 physical and mental component scores at 24 months compared with preoperative score
- No radiographic evidence of device subsidence > 3 mm
- No radiographic evidence of device migration > 3 mm
- No extensive radiolucency along the implant/bone interface (< 25% of the interface's length for each endplate defined as a success)
- Range of motion at the implanted level maintained or improved from the preoperative baseline for L-ADR; no motion on flexion/extension films (defined as < 3 mm translation and < 5° angulation)
- No loss of disc height > 3 mm
- No evidence of bony fusion for L-ADR; strong evidence of fusion, including > 50% trabecular bridging bone or bone mass maturation and increased or maintained bone density at the site for the control group

Success for this outcome in each study occurred when all the criteria in the respective study were met.

Other outcomes used as primary outcomes to answer the efficacy/effectiveness question for this technology assessment are the ODI, neurological success (defined as the maintenance or improvement of neurological status), and pain reduction. Secondary outcomes include satisfaction, quality of life (SF-36), and range of motion.

Safety outcomes
Primary outcomes assessed for safety include:

- Device failure (defined as reoperation due to revision, reoperation, or removal)
- Other adverse events/complications reported in the included studies

Economic outcomes
Two partial economic studies described costs using different costing methods and compared costs for arthroplasty with those for fusion.[68,100]

Cervical efficacy and effectiveness measures
There were sufficient data on the following outcomes to perform meta-analysis:

- Overall clinical success composite measure as defined by the FDA for PMA approval studies
- Individual components of the overall clinical success composite measure including
  - Functional success based on a 15 or greater point improvement in Neck Disability Index (NDI). The NDI is a patient-reported measure consisting of 10 categories (pain intensity, self-care, lifting, reading, headaches, concentration, work, driving, sleeping and recreation), each of which is scored from 0-5 for a maximum of 50 points. The higher the score, the greater the disability[76]
  - Neurological success (defined below)
  - Device success (defined below)
- Data for other outcomes (pain or pain relief, quality of life, adjacent segment disease and return to work) were not consistently reported by all trials or different trials used varying definitions or measures to assess these. Thus, summary data are given where possible and individual study data reported as appropriate.

Overall Clinical Success-Definitions and Meta-analysis
As defined by the FDA, "overall success" was a composite of measures as described below. Definitions were sufficiently similar such that pooling of data was considered appropriate for the overall composite as well as individual components where data were available. "Success" for this outcome in each study occurred when all the criteria in the respective study were met.
A summary of what was included in the composite scores is as follows:

Mummaneni (Prestige ST C-ADR):
- NDI ≥ 15 point improvement
- Neurological success: Maintenance/improvement in neurological status
- No serious implant associated or implantation procedure adverse event
- Device Success: No second surgery classified as a failure

Prodisc FDA report (Prodisc-C ADR):
- NDI ≥ 15 point improvement
- Neurological success: motor, sensory and reflexes are maintained or improved
- Device Success: No revisions, removals, reoperations, or supplemental fixation at the index level
- No adverse events related to the implant or implantation

Bryan FDA report: (Bryan C-ADR, based on interim PMA analysis):
- NDI ≥15 point improvement from baseline
- Neurological Success: Maintenance or improvement in neurological status
- No serious adverse event classified as implant-associated or implant/surgical procedure-associated
- Device Success: No additional surgical procedure classified as "failure"

Published reports by Nabhan and Peng-Fei did not report on these criteria, nor did they use other definitions of "success". Therefore, they could not be included in the meta-analysis.

Assessment of pain reduction when reported was also considered as a primary outcome to help answer the efficacy/effectiveness question. Secondary outcomes used include satisfaction, quality of life (SF-36), adjacent segment disease and range of motion.

3. Results

3.1 Key question 1 - What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

Lumbar

There were no studies found comparing lumbar ADR with continued nonoperative care. The only comparison of L-ADR with surgical procedures was with spinal fusion. Therefore, the results presented refer to the efficacy and effectiveness of L-ADR compared with lumbar spinal fusion.

Overall Clinical Success

The FDA criterion of at least a 15-point improvement from baseline ODI scores was used for both RCTs to minimize heterogeneity in the meta-analysis. The definition of overall clinical success was similar in the two studies, but not identical. In the Prodisc-L study, success was defined more conservatively than the Charité study in that it required improvement in the SF-36 and radiological success as additional criteria. The addition of these parameters would make success more difficult to achieve resulting in a lower proportion of patients attaining overall clinical success, but not likely biasing the results between study groups. Therefore, these two studies were pooled.

Using the baseline sample size as reference (ITT analysis), 52% of patients receiving the Charité L-ADR compared with 44% of those receiving lumbar fusion achieved success 24 months following surgery. In those receiving the Prodisc-L ADR, 49% were clinically successful compared with 39% receiving fusion. The meta-analysis of clinical success resulted in 51% (186/366) of patients receiving L-ADR compared with 42% (73/174) of those receiving fusion obtaining clinical success at 24 months, risk difference of 9% (95% CI, 0, 18%, $P = .05$), Figure 4. Using data from only those who completed the study, the risk difference was 8% (95% CI, 2%, 17%, $P = .11$), Figure 5. Since superiority of L-ADR was demonstrated in the ITT analysis but not the completer-only analysis, superiority was rejected. Non-inferiority at -10% inferiority margin was then assessed and non-inferiority was found to be supported by evaluating the lower bounds of the confidence intervals of the pooled results (0% ITT and -2% for completer-only analysis).

Sensitivity analyses to assess the effect of missing data supported non-inferiority at the -12.5% non-inferiority margin of lumbar ADR compared with spinal fusion, Table 16 and Figure 6.

Figure 4. Clinical Success (using ≥ 15 point difference over baseline for ODI) 24 months following L-ADR (intention-to-treat analysis)

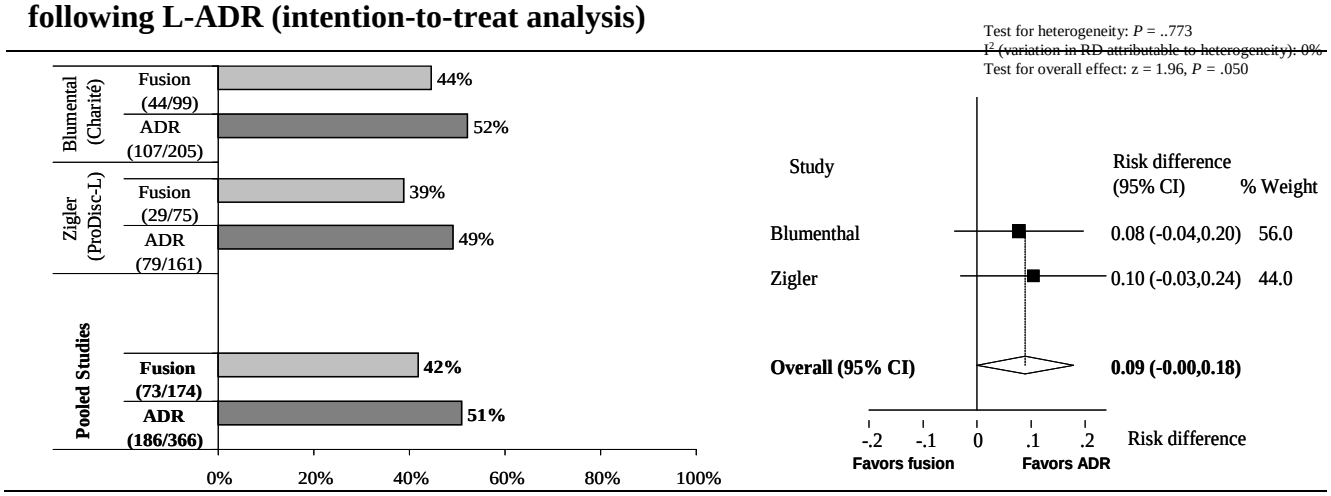


Figure 5. Clinical Success (using ≥ 15 point difference over baseline for ODI) 24 months following L-ADR (completer-only analysis)

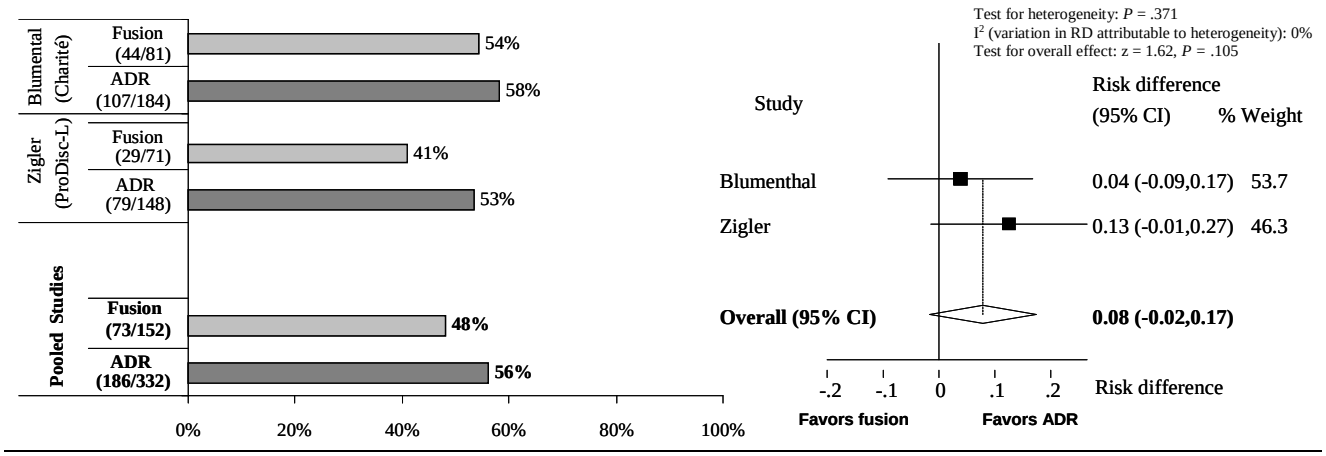
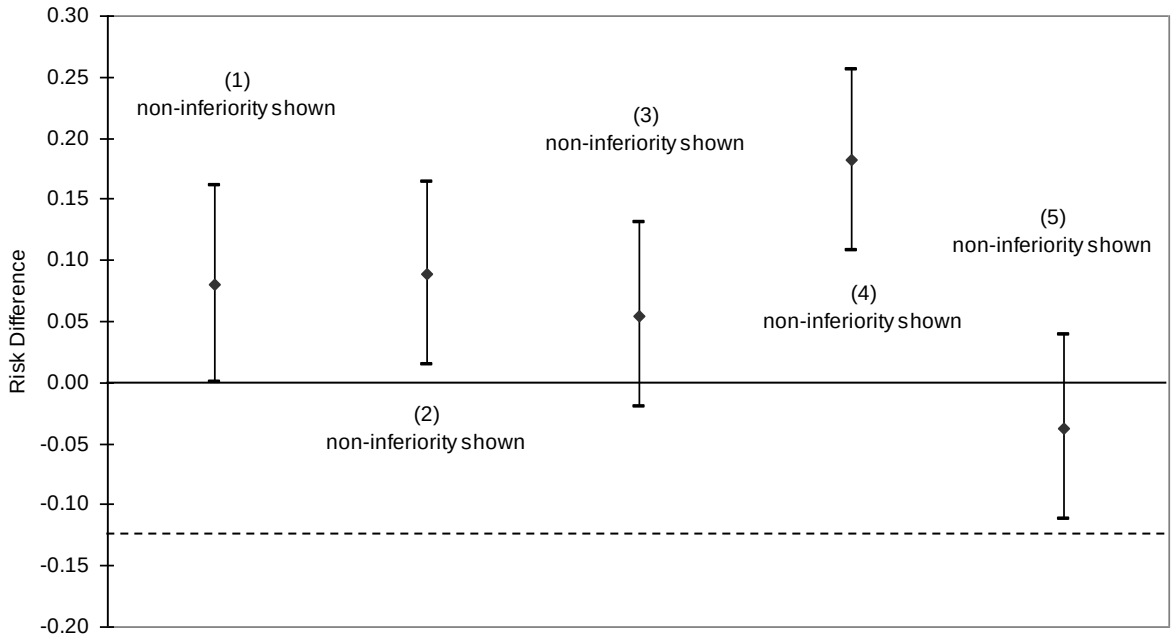


Table 16. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for the pooled results of the Blumenthal (Charité) and Zigler (Prodisc-L) studies

	L-ADR (n = 366)	Fusion (n = 174)	
Overall clinical success			
Yes	186	73	
No	146	79	
Unknown	34	22	
Rate of clinical success	n/N (%)	n/N (%)	Absolute difference (90% CI)*
Completer-only	186/332 (56.0)	73/152 (48.0)	.080 (-.016, .176)
Assuming poor outcome	186/366 (50.8)	73/174 (42.0)	.089 (-.001, .178)
Assuming good outcome	220/366 (60.1)	95/174 (54.6)	.055 (.-034, .144)
Extreme case favoring ADR	220/366(60.1)	73/174 (42.0)	.182 (.093, .270)
Extreme case favoring fusion	186/366 (50.8)	95/174 (54.6)	-.038 (-.128, .052)

*Two-sided 90% CI are shown for display purposes. The analysis was based on 1-sided 95% lower bound CI which is used in non-inferiority studies and corresponds to the 2-sided lower 90% CI shown in the figure (ie, the lower error bar on each plot can be read as either a 1-sided 95% CI or a 2-sided 90% CI).

Figure 6. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for L-ADR



(1): Completer-only
(2): ITT assuming failure for all missing data
(3): ITT assuming success for all missing data
(4): Missing data in ADR group = success, fusion group = failure
(5): Missing data in ADR group = failure, fusion group = success

ODI

Patients treated with L-ADR more often experienced substantial improvement (≥ 15 points over baseline) in ODI than those treated with fusion, 60% versus 49% for ITT analysis (P = .027) and 66% versus 57% for completer-only analysis (P = .062) 24 months following surgery, Figures 7 and 8. The completer-only analysis did not reach statistical significance. In both studies, mean percent improvement in ODI was greater for L-ADR patients than fusion patients at six weeks, three months, and six months, Figure 9. The differences between treatment groups diminished at 12 and 24 months.

Figure 7. ODI (≥ 15 point difference over baseline) 24 months following L-ADR (intention-to-treat analysis)

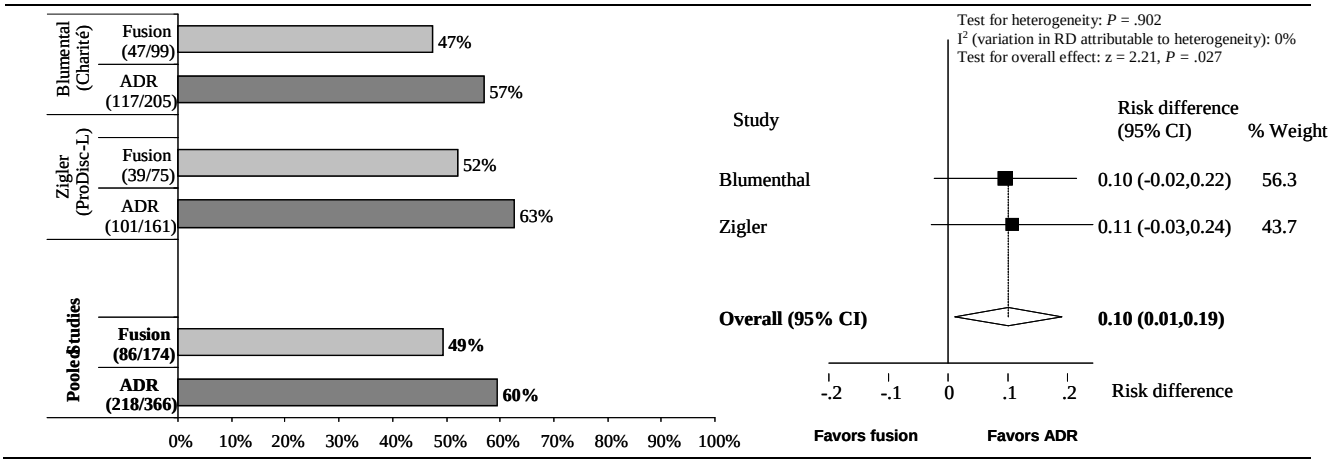


Figure 8. ODI (≥ 15 point difference over baseline) 24 months following L-ADR (completer-only analysis)

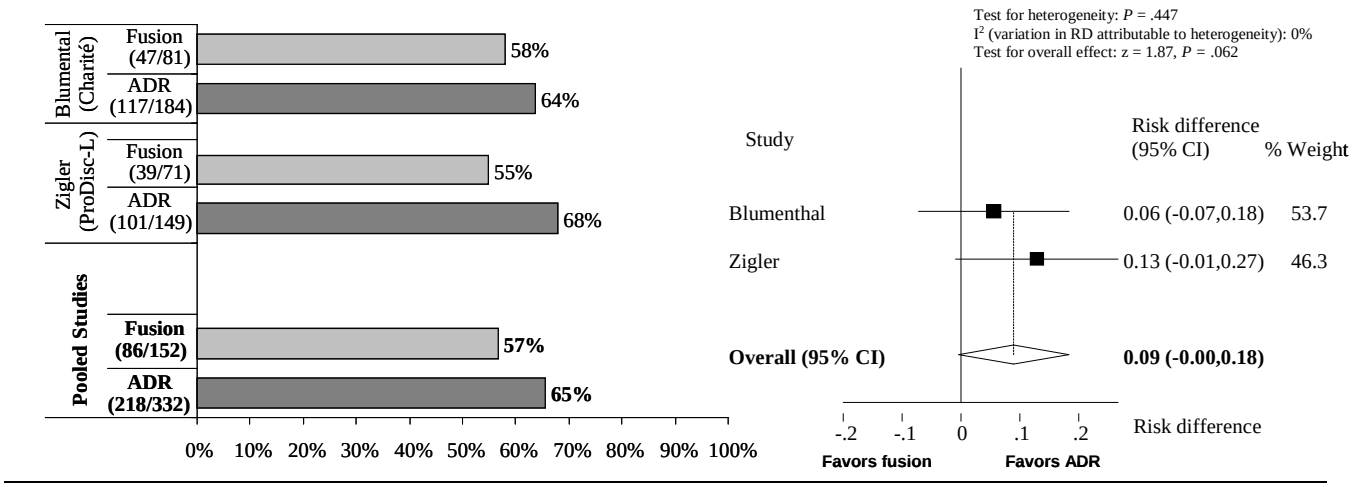
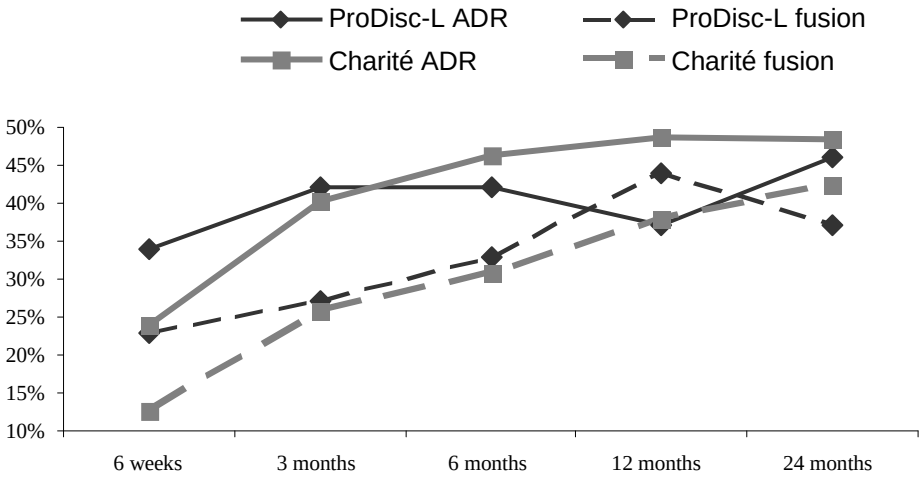


Figure 9. ODI (≥ 15 point difference over baseline) results over time following L-ADR*



*The differences were statistically better for the L-ADR group compared with fusion group at 6 weeks, 3 months, 6 months, and 12 months in the Blumenthal et al study, and at 6 weeks, 3 months, and 6 months in the Zigler et al study.

One nonrandomized trial[149] examined differences in ODI according to spinal segment treated. That study reported that patients treated by the Charité L-ADR only at L4-L5 experienced a greater mean reduction in ODI (63.4%), compared with those treated only at L5-S1 (53.9%) or those treated at both of these segments (43.2%). These differences were not statistically significant, perhaps due to the small size of the study (N = 99).

Neurological Success

Neurological success was defined as the maintenance or improvement of neurological status 24 months following surgery. Generally, neurological success was achieved by approximately 80% of all patients in the ITT analysis, and 90% of all patients in the completers-only analysis, Figures 10 and 11. There was no statistical difference between L-ADR and fusion with respect to neurological status. Data from completer-only analysis were not pooled due to heterogeneity between studies.

Figure 10. Neurological success 24 months following L-ADR (intention-to-treat analysis)

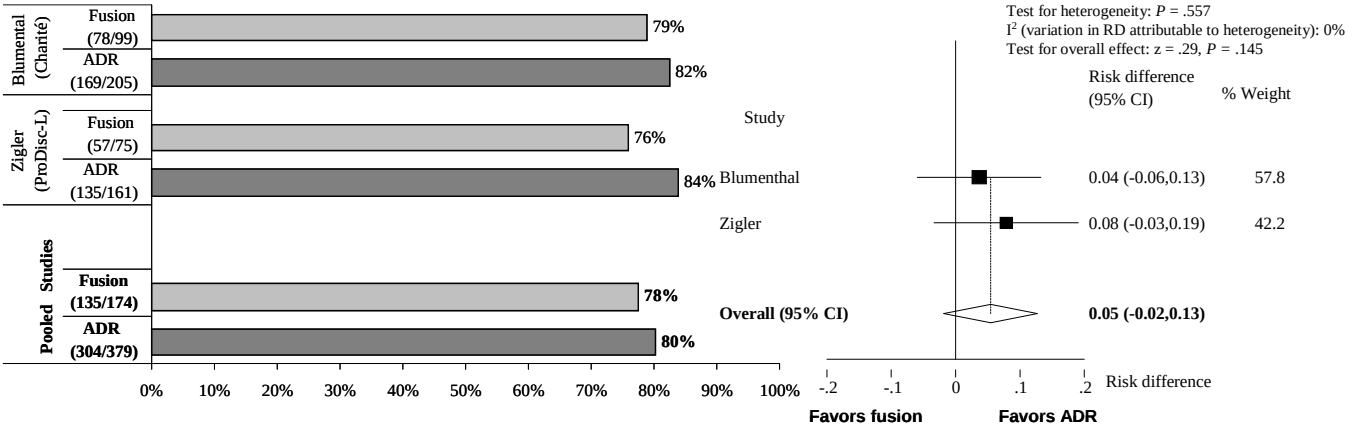
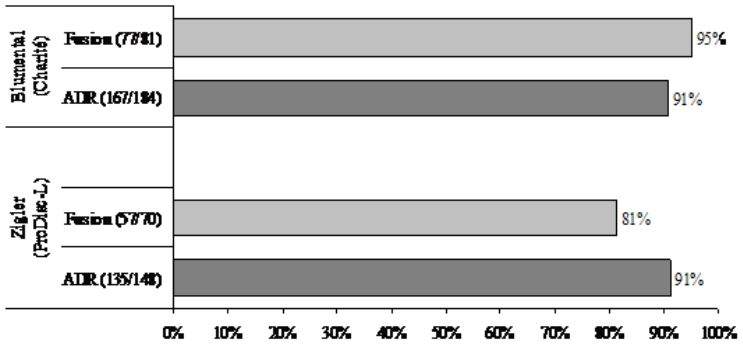


Figure 11. Neurological success 24 months following L-ADR (completer-only analysis)



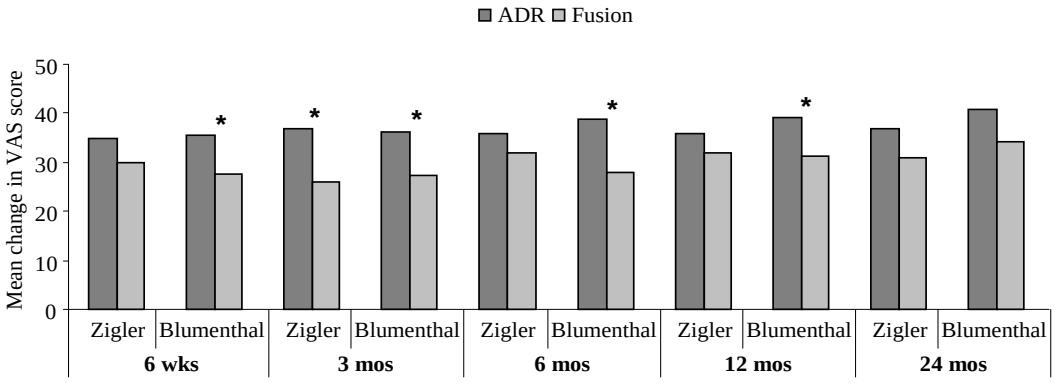
Pain reduction

L-ADR appears to provide as good or greater relief from pain than fusion procedures for those with single-level degenerative disc disease. There is no evidence that this effect varies with the type of artificial disc used, and some evidence that the effect is more pronounced in those with disease treated at L4-L5 than those with disease treated at L5-S1. Results are less clear for the use of narcotics, perhaps because of differences between studies in how this outcome was measured or due to the fact that use of narcotics is influenced by factors other than pain, such as patient preference, comorbidities, dependency, or practice style.

- *VAS Pain*

  Patients in both index studies receiving either treatment reported statistically significant pain reduction compared with preoperative pain levels. This occurred at every time point up to 2 years following surgery. Patients receiving L-ADR had a slightly greater mean improvement in VAS pain scores than patients receiving fusion in both index studies. However, this comparison reached statistical significance only once in the Zigler et al study (3 months) and in all the time periods except at 2 years in the Blumental et al study, Figure 12.

Figure 12. Mean change in pain (VAS) from preoperative pain scores at various time periods following L-ADR



* denotes statistically significant difference between L-ADR and fusion.

A single nonrandomized study compared improvements in VAS for pain among those with degenerative disc disease treated with a Charité artificial disc at L4-L5 with those treated at L5-S1 and those treated at both levels.[149] VAS improvements were statistically better comparing monolevel L4-L5 patients to bisegmental patients (74% versus 41%, *P* = .02) and better than monolevel L5-S1 patients (74% versus 58%, *P* > .05). The latter difference was not statistically significant, but this may be due to the modest size of the groups being compared (n = 22 for L4-L5 and n = 57 for L5-S1).

- *Use of narcotics*
  Blumenthal et al reported that among those using narcotics at baseline, 64% of patients treated with the Charité L-ADR were still using narcotics at 24 month follow-up, compared with 80% among those treated with fusion (*P* = .04).[28]

  Zigler et al, which did not report continued use of narcotics explicitly, suggests a lower proportion of continued narcotic users. Eight-four and 76% of the Prodisc-L and fusion patients were using narcotics at baseline, and 48% and 46% in each group were using at 24 months, implying a maximum of approximately 57% and 61% of each group continued to use narcotics. (No tests of significance were reported for this outcome). [171]

SF-36

Blumenthal et al reported on the proportion of patients experiencing substantial improvement, defined as ≥ 15% improvement from baseline on the SF-36 questionnaire. Those receiving the Charité L-ADR more often experienced a ≥ 15% improvement from baseline in the physical component score of the SF-36 questionnaire compared with those receiving fusion (72% versus 63%, test of significance not reported). Fifty percent of the L-ADR group and 51% of the control group had a ≥ 15% improvement from baseline in the mental component score section of the SF-36 questionnaire (test of significance not reported).

Zigler et al reported on the proportion of patients reporting any improvement compared with their preoperative SF-36 score. A slightly greater proportion of those receiving L-ADR experienced some improvement in SF-36 at 24 months than those receiving fusion, although this difference was not statistically significant (79% versus 70%, *P* = .09). Those receiving L-ADR more often experienced some improvement in SF-36 than those receiving fusion at six weeks (72% versus 56%, *P* = .02), three months (87% versus 70%, *P* = .004), six months (80% versus 75%, *P* = .2), and twelve months (81% versus 77%, *P* = .3) following surgery.

Patient satisfaction

- *Satisfaction.* When asked if they were "satisfied", "slightly satisfied", "slightly dissatisfied", or "dissatisfied" with their treatment, patients receiving the Charité L-ADR were statistically more likely to report they were "satisfied" (74%) than patients treated by fusion (53%, *P* = .001).[28] Zigler et al reported greater patient satisfaction with the Prodisc-L compared with fusion using a visual analog scale, mean 76.7 ± 29.2 mm versus 67.3 ± 31.5 mm, *P* = .015.[171]

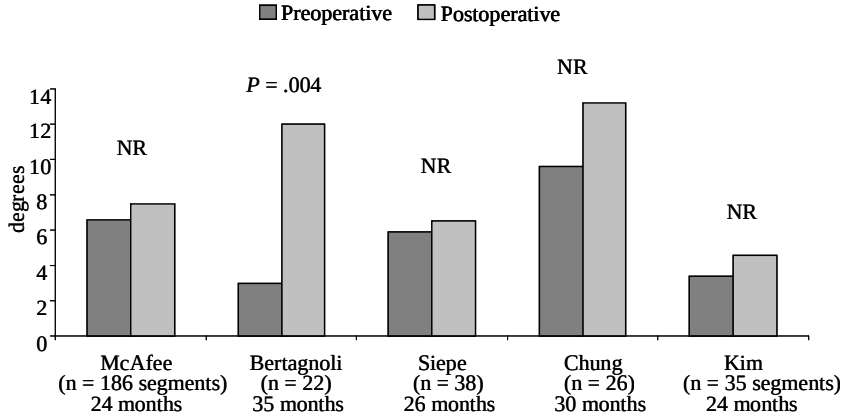
- *Willingness to choose again.* Both index studies asked patients if they would choose their treatment again. In each, a significantly higher proportion of patients receiving L-ADR responded affirmatively compared with patients treated by fusion (70% versus 50% in Blumenthal et al, *P* = .006 and 81% versus 69% in Zigler et al, *P* = .0004).

Preservation of motion

- *Preoperative versus postoperative flexion-extension (Figure 13)*
  McAfee et al[109] in a companion study to the Blumenthal et al RCT reported on maintenance of motion following L-ADR. They reported a slight increase in flexion-extension 24 months following surgery (7.5°) compared with preoperative measurements (6.6°) at the instrumented segment. When the investigators divided the surgical technical accuracy of the L-ADR into three groups (ideal, suboptimal, and poor), they found that flexion-extension improved with the surgical technical accuracy (*P* = .003).

  Four nonrandomized trials also reported pre- and postoperative flexion-extension and found increased movement 24 to 35 months following surgery compared with preoperative measurements at the instrumented segment.[22,40,89,150] This increase was statistically significant in one study (n = 22), which found on average patients increased from 3° preoperative flexion-extension to 12° post-operation (*P* = .004).[150] It should be noted that this population consisted of high level athletes only.

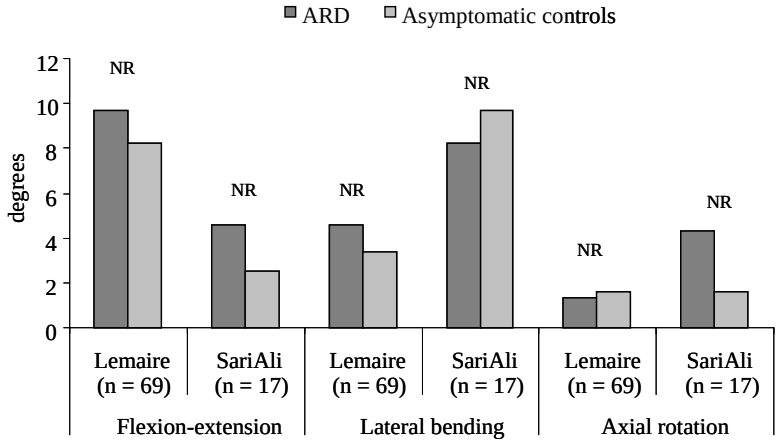
Figure 13. Mean flexion-extension before surgery and at follow-up for L-ADR



NR = *P* value not reported.

- *Postoperative range of motion versus asymptomatic controls (Figure 14)*
  Two small cohort studies[97,140] evaluated the long term motion at L4-L5 in people receiving a Charité L-ADR compared with asymptomatic controls after > 10 years follow-up. Segmental motion was generally slightly greater or similar to asymptomatic controls in flexion-extension, lateral bending, and axial rotation.

Figure 14. Long term motion at L4-L5 in patients receiving Charité L-ADR compared with asymptomatic controls after > 10 year follow-up

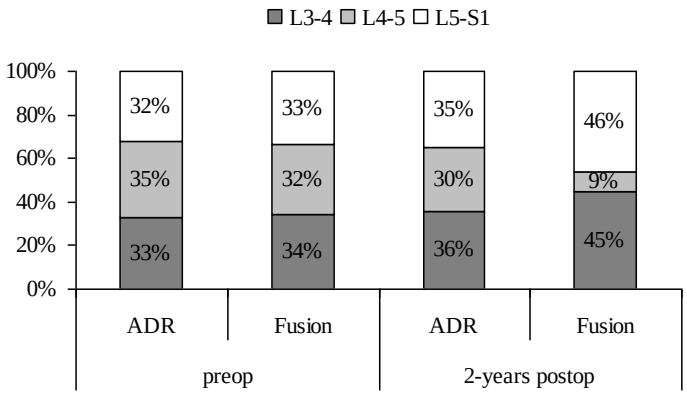


NR = *P* value not reported.

- *Postoperative range of motion versus normative data*
  One small study (N = 41) compared flexion-extension of the instrumented (Prodisc-L) and adjacent (untreated) segments with normative values 24 months following L-ADR.[96] The investigators found that the L-ADR failed to restore segmental sagittal rotation compared with the normative values. It should be noted that the normative values were obtained in a population different in demographics from the study population with respect to sex and age (74% males ranging in age from 19-57 years in the normative group versus 46% males ranging in age from 31-60 years in the study group). Also, worth noting is that nearly half of the 61 normative subjects performed the motion passively and half actively. Furthermore, imaging was unobtainable in 20% and 40% of the L4-L5 and L5-S1 segments, respectively.

- *Motion profile of the lowest three motion segments comparing L-ADR with fusion*
  One study[44] evaluated the motion profile (flexion-extension) at three motion segments (L3-4, L4-5, L5-S1) in 93 patients who received implants at L4-5 as part of the Charité index study. Comparison was made between L-ADR (n = 61) and fusion patients (n = 32). The proportion of motion following L-ADR more closely resembled preoperative motion compared with fusion, Figure 15. The authors concluded that one-level arthroplasty may replicate the normal distribution of motion of the intact spine at the implanted and adjacent levels.

Figure 15. Motion profile of L3-4, L4-5, and L5-S1 comparing L-ADR with lumbar fusion in patients who received implants at L4-5.



Adjacent segment disease (ASD)

Among non-randomized studies reporting radiologic lumbar ASD rates among patients receiving L-ADR, two studies with ≤ 10 years of follow-up reported 0% and 24% of patients had lumbar ASD,[82,158] and one study with > 10 years of follow-up found 17.0% of patients had lumbar ASD.[131] In the later study, ASD was only seen in patients with loss of motion at the instrumented segment. When patients were divided into those with motion of 5º or greater versus less than 5º, the rate of ASD was 0% (0/13) in the high motion group and (10/29) 34% in the low motion group (odds ratio = 13.5, *P* = .021). There were no differences in preoperative age, weight, or gender between patients with or without L-ASD.

Cervical

No studies were found comparing C-ADR with nonoperative care. The only comparison of C-ADR with surgical procedures was with spinal fusion. Therefore, the results presented refer to the efficacy and effectiveness of C-ADR compared with cervical spinal fusion.

Overall Clinical Success

Using the baseline sample size as reference (ITT analysis), 64% of patients receiving the Prestige ST C-ADR compared with 51% of those receiving anterior cervical fusion achieved success 24 months following surgery. In those receiving the Prodisc-C ADR, 71% were clinically successful compared with 65% receiving fusion. The pooled estimate from meta-analysis of clinical success resulted in 66% (250/379) of patients receiving C-ADR compared with 55% (203/371) of those receiving anterior cervical fusion obtaining clinical success at 24 months, risk difference of 11% (95% CI, 4, 18%, *P* = .002), Figure 16. Using data from only those who completed the study, the risk difference was 9% (95% CI, 2%, 16%, *P* = .009), Figure 17. The risk difference of 9%

equates to a number-needed-to-treat (NNT) of 11; that is, for every 11 patients who receive C-ADR instead of anterior fusion among patients with the same cervical disease as those in the studies, 1 additional patient will achieve overall success 24 months following surgery. Adding the interim analysis from the FDA Bryan report did not influence the pooled results or conclusions drawn, Figure 18.

Figure 16. Clinical success 24 months following C-ADR (intention-to-treat analysis)

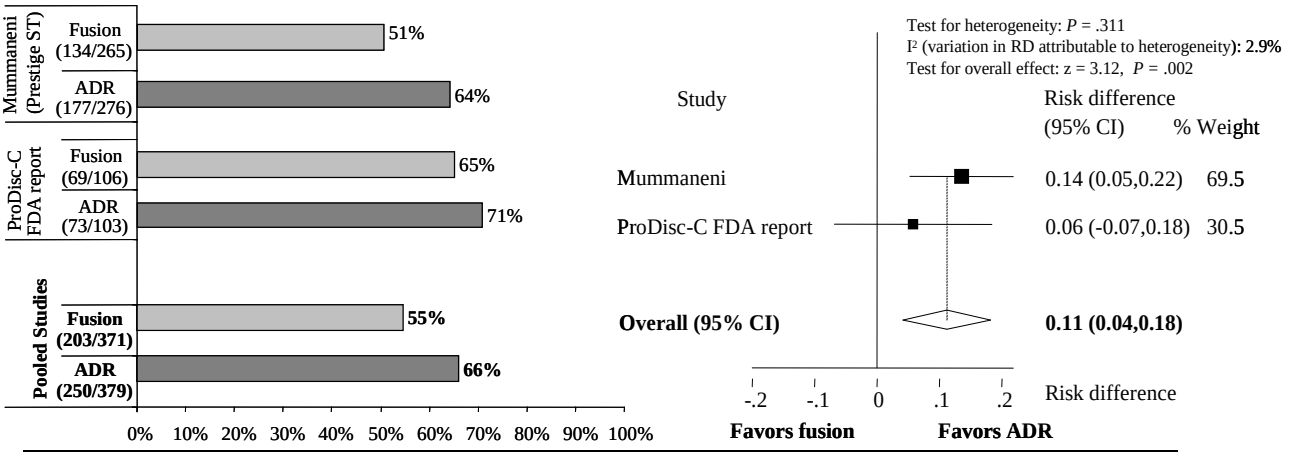


Figure 17. Clinical success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA interim report)

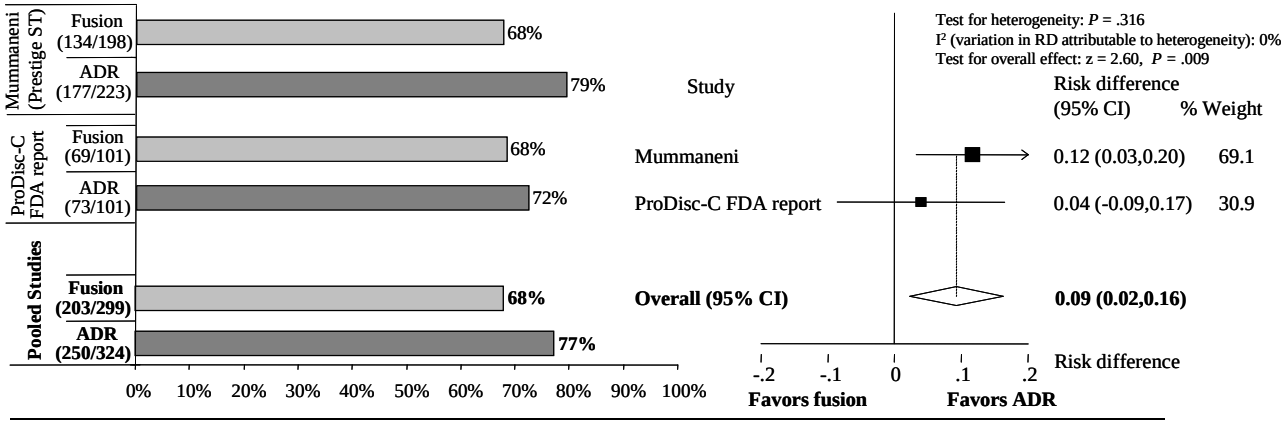
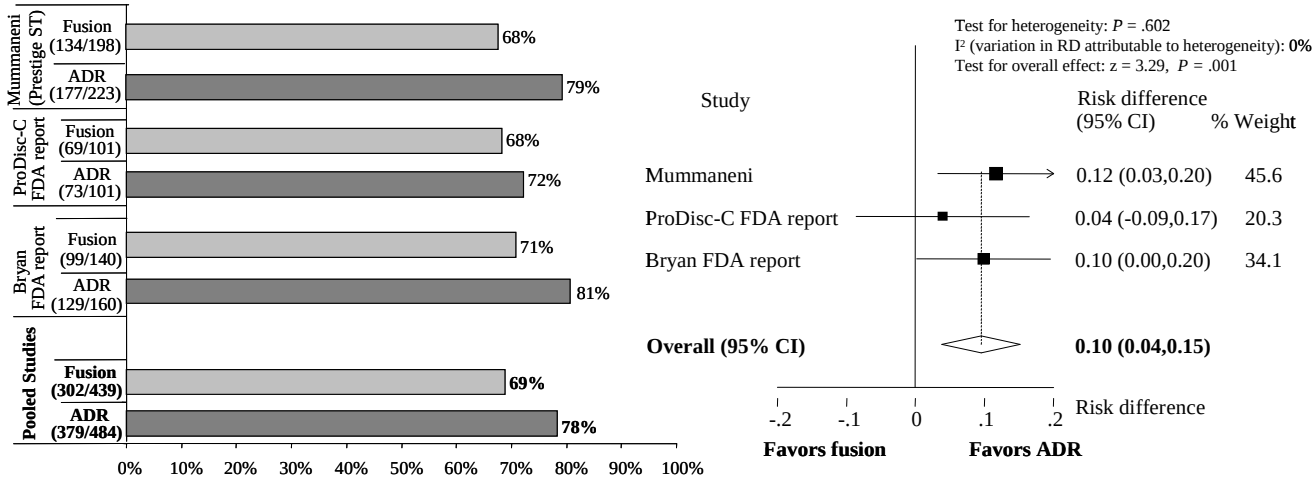


Figure 18. Clinical success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



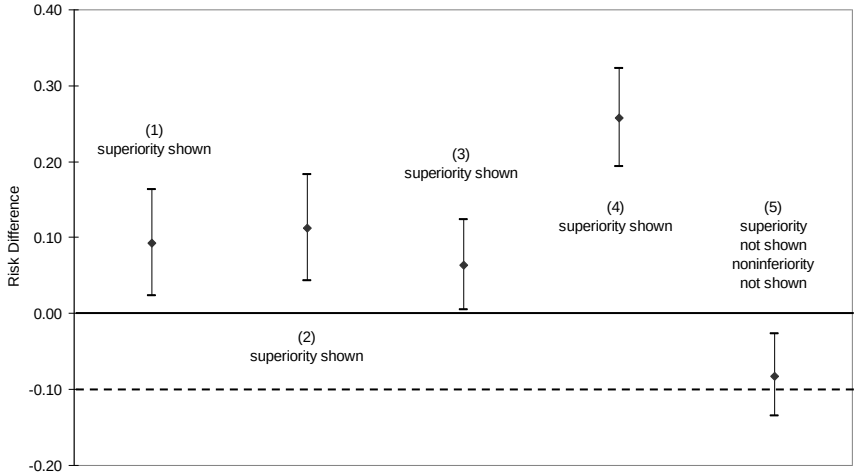
Sensitivity analysis was done to assess the effect of missing data on the pooled estimate for overall success for the Prestige ST (Mummaneni) and Prodisc-C FDA studies. Superiority was shown in four of the five scenarios, Table 17 and Figure 19. A description of each scenario appears with Figure 6. In the extreme case where all missing data in C-ADR group were assigned as "failure" and all missing data in the fusion group were assigned as "success", superiority of C-ADR was not shown. In fact in this extreme case, non-inferiority was not demonstrated at the 10% inferiority margin. Though this outcome is unlikely, the results of the sensitivity analysis leave open the remote possibility that missing data can have an important effect on the results of these studies.

Table 17. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for the pooled results of the Mummaneni (Prestige ST) and Prodisc-C FDA studies

	C-ADR (n = 379)	Fusion (n = 371)	
Overall clinical success			
Yes	250	203	
No	74	96	
Unknown	55	72	
Rate of clinical success	n/N (%)	n/N (%)	Absolute difference (95% CI)
Completer-only	250/324 (77.2)	203/299 (67.9)	.093 (.023, .163)
Assuming poor outcome	250/379 (66.0)	203/371 (54.7)	.112 (.043, .182)
Assuming good outcome	305/379 (80.5)	275/371 (74.1)	.064 (.004, .123)
Extreme case favoring ADR	305/379 (80.5)	203/371 (54.7)	.258 (.193, .322)
Extreme case favoring fusion	250/379 (66.0)	275/371 (74.1)	-.082 (-.136, -.027)*

*Two-sided 90% CI is shown for display purposes. The analysis was based on 1-sided 95% lower bound CI which is used in non-inferiority studies and corresponds to the 2-sided lower 90% CI shown in the figure (i.e., the lower error bar on each plot can be read as either a 1-sided 95% CI or a 2-sided 90% CI).

Figure 19. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for C-ADR



(1): Completer-only
(2): ITT assuming failure for all missing data
(3): ITT assuming success for all missing data
(4): Missing data in ADR group = success, fusion group = failure
(5): Missing data in ADR group = failure, fusion group = success

NDI

Patients treated with C-ADR more often experienced substantial improvement (≥ 15 points over baseline) in NDI than those treated with fusion, 70% versus 62% for ITT analysis (*P* = .027) and 82% versus 80% for completer-only analysis 24 months following surgery, Figures 20 and 21. The completer-only analysis did not reach statistical significance, risk difference of 2% (95% CI -4%, 9%; *P* = .465). Adding the

interim analysis from the FDA Bryan report did not change the statistical conclusions, Figure 22.

Figure 20. NDI success 24 months following C-ADR (intention-to-treat analysis)

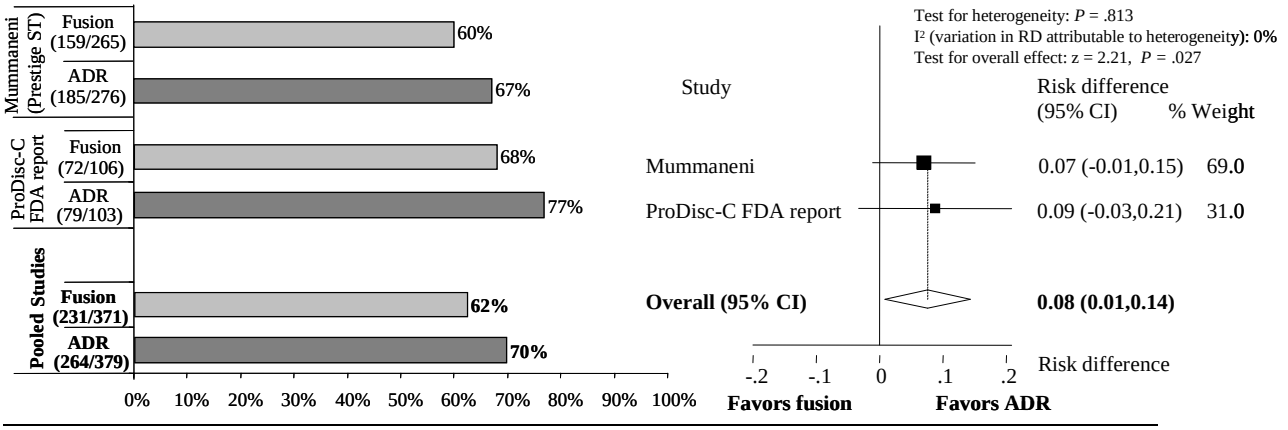


Figure 21. NDI success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA report)

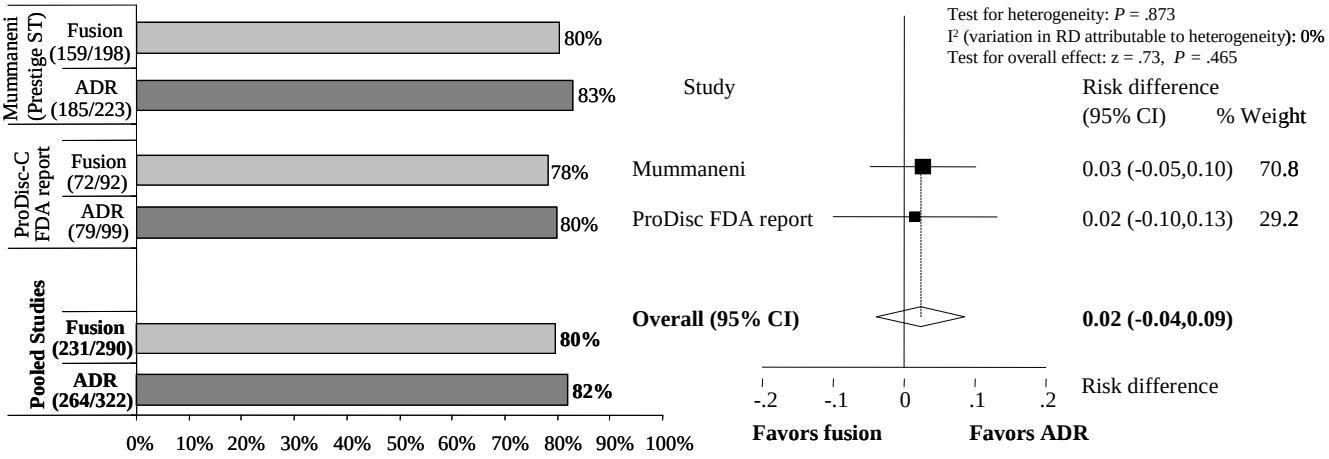
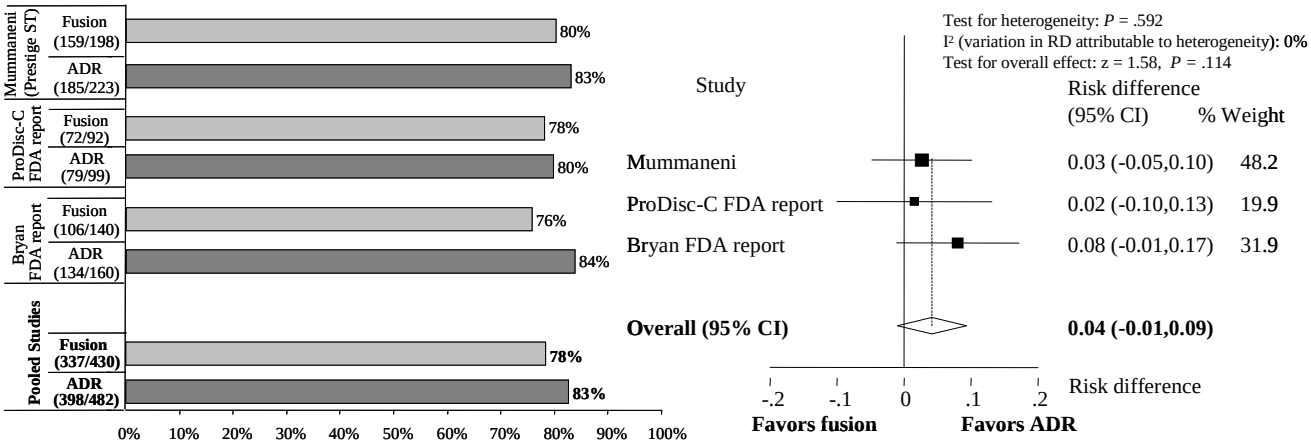


Figure 22. NDI success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



Neurological Success

Neurological success was defined as the maintenance or improvement of neurological status 24 months following surgery. Using the baseline sample size as reference (ITT analysis), neurological success was achieved by 78% of patients receiving C-ADR compared with 67% of those receiving fusion 24 months following surgery, risk difference of 12% (95% CI 5%, 18%, $P < .0001$), Figure 23. Using data from only those who completed the study, the risk difference was 7% (95% CI, 1%, 12%, $P = .022$), Figure 24. Adding the interim analysis from the FDA Bryan report lowered the risk difference to 5%, but did not influence the conclusions drawn, Figure 25.

Figure 23. Neurological success 24 months following C-ADR (intention-to-treat analysis)

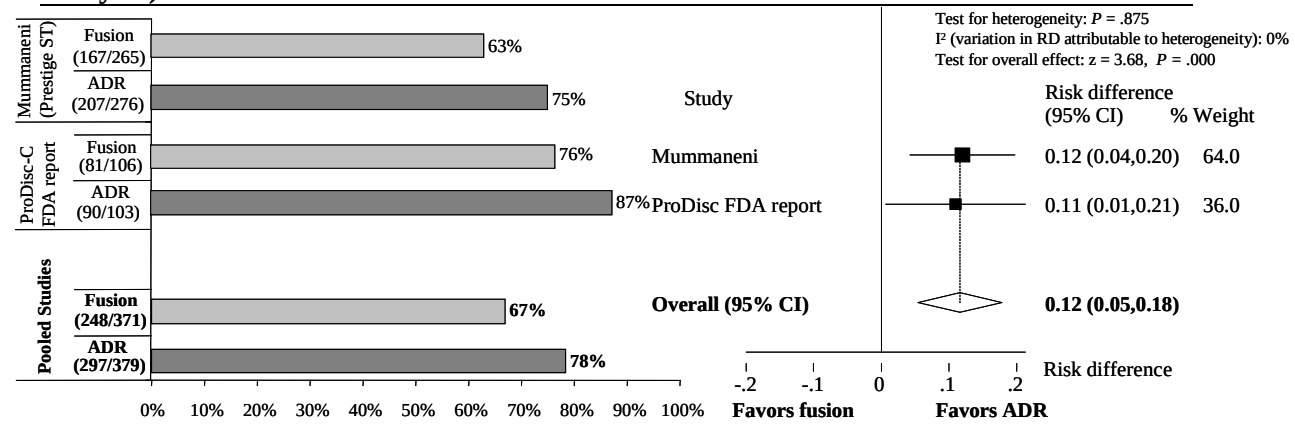


Figure 24. Neurological success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA report)

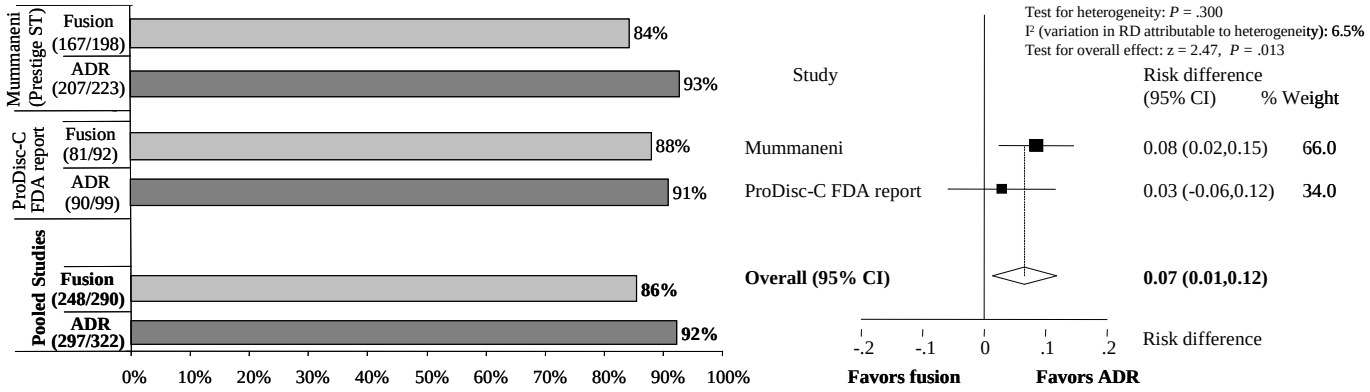
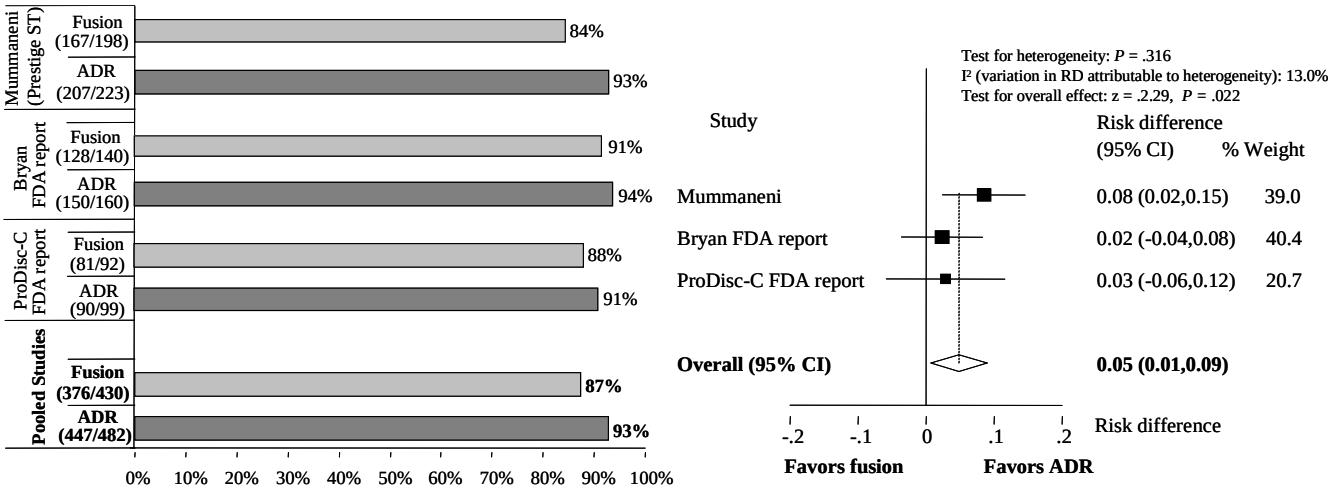


Figure 25. Neurological success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



Pain

Pain was assessed differently among the RCTs. Two studies measured the intensity of pain only, one on a 10 point scale[118] and one on a 100 point scale.[6] One study measured pain on a 100 point scale as the product of intensity (0-10) and frequency (0-10), [115] and another measured pain intensity and frequency separately.[5] Lastly, Peng-Fei et al[121] did not specify how pain was assessed.

Comparison of scores between baseline and follow-up: Patients undergoing either C-ADR or ACDF for cervical degenerative disc disease experienced significant relief of

neck and arm pain, as measured by the various methods described above, at 24 month follow-up compared with baseline.[5,6,115]

Comparison between treatment groups at 24 months: There were no statistical differences in the change of the intensity of neck or arm pain comparing the C-ADR group with the fusion group at follow-up. In the Bryan study[6], arm pain score changed by 50.1 in the C-ADR group compared with 50.0 in the fusion group 24 months following surgery. Neck pain and arm pain were reduced to equal degrees comparing C-ADR and fusion after 12 months in another RCT, 4.2 versus 4.2 for neck pain and 6.3 versus 6.0 for arm pain.[118] The proportion of patients who reported at least a 20 mm improvement in pain intensity comparing preoperative pain with pain at 24 months was similar in the Prodisc-C study,[5] 78.6% versus 75.6% for neck pain and 71.4% versus 76.7% for arm pain. Similar proportions were reported for at least 20 mm improvement in pain frequency in the same population for neck and arm pain. A composite score representing the product of pain intensity and duration was used in one study,[115] again with similar results between groups; a change composite score of 53 versus 53 for the C-ADR and fusion groups for neck pain, and 46 versus 49 for arm pain.

SF-36

The Prodisc-C SSED reported on the proportion of patients experiencing substantial improvement, defined as $\geq$ 15 point improvement from baseline on the SF-36 questionnaire. Those receiving the Prodisc-C ADR more often experienced a $\geq$ 15point improvement from baseline in the physical component score (PCS) of the SF-36 questionnaire compared with those receiving fusion (52% versus 34 %, test of significance not reported). Thirty six percent of the C-ADR group and 42% of the fusion group had a $\geq$ 15point improvement from baseline in the mental component score (MCS) section of the SF-36 questionnaire (test of significance not reported).

Mummaneni et al reported on the improvement in mean postoperative SF-36 scores compared with mean preoperative scores. A change in the scores for the C-ADR and fusion groups were 13.1 and 11.8, respectively, for the PCS, and 7.4 and 7.5 for the MCS 24 months after surgery (test of significant not reported).

The Bryan FDA executive summary reported a mean improvement from baseline for the PCS (C-ADR = 14.4, ACDF = 14.5) and the MCS (C-ADR = 8.1, ACDF = 7.3). Twenty four months following surgery, the C-ADR group compared with the fusion group had a 85.5% versus 90.6% success rate in the PCS and a 69.8 versus 72.5% in the MCS. Success for the SF-36 was not defined, however.

JOA score

In one small RCT, the functional outcome assessed was the Japanese Orthopaedic Association cervical myelopathy measure (JOA score). This study found no difference in the JOA score after a short follow-up ranging from 10 to 35 months. The JOA score of the group with C-ADR increased from an average of 8.6 to 15.8 (the higher the score, the better the function) compared with the ACDF group which increased from an average of 9.0 to 16.2.

Patient satisfaction

One study, the Prodisc-C FDA trial, reported on this important outcome. Using a VAS, the investigators asked the patient how satisfied they were with the surgery they received on a 100 mm scale with 100 representing the maximum satisfaction. Seventy one percent of those receiving C-ADR reported an 80 mm or higher for satisfaction compared with 68% in the ACDF group (test of significance not reported). When asked whether they would have the same surgery again, 86% of the C-ADR patients and 81% of the ACDF patients responded affirmatively.

Preservation of motion

The five RCTs and nine nonrandomized studies evaluated cervical C-ADR by comparing postoperative motion with preoperative motion, or by comparing postoperative motion between a C-ADR group and a fusion or an asymptomatic control group. Five studies had follow-up of two years or more.

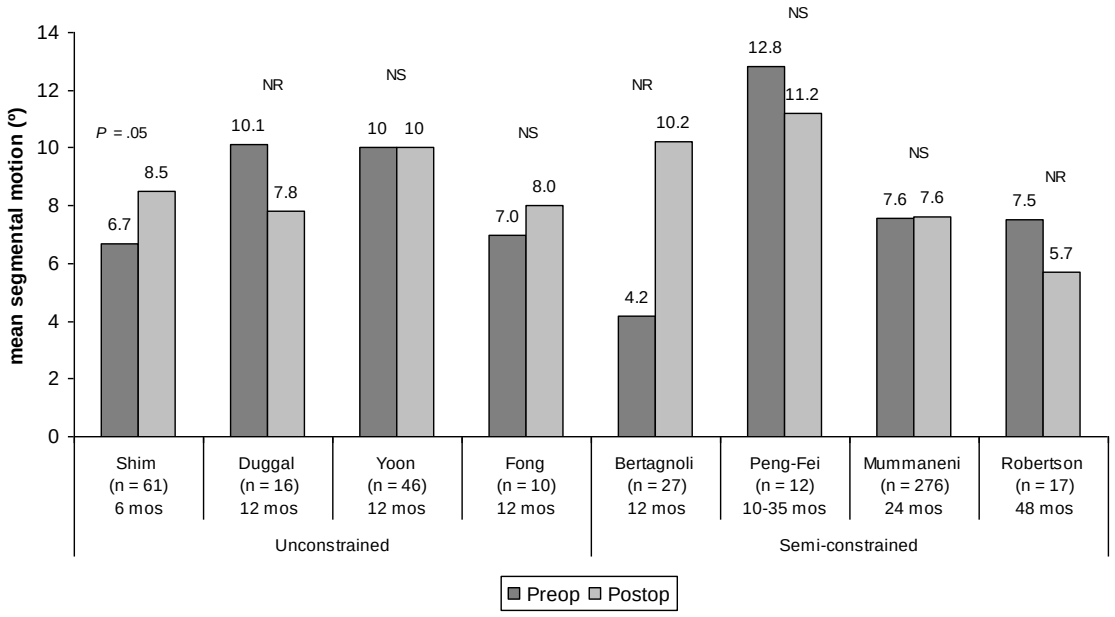
Preoperative versus postoperative flexion-extension (Figure 26)

Segmental flexion-extension at the level of instrumentation was generally maintained after C-ADR comparing preoperative motion with postoperative motion from 6–48 months following surgery. In some cases, motion was slightly increased postoperatively,[24,55,147] in some cases the motion was slightly decreased,[50,121,136] and in some cases the motion was the same compared with preoperative motion.[115,166] This pattern occurred with both the unconstrained and semiconstrained devices.

Postoperative range of motion in C-ADR versus fusion

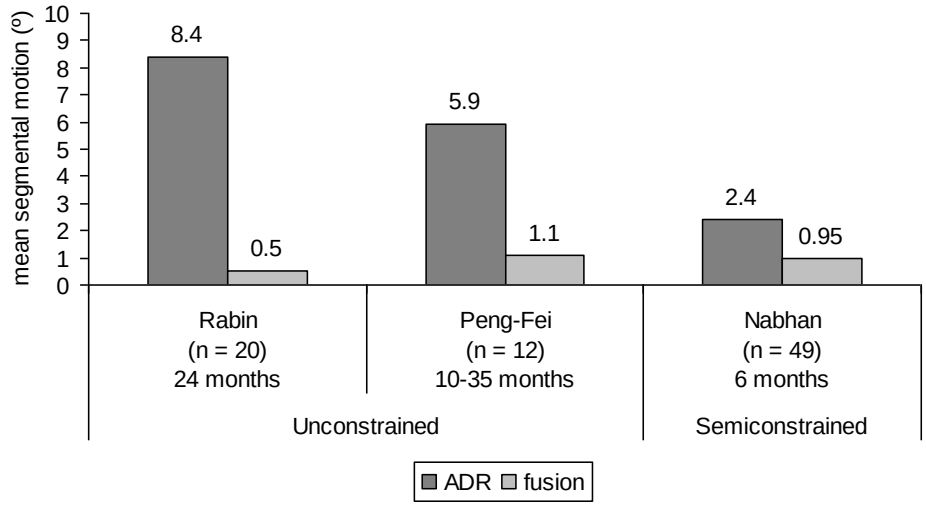
Three studies evaluated segmental motion comparing C-ADR with fusion at various follow-up periods.[118,121,132] Mean flexion-extension at the instrumented level was consistently and substantially higher in the C-ADR groups, for both an unconstrained and semiconstrained model at final follow-up, Figure 27. In one study, mean motion in the frontal and horizontal planes also was greater in the C-ADR group compared with ACDF group at the instrumented level.[117]

Figure 26. Average segmental flexion-extension at the C-ADR instrumented level comparing preoperative with postoperative motion at final follow-up



NR = not reported
NS = not statistically significant

Figure 27. Average segmental flexion-extension at the instrumented level comparing C-ADR with ACDF

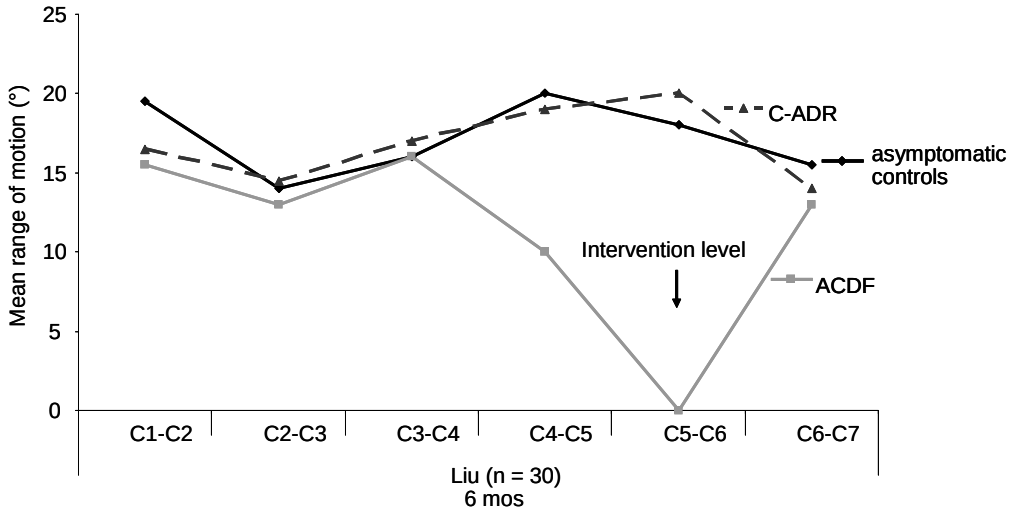


Postoperative range of motion in C-ADR versus asymptomatic controls
One small study evaluated motion in C-ADR (n = 10) and age- and sex-matched asymptomatic control (n = 10) groups. Segmental motion was similar in the ADR group (20°) compared with the controls (18°). [102]

Postoperative range of motion in adjacent segments for ADR, fusion, and control groups (Figure 28)

One small study evaluated segmental motion in ADR (n = 10), fusion (n = 10), and asymptomatic control (n = 10) groups. The motion patterns in the adjacent segments for ADR were similar to the motion of asymptomatic controls in terms of percent of total motion. The relative contribution of motion in the adjacent segment one level cephalad in the fusion group was decreased compared with ADR or asymptomatic controls.[102]

Figure 28. Average proportion adjacent segment motion (flexion-extension) at follow-up for C-ADR, ACDF, and asymptomatic controls



Adjacent segment disease (ASD)

Mummaneni et al reported a rate of symptomatic cervical ASD requiring surgical intervention of 1.1% in C-ADR patients and 3.4% in anterior cervical fusion patients after 2 years of follow-up [115], a relative risk decrease of 67% (absolute risk difference of 2.3%), *P* = .049. One retrospective cohort study reported a lower risk of cervical ASD requiring surgery following C-ADR compared with fusion (0% versus 7.0%).[137] In this study's analysis of symptomatic C-ASD patients only, (i.e., those with symptoms who received conservative or operative care), there was a marked difference between the ADR group (1.3%) compared with the fusion group (33%). The interpretation of these results should be tempered given that the groups were treated at two different time periods, there were no detailed comparisons of population characteristics at baseline, and there was no attempt to control for potential confounding that often affects cohort studies.

Two case-series report 1%[66] and 7%[161] symptomatic cervical ASD 24 months following a Bryan and Prestige C-ADR, respectively.

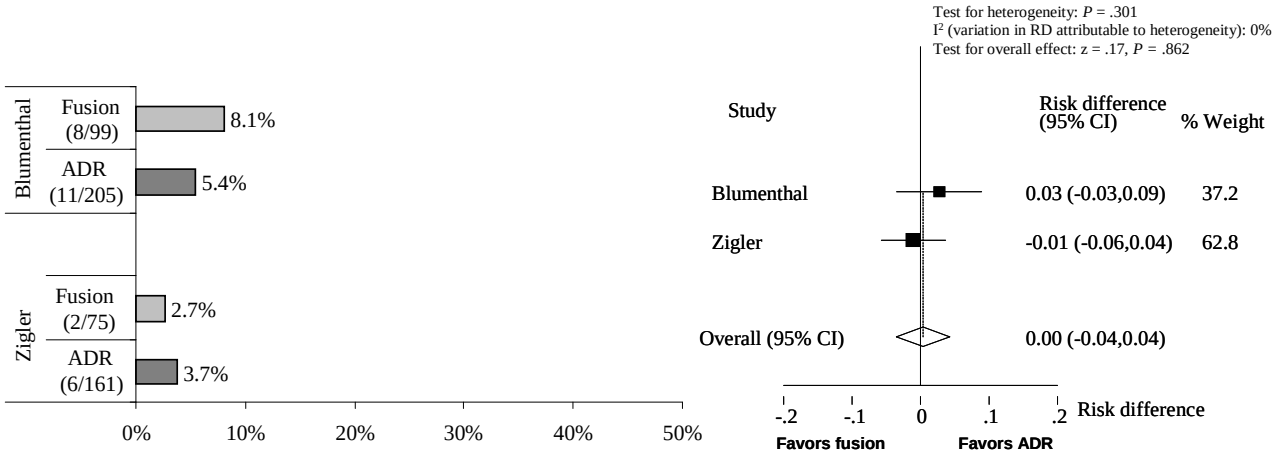
Few studies report on radiographic (asymptomatic) cervical ASD following C-ADR. One small RCT found no cases of radiographic C-ASD in either group after one year follow-up.[117] Robertson et al reported a high rate of radiographic cervical ASD after two years follow-up, 17.5% among C-ADR patients and 34.2% among fusion patients.[137] Again, caution interpreting the results from Robertson should be exercised based on the methodological issues above. Two small case-series report no cases of radiographic C-ASD 12 months following a Bryan or Prodisc C-ADR.[19,84] In general, radiographic evidence of changes to adjacent segments do not highly correlate with patient symptoms.

3.2 Key question 2 - What is the evidence related to the ADR safety profile (including device failure, reoperation)?

Device failure

The frequency of device failure (defined as reoperation, revision, or removal of the implant) was 5.4% and 3.7% in patients receiving L-ADR, and 8.1% and 2.7% in those receiving fusion in the Blumenthal et al and Zigler et al studies, respectively. There was no statistical difference in device failure between L-ADR and fusion, Figure 29.

Figure 29. Device failure for L-ADR (reoperation, revision, or removal of the implant)



Complications or adverse events

Blumenthal et al reported three major complications (defined as major vessel injury, neurological damage, nerve root injury, or death), two in the L-ADR group and one in the fusion group. One in the L-ADR group led to death (associated with narcotic use). Approach related complications (venous injury, retrograde ejaculation, ileus, perioperative vein thrombosis, clinically significant blood loss [> 1500 cc], incisional hernia, epidural hematoma, dural tear, deep vein thrombosis, arterial thrombosis) occurred in 20 L-ADR patients (9.8%) and 10 fusion patients (10.1%). Infections (superficial wound with incision site pain, other nonwound related, UTI, wound swelling, pulmonary, peritonitis, graft site) were reported in 26 patients (12.7%) and eight patients (8.1%) in the L-ADR and lumbar fusion groups, respectively. Device collapse, subsidence, or displacement was reported in eight L-ADR patients (3.9%) and one fusion patient (1.0%). Additional surgery at the index level was necessary in eleven patients (5.4%) in the L-

ADR group and nine patients (9.1%) in the fusion group. Neither group reported any catastrophic device failure.

Zigler et al reported no major complications in either group of the Prodisc-L study. However, two patients (2.7%) in the fusion group and none in the L-ADR group experienced clinically significant blood loss of > 1500 cc. Retrograde ejaculation occurred in two L-ADR patients (1.2%) and in no fusion patient. Deep vein thrombosis was reported in two patients (1.2%) in the L-ADR group and in one patient (1.3%) in the fusion group. No infection occurred in those receiving L-ADR, but did occur in two patients (2.7%) who underwent fusion. Device migration or subsidence was reported in four L-ADR patients (2.5%) and in one fusion patient (1.3%). Loss of disc height or radiolucency was not seen in the L-ADR group but occurred in six patients (8.0%) in the fusion group. In the fusion group, there were two cases (2.7%) of nonunion. No cases of spontaneous fusion were seen in the L-ADR group.

There were no statistical differences in the risk of all, device related, or major adverse events/complications between patients receiving L-ADR compared with fusion in the two index randomized controlled trials, Table 18. There were no reports of death relating to the device or surgical procedure with either ADR or fusion in either study. A list of all recorded adverse events from each study is found in Appendix F.

Table 18. Risk of all, device related and major adverse events/complications for the two index randomized controlled trials comparing L-ADR with fusion

	Blumenthal			Zigler		
Adverse events/complications	ADR (n = 205) no. (%)	Fusion (n = 99) no. (%)	Risk difference* (95% CI)	ADR (n = 162) no. (%)	Fusion (n = 80) no. (%)	Risk difference* (95% CI)
All irrespective of relationship to treatment	156 (76.1)	77 (77.8)	-0.02 (-0.12, 0.08)	136 (84.0)	70 (87.5)	-0.04 (-0.13, 0.06)
Device related	15 (7.3)	4 (4.0)	0.03 (-0.02, 0.09)	29 (17.9)	16 (20.0)	-0.02 (-0.13, 0.08)
Major complications	2 (1.0)	1 (1.0)	-0.00 (-0.02, 0.02)	0 (0.0)	0 (0.0)	0

*A negative risk difference signifies a benefit for L-ADR. There is no statistical difference between L-ADR and fusion groups in either study.

Other complications reported in case-series

Complications following L-ADR were reported for 1319 patients from 22 case-series. Risks of complication were calculated using the number of patients at follow-up when available. When follow-up data were not available, risks were calculated using the number of patients at the start of the study, which may underestimate the actual rate of complications for some studies. Mean follow-up ranged from 6 months to 17 years. In general, complication risks varied widely between studies, Table 19. Different length of follow-up, different patient populations and varying definitions of complications could partially explain the wide range in risks.

Two case-series with a minimum follow-up of at least 10 years have been reported evaluating the rate of heterotopic ossification or spontaneous fusion.[45,131] David et al[45] reported a heterotopic ossification or spontaneous fusion frequency of 2.8% for Charité ADR while Putzier et al[131]

reported a frequency of 60%. The former study changed the postoperative regimen to active physiotherapy beginning on the sixth postoperative day while Putzier et al kept patients in a brace with no active motion for 8 weeks following surgery. The postoperative motion protocol may explain the large difference in the incidence of heterotopic ossification or spontaneous fusion between these two studies.

Table 19. Complications following L-ADR reported from case-series

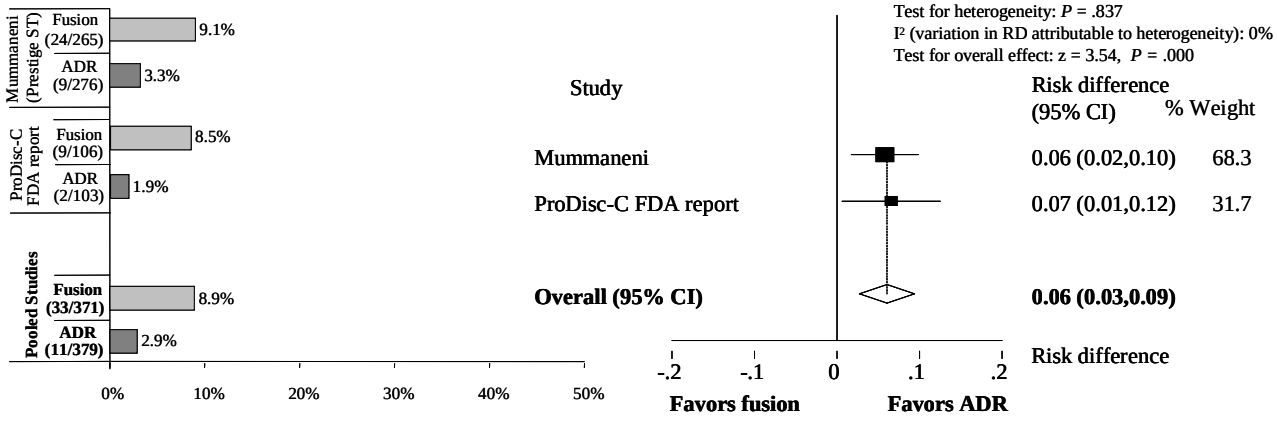
Complication	No. of studies	No. of patients with complication	Range of rates reported
New or residual pain	13 [20,25,39,42,45,56,95,107,131,157,158,170]	67	1.0%-36.9%
Vein or vessel laceration	7 [39,95,97,148,157,164,170]	10	1.6%-5.6%
Hematoma	3 [25,149,170]	17	1.0%-28.3%
Retrograde ejaculation	5 [24,25,56,97,157,170]	5	1.0%-4.0%
Heterotopic ossification	8 [35,42,45,56,95,97,131,149]	28	1.0%-60.0%
Prosthesis migration	3 [35,95,130]	15	7.8%-10.7%
Subsidence	8 [24,45,95,97,130,131,148,157]	54	1.6%-52%
Prosthesis malposition	4 [42,149,158,170]	8	1.0%-7.0%
Secondary fusion	4 [35,42,45,131]	37	5%-23%
Disc replacement surgery	1 [45]	6	5.7%

Cervical

Device failure

Using the baseline sample size as reference (ITT analysis), the frequency of device failure (defined as reoperation, revision, or removal of the implant) was 2.9% in the C-ADR group compared with 8.9% in the ACDF group, risk difference of 6.0% (95% CI 2.6%, 9.3%; *P* = .0005), Figure 30. The risk difference of 6% equates to a number-needed-to-treat (NNT) of 17; that is, for every 17 patients who receive C-ADR instead of anterior cervical fusion among patients with the same cervical disease as those in the studies, 1 additional patient will avoid device failure during the first 24 months following surgery.

Figure 30. Device failure for C-ADR (reoperation, revision, or removal of the implant)



Complications or adverse events

The Prestige ST FDA SSED reported five cases of hardware removal in the C-ADR group (1.8%) compared with nine cases in the ACDF group (3.5%). There were four (1.4%) reoperations in the C-ADR group, two for unresolved neck pain, one for unresolved arm pain and one for both neck and arm pain. The ACDF group sustained five revisions (2%), eight supplemental fixations (3%), and two reoperations (1%). Device related or device/surgical procedure related adverse events occurred less frequently in the C-ADR group (3.3%) compared with the ACDF group (9.8%), risk difference of 7% (95% CI 2%, 11%), Table 11.

The Prodisc-C FDA SSED reported two implant related adverse events in two C-ADR patients and nine implant related adverse events in seven ACDF patients. There were no statistical difference between C-ADR and ACDF with respect to all adverse events (P=1.0), device-related adverse events (P = .17) or surgery-related adverse events (P = .41). Major complications (severe or life threaten adverse events) occurred less frequently in the C-ADR group (15.5%) compared with ACDF group (30.2%), risk difference of 15% (95% CI 3%, 26%), Table 11. Heterotopic ossification resulting in loss of motion (<2°) was found in three Prodisc-C patients.

The Bryan FDA Panel Executive Summary reported similar proportions of serious adverse events (WHO grade 3 or 4) between the C-ADR and ACDF groups, 26.4% versus 24.9%. Implant or surgical procedure related serious adverse events occurred in 1.7% of the C-ADR group and 3.2% in the ACDF group. Subsequent surgical interventions and implant migration/failure related adverse events were reported in 2.5% and 2.9% in the C-ADR group, and 4.1% and 5.4% in the ACDF group, respectively.

Additional detail of complications for the five clinical trials is found in Appendix F.

Table 20. Risk of all, device related and major adverse events/complications for the three FDA randomized controlled trials comparing C-ADR with fusion

	Prestige ST FDA trial				Prodisc FDA trial				Bryan FDA trial*		
Adverse events/complications	ADR (n = 276) no. (%)	Fusion (n = 265) no. (%)	Risk difference† (95% CI)		ADR (n = 103) no. (%)	Fusion (n = 106) no. (%)	Risk difference† (95% CI)		ADR (n = 242) no. (%)	Fusion (n = 221) no. (%)	Risk difference† (95% CI)
All irrespective of relationship to treatment	226 (81.9)	212 (80.0)	0.01 (-0.04, 0.07)		84 (81.6)	86 (81.1)	-0.0 (-0.10, 0.11)		202 (83.5)	174 (78.7)	0.05 (-0.02, 0.12)
Major complications (severe or life threatening)	NR	NR	NR		16 (15.5)	32 (30.2)	-0.15 (-0.26, -0.03)		64 (26.4)	55 (24.9)	0.02 (-0.06, 0.10)
Device related or device/surgical procedure related	9 (3.3)	26 (9.8)	-.07 (-0.11, -0.02)		13 (12.6)	23 (21.7)	-0.09 (-0.19, 0.01)		7 (2.9)	12 (5.4)	-0.03 (-0.06, 0.01)

NR = not reported.

*As reported in the FDA Executive Summary for the full enrolled population, even though the primary analysis focused on 300 who had completed 24 months follow-up.

†A negative risk difference signifies a benefit for C-ADR. There is a statistical difference between C-ADR and fusion groups in for device related adverse events for the Prestige ST trial and for major complications for the Prodisc trial in favor of C-ADR.

Complications from case-series

Other complications reported in case-series (Table 21)
Complications following cervical ADR were reported for 950 patients from 22 case-series. Complication rates were calculated using the number of patients at follow-up when available. When follow-up data was not available, rates were calculated using the number of patients at the start of the study, which may underestimate the actual rate of complications for some studies. Mean follow-up ranged from 4 to 48 months.

Increased or new pain was reported in 42 patients in eight of the studies[50,66,125,128,137,145,147,162] ranging from 1.3%[137] to 33.3%.[162] Hematomas were observed in nine patients over eight studies[19,23,66,74,84,125,137,166] ranging from 0%[19,23] to 4.0%.[84] Dysphonia or other vocal cord problems were reported in six patients in four of the studies[50,90,93,162] ranging from 0%[90] to 13.3%.[162] Dysphagia was also noted in 51 patients in three studies[50,84,90] ranging from 0%[90] to 100%.[84] Heterotopic ossification was reported in 23 patients (grades 1 and 2 in ten; grades 3 and 4 in 13) over six studies[12,19,74,98,125,165] ranging from 0%[12,19,165] to 17.8%[98] and in 48 levels/segments (all grades 1 and 2) in two studies, rate of disease ranging from 0% to 62.2%.[74,113]

Device migration or suspected migration was observed in seven patients in eight of the studies[19,23,50,55,66,74,125,127] ranging from 0%[19,23,55,74] to 4.1%.[125] Revision decompression surgery was necessary in three patients over two studies ranging from 1.4%[66] to 1.6%.[147] Removal of the artificial disc and subsequent fusion was reported in four patients over four studies[128,136,137,162] ranging from 1.3%[137] to 10.0%.[128] Adjacent level surgery was performed in three patients over three studies[66,137,162] ranging from 1.3%[137] to 6.7%.[162]

Since case-series do not include comparisons to other treatments, have variable lengths of follow-up, often do not provide adequate information on loss to follow-up and may be subject to bias, rates should be interpreted with some caution.

Table 21. Complications following C-ADR reported from case-series

Complication	No. of studies	No. of patients with complication	Range of rates reported
New or residual pain	8[50,66,125,128,137,145,147,162]	42	1.3%-33.3%
Hematoma	8[19,23,66,74,84,125,137,166]	9	0%-4.0%
Dysphonia	4[50,90,93,162]	6	0%-13.3%
Dysphagia	3[50,84,90]	51	0%-100%
Heterotopic ossification	7[12,19,74,98,113,125,165]	23	0%-17.8% 62.2%*
Migration or suspected migration of the device	8[19,23,50,55,66,74,125,127]	7	0%-4.1%
Revision decompression surgery	2[66,147]	3	1.4%-1.6%
Device removal	4[128,136,137,162]	4	1.3%-10.0%
Adjacent level surgery	3[66,137,162]	3	1.3%-6.7%

*Proportion based on number of segments with signs of ossification

FDA's Manufacturer and User Facility Device Experience (MAUDE)
The FDA's MAUDE data base of adverse events (updated on March 27, 2008) was searched. Approximately 500 adverse event reports have been made related to artificial discs overall. Report initiators include manufacturers, clinical users/providers, attorneys, and patients. It is unclear how many are unique reports. Some provide information regarding the severity, type, and resolution of adverse events while others do not. Summary and categorization of these is beyond the scope of this report and since no denominator information is available to provide rate information, it is not possible to put these reports into a meaningful context.

3.3 Key Question 3 - What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

Lumbar
Three reports were found evaluating the L-ADR in subpopulations: the elderly (> 60 years of age), athletes, and smokers. No studies were found evaluating L-ADR in workers compensation populations. Due to the nature of the study design (two case-series and one cohort study), the size of the populations and the length of follow-up, no firm conclusions can be drawn with respect to L-ADR in special populations.

The elderly (> 60 years of age)
Bertagnoli et al[22] reported on 22 patients with mean age of 63 years (range 61-71 years) presenting with discogenic low back pain (LBP) with or without radicular pain. Patients had no evidence of spinal stenosis and minimal or no facet joint degeneration. Seventeen patients received single-level replacement, four two-level replacement, and one three-level replacement. Statistical improvements in VAS, ODI, and patient satisfaction scores were observed at early (3 months postoperatively) and late (24 month postoperatively) time periods. Patient satisfaction was reported by 94% of the patients at 24 months. There were two cases involving neurological deterioration; both occurred in patients in whom there was evidence of circumferential spinal stenosis before surgery. There were two cases of implant subsidence and no thromboembolic phenomena. The investigators cautiously recommend the use of artificial disc replacement in the treatment of chronic discogenic LBP in patients older than age 60 years in whom bone quality is adequate in the absence of circumferential spinal stenosis.

Athletes
Siepe et al[150] evaluated the results of Prodisc-L in 39 patients involved in high level athletics or extreme sport. Significant pain relief was attained following L-ADR with a mean follow-up of 26.3 months (range 9-50.7 months). Thirty-seven patients (94.9%) resumed their sporting activity, most improving their performance significantly. Minor subsidence was observed in 13 patients (30%). Preoperative participation in sport was strong positive predictor for highly satisfactory postoperative outcome. The investigators concluded that due to the young age of the patients and significant load increase exerted during athletic activities, a longer follow-up will be required to assess the effectiveness of L-ADR in this population.

Smokers
Bertagnoli et al[21] conducted a prospective cohort study in 104 patients with disabling discogenic low back pain treated with single-level Prodisc-L ADR. Smokers and nonsmokers were assessed before surgery and after surgery using patient satisfaction, Oswestry, and Visual Analog Scores. There were no differences between smokers and nonsmokers at two year follow-up with respect to any of the effectiveness outcomes. There were no cases of loosening, dislodgment, mechanical failure, infection, or fusion of the affected segment in either group. The authors concluded that smokers do equally well compared with nonsmokers when Prodisc-L ADR is used in the treatment of debilitating lumbar spondylosis.

Cervical

No studies evaluating C-ADR within special populations or subpopulations were identified.

3.4 Key Question 4: What are the cost implications and cost effectiveness for ADR?

Critical Appraisal, lumbar

Two studies comparing arthroplasty costs with fusion costs as a competing alternative were included.[68,100] Neither is a full economic evaluation. Critical appraisal, based on the items of the Quality of Health Economic Studies (QHES) instrument and epidemiologic principles, indicates that there are insufficient data for full economic evaluation or extensive conclusions and that potential biases should be considered in the interpretation of these studies. Weighted QHES scores were low at 57 and 59 [possible score 0 (worst) to 100 (best)] for Guyer and Levin respectively.

Both papers are costing studies, not cost-effectiveness or cost-utility analyses, and therefore are considered partial economic analyses. It is well accepted that cost analyses are not considered full economic evaluations. Theoretically, a cost-minimization study (one that compares costs of the alternatives assuming equal effectiveness) might provide a complete economic evaluation, but because of uncertainty around costs and quality of life outcomes that likely differ between alternative interventions this is rarely possible.[49] In addition, when data from trials using a non-inferiority design are used to establish equivalence, the choice of outcome, methods of evaluating outcome proportions and determination of statistical power need to be considered in the design of cost-minimization studies.[153]

Both papers make the assumption that L-ADR and any type of fusion have equivalent clinical outcomes. Both studies, however mention that outcomes for different types of fusion may be different. The assumption of equivalent outcomes, even if appropriate on some outcome measures, prohibits a rigorous examination of qualitative differences between treatment alternatives considering patient experience and long-term clinical outcomes. Neither paper provides a transparent assessment of how, and for which outcomes, they established equivalence. These two papers do provide data that begin to describe the cost of lumbar ADR in the short term. However, neither paper adequately describes the cost of longer-term complications (eg, adjacent segment disease) or lost productivity and other quality of life considerations. Neither study was designed to provide an incremental analysis of the overall *value* of L-ADR, measured

as a cost per clinical outcome achieved, compared with fusion in the context of patient-reported outcomes.

The Levin study provides cost data only for operating room, devices, and physician (surgeon and anesthesiologist) Medicare fees at the time of the index procedure. Since the long-term effects of ADR as a surgical treatment alternative for DDD could vary significantly and could involve hospital charges, a model that includes an appropriate time horizon would provide a more complete picture of costs and should be linked to specific patient outcomes. The Guyer study provides a series of direct cost models from hospital or payer perspectives, and assumes equivalent clinical benefit for each alternative. Costs for single-level L-ADR are compared with different fusion options which included an unknown number of multilevel fusions, Table 22. Although the authors made an adjustment which they believe would adjust the fusion costs downward, it is unclear what the true effect may be. In addition, the patient population used in building these models was not clearly described, so the comparability of patients, generalizability, and potential for selection bias are unknown. Both report mean costs (without ranges or standard deviations), which may or may not reflect the typical values as costs frequently have skewed distributions.

Table 22. Overview of included partial economic analyses comparing lumbar ADR and fusion

	Design	Data sources and Population	Primary Strengths	Primary Limitations
Levin	▪ Cost analysis ▪ Hospital perspective ▪ 2006 USD (inflation corrected) ▪ Authors indicate no funding received for study	▪ Hospital charges ▪ Physician Medicare reimbursement scale used ▪ Demographics N = 53 Female: 38%; Age 39 (22-55); BMI mean 26.9	▪ Prospective design ▪ Data from RCT (FDA IDE trial) ▪ Provided demographic information and inclusion/exclusion criteria	▪ Inpatient costs not reported ▪ Small sample size (N = 53) particularly when divided into 1 and 2 level procedures. ▪ Sample reflects data from one site of multicenter trial ▪ Only short term costs included (index operation only) ▪ Did not compare effectiveness of alternatives ▪ Sensitivity analyses not reported
Guyer	▪ Cost minimization analysis ▪ Hospital and payer perspectives ▪ 2006 USD ▪ Authors acknowledge financial relationship with DePuy and use of DePuy consultant for the study	▪ Commercial payers claims data from hospital and Milliman Database ▪ Demographics: Not reported	▪ Description of included costs and assumptions is reasonably complete ▪ Provision of several models based on different perspectives and different types of fusion ▪ Authors attempted to adjust for inconsistencies in cost related to number of levels.	▪ No demographic description of patient populations to evaluate comparability or generalizability ▪ Method of selecting patients and claims data unclear ▪ Fusion costs included unknown numbers of multi-level procedures while ADR is single-level ▪ Discounting of costs beyond one year not reported ▪ Comparison of outcomes, effectiveness of alternatives not reported ▪ Sensitivity analyses not reported

Results:

Both studies suggest that mean L-ADR costs may be lower or at least similar to those for fusion, depending on the levels compared, types of fusion, and perspective. However, the limitations of the studies should be borne in mind.

From a hospital cost perspective, both studies suggest that L-ADR may be less costly than fusion.

- In one study, one-level L-ADR had significantly lower mean total cost compared with one-level fusion (difference, $10,688 or 23% less) while there was no statistically significant difference between groups when two-level procedures were compared. Mean totals are based on a sum of mean charges for operating room and implants with Medicare-based fees for surgeon and anesthesiologist (Figure 31).[100]
- Total costs for lumbar single-level L-ADR were also less by 12%-36% (difference, $1995-$6087) compared with various fusion options in the other study (Figure 32).[68] Cost included facility, therapy, devices/medications/supplies, diagnostic tests, and other costs. Costs for fusion include an unknown number of multilevel procedures and authors adjusted the estimates downward by a factor of 0.78 to account for this.

Figure 31. Comparison of mean total hospital charges for ProDisc-L ADR and circumferential fusion based on numbers of levels involved[100]

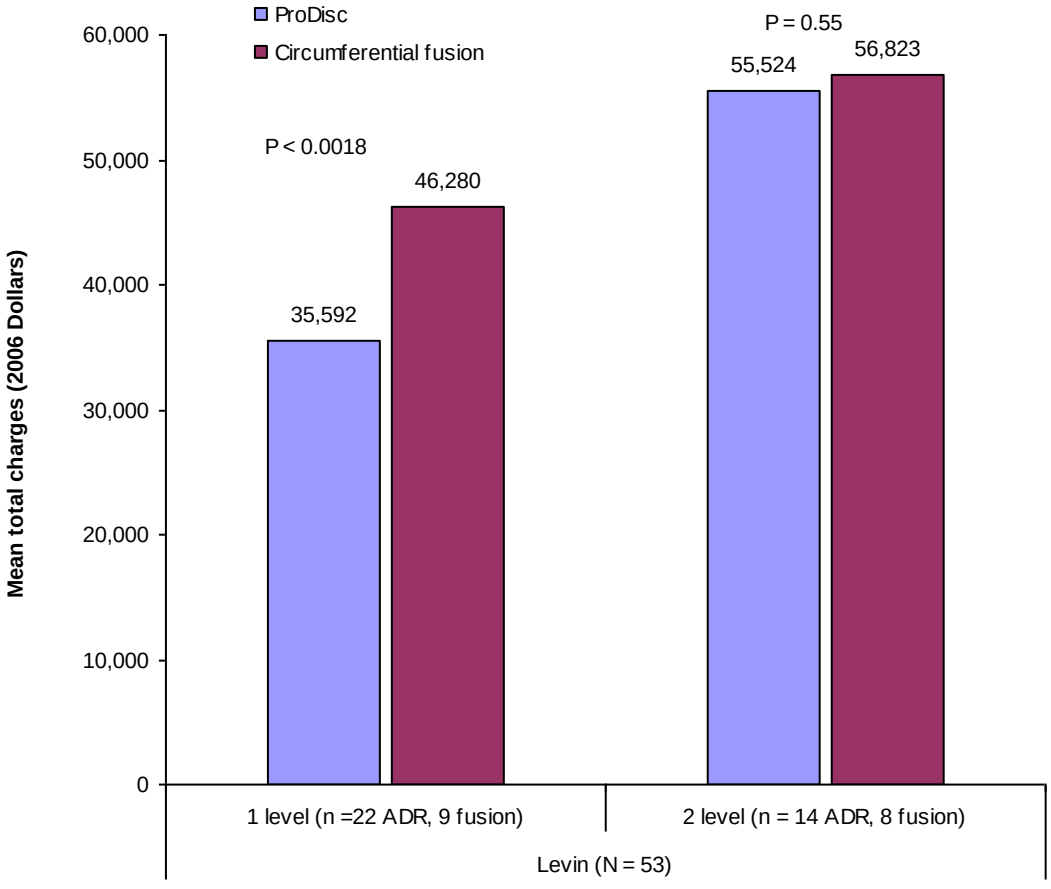
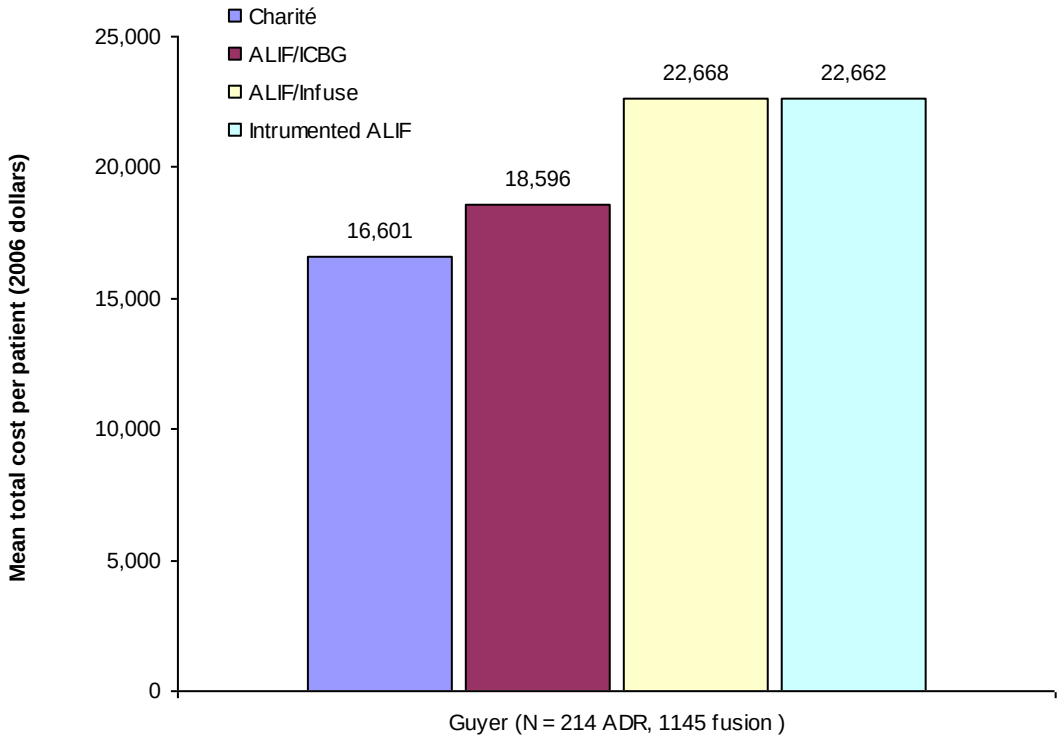


Figure 32. Comparison of mean total costs from hospital perspective (per diem and DRG payment arms) for Charité L-ADR and various fusion procedures[68]



The Guyer study demonstrates that different perspectives can provide different cost estimates (see table 23). The only difference between the perspectives is in the cost of the index procedure implant, with the other cost estimates remaining the same (including follow-up care, revision surgery, and complications). The per diem methodology is based on payer costs using a pre-established, fixed payment for a patient care-day and 100% of implant costs. Compared with ALIF with Infuse or ALIF with instrumentation, the Charité L-ADR total costs were lower in both scenarios.

Table 23. Summary of mean total costs (2006 USD) from different payer perspectives as reported by Guyer for L-ADR

	Payer perspective: DRG arm				Payer perspective: Per diem payment			
Cost Category	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**
Index Procedure	9611	22,338	22,165	24,663	16,822	13,156	18,861	21,231
Other costs	8002	10,621	10,031	10,389	8002	10,621	10,031	10,389
Total per patient cost	17,614	32,960	32,196	35,,052	24, 885	23,778	18,892	31,620
Compared with Charité (%)	-	+ 87%	+82.8%	+99.0%	-	-.4.4	+16.1	+27.1

ALIF = anterior lumbar interbody fusion.
ICBG = iliac crest bone graft.
PLIF = posterior lumbar interbody fusion.

Levin describes mean length of hospital stay, estimated blood loss, and average length of surgery but does not describe in terms of a cost analysis or impact. No significant differences were reported with regard to mean length of stay with L-ADR patients averaging 4.78 days versus 4.32 days for fusion. Mean estimated blood loss was significantly higher in the L-ADR group (794 mL) compared with fusion (412 mL, $P = .0058$) however the length of surgery for L-ADR was significantly less (185 minutes) compared with fusion (344 minutes, $P < .0001$).[100]

Research recommendations:

These papers could be considered a starting point for full economic evaluation as they present data on hospital charges that may be useful in the development of a more complete model of the cost-effectiveness for L-ADR compared with fusion. Such a model would include a clear statement of perspective, time horizon, and quality-adjusted outcome measures. The downstream outcomes for both ADR and fusion need to be articulated and the potential influence of different types of fusion needs to be more fully considered. In addition, specification of patient populations is needed. Sensitivity analyses incorporating the ranges of various costs and examining the various assumptions are necessary as well to examine the stability of estimates.

Economic analyses from other HTAs

Two previously performed HTAs, one from Ontario and one from Australia provided economic analyses. Differences in health care systems, practice patterns and reimbursement mechanisms need to be considered when reviewing the results. For example, in Ontario, diffusion of artificial discs is controlled by hospitals based on global budgets.

The most thorough evaluation was reported by the Medical Services Advisory Committee (MSAC) of the Commonwealth of Australia. Direct costs (discounted at 5% per annum) for hospital care, prostheses, and medical fees for both public and private hospitals were used to compare the Charité device (based on the index RCT) with two different fusion methods (screw and rod/plate or interbody fusion). Overall clinical success as defined in the Charité trial was used as the best comparator of clinical effectiveness and equivalence of L-ADR and fusion was

assumed for this outcome. However, not all randomized patients had completed the 24 month follow-up and it is not clear what denominator may have been used for success rates (ie, intention to treat or other). In addition to a base case scenario, one-way sensitivity analyses which first assumed a lower devices price and then the higher device prices from price ranges provided by manufacturers. An incremental increase in cost of L-ADR was estimated at $1054 (Australian Dollars) when all fusion methods were included up to a higher estimate of $7570 based on sensitivity analysis. When interbody fusion alone was considered as the competing alternative, a cost *savings* of $3458 for L-ADR was projected as a base case ranging to an increased cost of $262 based on sensitivity analysis. The prosthesis costs were the primary driver of the differences.

The Ontario assessment estimates an incremental increase of $4060 (Canadian Dollars) for use of L-ADR verses fusion, based on a mean prosthesis costs obtained from manufacturers, professional fee schedules, and median hospital costs for 148 fusion cases and five L-ADR cases.[155] Discounting of 3%-5% is mentioned in the standardized methods description. Sensitivity analyses, method of case selection and fusion methods compared are not reported. In addition, a very small number of ADR cases (5) were used for analyses.

Both reports suggest that approximately 5% of those patients eligible for lumbar fusion would be candidates for L-ADR based on indications and contraindications for the use of L-ADR,[112,155] an assumption also made by Huang and colleagues.[81] Assuming 5% substitution of L-ADR in lieu of fusion, estimated incremental costs incurred by the health sector ranged from $218,618 to $1,570,151(Australian Dollars) in the MSAC report. Budgetary impacts from these HTAs are difficult to interpret since long-term benefits and effectiveness are not well delineated.

The following limitations to the evaluations need to be considered:

- Data for some estimates may not be of the highest quality for either L-ADR or fusion
- Data on benefits and safety beyond 24 months are sparse and are of poor quality such that downstream costs cannot be determined. For example there are insufficient data on the rates of adjacent segment disease (ASD) and the extent to which they may differ for ADR compared with fusion or what the influence of follow-up care for graft site pain or use of synthetic proteins in fusion patients may have on estimates. In addition, it is unclear how L-ADR device failure in the long term may influence revision options and costs.
- The impact of rehabilitation following surgery was not included.
- The relative long term advantages of either procedure compared with nonsurgical treatment are not clear.

Implications of economic analyses:
The costing studies by Guyer and Levin suggest that L-ADR costs may be at least similar and perhaps less than those for fusion. This seems to be supported by the MSAC assessment if interbody fusion only is considered as the alternative; however it is not supported by the findings of the Ontario assessment. The fusion method used may influence cost and therefore differences in cost compared with L-ADR. Again the limitations of all of these evaluations need to be considered.

Within Washington State, the Comprehensive Hospital Abstract Reporting System (CHARS) contains hospital inpatient discharge information[10] including diagnostic and procedural information as well as billed charges based on DRGs (diagnosis-related groups). The data below provide a gross estimate of the numbers of ADR procedures since 2005 and costs. These charges include facility and ancillary charges but generally do *not* include physician charges.

Table 24. Summary of the number of lumbar ADR procedures performed and total charges for Washington State 2005-2007 based on CHARS data (DRG basis)

	L-ADR	
	number performed	**mean total charges x 0.50***
2005	29	$20,091
2006	44	$16,805
2007	16	$29,249
total	89	$20,113

*the multiplier of 50% provides a crude estimate of paid charges.

A number of limitations to these data need to be considered. First, this is not a formal economic analysis and is based on available data from CHARS. Second, there are a number of general limitations to the use of administrative data which include differences in coding practices across hospitals, possible miscoding of procedures and misclassification of diagnoses and the possibility of incomplete coding. Coding is primarily geared toward reimbursement. The ICD-9 CM codes capture conditions based on physician documentation and codes which may not relate to reimbursement may not be represented completely. While it is assumed that the primary diagnosis code is the most relevant to the respective procedures, this may not always be the case. Thus, numbers of unique cases may be underestimated.

With regard to actual device costs (or ranges) and diffusion of the technology, particularly in Washington State, Medtronic, DePuy, and Synthes were contacted but declined the opportunity to provide data.

Cervical

No formal economic analyses were found during the systematic literature search of peer-reviewed literature.

Economic analyses from other HTAs

One previously done assessment (Medical Services Advisory Committee (MSAC) of the Commonwealth of Australia) did provide an assessment for cervical arthroplasty.[112] Differences in health care systems, practice patterns and reimbursement mechanisms need to be considered when reviewing the results.

The analysis assumed that hospital costs for fusion and C-ADR were the same. The estimated incremental cost increase of $9,438 (range, $9,438 to $13,346) was attributed to the higher cost of the prosthesis when compared with any type of fusion. When interbody fusion only was the comparator, the incremental cost of C-ADR was slightly less at $8413 (range, $8,413 to $11,696). Although the report describes incremental cost for specific measures (e.g. quality

adjusted life year, QALY), data for outcomes were taken from a preliminary report of the Prestige-II disc randomized controlled trial representing four trial sites. Only 16% of the study population had reached 24 months of follow-up at the time of publication and thus, the evidence base for the determination is questionable.

Based on the assumption that 40% of cervical fusion patients would have C-ADR instead, estimated incremental costs incurred by the health sector ranged from $3,184,940 to $4,503,730 (Australian Dollars) based on sensitivity analyses around the lowest and highest ranges for C-ADR device costs. Budgetary impacts from this HTA are difficult to interpret since long-term benefits and effectiveness are not well delineated. In addition, there are a number of differences in health care delivery and reimbursement practices compared to the United States.

The following limitations to the evaluation need to be considered:

- Data for outcomes are from incomplete trial data supplied by sponsors
- Data on benefits and safety beyond 24 months are sparse and are of poor quality such that downstream costs cannot be determined. For example there are insufficient data on the rates of adjacent segment disease (ASD) and the extent to which they may differ for C-ADR compared with fusion over the long-term.
- The impact of rehabilitation following surgery was not included.

C-ADR in Washington State

Within Washington State, the Comprehensive Hospital Abstract Reporting System (CHARS) contains hospital inpatient discharge information[10] including diagnostic and procedural information as well as billed charges based on DRGs (diagnosis-related groups). The data below provide a gross estimate of the numbers of ADR procedures since 2005 and costs. These charges include facility and ancillary charges but generally do *not* include physician charges.

Table 25. Summary of the number of cervical ADR procedures performed and total charges for Washington State 2005-2007 based on CHARS data (DRG basis)

	C-ADR	
	number performed	**mean total charges x 0.50***
2005	17	$11,399
2006	14	$7,896
2007	25	$10,394
total	56	$14,344

*The multiplier of 50% provides a crude estimate of paid charges.

A number of limitations to these data need to be considered. First, this is not a formal economic analysis and is based on available data from CHARS. Second, there are a number of general limitations to the use of administrative data which include differences in coding practices across hospitals, possible miscoding of procedures and misclassification of diagnoses and the possibility of incomplete coding. Coding is primarily geared toward reimbursement. The ICD-9 CM codes capture conditions based on physician documentation and codes which may not relate to reimbursement may not be represented completely. While it is assumed that the primary

diagnosis code is the most relevant to the respective procedures, this may not always be the case. Thus, numbers of unique cases may be underestimated. Data may include patients who were part of IDE trials. The type of device or number of levels is unknown.

With regard to actual device costs (or ranges) and diffusion of the technology, particularly in Washington State, Medtronic, DePuy, and Synthes were contacted but declined the opportunity to provide data.

Summary and Implications

A summary of the overall strength of evidence for each key question can be found in Tables 26 and 27 below.

1. Efficacy/effectiveness of artificial disc replacement (ADR)

- Findings contained in this technology assessment reflect the use of lumbar or cervical ADR in patients who have failed conservative treatment. For the lumbar spine, conservative treatment for at least six months was required prior to study enrollment. For the cervical spine, six weeks of conservative treatment or a progression of neurological signs was an indication for ADR. Neither the type of conservative treatment nor the level of patient compliance with pre-study conservative treatment was detailed in the published studies used in this technology assessment and therefore, unknown.
- There is insufficient evidence to draw extensive efficacy/effectiveness conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the efficacy/effectiveness of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion. One study is underway that includes three surgical treatment arms for cervical radiculopathy: C-ADR versus anterior cervical discectomy without fusion versus anterior cervical discectomy with fusion (ACDF).
- With respect to the comparison of L-ADR and fusion, there is moderate evidence that the efficacy/effectiveness of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery. This evidence is based on two moderate quality randomized controlled trials conducted as FDA Investigational Device Exemption non-inferiority trials. Overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving L-ADR and 48% receiving lumbar fusion. Though the results suggest that 24 month outcomes for L-ADR are similar to lumbar fusion, it should be noted that a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question.
- There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index, and pain up to two years following surgery. The evidence is based on two moderate quality randomized controlled FDA Investigational Device Exemption non-inferiority trials. An

interim analysis of approximately 65% of a third RCT was reported in an FDA Panel Executive Summary. If the results following completion of the trial are similar to the interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase.

- There is evidence that segmental motion is maintained or improved up to three years in the L-ADR patients and up to four years in C-ADR patients compared with preoperative motion. It is unclear the true extent to which preserving segmental motion by using ADR instead of fusion influences rates of adjacent segment disease (ASD). Whether ASD is a continuation of a disease process necessitating fusion or a result of fusion continues to be disputed. Furthermore, there continues to be debate on whether the presence of ASD is clinically important given that patients with marked radiographic ASD often have no symptoms.

2. Safety of artificial disc replacement (ADR)

- There is insufficient evidence to draw extensive safety conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the safety of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion.

- There is moderate evidence that L-ADR is as safe as lumbar anterior or circumferential fusion, and that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery.
- There is insufficient data at this time to determine the longer term safety of both L-ADR and C-ADR.

3. Special or subpopulations

- There is insufficient evidence to draw conclusions regarding the safety and efficacy of L-ADR in the few special populations studied (elderly, smokers, athletes). No studies or sub-analyses were found on the use of C-ADR in special or subpopulations.

4. Economic implications

- There are inadequate data from partial economic studies reflecting short time horizons for L-ADR and no economic studies for C-ADR to truly assess the potential cost-effectiveness of ADR technology. One report and one previously done HTA suggest that the type of fusion may influence complication rates and therefore costs.

5. Additional implications

- The studies primarily reflect outcomes measured up to 24 months and therefore questions remain regarding the longer term safety and efficacy of L-ADR or C-ADR compared with fusion. This is an important matter, particularly in those receiving C-ADR where the

average age is near 45 years. Since these are mechanical devices, future failure is a possibility and may influence complication rates and costs in the longer-term.

- Findings contained in this report primarily reflect use of ADR at a single level and it may not be appropriate to extrapolate the results to patients with ADR at multiple levels or for indications other than those evaluated during the FDA trials. As diffusion of these devices increases and they are used for additional indications, the safety and efficacy profiles may change.
- Studies which met the inclusion criteria for this report encompassed only two biomechanical types, an unconstrained device and a semiconstrained device. While it was deemed reasonable to pool information from trials despite difference in device design, it is probably appropriate to consider that such differences may influence longer term outcomes. There are a variety of different biomechanical designs for ADR. There is limited data which directly compare outcomes and complications for different devices in the short-term or longer term and thus, the influence of different designs is unknown.
- One study suggests that surgeons and institutions with a high volume of L-ADR cases have shorter operating time and hospital stay, and lower complication rates which may have an economic effect. No effect on clinical outcomes was reported between high and low volume surgeons or institutions.

Table 26. Summary of overall strength of evidence for key questions pertaining to L-ADR

Key Question 1: Efficacy/effectiveness of L-ADR compared with nonoperative care, lumbar fusion, other surgical procedures					
		Domain Criterion Quality: ≥ 80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
L-ADR versus:	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Nonoperative care	**No evidence**	• There is no evidence from studies directly comparing L-ADR with non-operative care for degenerative disc disease	none	none	none
2. Lumbar fusion • Overall clinical success • ODI • Pain • Neurological success • SF-36 • Patient satisfaction • Preservation of motion	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that L-ADR is as good or slightly better than lumbar fusion with respect to overall clinical success, functional improvement (ODI), pain reduction, neurological success, SF-36 improvement, and patient satisfaction two years following surgery • Motion at the index segment for L-ADR is maintained or improved compared with preoperative levels up to 3 years following surgery, and in two small studies, similar to asymptomatic controls >10 years following surgery • There are no long-term follow-up data assessing efficacy/effectiveness from the two index RCTs at this time	+	–	+
3. Other surgical procedures	**No evidence**	• There is no evidence from studies directly comparing L-ADR with surgical procedures other than lumbar fusion for degenerative disc disease	none	none	none
Key Question 2: What is the evidence related to the L-ADR safety profile (including device failure, reoperation)?					
1. Device failure	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that the frequency of device failure (reoperation, revision or removal of the implant) among patients receiving L-ADR (< 6%) is similar to device failure among those receiving lumbar fusion (≤ 8%) • There is insufficient data at this time to determine the longer term safety of L-ADR.	+	–	+
2. Complications or adverse events	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that L-ADR results in a similar proportion of device-related complications (7 to 18%) compared with lumbar fusion (4 to 20%) • There is moderate evidence that L-ADR results in a similar proportion of major complications (0 to 1%) compared with lumbar fusion (0 to 1%) • There are no long-term follow-up data assessing safety from the two index RCTs at this time	+	–	+

Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations?					
		Domain Criterion Quality: ≥80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Age	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that L-ADR may be effective in select patients (those with good bone quality and absent circumferential spinal stenosis) older than 60 years	–	–	–
2. Athletes	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that L-ADR may be effective in high level athletes in the short term among those who were athletic participants preoperatively	–	–	–
3. Smokers	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that smoking status may not affect the short term results of L-ADR	–	–	–
Study Question 4: What are the cost implications and cost effectiveness for ADR?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Hospital perspective	**Very low** (Any effect estimate is uncertain)	• There is very low evidence from 2 costing reports (partial economic studies) to suggest that mean L-ADR costs may be less than those for fusion from a hospital perspective for the index procedure	–	–	+
2. Payer perspective	**Very low** (Any effect estimate is uncertain)	• There is very low evidence from 1 costing report to suggest that L-ADR costs may be lower than any type of fusion based DRGs • There is very low evidence from the same report that incremental cost savings from L-ADR may depend on type of fusion using a per diem approach • The time horizon of 2 years may be too short to adequately assess downstream costs or benefits • Analyses from previous HTAs in other countries had conflicting results and suggest that type of fusion may influence cost evaluations	–	–	–

*Majority of characteristics for high quality, full economic studies, and modeling as described in Appendix B are met.

Table 27. Summary of overall strength of evidence for key questions pertaining to C-ADR

Key Question 1: Efficacy/effectiveness of C-ADR compared with nonoperative care, cervical fusion, other surgical procedures					
		Domain Criterion Quality: ≥ 80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
C-ADR versus:	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Nonoperative care	**No evidence**	• There is no evidence from studies directly comparing C-ADR with non-operative care for degenerative disc disease	none	none	none
2. Anterior fusion • Overall clinical success • NDI • Pain • Neurological success • SF-36 • Patient satisfaction • Preservation of motion	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that the proportion of patients achieving overall clinical success and neurological success at 24 months for C-ADR was significantly higher compared with patients receiving anterior cervical fusion (77% vs. 68% for clinical success, 92% vs. 86% for neurological success). This result is based on FDA criteria for overall success and pooled estimates from two completed trials and an interim FDA analysis of a 3rd trial. • Patients receiving either C-ADR or ACDF can expect reduced neck and arm pain following surgery compared with baseline pain status. There is no statistical difference between those receiving C-ADR and those receiving ACDF with respect to intensity or frequency of neck or arm pain • Improvement in disability (≥ 15 points over baseline in the NDI) was achieved by a similar proportion of patients receiving C-ADR and ACDF. • Segmental flexion-extension at the level of instrumentation was generally similar after C-ADR comparing preoperative motion with postoperative motion from 6–48 months following surgery. • The effect of C-ADR on adjacent segment disease remains unanswered. Studies with similar definitions of symptomatic adjacent segment disease with longer follow-up than two years will need to be conducted to answer this question. • There are no long-term follow-up data assessing efficacy/effectiveness from the 5 RCTs at this time	+	–	+
3. Other surgical procedures	**No evidence**	• There is no evidence from studies directly comparing C-ADR with surgical procedures other than cervical fusion for degenerative disc disease	none	none	none

Key Question 2: What is the evidence related to the C-ADR safety profile (including device failure, reoperation)?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Device failure	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence to suggest that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery. • Device failure defined as reoperation, revision or removal of the implant, was less common among C-ADR recipients (3%) than anterior fusion patients (9%) within the 24 month trial period. • There is insufficient data at this time to determine the longer term safety of C-ADR.	+	–	+
2. Complications or adverse events	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• Complication rates varied among the studies but generally device related or device/surgical procedure related complications or adverse events occurred less frequently among the C-ADR patients (5%) than anterior fusion patients (10%). • There are no long-term follow-up data assessing safety from the five index RCTs at this time	+	–	+
Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Special populations	**No evidence**	• There were no studies or sub-analyses found which describe the efficacy or safety in special populations	none	none	none
Study Question 4: What are the cost implications and cost effectiveness for ADR?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Economic analyses	**No Evidence**	• There were no formal economic analyses found in the peer-reviewed literature	none	none	none

*Majority of characteristics for high quality, full economic studies, and modeling as described in Appendix B are met.

APPENDIX A. Search Strategies

Database: MEDLINE
Search Strategy: lumbar spine

For Key Question 1

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(CHARITÉ OR PRODISC* OR MAVERICK OR FLEXICORE OR MOBIDISC)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Lumbar Vertebrae"[Mesh] OR Lumbar[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	LIMIT: RCT

For Key Questions 2, 3

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(CHARITÉ OR PRODISC* OR MAVERICK OR FLEXICORE OR MOBIDISC)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Lumbar Vertebrae"[Mesh] OR Lumbar[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	#7 NOT (cadaver* OR case report OR finite element OR in vitro)
9	#8 NOT “Review “[Publication Type]
10	#9 NOT RCT
11	Limit: items with abstracts
12	English AND Human

Search Strategy: cervical spine

For Key Question 1

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(PRODISC* OR PRESTIGE OR Bryan OR porous coated motion OR PCM) OR mobi-c OR Kineflex* OR CerviCore or Discover)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Cervical Vertebrae"[Mesh] OR CERVICAL[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	LIMIT: RCT

For Key Questions 2, 3

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(PRODISC* OR PRESTIGE OR Bryan OR porous coated motion OR PCM) OR mobi-c OR Kineflex* OR CerviCore or Discover)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Cervical Vertebrae"[Mesh] OR CERVICAL[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	#7 NOT (cadaver* OR case report OR finite element OR in vitro)
9	#8 NOT “Review “[Publication Type]
10	Limit: items with abstracts

Database: EMBASE
Search Strategy: lumbar spine

1	exp Intervertebral Disk Degeneration/ or degenerative disc disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	exp Spine Fusion/
3	exp intervertebral disk/ or exp lumbar disk/ or exp lumbar vertebra/ or exp vertebra/
4	exp Spine Disease/
5	exp Lumbar Spine/ or exp Cervical Spine/
6	exp Backache/
7	exp intervertebral diskectomy/
8	or/1-7
9	(dis$ adj1 (prosthe$ or artificial or replacement$ or arthrodesis or arthroplasty)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10	exp joint prosthesis/
11	exp bone prosthesis/
12	exp arthroplasty/
13	or/9-12
14	8 and 13
15	(sb Charité or Prodisc or (Maverick adj1 disc) or (bryan adj1 disc) or active-l).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16	14 or 15 (802)
17	limit 16 to (human and english language and yr="2003 - 2008")
18	limit 17 to (editorial or letter or note)
19	Case Report/
20	17 not (18 or 19)

Search Strategy: cervical spine

1	exp Intervertebral Disk Degeneration/ or degenerative disc disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	exp Spine Fusion/
3	exp intervertebral disk/ or exp cervical disk/ or exp cervical vertebra/ or exp vertebra/
4	exp Spine Disease/
5	exp Cervical Spine/
6	exp Neckache/
7	exp intervertebral diskectomy/
8	or/1-7
9	(dis$ adj1 (prosthe$ or artificial or replacement$ or arthrodesis or arthroplasty)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10	exp joint prosthesis/
11	exp bone prosthesis/

12	exp arthroplasty/
13	or/9-12
14	8 and 13
15	(sb Prestige or Prodisc or (bryan adj1 disc) or active-l).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16	14 or 15 (802)
17	limit 16 to (human and english language and yr="2003 - 2008")
18	limit 17 to (editorial or letter or note)
19	Case Report/
20	17 not (18 or 19)

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches
The following databases have been searched for relevant information:
Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews (through 2007, Issue 2)
Cochrane Registry of Clinical Trials (CENTRAL) (through 2007, Issue 2)
Cochrane Review Methodology Database (through 2007, Issue 2)
Computer Retrieval of Information on Scientific Projects (CRISP)
Database of Reviews of Effectiveness (Cochrane Library) (through 2007, Issue 2)
EMBASE (1985 through April 15, 2007)
PubMed (1975 through April 15, 2007)
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database (Cochrane Library through 2007, Issue 2)
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases
AHRQ- Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX B. Level of Evidence Determination

Methods for critical appraisal and level of evidence assessment

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine,[123] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[16] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[160] Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Procedures for determining adherence to level of evidence (LoE) criteria

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table. For therapeutic articles, the criteria are listed in the Table below and an example is given. All criteria met are marked. A blank for the criterion indicates that the criterion was not met, could not be determined or was not reported by the author.

Table B.1. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size
II	Moderate or Poor quality RCT	• Violation of any of the criteria for good quality RCT
	Good quality Cohort	• Blind or independent assessment in a prospective study or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size • Controlling for possible confounding†
III	Moderate or Poor quality Cohort	• Violation of any of the criteria for good quality cohort
	Case Control	
IV	Case Series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Table B.2. Example of methods evaluation for articles on therapy

Methodological Principle	Author 1	Author 2	Author 3	Author 4
Study design Randomized controlled trial Cohort Study Case-series	■	■	■	■
Statement of concealed allocation*	■	■		
Intention to treat*	■	■		
Independent or blind assessment	■		■	
Co-interventions applied equally	■	■	■	
Complete follow-up of ≥85%	■			■
Adequate sample size	■	■	■	
Controlling for possible confounding	■	■	■	
Evidence Level	**I**	**II**	**III**	**IV**

* Applies to randomized controlled trials only.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence for diagnostic studies are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ.[160]

The following definitions are used by SRI to determine whether or not the body of evidence meets the criteria for each domain:

Domain	Definition/Criterion
Quality	• At least 80% of the studies are LoE I or II
Quantity	• There are at least three studies which are adequately powered to answer the study question
Consistency	• Study results would lead to a similar conclusion (similar values, in the same direction) in at least 70% of the studies

Based on the criteria described above, the possible scenarios that would be encountered are described below. Each scenario is ranked according to the impact that future research is likely to have on both the overall estimates of an effect and the confidence in the estimate. This ranking describes the overall "Strength of Evidence" (SoE) for the body of literature on a specific topic. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group[16] for the development of clinical guidelines.

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[119] QHES embodies the primary components relevant for critical appraisal of economic studies.[36,119] It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention

comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (eg, complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (eg, were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:
- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument[119] **Study** _____

Questions	Points	Yes	No
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**		
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**		
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**		
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**		
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**		
6. Was incremental analysis performed between alternatives for resources and costs?	**6**		
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**		
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**		
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**		
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**		
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**		
16. Was there a statement disclosing the source of funding for the study?	**3**		
TOTAL POINTS	**100**		

APPENDIX C. Inclusion and Exclusion Criteria for the Index Randomized Controlled Trials Assessing ADR

Inclusion and Exclusion Criteria for the Two Index Randomized Controlled Trials Assessing L-ADR

Blumenthal et al (Charité L-ADR)

INCLUSION	EXCLUSION
• Male or female • Age 18 to 60 years • Symptomatic degenerative disc disease with objective evidence of lumbar DDD by CT or MR scan, followed by discogram • Single level disease at L4-L5 or L5-SI • Minimum of 6 months of unsuccessful conservative treatment • Oswestry Low Back Pain Disability Questionnaire ≥30 points • Patient a surgical candidate for an anterior approach to the lumbar spine (<3 abdominal surgeries) • Back pain at the operative level only (by discogram) • Leg pain and/or back pain in the absence of nerve root compression, per MRI or CT scan, without prolapse or narrowing of the lateral recess. • VAS ≥40mm • Able to comply with protocol • Informed consent • DDD is defined as discogenic back pain with degeneration of the disc as confirmed by history and radiographic studies with one or more of the following factors: • Contained herniated nucleus pulposus • Facet joint degeneration/changes • Decreased disc height by >2mm, and/or • Scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule	• Previous or other spinal surgery at any level, except prior discectomy, laminotomy, laminectomy, or nucleolysis at the same level • Multiple level degeneration • Previous trauma to the L4, L5, or S1 levels in compression or burst • Non-contained or extruded herniated nucleus pulposus • Mid-sagittal stenosis of <8mm (by CT or MR) • Spondylolisthesis >3mm • Lumbar scoliosis (>11° sagittal plane deformity) • Spinal tumor • Active systemic or surgical site infection • Facet joint arthrosis • Arachnoiditis • Isthmic spondylolisthesis • Chronic steroid use • Metal allergy • Pregnancy • Autoimmune disorders • Psychosocial disorders • Morbid obesity (BMI >40) • Bone growth stimulator use in spine • Investigational drug or device use within 30 days • Osteoporosis or osteopenia or metabolic bone disease • Positive single or bilateral straight leg raising test

Zigler et al (Prodisc-L ADR)

INCLUSION	EXCLUSION
• Degenerative Disc Disease (DDD) in one vertebral level between L3 and S1. Diagnosis of DDD requires back and/or leg (radicular pain); and radiographic confirmation of any 1 of the following by CT, MRI, discography, plain film, myelography and/or flexion/extension films: o Instability (≥ 3mm translation or ≥ 5° angulation); o Decreased disc height > 2mm; o Scarring/thickening of annulus fibrosis; o Herniated nucleus pulposus; or o Vacuum phenomenon • Age between 18 and 60 years • Failed at least 6 months of conservative treatment • Oswestry Low Back Pain Disability Questionnaire score of at least 20/50 (40%) (Interpreted as moderate/severe disability) • Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements and filling out of forms • Signed informed consent	• No more than 1 vertebral level may have DDD, and all diseased levels must be treated • Patients with involved vertebral endplates dimensionally smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions • Known allergy to titanium, polyethylene, cobalt, chromium or molybdenum • Prior fusion surgery at any vertebral level • Clinically compromised vertebral bodies at the affected level due to current or past trauma • Radiographic confirmation of facet joint disease or degeneration • Lytic spondylolisthesis or spinal stenosis • Degenerative spondylolisthesis of grade > 1 • Back or leg pain of unknown etiology • Osteopenia or osteoporosis: A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients to determine if a DEXA scan is required. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score < -2.5. • Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis which is addressed above) • Morbid obesity defined as a body mass index > 40 or a weight more than 100 lbs. over ideal body weight • Pregnant or interested in becoming pregnant in the next 3 years • Active infection – systemic or local • Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids) • Rheumatoid arthritis or other autoimmune disease • Systemic disease including AIDS, HIV, Hepatitis • Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years

Inclusion and Exclusion Criteria for the Five Index Randomized Controlled Trials Assessing C-ADR

Bryan Panel meeting (Bryan C-ADR)

INCLUSION	EXCLUSION
• DDD at single level between C3 and C7 • Disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy • 6 weeks minimum unsuccessful conservative unless myelopathy requiring immediate treatment • CT, myelography and CT, and/or MRI demonstration of need for surgical treatment • ≥21 years old • Preoperative NDI ≥ 30 and minimum one clinical sign associated with level to be treated • Willing to sign informed consent and comply with protocol	• Significant cervical anatomical deformity • Moderate to advanced spondylosis • Any combination of bridging osteophytes, marked reduction or absence of motion • Collapse of intervertebral disc space of > 50% normal height, radiographic signs of subluxation > 3.5 mm, angulation of disc space > 11° greater than adjacent segments, significant kyphotic deformity or reversal or lordosis • Axial neck pain as solitary symptom • Previous cervical spine surgery • Metabolic bone disease • Active systemic infection or infection at operative site • Known allergy to components of titanium, polyurethane, ethylene oxide residuals • Concomitant conditions requiring steroid treatment • Daily insulin management • Extreme obesity • Medical condition which may interfere with postop management program or may result in death prior to study completion • Pregnancy • Current or recent alcohol and/or drug abuser • Signs of being geographically unstable

Mummaneni et al (Prestige C-ADR)

INCLUSION	EXCLUSION
• adults >18 years of age • single level symptomatic DDD between C3-7 • intractable radiculopathy, myelopathy or both • NDI scores ≥ 30 • VAS neck pain scores ≥ 20 • preserved motion at the symptomatic level found in all included patients • unresponsive to ≥ 6 weeks conservative treatment or progressive neurological worsening despite conservative treatment • no previous procedures at the operative level • negative for several radiographic findings, medications, and diagnoses	• multilevel symptomatic DDD or evidence of cervical instability • sagittal plane translation of greater than 3.5 mm or sagittal plane angulation of greater than 20 degrees at a single level • symptomatic C2-C3 or C7-T1 disc disease • previous surgery at the involved level • severe facet joint disease at the involved level • history of discitis • osteoporosis • metastases • medical condition that required long-term use of medication such as steroid or nonsteroidal antiinflammatory drugs that could affect bone quality and fusion rates

Nabhan et al (Prodisc C-ADR)

INCLUSION	EXCLUSION
• monosegmental cervical DDD between C3-C7 • unresponsive to conservative treatment or presence of signs of nerve root compression with paresis • soft disc herniation • no myelopathy • age between 20-60 years • negative for specific radiographic findings, medications, and diagnoses • signed informed consent	• marked cervical instability on resting or flexion-extension radiographs • >11 of angulations • translation >3 mm • more than one level pathology • myelopathy • radiographic confirmation of severe facet joint degeneration • hard disc disease • osteoporosis, infection, rheumatiod arthritis • spondylodiscitis and active infection • malignant disease • system disease, eg hepatitis, HIV, AIDS • known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • traumatic injury of spine • pregnant or possible pregnancy in the next 3 years

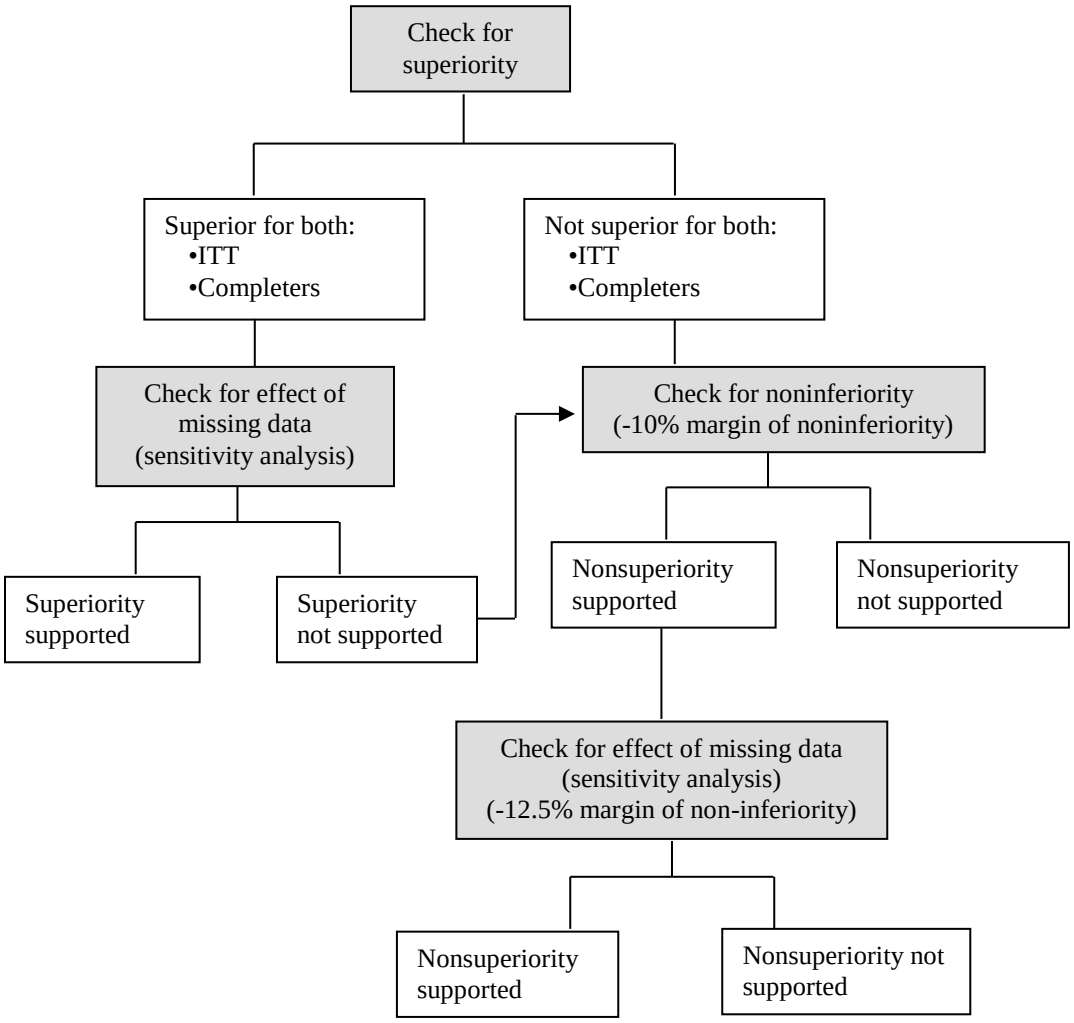
Sun Peng-Fei et al (C-ADR)

INCLUSION	EXCLUSION
• single C5-6 intervertebral disc hernia • failed conservative treatment w/ worsening symptoms	• NR

Prodisc C FDA (Prodisc C-ADR)

INCLUSION	EXCLUSION
• Symptomatic cervical disc disease (SCDD) in one level between C3-C7 • Age 18-60 years • Unresponsive to nonoperative treatment for six weeks or progressive symptoms • NDI ≥ 15/50 (30%) • Able to comply with protocol • Informed consent	• More than one vertebral level requiring treatment • Marked cervical instability ; translation > 3 mm or > 11° rotational difference • Fused level adjacent to level to be treated • Radiographically confirmed severe facet joint disease or degeneration • Allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • Clinically compromised vertebral bodies at affected level due to trauma • Prior surgery at level to be treated • Severe spondylosis at level to be treated • Neck or arm pain of unknown etiology • Osteoporosis • Metabolic bone disease • Daily insulin management • Pregnancy • Active infection, systemic or local • Medications or drug known to potentially interfere with healing (steroids) • Autoimmune disease including RA • Systemic disease including AIDS, HIV, hepatitis • Active malignancy within last 5 years

APPENDIX D. Decision Tree in Assessing Results for Clinical Success



APPENDIX E. Data Used for ADR Meta-Analysis

Spectrum Research, Inc. uses the statistical program STATA for meta-analysis. The following tables list the data used for meta-analyses.

LUMBAR ADR

1) Overall success at 24 months

1.1) Using baseline sample size as reference (ITT analysis)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	107	98	99	44	55
2	Zigler	161	79	82	75	29	46

1.2) Using completers only

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	184	107	77	81	44	37
2	Zigler	148	79	69	71	29	42

2) ODI success at 24 months

2.1) Using baseline sample size as reference (ITT analysis)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	117	88	99	47	52
2	Zigler	161	101	60	75	39	36

2.1) Using data for completers only

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	184	117	67	81	47	34
2	Zigler	149	101	48	71	39	32

3) Device Success at 24 months (relative to baseline sample size, ITT analysis only)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	194	11	99	91	8
2	Zigler	161	155	6	75	73	2

4) Neurological success at 24 months (relative to baseline sample size, ITT analysis only)

4.1) Using baseline sample size as reference

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	169	36	99	78	21
2	Zigler	161	135	26	75	57	18

CERVICAL ADR

1) Overall Clinical Success (FDA ≥ 15 point) at 24 months –

1.1) Using the baseline sample size as reference for ITT analysis.

	studname	ADR succ	ADR fail	ACDF succ	ACDF fail
1.	Mummaneni	177	99	134	131
5.	Bryan FDA report	129	.	99	.
6.	Prodisc-C FDA report	73	30	69	37

1.2) Using the sample size at 24 months follow-up as reference.**- completers**

Clinical outcome using the sample size at 24 months follow-up as reference. 101 = n for ACDF

	studname	ADR succ	ADR fail	ACDF succ	ACDF fail
1.	Mummaneni	177	46	134	64
2.	Prodisc-C FDA report	73	28	69	32
3.	Bryan FDA report	129	31	99	41

2) NDI success (FDA ≥ 15 point) at 24 months of follow-up

2.1) Data used for the meta analysis are shown in the next two tables. – ITT analysis uses baseline N and "completer" analysis uses 24 month N

Table for ADR

	studnum	studname	base N	24mo N	Succ24	Fail24 (base N)	Fail24 (24mo N)
1.	1	Mummaneni	276	223	185	91	38
2.	6	Prodisc FDA report	103	99	79	24	20
3.	5	Bryan FDA report	242	160	134	.	26

Table for ACDF

	studnum	studname	base N	24mo N	Succ24	Fail24 (base N)	Fail24 (24mo N)
1.	1	Mummaneni	265	198	159	106	39
2.	6	Prodisc FDA report	106	92	72	34	20
3.	5	Bryan FDA report	221	140	106	.	34

3) Neurological Success-

3.1) ITT analysis

Table for ADR group

	studnum	studname	ADRbaseN	ADR_ne~e	ADR_ne~s
1.	1	Mummaneni	276	69	207
3.	6	Prodisc FDA report	103	13	90

Table for ACDF Group

	studnum	studname	ACDFba~N	ACDF_n~e	ACDF_n~s
1.	1	Mummaneni	265	98	167
3.	6	Prodisc FDA report	106	25	81

3.2) Completer analysis

Table for ADR group

	studnum	studname	N at 24mo	Failures	Successes
1.	1	Mummaneni	223	16	207
2.	5	Bryan FDA report	160	10	150
3.	6	Prodisc FDA report	99	9	90

Table for ACDF

	studnum	studname	N at 24mo	Failures	Successes
1.	1	Mummaneni	198	31	167
2.	5	Bryan FDA report	140	12	128
3.	6	Prodisc FDA report	92	11	81

4) Device Success-

4.1) ITT analysis

Table for ADR – ITT analysis

	stu~m	studname	ADR..	ADR..
1.	1	Mummaneni	267	9
2.	6	Prodisc FDA report	101	2

Table for ACDF – ITT analysis

	stu~m	studname	ACD..	ACD..
1.	1	Mummaneni	241	24
2.	6	Prodisc FDA report	97	9

APPENDIX F. A List of Adverse Events/Complications Given for the Randomized Controlled Studies

Adverse events comparing the Charité L-ADR with lumbar spinal fusion*

Adverse event	L-ADR (n = 205) No. (%)	Spinal fusion (n = 99) No. (%)
Adverse events irrespective of relationship to treatment		
Any	156 (76.1)	77 (77.8)
Severe or life-threatening	30 (14.6)	9 (9.1)
Adverse events related to treatment		
Device-related	15 (7.3)	4 (4.0)
Device failures	10 (4.9)	8 (8.1)
Adverse events irrespective of relationship to treatment		
Pain (back or lower extremity)	107 (52.2)	52 (52.5)
Pain (other)	27 (13.2)	9 (9.1)
Neurological	34 (16.6)	17 (17.2)
Infection	25 (12.2)	6 (6.1)
Approach problems (abdominal)	18 (8.8)	8 (8.1)
DDD progression, natural history	6 (2.9)	4 (4.0)
Additional surgery, index level	10 (4.9)	8 (8.1)
Intraoperative complications	2 (1.0)	3 (3.0)
Abnormal bone formation	2 (1.0)	0 (0.0)
Severe or life-threatening adverse events irrespective of relationship to treatment		
Pain (back or lower extremity)	10 (4.9)	5 (5.1)
Other	11 (5.4)	3 (3.0)
Other, cardiovascular	0 (0.0)	1 (1.0)
Infection	3 (1.5)	2 (2.0)
Additional surgery, index level, removal	4 (2.0)	0 (0.0)
Additional surgery, index level, delayed fusion	1 (0.5)	0 (0.0)
Additional surgery, index level, reoperation	1 (0.5)	0 (0.0)
Approach problems (abdominal)	2 (2.0)	1 (1.0)
Approach problems (hernia)	1 (0.5)	0 (0.0)
Approach problems (retrograde ejaculation)	1 (0.5)	1 (1.0)
Additional surgery, unrelated to index level	1 (0.5)	1 (1.0)
Neurological (nerve root injury)	1 (0.5)	0 (0.0)
Device failures		
Reoperation	0 (0.0)	1 (1.0)
Revision	0 (0.0)	1 (1.0)
Removal	2 (1.0)	0 (0.0)
Supplemental fixation	8 (3.9)	6 (6.1)

*From the FDA Clinical Review Report, P040006.

Adverse events comparing the Prodisc-L ADR with lumbar spinal fusion*

Adverse event	L-ADR (n = 162) No. (%)	Spinal fusion (n = 80) No. (%)
All adverse event	136 (84.0)	70 (87.5)
Anemia	6 (3.7)	2 (2.5)
Burning or dysesthetic pain	8 (4.9)	3 (3.8)
Cardiovascular	2 (1.2)	5 (6.3)
Significant blood loss (> 1500 cc)	0 (0.0)	2 (2.5)
Degenerative Disease progression, other lumbar	9 (5.6)	0 (0.0)
Dermatological	6 (3.7)	2 (2.5)
Dermatological drug allergy	2 (1.2)	0 (0.0)
Dizziness	4 (2.5)	3 (3.8)
Drug allergy	2 (1.2)	1 (1.3)
Dural tear	0 (0.0)	2 (2.5)
Edema	8 (4.9)	3 (3.8)
Fever	10 (6.2)	10 (12.5)
Fracture (nonvertebral)	2 (1.2)	0 (0.0)
Gastrointestinal	32 (19.8)	22 (27.5)
Genitourinary	14 (8.6)	4 (5.0)
Headache	11 (6.8)	5 (6.3)
Herniated Nucleus Pulposus	1 (0.6)	0 (0.0)
Incontinence	3 (1.9)	4 (5.0)
Infection (nonwound related)	5 (3.1)	5 (6.3)
Infection (superficial wound with incision site pain)	0 (0.0)	2 (2.5)
Infection (UTI)	0 (0.0)	1 (1.3)
Insomnia	8 (4.9)	4 (5.0)
Migration not requiring surgery	3 (1.9)	1 (1.3)
Migration requiring surgery	4 (2.5)	0 (0.0)
Motor deficit/index level	4 (2.5)	0 (0.0)
Musculoskeletal spasm, back	1 (0.6)	2 (2.5)
Musculoskeletal spasm, back and leg	0 (0.0)	0 (0.0)
Musculoskeletal spasm, leg	2 (1.2)	0 (0.0)
Narcotic use	2 (1.2)	1 (1.3)
Nerve root injury	1 (0.6)	0 (0.0)
Non-specific musculoskeletal spasms	6 (3.7)	1 (1.3)
Numbness index level related	0 (0.0)	1 (1.3)
Numbness peripheral nerve or nonindex level related	17 (10.5)	5 (6.34)
Other musculoskeletal	21 (13.0)	13 (16.3)
Other	11 (6.8)	8 (10.0)
Pain, back	55 (34.0)	27 (33.8)
Pain, back and lower extremities	29 (17.9)	10 (12.5)
Pain, back and lower extremities with burning	3 (1.9)	0 (0.0)
Pain, back and lower extremities with numbness at index	4 (2.5)	4 (5.0)
Pain, back and other	8 (4.9)	5 (6.3)
Pain, groin area	5 (3.1)	0 (0.0)
Pain, incision site	2 (1.2)	6 (7.5)
Pain, lower extremities	32 (19.8)	16 (20.0)
Pain, lower extremities with numbness at index level	3 (1.9)	1 (1.3)
Pain other (not back/hip/leg)	25 (15.4)	12 (15.0)

Pruritus	8 (4.9)	4 (5.0)
Psychological	19 (11.7)	6 (7.5)
Pulmonary infection	0 (0.0)	1 (1.3)
Radiolucency, graft	0 (0.0)	1 (1.3)
Reflex change	1 (0.6)	0 (0.0)
Respiratory	4 (2.5)	0 (0.0)
Retrograde ejaculation	2 (1.2)	1 (1.3)
Subsidence not requiring surgery	2 (1.2)	1 (1.3)
Subsidence requiring surgery	0 (0.0)	0 (0.0)
Surgery, adjacent level	2 (1.2)	1 (1.3)
Surgery, index level (revision)	1 (0.6)	4 (5.0)
Surgery, index level (supplemental fixation)	1 (0.6)	0 (0.0)
Surgery, other	7 (4.3)	3 (3.8)
Thrombosis	0 (0.0)	0 (0.0)
Thrombosis (DVT leg)	2 (1.2)	1 (1.3)
Vessel damage/bleeding, major	1 (0.6)	1 (1.3)
Vessel damage/bleeding, minor	4 (2.5)	5 (6.3)
Wound issues, other	5 (3.1)	7 (8.8)
All device related adverse events	29 (17.9)	16 (20.0)
Pain, back	8 (4.9)	5 (6.3)
Pain, back and lower extremities	6 (3.7)	2 (2.5)
Numbness peripheral nerve or non index level related	4 (2.5)	0 (0.0)
Edema	2 (1.2)	0 (0.0)
Other musculoskeletal	2 (1.2)	3 (3.8)
Degenerative Disease progression, other lumbar	3 (1.9)	0 (0.0)
Burning or dysesthetic pain	1 (0.6)	0 (0.0)
Fracture (non-vertebral)	1 (0.6)	0 (0.0)
Herniated Nucleus Pulposus	1 (0.6)	0 (0.0)
Motor deficit in index level	1 (0.6)	0 (0.0)
Pain, back and lower extremities with burning	1 (0.6)	0 (0.0)
Pain, back and lower extremities with numbness at index level	1 (0.6)	1 (1.3)
Pain, lower extremities with numbness at index level	1 (0.6)	0 (0.0)
Musculoskeletal spasms, back	0 (0.0)	1 (1.3)
Nerve root injury	0 (0.0)	0 (0.0)
Pain other (not back/hip/leg)	0 (0.0)	1 (1.3)
Radiolucency (graft)	0 (0.0)	1 (1.3)
Headache	0 (0.0)	1 (1.3)
Cardiovascular	0 (0.0)	2 (2.5)
Gastrointestinal	0 (0.0)	1 (1.3)
Pruritus	0 (0.0)	1 (1.3)
Other	0 (0.0)	1 (1.3)
Subsidence	2 (1.2)	1 (1.3)
Migration requiring surgery	4 (2.5)	0 (0.0)
Migration not requiring surgery	3 (1.9)	1 (1.3)
Surgery, index level (supplemental fixation)	1 (0.6)	0 (0.0)
Surgery, index level (revision)	1 (0.6)	4 (5.0)

*From the FDA SSED, P050010.

Adverse events comparing the Bryan C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 242) No. (%)	Spinal fusion (n = 221) No. (%)
All adverse events	202 (83.5)	174 (78.7)
Anatomical/technical difficulty	0 (0.0)	1 (0.5)
Cancer	2 (0.8)	0 (0.0)
Cardiovascular	4 (1.7)	2 (0.9)
Carpal tunnel syndrome	12 (5.0)	4 (1.8)
Death	0 (0.0)	1 (0.5)
Dysphagia/dysphonia	26 (10.7)	19 (8.6)
Gastrointestinal	9 (3.7)	6 (2.7)
Infection	17 (7.0)	10 (4.5)
Malpositioned implant	2 (0.8)	0 (0.0)
Neck or arm pain	115 (47.5)	96 (43.4)
Neurological	48 (19.8)	46 (20.8)
Nonunion	0 (0.0)	5 (2.3)
Other	59 (24.4)	39 (17.6)
Other pain	49 (20.2)	44 (19.9)
Pending nonunion	0 (0.0)	5 (2.3)
Respiratory	4 (1.7)	6 (2.7)
Spinal event	21 (8.7)	20 (9.0)
Trauma	34 (14.0)	22 (10.0)
Urogenital	6 (2.5)	3 (1.4)
Vascular intra-op	2 (0.8)	3 (1.4)
Subsequent surgical interventions†	6 (2.5)	9 (4.1)

*As reported in the FDA Executive Summary, P060023 based on full study population.
†For purposes of revision, removal, reoperation, or supplemental fixation.

Adverse events comparing the Prestige C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 276) No. (%)	Spinal fusion (n = 265) No. (%)
All perioperative adverse events	17 (6.2)	11 (4.2)
Neurological (numbness, paresthesia, back and leg, paresthesia/pain in arm, Lhermitte phenomenon)	4 (1.4)	1 (0.4)
Pain (bursitis, headaches, neck and/or arm pain)	3 (1.1)	2 (0.8)
Venous bleeding	1 (0.4)	0 (0.0)
Infections (UTI and sinusitis)	2 (0.7)	0 (0.0)
CSF leaks	0 (0.0)	2 (0.8)
Spinal fluid leak	1 (0.4)	0 (0.0)
Respiratory (sleep apnea)	1 (0.4)	0 (0.0)
Dysphagia/dysphonia	2 (0.7)	3 (1.1)
Anatomical/technical (screw fixation) difficulty	1 (0.4)	0 (0.0)
Hematoma	2 (0.7)	0 (0.0)
Low bone density	1 (0.4)	0 (0.0)
Nausea	0 (0.0)	1 (0.4)
Vomiting	0 (0.0)	1 (0.4)
Device failure		
Revisions	0 (0.0)	5 (1.9)
Hardware removals	5 (1.8)	9 (3.4)
Supplemental fixations	0 (0.0)	8 (3.4)

*Data from Mummaneni et al report.

Adverse events comparing Prodisc C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 25) No. (%)	Spinal fusion (n = 24) No. (%)
Mortality during surgery	1 (4.0)	0 (0.0)

*Data from Nabhan et al report.

Adverse events comparing C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 12) No. (%)	Spinal fusion (n = 12) No. (%)
All adverse event	0 (0.0)	0 (0.0)

*Data from Sun Peng-Fei report, Bryan disc used.

Adverse events comparing the Prodisc C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 103) No. (%)	Spinal fusion (n = 106) No. (%)
All adverse events	84 (81.6)	86 (81.1)
Adjacent level DDD or DJD	0 (0.0)	4 (3.8)
Burning or dysesthetic pain	1 (1.0)	0 (0.0)
Cancer	1 (1.0)	0 (0.0)
Cardiovascular	5 (4.9)	7 (6.6)
DDD progression, non-cervical	1 (1.0)	1 (0.9)
Dermatological	1 (1.0)	1 (0.9)
Dizziness	1 (1.0)	0 (0.0)
Dural tear	1 (1.0)	0 (0.0)
Dysphagia	6 (5.8)	9 (8.5)
Dysphonia	0 (0.0)	1 (0.9)
Edema	2 (1.9)	1 (0.9)
Fatigue	1 (1.0)	0 (0.0)
Fracture, vertebral	0 (0.0)	1 (0.9)
Gastrointestinal	16 (15.5)	15 (14.2)
Genitourinary	5 (4.9)	3 (2.8)
Headache	18 (17.5)	12 (11.3)
Infection, non-wound	2 (1.9)	6 (5.7)
Infection, superficial wound	0 (0.0)	1 (0.9)
Insomnia	6 (5.8)	3 (2.8)
Musculoskeletal	18 (17.5)	16 (15.1)
Musculoskeletal, back spasms	1 (1.0)	1 (0.9)
Musculoskeletal, neck spasms	3 (2.9)	5 (4.7)
Musculoskeletal, non-specific	3 (2.9)	4 (3.8)
Narcotics use	1 (1.0)	0 (0.0)
Neurological	4 (3.9)	1 (0.9)
Numbness, index level	0 (0.0)	2 (1.9)

Numbness, nonindex level	11 (10.7)	7 (6.6)
Ossification	1 (1.0)	0 (0.0)
Other	4 (3.9)	6 (5.7)
Pain, back	11 (10.7)	8 (7.5)
Pain, back and lower extremities	4 (3.9)	2 (1.9)
Pain, incision site	1 (1.0)	1 (0.9)
Pain, neck	16 (15.5)	22 (20.8)
Pain, neck and other	1 (1.0)	0 (0.0)
Pain, neck and shoulder	7 (6.8)	6 (5.7)
Pain, neck and upper extremities	3 (2.9)	6 (5.7)
Pain, neck and upper extremities with numbness	6 (5.8)	6 (5.7)
Pain, other	5 (4.9)	7 (6.6)
Pain, shoulder	9 (8.7)	9 (8.5)
Pain, upper extremities	8 (7.8)	5 (4.7)
Pain, upper extremities with numbness	4 (3.9)	5 (4.7)
Pseudoarthrosis	0 (0.0)	2 (1.9)
Psychological	4 (3.9)	5 (4.7)
Pulmonary infection	1 (1.0)	0 (0.0)
Puritis	0 (0.0)	2 (1.9)
Reflex change	1 (1.0)	0 (0.0)
Respiratory	4 (3.9)	3 (2.8)
Seizures	0 (0.0)	2 (1.9)
Sore throat	1 (1.0)	1 (0.9)
Surgery, index level	2 (1.9)	10 (9.4)
Surgery, other	12 (11.7)	21 (19.8)
Wound issues, other	3 (2.9)	2 (1.9)
All implant related adverse events	2 (1.9)	7 (6.6)
Dysphagia	0 (0.0)	1 (0.9)
Infection (superficial wound)	0 (0.0)	1 (0.9)
Musculoskeletal	0 (0.0)	1 (0.9)
Pain (neck)	0 (0.0)	1 (0.9)
Surgery (index level)	2 (1.9)	5 (4.7)
All surgery related adverse events	11 (10.7)	16 (15.1)
DDD progression (other cervical)	0 (0.0)	1 (0.9)
Dural tear	1 (1.0)	0 (0.0)
Dysphagia	2 (1.9)	4 (3.8)
Edema	1 (1.0)	0 (0.0)
Gastrointestinal	6 (5.8)	4 (3.8)
Genitourinary	1 (1.0)	0 (0.0)
Pain (back)	1 (1.0)	0 (0.0)
Pain (neck)	0 (0.0)	1 (0.9)
Pain (neck and upper extremities)	0 (0.0)	2 (1.9)
Pain (upper extremities)	2 (1.9)	0 (0.0)
Pseudoarthrosis	0 (0.0)	2 (1.9)
Surgery (index level)	0 (0.0)	2 (1.9)
Wound issues (other)	0 (0.0)	2 (1.9)
All severe or life-threatening adverse events	16 (15.5)	32 (30.2)
Cardiovascular	0 (0.0)	1 (0.9)
Dermatological	1 (1.0)	0 (0.0)
Dural tear	1 (1.0)	0 (0.0)
Gastrointestinal	0 (0.0)	1 (0.9)
Infection (non-wound)	0 (0.0)	1 (0.9)
Infection (superficial wound)	0 (0.0)	1 (0.9)

Other	0 (0.0)	1 (0.9)
Surgery (index level)	2 (1.9)	10 (9.4)
Surgery (other)	13 (12.6)	21 (19.8

*Data from the FDA Summary of Safety and Effectiveness Data, P-070001 .

APPENDIX G. Evidence Tables: Demographics, Study Design, and Characteristics of Included Studies for ADR

Table G1. Demographics and characteristics of included RCTs for L-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Blumenthal (2005) ‡ McAfee (2005) ‡ Geisler (2004) ‡ Statistical Review for Expedited PMA (2004) ‡ Summary of Safety and Effectiveness (2004) ‡	RCT (II) • assignment via central computer • 2:1 allocation • noninferiority • multicenter prospective cohort (II)	N = 304 n = 205 (ADR) n = 99 (fusion) male %: 51.6 mean age: years (sd) ADR: 39.6 (8.2) fusion: 39.6 (9.1)	duration: 24 months *24 months* including out of window: F/U % : 82.2 (250/304) § ADR: 85.9 (176/205) fusion: 74.7 (74/99) per protocol: F/U %: 74.7 (227/304) ADR: 78.5 (161/205) fusion: 66.7 (66/99) *12 months* F/U%: 87.2 (265/304) ADR: 89.8 (184/205) fusion: 81.8 (81/99)	• age 18-60 years • symptomatic DDD confirmed by discogram • single level L4-5 (n = 61) or L5-S1 (n = 144) • ODI ≥ 30 • VAS pain ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive list of medications and diagnoses • able to comply • informed consent	• prior fusion • current or prior fracture L4, L5 or S1 • other spinal surgery at the affected level • symptomatic multilevel degeneration • allergies • noncontained herniation • facet disease • spondylosis • spondylolisthesis > 3 mm or midsagittal stenosis > 8 mm • scoliosis > 11° • osteoporosis or osteopenia • positive straight leg raise or established nerve root compression • additional diagnoses: spinal tumor, metabolic bone disease, infection, psychosocial disorder, morbid obesity, arachnoiditis, autoimmune	• Charite artificial disc via the anterior retroperitoneal approach • ALIF with BAK cages at 1 or 2 contiguous levels	• binary clinical success score based on meeting four criteria • pain using VAS • narcotic use • function using ODI • QoL using SF-36 • neurological status • radiological evaluation • satisfaction questionnaire • work status • complications • intraoperative parameters	• industry funds received to support work • 1 or more authors has or will receive benefits from commercial party related to the subject of the manuscript

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					disease, pregnancy • additional perscriptions: chronic steroids, bone growth stimulator • participation in another study			
Zigler (2007)	RCT (II) • randomization held by sponsor until individual enrolled • 2:1 allocation • noninferiority • multicenter	N = 236 (paper) n = 161 (ADR) n = 75 (fusion) male %: 49.2 mean age: years (sd) ADR: 40.4 (7.6) fusion: 38.7 (8.0) FDA report N = 292 n = 162 (ADR) n = 80 (fusion) n = 50 (nonrandomized ADR) male %: 50 mean age: years (sd) ADR: 39.6 (8.0) fusion: 40.2 (7.6)	duration : 24 months F/U % : 98.2%** ADR : 98.6% (159/161) fusion : 97.1% (73/75) with complete data (paper) : ADR : 91% (147/161) fusion : 88.5% (66/75) FDA report : ADR : 91% (148/162) fusion : 88.5% (71/80)	• age 18-60 years • symptomatic DDD confirmed by any of several radiographic confirmations • single level L3-S1 • ODI ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive list of diagnoses • able to comply • informed consent	• prior fusion • no DDD > 1 • allergies • small endplates • compromised vertebral bodies • facet disease • lytic spondylolisthesis or spinal stenosis • osteoporosis • back or leg pain of unknown etiology • metabolic bone disease (long list)	• Prodisc-L total disc replacemen per IDE No. G010133 • circumferential fusion	• binary clinical success score based on meeting 10 primary endpoints • 1.function using ODI • 2.QoL using SF-36 • 3. neurologic exam • 4. “device success” • 5-10. radiographic endpoints • pain using VAS • narcotic use • satisfaction using VAS • would have again • work status • recreation status • complications • intraoperative parameters	• no industry funds received to support work • 1 or more authors has or will receive benefits from commercial party related to the subject of the manuscript

BMI = body mass index.
DDD = degenerative disc disease.
ODI = Oswestry Disability Index.
NR = not reported.
QoL = quality of life.

VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡These three published studies and two FDA reports all refer to a single RCT. Blumenthal was used for most information included in the assessments, except for neurological outcomes and one subgroup analysis.
§These percentages include all individuals followed-up at ≥ 24 months, including 15 in ADR group and 8 in control group evaluated after the window specified in the protocol.
**Percentage that followed-up at 24 months for which complete data are available is less; ADR: 91% and fusion: 88.5%.

Table G2. Demographics and characteristics of included nonrandomized studies for L-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Bertagnoli (2006)	prospective cohort (III) multicenter	N = 22 male%: 41 age: 63 years (61-71)	mean F/U: 2.9 years (1-4.7) F/U %: NR	• DDD (n = 19) or failed disc surgery syndrome (n = 3) • discogenic LBP with or without radiculopathy	• Prodisc II ADR • number of levels monolevel: n = 17 bilevel: n = 4 trilevel: n = 3	• ODI • VAS for back pain • patient satisfaction • general back pain • radicular pain • medication usage • complications • radiography: disc heights of affected and adjacent levels, disc motion, subsidence	• NA
Bertagnoli (2006)	case-series (IV)	N = 110 male%: NR ‡mean age: smokers: 45 years (30-60) nonsmokers: 49 years (29-60)	duration of F/U: 24 months mean F/U: smokers: 33 months (24-49) nonsmokers: 34 months (24-47) F/U %: 94.5	• age 18-60 years • disabling discogenic back pain • minimal radicular pain • failed ≥ 9 months conservative treatment • no spinal stenosis, osteoporosis, chronic infections, metal allergies, facet arthrosis, neuromuscular disease, pregnancy, Worker's Compensation, litigation, isthmic or degenerative spondylolisthesis greater than Grade 1 • BMI < or = 35 • adequate vertebral endplate size	• ADR with Prodisc • number of levels monolevel: all • spinal segments L3-4: n = 7 L4-5: n = 17 L5-S1: n = 76 L5-6: n = 5	• ODI • VAS • patient satisfaction • general back pain • radicular pain • medication use • several radiological outcomes (not ROM or segmental disease) • complications	• smokers v. nonsmokers
Cakir (2005)	case-series (IV) Germany	N = 29 male %: 34 mean age ± sd: 40.8 years ± 6.4 (29-56)	mean F/U: 15.3 months (12-35) F/U%: 100	• symptomatic DDD (n = 21) or postdiscectomy syndrome (n = 8) • low back pain ≥ 12 months • failed ≥ 6 months conservative treatment	• Prodisc ADR via retroperitoneal approach using a pararectal incision for level L3-4 and L4-5 or a horizontal incision for level L5-S1 • number of levels:	• ODI • SF-36 • evaluation of the segmental lordosis at the operated level and the total lumbar lordosis using standard Cobb	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
					monosegmental: all	measurements before and after surgery • segmental/lumbar lordosis classified as: insufficient (< 16°/< 41°); normative (16°-30°/41°-75°); excessive (> 30°/> 75°)	
Caspi (2003)	case-series (IV) Israel	N = 20 male %: 55 age range: 24–50 years	duration of F/U: 48 months F/U %: NR	• low back pain with or without radicular pain • mean duration of disease = 5 years	• Charite SB III ADR via anterior retroperitoneal approach • number of levels: monolevel: n = 17 bilevel: n = 3	• clinical results rated as poor, fair, good, or excellent • return to work • radiological assessment	• NA
Chung (2006)	retrospective cohort (III) Seoul, Korea	N = 26 male %: 44 mean age: 44.2 years (30-57)	mean F/U: 30 months (24-36) F/U %: 100	• age 18-60 years • symptomatic DDD confirmed by any of several radiographic criteria • no radicular leg pain or claudication • primary complaint of back pain • disc height ≥ 4mm • ODI ≥ 40 • failed ≥ 6 months conservative treatment	• ADR with Prodisc • number of levels monolevel: n = 19 bilevel: n = 7 • spinal segment L3-4: n = 2 L4-5: n = 18 L5-S1: n = 13	• radiological evaluation: lumbar lordosis, sacral tilt, pelvic tilt, ROM	• NA
Chung (2006)	case-series (IV) Seoul, Korea	N = 38 ‡male %: 44.4 ‡mean age: 43 years (25-58)	mean F/U: 37 months (25-42) F/U %: 94.7	• 18-60 years of age • symptomatic DDD at 1 or 2 levels • primary complaint of back pain • disc height ≥ 4mm • ODI ≥ 40 • failed ≥ 6 months conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 25 bilevel: n = 11 • spinal segments L3-4: n = 2 L4-5: n = 24 L5-S1: n = 25	• VAS for back and leg pain • ODI • work status • medication usage • segmental ROM and intervertebral disc height via anteroposterior, lateral, and flexion-extension radiographs	• age • gender • body mass index • single or double level • previous operations on the same level (discectomy)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
							• estimated blood loss during surgery • operation time • segmental ROM • prosthesis position
David (2007)	case-series (IV) Bois-Bernard, France	N = 108 male %: 41.7 mean age: 36.4 years (23-50)	mean F/U: 13.2 years (10.0-16.8) F/U%: 98.1	• single level DDD with (n = 68) or without (n = 44) radiculopathy • failed ≥ 6 months conservative treatment	• ADR with SB Charite III via anterior retroperitoneal approach • spinal segment: L3-4: n = 1 L4-5: n = 25 L5-S1: n = 82	• modified Stauffer-Coventry • return to work among previously employed, divided into heavy and light/sendentary labor • complications • ROM	• NA
Fraser (2004	case-series (IV) Adelaide, Australia	N = 28 AcroFlex I: n = 11 AcroFlex II: n = 17 male%: 50 mean age: 41years (30-54)	duration of F/U: 24 months F/U %: NR	• 30-55 years of age • symptomatic DDD, with o without leg symptoms, confirmed by discography • failed ≥ 6 months conservative treatment • consenting, able to f/u • no previous lumbar surgery • lumbosacral angle not too steep • no significant lateral or recess spinal stenosis • no spondylolisthesis, systemic disease that would limit ability to assess in f/u, morbid obesity, EtOH or drug abuse, structural scoliosis • < 3 positive Waddell signs	• ADR with AcroFlex via direct anterior retroperitoneal approach • number of levels monolevel: n = 24 bilevel: n = 4 • spinal segments L4-5: n = 9 L5-S1: n = 23	• ODI • low back outcome score • complications • operative characteristics	• generation of AcroFlex disc

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
				• no major psych disorder or other condition limiting ability to comply • no current litigation			
Kim (2007)	prospective cohort (III) Seoul, Korea	N = 32 ‡male %: 40% ‡mean age: 38.9 years (24-60)	mean F/U: 30.2 months (24-41) F/U %: 93.8 (30/32)	• 18-60 years • DDD confirmed by any of several radiographic criteria • axial back pain, back + buttock or thigh pain, or back + leg pain • failed ≥ 6 months conservative treatment • no spinal stenosis, advanced facet arthrosis, osteoporosis, prior fusion, obesity, instability, deformity, chronic infection or pregnancy • excluded if moderate facet arthrosis treated with facet block and pain went away	• ADR with Prodisc II via median retroperitoneal approach • number of levels: monolevel: n = 19 bilevel: n = 11	• global lumbar lordosis • segmental lordosis at affected level • ROM	• gender • age • BMI • preoperative ROM • spinal segment • position and size of prosthesis
Le Huec (2005)	case-series (IV) France	N = 64 male %: 39 mean age: 44 years (20-60)	mean F/U: 18 months (12-26) F/U%: 100	• chronic back pain • failed ≥ 12 months conservative treatment • received medical and rheumatologic follow-up and rehabilitation physiotherapy	• Maverick ADR via mini-invasive anterior approach • number of levels monolevel: all • spinal segment: L5-S1 (n = 35) L4-5 (n = 27) L3-4 (n = 2)	• clinical success§ • ODI • VAS for pain • neurological function • use of analgesics • SF-36 • patient satisfaction	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Leivseth (2006)	prospective cohort (III) multicenter trial	N = 41 male %: 46.3 median age: 45 years (31-60)	mean F/U: 2 years F/U%: 100	• DDD or postdiscetomy syndrome • low back and/or leg pain > 1 year • failed conservative treatment	• Prodisc II • spinal segment: L1-2 (n = 1) L2-3 (n = 4) L3-4 (n = 7) L4-5 (n = 21) L5-S1 (n = 23)	• ODI • ROM • disc space height	• NA
Lemaire (2005)	case-series (IV) prospective cohort (III) France	N = 107 ‡male %: 41 ‡mean age: 39.6 years (24-51)	mean F/U: 11.3 years (10.0-13.4) F/U %: 93.4 (100/107)	• DDD with intractable low back pain • failed nonsurgical treatment • mean duration of disease = 6 years	• Charité SB III ADR via the anterior retroperitoneal approach • number of levels: monolevel: n = 54 bilevel: n = 45 trilevel: n = 1 • spinal segment: L3-4: n = 6 L4-5: n = 69 L5-S1: n = 72	• clinical evaluation: modified Stauffer Coventry score • radiological evaluation: disc height, sagittal alignment, ROM	• NA
Mayer, (2002)**	case-series (IV) Munich, Germany	N = 26 ADR male %: 42 mean age (range): 44 years (25.2-65)	average F/U: 6 months (3-18) F/U%: NR	• DDD with discogenic lower back pain	• ADR with Prodisc II • spinal segment L5-S1: n = 24 L5-6: n = 2	• ODI • VAS pain • operative parameters • complications	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Putzier (2006)	case-series (IV) Berlin, Germany	N = 71 (84 segments) male %: 38 (after loss to f/u) age 44 years (30-59) (after loss to f/u)	mean F/U: 17.3 years (14.5-19.2) F/U%: patients 74.6% (53/71) segments 75.0% (63/84)	• DDD at 1 or 2 levels • moderate to severe osteochondrosis • some with previous disc surgery or history of spondylolisthesis	• ADR with Charite total disc prosthesis Type I, II or III • Type I: n = 15 Type II: n = 22 Type III: n = 16 • number of levels monolevel: n = 43 bilevel: n = 10 • spinal segments L3-4: n = 2 L4-5: n = 25 L5-S1: n = 16 L4-S1: n = 10 Type I: n = 16 Type II: n = 25 Type III: n = 22	• ODI • VAS pain • perception of overall outcome • radiological parameters: segmental mobility, heterotopic ossification, implant failure, adjacent segment disease (disc height and dynamic translation), subsidence, dislocation • secondary surgery for implant fracture, subsidence, dislocation or persistent pain	• generation of Charite
SariAli (2006)	retrospective cohort (III) Paris, France	N = 23 ††male %: 52.9 ††mean age ± sd: 38.6 ± 9 (25-47)	mean F/U: 12.4 years ± 1 (10.8-14.3) F/U %: NR	• severe discopathy OR • healthy controls with no history of lumbalgia	*In patients* • ADR with SB Charite III (n = 17) • number of levels monolevel: n = 5 bilevel: n = 12 • spinal segment L4-5: n = 17 L5-S1: n = 12 OR *In healthy controls* • none (n = 6)	• degree of right axial motion • occurrence of increased right axial motion	• DDD patients receiving ADR vs. healthy controls

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Shim (2007)	retrospective cohort (III) Seoul, Korea	N = 61 Charite: n = 33 Prodisc: n = 24 (data available on 57 patients followed) male %: 52.6 Charite: 51.5 Prodisc: 54.2 mean age Charite: 44.4 years (31-63) Prodisc: 44 years (31-66)	mean F/U Charite: 41 months (36-48) Prodisc: 38 months (36-40) clinical F/U %: 93 (57/61) radiographic F/U %: 91.2 (52/57)	• DDD • low back pain • failed conservative treatment ≥ 6 months • disc herniation and significant space narrowing	• ADR with Charite or Prodisc • number of levels monolevel: n = 50 bilevel: n = 7 • spinal segment L4-5: n = 36 L5-S1: n = 14 L4-5/L5-S1: n = 7	• ODI • VAS back pain • subjective improvement rate • satisfaction rate • clinical success rate • ROM of L4-5 and L5-S1 • complications	• ADR with Charite vs. Prodisc
Siepe (2007)	case-series (IV) Munich, Germany	N = 99 male %: NR mean age: NR	F/U: ≥ 12 months F/U %: NR	• DDD without accompanying pathologies or transitional vertebrae • low back pain > sciatica • failed conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 79 bilevel: n = 20 • spinal segment L4-5: n = 42 L5-S1: n = 77 • fluoroscopically guided spine infiltration (in some pts.)	• ODI • VAS pain • clinical and radiographic parameters • patient satisfaction rating • would do again • return to work • intraoperative parameters • complications • pain relief with fluoroscopically guided spine infiltrations	• number of levels • spinal segment
Siepe (2007)	prospective cohort (III) Munich, Germany	N = 39 male %: 53.8 mean age: 39.8 years (26-58) athlete active in contact or professional sport	F/U: 2.2 years F/U%: 97.4	• DDD at one or more levels • no accompanying pathologies or transitional vertebrae • low back pain > sciatica • failed conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 36 bilevel: n = 3 • fluoroscopically guided spine infiltration	• ODI • VAS pain • clinical and radiographic parameters • sports related issues questionnaire • patient satisfaction rating • return to work • return to sports • range of motion	• preoperative participation in sport

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
		at least twice per week				• complications	
Tortolani (2007) ‡‡ Regan (2006) ‡‡	case-series within an RCT multicenter trial	N = 276 **n = 205 trial (late)** ---------- n = 91 high-volume surgeon n = 114 low-volume surgeon ---------- n = 120 high-volume institution n = 85 low-volume institution ---------- **n = 71 pretrial (early)** male %: 55.8% mean age, range: 39.3 (18-60)	Duration of F/U: 24 months *Tortolani* F/U %: NR *Regan* trial: 90.7% pretrial: 85.6%	• age 18-60 years • symptomatic DDD confirmed by discogram • ODI ≥ 30 • VAS pain ≥ 40 • failed ≥ 6 months conservative treatment • prior fusion, current or prior fracture L4, L5 or S1 other spinal surgery at the affected level, symptomatic multilevel degeneration, allergies, noncontained herniation, facet disease, spondylosis, spondylolisthesis, scoliosis, osteoporosis or osteopenia, positive straight leg raise or established nerve root compression, several additional dx or rx, or participation in another study	• Charite ADR via the anterior retroperitoneal approach	*Tortolani* • heterotropic ossification classification • segmental range of motion • ODI • VAS pain *Regan* • surgical parameters • adverse events • ODI • VAS pain • neurologic status • patient satisfaction • work status • range of motion flexion-extension	• high vs. low-volume surgeon • high vs. low-volume institution • early (pretrial) vs. late (trial) experience

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Tropiano (2003)	prospective case-series (IV) multicenter trial	N = 53 male %: 34 mean age: 45 years (28-67)	F/U: 1.4 years (1-2) F/U %: 100	• DDD (n = 33) or failed spine surgery (n = 20) • 6 months severe back pain • failed conservative treatment	• Prodisc II • approach retroperitoneal: n = 48 transperitoneal: n = 5 • number of levels monolevel: n = 40 bilevel: n = 11 trilevel: n = 2 • spinal segment L3-4: n = 4 L4-5: n = 26 L5-S1: n = 38	• VAS for back and leg pain • Oswestry Disability Questionnaire • qualitative scales for quality of life, return to work, and patient satisfaction • radiography: Cobb angle, implant position, interface ingrowth, angular motion, and degenerative changes in adjacent motion segments	• single vs. multilevel surgery • previous lumbar surgery vs. none
Tropiano (2005) §§ Huang (2006) §§	case-series (IV) Caselnau-le-Lez, France	N = 64 ‡male %: 54.5% ‡mean age: 46 years (25-65)	mean F/U ± sd (range): 8.7 years ± 1 (6.9 – 10.7) F/U %: overall: 85.9% with complete ASD and ROM data: 65.6%	• symptomatic DDD confirmed by any of several radiographic criteria • discogenic back pain • failed ≥ 6 months conservative treatment • no facet arthrosis, central or lateral recess stenosis, osteoporosis, sagittal or coronal plane deformity, absence of posterior elements, sequestrated herniated nucleus	• ADR with first-generation Prodisc • approach retroperitoneal: n = 45 transperitoneal: n = 10 • number of levels monolevel: n = 35 bilevel: n = 17 trilevel: n = 3 • spinal segment L3-4: n = 8 L4-5: n = 43 L5-S1: n = 28	• category of relative improvement for 20-point modified Stauffer-Coventry score • 3-point scales for low-back pain, lower-limb pain, and ability to perform work, and ADLs • satisfaction • radiography: periprosthetic radiolucent lines, implant migration, mechanical failure, wear of bearing, height of polyethylene core, ASD, ROM	• gender • age • previous surgery • multilevel surgery • ROM
Xu (2004)	case-series (IV) China	N = 34 male %: 59 mean age: 41.1 years (21-65)	mean F/U: 18.6 months (3-28) F/U %: 100	• DDD	• Charite SB III ADR via anterior extra-peritoneal approach • number of levels: monolevel: n = 27 bilevel: n = 7 • spinal segment: L3-5: n = 2 L4-5: n = 18 L5-S1: n = 7 L3-4, L4-5: n = 1 L4-5, L5-S1: n = 6	• radiological evaluation: lumbar spine stability, angle between superior and inferior endplates in flexion and extension, intervertebral space height, and intervertebral foramen size	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated

ADL = activities of daily living.
BMI = body mass index.
DDD = degenerative disc disease.
NA = not applicable.
ODI = Oswestry Disability Index.
ROM = range of motion.
VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡Demographics reported in this study are after loss to follow-up.
§"Clinical success" = improvement on ODI of $\geq 25\%$.
**Mayer and Wiechart also report on a series of patients receiving fusion surgeries for other indications (spondylolisthesis, spinal stenosis, and more), but only DDD patients receiving ADR are included here.
††Demographic information is given only for patients, not healthy controls.
‡‡Tortolani et al and Regan et al studied subjects in the RCT reported by Blumenthal et al and McAfee et al that were randomized to receive ADR (n = 205) plus all subjects in the nonrandomized, pretrial study (n = 71). Tortolani et al evaluated whether heterotopic ossification is associated with ODI, VAS pain, or range of motion. Regan et al evaluated whether surgery or hospital experience was associated with ADR and whether ADR was associated with other outcomes.
§§Tropiano et al and Huang et al studied the same patients. Tropiano et al evaluated whether gender, age, previous surgery or multiple levels were associated with clinical and radiographic outcomes. Huang et al reported the frequency of ASD and whether it was associated with ROM or clinical outcome. Not all patients in the entire series reported by Tropiano et al had complete ASD and ROM data to be included in Huang et al's analysis, but distribution of age, gender, number of levels and segment treated were similar in both reports.

Table G3. Demographics and characteristics of included RCTs for C-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Bryan Panel meeting 2007	• RCT (II) • Multisite; up to 35 sites approved number of sites represented in the report are not clear	N = 463 n = 242 (ADR) n = 221 (ACDF) male %: 48% age: 44.5 (25-78) ADR: 44.4 (25-78) ACDf: 44.7 (27-68) mean weight: ADR: 173 lbs (108-312) ACDF: 180 (100-285) worker's comp: ADR: 15 (16.2%) ACDF: 11 (5.0%) tobacco user: ADR: 61 (25.5%) ACDF: 53 (24.0%)	Duration: 24 months; % NR ‡	• DDD at single level between C3 and C7 • Disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy • 6 weeks minimum unsuccessful conservative unless myelopathy requiring immediate treatment • CT, myelography and CT, and/or MRI demonstration of need for surgical treatment • ≥21 years old • Preopearative NDI ≥ 30 and minimum one clinical sign associated with level to be treated • Willing to sign informed consent and comply with protocol	• Significant cervical anatomical deformity • Moderate to advanced spondylosis • Any combination of bridging osteophytes, marked reduction or absence of motion • Collapse of intervertebral disc space of > 50% normal height, radiographic signs of subluxation > 3.5 mm, angulation of disc space > 11° greater than adjacent segments, significant kyphotic deformity or reversal or lordosis • Axial neck pain as solitary symptom • Previous cervical spine surgery • Metabolic bone disease • Active systemic infection or infection at operative site	• BRYAN Cervical Disc • Standard anterior cervical discectomy and fusion (ACDF) using allograft and MEDTRONIC Sofamor Danek ATLANTIS Cervical Plate system • Treatment levels: C3-4 n = 3 C4-5 n = 29 C5-6 n = 250 C6-7 n = 181	• Overall success defined as improvement of at least 15 points on NDI, maintenance or improvement in neurological status, no serious adverse event which was implant associated or implant-surgical procedure associated, and no additional surgical procedure classified as "failure" • Overall neuro status • NDI score • Neck pain score • Arm pain score • SF-36 health survey • FSU (functional spinal unit) height/implant subsidence • AP implant migration • Angular motion • Translation • Radiographic success • Bending at target level • Fusion status • Angular motion at adjacent levels • Gait • Patient satisfaction • Adverse events	• (Medtronic)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					• Known allergy to components of titanium, polyurethane, ethylene oxide residuals • Concomitant conditions requiring steroid treatment • Daily insulin management • Extreme obesity • Medical condition which may interfere with postop management program or may result in death prior to study completion • Pregnancy • Current or recent alcohol and/or drug abuser • Signs of being geographically unstable			
Mummaneni (2007)	• RCT (II) • multisite (32 sites) • patients given sequential clinical trial number then randomly assigned according to randomization schedule using Plan Procedure in Statistical Analysis System	N = 541 n = 276 (ADR) n = 265 (ACDF) male %: 46.2 age: 43.6 years (22-73) ADR: 43.3 (25-72) ACDF: 43.9 (22-73)	duration: 24 months 24 month F/U %: 79% ADR: 80% (n = 223/276) ACDF: 75% (n = 198/265) 12 month F/U: ADR: 96% (265/276) ACDF: 86% (228/265)	• adults >18 years of age • single level symptomatic DDD between C3-7 • intractable radiculopathy, myelopathy or both • NDI scores ≥ 30 • VAS neck pain scores ≥ 20 • preserved motion at the	• multilevel symptomatic DDD or evidence of cervical instability • sagittal plane translation of greater than 3.5 mm or sagittal plane angulation of greater than 20 degrees at a single level	• ADR: Prestige ST Cervical Disc System prosthesis • ACDF: interbody fusion with cortical ring allograft spacers and Atlantis Cervical Plate System	• SF-36 • NDI • neck pain (VAS) • arm pain (VAS) • neurological status • work status • angulation • sagittal plane angulation • secondary surgical procedures including for adjacent segment disease • adverse events • overall success	• "Authors have or will receive benefits for personal or professional use Medtronek Sofamor Danek in relation to products named in this article."

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
	(version 6.12 or higher, SAS) • treatment 1:1 on a site basis		6 month F/U: ADR 94% ACDF: 88% 3 month F/U: ADR 93% ACDF: 91% 1.5 month F/U: ADR: 99% ACDF: 97%	symptomatic level found in all included patients • unresponsive to ≥ 6 weeks conservative treatment or progressive neurological worsening despite conservative treatment • no previous procedures at the operative level • negative for several radiographic findings, medications, and diagnoses	• symptomatic C2-C3 or C7-T1 disc disease • previous surgery at the involved level • severe facet joint disease at the involved level • history of discitis • osteoporosis • metastases • medical condition that required long-term use of medication such as steroid or nonsteroidal antiinflammatory drugs that could affect bone quality and fusion rates			
Nabhan (2007)	• RCT (II) • drawing cards in sealed envelops • single site	N = 49 n = 25 (disc) n = 24 (ACDF) 8 patients excluded after randomization due to markers obscured (n = 5 of disc group, n = 3 of ACDF group) which leaves: N = 41 n = 20 (disc) n = 21 (ACDF) male %: 56 age: 44 years	duration: 52 weeks F/U % at 52 weeks: 82% (40/49)	• monosegmental cervical DDD between C3-C7 • unresponsive to conservative treatment or presence of signs of nerve root compression with paresis • soft disc herniation • no myelopathy • age between 20-60 years • negative for specific radiographic findings,	• marked cervical instability on resting or flexion-extension radiographs • >11 of angulations • translation >3 mm • more than one level pathology • myelopathy • radiographic confirmation of severe facet joint degeneration • hard disc disease • osteoporosis, infection,	• Prodisc-C prosthesis implant: metal polyethylene ball-in-socket design with 2 metal fins; interface UHMW polyethylene inlay, and cobalt-chrome alloy with titanium surface superior and inferior plate (Synthes) • ACDF with "Solis" cage	• neck pain (VAS) • arm pain (VAS) • intervertebral mobility (translation) • complications	• no funds received in support of the work • no benefits in any form from a commercial party

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
				medications, and diagnoses • signed informed consent	rheumatiod arthritis • spondylodiscitis and active infection • malignant disease • system disease, eg hepatitis, HIV, AIDS • known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • traumatic injury of spine • pregnant or possible pregnancy in the next 3 years	(PEEK) and nonconstrained plate for anterior osteosynthesis		
Sun Peng-Fei (2008)	• RCT (II) • single site	N = 24 n = 12 (ADR) n = 12 (ACDF) male %: 70.8 age: 42 years (24-53)	average: 17 months (range, 10-35) F/U %: NR	• single C5-6 intervertebral disc hernia • failed conservative treatment w/ worsening symptoms	• NR	• Bryan ADR • interbody ACDF	• JOA score • ROM of adjacent space • degree of alleviation of clinical symptoms according to the Odom criteria • neurological or vascular complications • mechanical failure	• NR
Prodisc-C FDA report (2007)	RCT (II) multisite (13) non-inferiority study	N = 209 n = 103 (ADR) n = 106 (ACDF) % male: 45 ADR: 44.7% ACDF: 46.2% mean age: 43 years ADR: 42.1 years ACDF: 43.5 years smoking status:	duration 24 months ADR: 96.1% (99/103) § ACDF: 86.8% (92/106) §	• Symptomatic cervical disc disease (SCDD) in one level between C3-C7 • Age 18-60 years • Unresponsive to nonop treatment for six weeks or progressive symptoms • NDI ≥ 15/50 (30%)	• More than one vertebral level requiring treatment • Marked cervical instability ; translation > 3 mm or > 11° rotational difference • Fused level adjacent to level to be treated	• ADR: Prodisc-C • ACDF • Treatment levels: C3-C4 n = 4 C4-C5 n = 16 C5-C6 n = 119 C6-C7 n = 70	• Overall clinical success • NDI > 20% improvement • NDI > 15 point improvement • SF-36 • VAS pain intensity • device failure • neurological failure	• (Synthes Spine)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding

		former:
		n = 38 (18%);
		ADR n = 18 (18%);
		ACDF n = 20 (19%)
		current:
		n = 71 (34%);
		ADR n = 34 (33%);
		ACDF n = 37 (35%)
		
		weight:
		ADR 171 lbs;
		ACDF 180 lbs
				• Able to comply with protocol
				• Informed consent
					• Radiographically confirmed severe facet joint disease or degeneration
					• Allergy to cobalt, chromium, molybdenum, titanium, or polyethylene
					• Clinically compromised vertebral bodies at affected level due to trauma
					• Prior surgery at level to be treated
					• Severe spondylosis at level to be treated
					• Neck or arm pain of unknown etiology
					• Osteoporosis
					• Metabolic bone disease
					• Daily insulin management
					• Pregnancy
					• Active infection, systemic or local
					• Medications or drug known to potentially interfere with healing (steroids)
					• Autoimmune disease including RA
					• Systemic disease including AIDS, HIV, hepatitis
					• Active malignancy			

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					within last 5 years			

ACDF = anterior cervical decompression and fusion.
DDD = degenerative disc disease.
NDI = Neck Disability Index.
NR = not reported.
SF-36 = Short Form 36.
VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡Patients included are those with 24 months of follow-up at time of paper preparation; of the original group, 160 of 168 ADR and 140 of 165 ACDF patients had passed the 24 month point in the course of their treatment.
§Follow-up n's are from table 13 of report (based on number of patients who complete trial); percent is calculated from those n's.

Table G4. Demographics and characteristics in included nonrandomized studies for C-ADR

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
Amit (2007)	case-series (IV) London, England	N = 22 male %: 59.1 mean age: 51 years (39-79)	mean F/U: 15 months (range, 12-20 months) F/U %: NR	• cervical spondylosis with myelopathy (n = 4) or radiculopathy (n = 18)	• single level anterior decompression and Bryan ADR	• VAS pain • SF-36 • myelopathy disability index (MDI) • NDI • Odom's criteria • Cobb angle measured at 6 months and 12 months
Bertagnoli (2005)	case-series (IV) multicenter trial	N = 16 male %: 50 mean male age: 45.6 years (33-60) mean female age: 51 years (32-59) overall median age: 50.5 years	median F/U: 12.7 months (12-14 months, range) F/U%: 100	• one or two level cervical spondylosis with: 1) severe axial neck pain of greater than 6 months' duration and secondary to intervertebral DDD without radicular and/or myelopathic symptoms (n = 4); and 2) with persistent radicular symptoms of greater than 2 months' duration with axial neck pain and absent or minimal clinical signs of myelopathy (n = 12) • overall median duration of pain: 50 months (6 weeks to 400 months, range) • previous anterior cervical ADR with Bryan disc experiencing ASD (n = 2)	• Prodisc C ADR via anterior approach • spinal segment: C4-5 (n = 3) C5-6 (n = 7) C6-7 (n = 6)	Patients assessed preoperatively and postoperatively at 3 and 6 weeks and at 3, 6, and 12 months • ODI for disability • VAS for pain • patient satisfaction • general neck pain • radicular pain • medication usage • approach-related complications • radiographic assessment of ROM, intervertebral disc height of affected and adjacent levels, device related complications
Bertagnoli (2005)	case-series (IV) multicenter trial	N = 27 male %: 48 mean age: 49 years (31-66)	F/U: 12 months F/U %: NR	• single level cervical DDD	• Prodisc-C ADR • spinal segment C4-5 (n = 2) C5-6 (n = 16) C6-7 (n = 9)	Patients assessed preoperatively and postoperatively at 3 and 6 weeks and at 3, 6, and 12 months • NDI • VAS pain • patient satisfaction • general neck pain • radicular pain • medication usage • complications • radiographic assessment of ROM, device-related loosening, dislodgment, or subsidence

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes

Bryan (2002)
 	
population same as Goffin 2002 with different f/u and outcomes
	case-series (IV)
	
	multicenter trial
		N = 97
		male %: 42
		age range: 26-79 years
			number of eligible and lost to follow-up not reported
			
			*at time of publication 49 patients had reached 1 year f/u and 10 had reached 2 year f/u
				• single level cervical DDD
				• disc herniation (n = 75) or spondylosis (n = 33) with radiculopathy (n = 90) and/or myelopathy (n = 13)*
				• failing conservative treatment
				• duration of symptoms (range) = 6 weeks to 24 months
				
				*several patients presented with multiple diagnoses and/or cause
					• Bryan cervical ADR via anterior cervical discectomy
					• spinal segment:
					C4-5 (n = 11)
					C5-6 (n = 42)
					C6-7 (n = 44)
						• Cervical Spine Research Study (CSRS) questionnaire
						• SF-36 questionnaire
						• relief of objective neurological signs as assessed by physician in a neurological exam preoperatively, postoperatively, and then 6 weeks, and 3, 6, 12 and 24 months:
						  • motor strength on five point scale (right and left sides)
						  • gait on four point scale
						  • reflexes on four point scale (right and left sides)
						  • sensory function on four point scale (right and left sides)
						  • neck pain severity
						  • arm pain severity
						  • ability to function with respect to activities of daily living
						• radiographic evaluation to assess stability, subsidence, or migration of the prosthesis
						• results categorized according to a modified version of Odom's Criteria: excellent, good, fair, poor

Duggal (2004)	case-series (IV) Canada	N = 26 male %: 62 mean age (SD): 43.3 (7.9) years (30-67)	mean F/U: 12.3 months (1.5-27 months, range) F/U%: 100	• cervical DDD with radiculopathy and/or myelopathy whose main symptom was arm pain and NOT neck pain • mean duration of symptoms for radiculopathy = 12.5 months (2.5- 60 months, range) • mean duration of symptoms for myelopathy = 6.2 months (1-14 months, range) • failed nonsurgical medical therapy: activity modification, nonsteroidal anti-inflammatory medications, physiotherapy, massage • preoperative motion at the symptomatic level • previous anterior cervical discectomy and fusion (n = 4)	• **Bryan** cervical ADR via anterior approach and a transverse skin incision made on the right side of the neck • number of levels: monolevel at C5-6 or C6-7: (n = 22) bilevel at C5-6 & C6-7: (n = 4) • spinal segment C4-5 (n = 1) C5-6 (n = 13) C6-7 (n = 16)	• neurological examination • Oswestry NDI (self-administered) • SF-36 (self-administered) • static and dynamic cervical X-rays • duration of surgery • blood loss • complications

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
Fong (2006)	case-series (IV) Canada	N = 10 male %: 60 mean age: 44 years (36-52) subpopulation from larger, ongoing, prospective study	median F/U: 4 months (3-12 months, range) F/U %: 100	• single level disease with cervical radiculopathy and/or myelopathy • duration of symptoms ranged from 6-36 months • disc herniation was the cause of foraminal or central canal stenosis, or both, in all patients • previous anterior discectomy and fusion (n = 1)	• Bryan ADR via a standard right-sided cervical exposure through a transverse incision • spinal segment: C5-6 (n = 7) C6-7 (n = 3)	• Oswestry NDI • SF-36 questionnaire • radiographic evaluation to determine endplate angle, functional spinal unit angle and height, Cobb angle

Goffin (2003)	case-series (IV)
	
	Belgium
		single level study:
		N = 103
		male %: 41
		age range: 26-79 years
		
		bilevel study:
		N = 43
		male %: 58
		age range: 28-62 years
			F/U: 24 months
			
			single level study*:
			12 month F/U%: 97.1
			24 month F/U%: 49.5
			
			bilevel study*:
			12 month F/U%: 67.4
			24 month F/U%: 2.3
			
			*% F/U based on author's report of patients who had reached 12 & 24 month F/U at time of publication
				• disc herniation or spondylosis with radiculopathy and or myelopathy
				• failed conservative treatment during at least 6 weeks
					• Bryan ADR	• primary outcome: classification based on relief of each preoperative symptom as assessed by the patient using the Cervical Spine Research Society questionnaire and relief of each objective neurologic sign as assessed by the physician in a neurologic examination.
						• surgeons assessments preoperatively and postoperatively, then 6 weeks, 3, 6, 12, 24 months after surgery:
						  • motor strength in 5-point scale (left and right sides)
						  • Reflexes in 4-point scale (right and left sides)
						  • Sensory in 4-point scale (right and left sides)
						  • Babinski's Sign
						  • Spurling's Sign
						  • Clonus
						  • Hoffman's Sign
						  • patient assessments preoperatively and postoperatively and then 6 weeks, and 3, 6, 12, and 24 months after surgery. Assessed were neck pain severity in 6-point scale, arm pain severity in 6-point scale, and ability to function at activities of daily living in 4-point scale
						• all outcomes categorized according to Odom's criteria: excellent, good, fair, or poor

Goffin (2002)
 	
population same as Bryan 2002 with different f/u and outcomes
	case-series (IV)
	
	multicenter trial
		N = 97
		male %: 42.2
		age range: 26-79 years
			number of eligible and lost to follow-up not reported
			
			*at time of publication 60 patients had reached 6 month f/u and 10 had
				• single level cervical DDD
				• disc herniation (n = 75) or spondylosis (n = 33) with radiculopathy (n = 90) and/or myelopathy (n = 13)*
				• failing conservative treatment
				• duration of symptoms (range) = 6 weeks to 24 months
					• Bryan cervical ADR via anterior cervical discectomy
					• spinal segment:
					C4-5 (n = 11)
					C5-6 (n = 42)
					C6-7 (n = 44)
						• primary outcome: Cervical Spine Research Study and SF-36 questionnaires and relief of each objective neurologic sign as assessed by the physician
						• surgeons assessments preoperatively and postoperatively, then 6 weeks, 3, 6, and 12 months after surgery:
						  • Motor strength in 5-point scale (left and right sides)
						  • Reflexes in 4-point scale (right and left sides)

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
			reached 12 month f/u	*several patients presented with multiple diagnoses and/or cause		• Sensory in 4-point scale (right and left sides) • Babinski's Sign • Spurling's Sign • Clonus • Hoffman's Sign • patients assessments preoperatively and postoperatively and then 6 weeks, and 3, 6, and 12 months after surgery. Assessed were neck pain severity in 6-point scale, arm pain severity in 6-point scale, and ability to function at ADL in 4-point scale • radiographic evaluation to assess stability, subsidence, or migration of the prosthesis • Odom's criteria: excellent, good, fair, or poor
Heidecke (2008)	case-series (IV) Germany	N = 54 male %: 41% mean age: 47 years (26-58)	F/U: 2 years F/U %: NR	• disc herniation and/or spondylosis with preserved mobility in the affected segment • cervical radiculopathy and/or myelopathy with or without neck pain • exclusion criteria included: advanced kyphotic deformity, spondylolisthesis, translational instability of the cervical spine, insulin-dependent diabetes, advanced osteoporosis, ankylosing spondylitis, rheumatoid arthritis, age > 60 years	• Bryan cervical disc prosthesis in standard anterior cervical discectomy • number of levels treated single level (n = 49) two levels (n = 5) • 59 total spinal segments replaced: C4-5 n = 18 discs C5-6 n = 33 discs C6-7 n = 8 discs	• radiographic evaluation to assess migration, dislocation • heterotopic ossification • intraoperative or early postoperative complications related to disc • neurological symptoms • Odom's criteria: excellent, good, fair, or poor
Jollenbeck (2004)	case-series (IV) Germany	N = 50 male%: 52 mean age: 46.2 years (32-65)	number of eligible patients not reported F/U: range, 1-14 months 6 month F/U%: 82 12 month F/U%: 26	• prolapse or protruding degenerative cervical disc with local neck pain and radicular pain (n = 13), sensory loss and some motor deficits (n = 38), and myelopathy with gait ataxia and increased tendon reflexes (n = 7)	• unspecified cervical disc used for ADR via anterior approach (? Bryan) • number of levels: monolevel (n = 49) bilevel (n = 1) • spinal segments C3-4 (n = 2) C4-5 (n = 2) C5-6 (n = 35) C6-7 (n = 10) C5-6 & C6-7 (n = 1)	• VAS for duration and intensity of neck ache, radicular pain, and difficulties swallowing daily for 7 days post-op • rate of hemorrhage and infection • duration of hospital stay • radiological and neurological f/u and assessment of ROM at 3, 6, and 12 months • self-assessment of pain and return to work via Odom's scale at all f/u intervals

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
Kim (2007)	case-series (IV) Korea	N = 23 male %: 70 mean age: 43 years (31-62)	mean F/U: 6 months F/U %: NR	• cervical DDD with axial pain, radiculopathy, or myelopathy (n = 8) • mean symptom duration: 7.5 months (2 weeks to 36 months, range) • previous anterior cervical fusion (n = 2)	• Mobi-C cervical ADR via anterior approach, with anterior cervical interbody fusion also in different levels (n = 6) • number of levels: monolevel (n = 22) bilevel (n = 1) • spinal segment: C3-4 (n = 2) C4-5 (n = 4) C5-6 (n = 11) C6-7 (n = 6)	• radiographic analysis to determine Cobb's angle, functional spinal unit angle, and ROM • VAS for axial pain and radiculopathy • modified Japanese Orthopaedic Association (JOA) scoring system for severity of myelopathy • Prolo economic and functional rating scale • results scored according to modified Odom's criteria: excellent, good, fair, poor
Lafuente (2005)	case-series (IV) United Kingdom	N = 46 male %: 61 mean age (SD): 47.6 (10.5) years (33-70)	mean F/U: 14 months F/U%: 100	• single level disease with either radiculopathy or myelopathy • failing nonsurgical treatment • mean (SD) duration of symptoms = 13.8 (11.9) months (1-6 months, range) • previous lumbar discectomy (n = 2) and cervical fusion at one level (n = 3)	• **Bryan** ADR via anterior cervical discectomy • number of levels: all between C3-5 and C6-7	• neurological examination • radiological evaluation to assess movement, stability, and subsidence or the prosthesis • VAS for pain • SF-36 for general health • Oswestry NDI for functionality • results were categorized as excellent, good, fair, or poor according to modified Odom's criteria
Leung (2005)	case-series (IV) multicenter trial	N = 103 male%: 43 mean age (SD): 45 (9.8) years (26-79)	F/U: 12 months x-ray F/U%: 87.3 clinical F/U%: 86.4	• disc herniation or spondylosis with radiculopathy and/or myelopathy • failed conservative treatment: relative rest, soft collar, physiotherapy, and medication for at least 6 weeks	• Bryan cervical ADR	• McAfee classification for heterotopic ossification (OH) • Odom's criteria: poor = unfavorable; fair, good, and excellent = favorable • SF-36
Liu (2007)	retrospective cohort (III)	N = 30 male: NR age: NR	NR	• normal subjects (n = 10) • patients treated with an anterior cervical decompression and fusion (ACDF) (C5–C6) (n = 10) • patients having cervical artificial disc replacement (CADR) (C5–C6) (n = 10)	• full flexion to extension motions under fluoroscopic surveillance in the sagittal plane • kinematic data were obtained from the fluoroscopic images • kinetic data were derived based on an inverse dynamic	Intersegmental ROM

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
					model of the entire cervical spine.	
Mehren (2006)	case-series (IV) multicenter trial	N = 54 male%: NR mean age: NR	F/U: 12 months F/U%: NR	• disc herniation or other degenerative changes leading to neurological deficits, and/or arm and/or neck pain	• Pro-disc C ADR via anterior approach • number of levels: monolevel (n = 34) bilevel (n = 17) trilevel (n = 3) • spinal segment: C3-4 (n = 3) C4-5 (n = 9) C5-6 (n = 36) C6-7 (n = 29)	• radiography to determine McAfee classification for heterotopic ossification (OH) • VAS for neck and arm pain • NDI
Pickett (2006)	case-series (IV) multicenter trial	N = 74 male %: 50 mean age: 44 years	mean F/U: 12 months (maximum 39 months) F/U%: NR	• cervical disc herniation or spondylosis with radiculopathy and/or myelopathy or neck pain • 12 patients had prior neck surgery, 11 of whom had ACDF	• Bryan ADR	• NDI • Oswestry NDI • VAS for pain • SF-36 • patient satisfaction (ie, would have the procedure again) • radiographic parameters • complications
Pimenta (2004)	case-series (IV) Brazil	N = 53 male %: 40 mean age: 45 years (28-68)	F/U: 12 months F/U %: NR	• DDD (n = 43), degenerative adjacent segment disease (n = 10) • Radicular or medullary compression symptoms • Age 20-70 years • Neurological compression of one, two or three levels from C3-C4 to C7-T1 • Herniation of the nucleus pulposus • Cervical spondylosis • Nontraumatic segmental instability • Exclusion criteria included metabolic and bone diseases, terminal phase of chronic disease, pyogenic infection or	• PCM (Cervitech) discs implanted by PRESS FIT Model or Flange Fixed Model • 81 discs in 53 patients One level in n = 28 Two level in n = 22 Three level in n = 3 • Levels receiving implants: C3-C4 n = 28 C4-C5 n = 15 C5-C6 n = 34 C6-C7 n = 22 C7-T1 n = 2	• VAS for pain • NDI • Treatment Intensity Gradient Test • Odom's criteria: excellent, good, fair, bad • radiographic parameters • heterotopic ossification

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
				active granulomatosis, neoplasty or traumatic disease of the cervical column, biomechanical instability of traumatic origin		
Pointillart (2001)	case-series (IV) France	N = 10 male %: 50% mean age: 36 years (25-49)	F/U: 1 year F/U %: NR	• cervicobrachial pain for over 3 months • soft disc herniation by MRI • exclusion criteria included intervertebral instability	• prototype prosthesis (not otherwise specified) • levels receiving implants: C5-C6 n = 6 C6-C6 n = 4	• further procedures • pain • mobility • complications
Rabin (2007)	retrospective cohort (III)	N = 20 male: 80% age: 34.8 (ACDF) 35.8 (AD)	ACDF: 24.8 months AD: 15 months	• single-level Bryan cervical disc (n = 10) • single-level ACDF matched based on age and sex (n = 10)	• lateral neutral, flexion and extension cervical x-rays were obtained preoperatively and at regular intervals up to 24 months postoperatively.	ROM at operated level
Robertson (2004) pilot study and extension of the Wigfield 2002 study, 2 additional patients enrolled	case-series (IV) United States	N = 17 male %: 59 mean age (SD): 50.1 (11.4) years (31.9-74.5)	F/U: 36 and 48 months x-ray F/U% at 36 months: 64.7 x-ray F/U% at 48 months: 70.5 clinical F/U% at 48 months: 82.4	• radiculopathy or myelopathy with cervical disc herniation or posterior vertebral body osteophytes AND have either a previous adjacent-level surgical or congenital spinal fusion or radiologic evidence of ASD • previous surgical fusions (n = 9)	• Prestige I ADR • discs inserted between C3-4 and C6-7	• radiological evaluation to assess motion preservation and device stability • neurological examination • VAS for arm and neck pain • NDI • SF-36 physical and mental component scores • European myelopathy scale (EMS)
Robertson (2005)	retrospective cohort using nonconcurrent controls (III)	ADR N = 310 male: 41% age: 55.9 years (28-79) fusion: N = 202 male: 49% age: 44.5 years	24 months F/U %: 75	• symptomatic single level disc herniation or spondylosis (C2-3 to C7-T1) with radiculopathy and/or myelopathy	• Bryan ADR (n = 74) or fusion using an Affinity Anterior Cervical Cage System (n = 158) • anteroposterior, neutral, and lateral flexion-extension x-rays were collected pre-, peri-, and postoperatively at 6 weeks, and 3, 6, 12, and 24 months	*Bryan protocol:* • Odom criteria • Cervical Spine Research Study outcome forms • qualitative scale of the SF-36 *Affinity system protocol:* • neck disability score • VAS pain scores • qualitative scale of the SF-36

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
						rate of adjacent segment disease based on new anterior osteophyte formation or enlargement of existing osteophytes, increased or new narrowing of a disc space, and new or increasing ALL calcification
Sekhon (2004)	case-series (IV) Australia	N = 11 male %: 64 mean age: 43.7 years (31-55) 7 patients presented in a previous report with shorter f/u	mean F/U: 18.4 months (10-32 months, range) F/U%: 100	• spinal cord compression and/or clinically confirmed cervical myelopathy • mean duration of symptoms = 15.2 months (.75-72 months, range)	• Bryan ADR via left-sided transverse cervical incision or an oblique left-sided paramedian incision for a bilevel disease • number of levels: single level (n = 7) bilevel (n = 4) • spinal segment: C3-4 (n = 1) C4-5 (n = 1) C5-6 (n = 2) C6-7 (n = 3) C4-5, C5-6 (n = 2) C5-6, C6-7 (n = 2)	• neurological exam • Nurick grading • Oswestry NDI assessment • neck and arm symptoms rated on a scale from 0 (none), 1 (mild), 2 (moderate), and 3 (severe) • results were categorized using Odom's criteria
Shim (2006)	case-series (IV) Korea	N = 61 male %: 70 mean age: 45.6 years (32-64) (% male and mean age available for only 47 patients with 3 months f/u)	mean F/U: 6 months F/U%: 77	• cervical radiculopathy or myelopathy with (n = 41) or without (n = 6) soft disc herniation	• Bryan cervical ADR (n = 43) in combination with ACDF (n = 4) • number of levels: monolevel (n = 39) bilevel (n = 8)	• NDI • VAS for neck and shoulder/arm pain • patient's subjective improvement rate of symptoms • patient's satisfaction with procedure • radiological evaluation to determine segmental angle, total sagittal alignment, and ROM
Wigfield (2002)	case-series (IV) United Kingdom	N = 15 male %: 67 mean age (SD): 47.6 (18.1) years	F/U: 24 months F/U%: 93.3	• radiculopathy or myelopathy with cervical disc herniation or posterior vertebral body osteophytes AND have either a previous adjacent-level surgical or congenital spinal fusion or radiologic evidence of ASD • previous surgical fusions (n = 9) • mean (SD) duration of symptoms = 5 (5.4) years	• Frenchay ADR via a standard anterolateral approach using the Smith and Robinson technique • discs inserted between C3-4 and C6-7	• operative time • blood loss • infection • radiological evaluation to assess motion preservation and device stability • neurological examination • VAS for arm and neck pain • NDI • SF-36 physical and mental component scores • European myelopathy scale (EMS)

Author (year)	Study design (LoE)	Demographics	Follow-up	Characteristics	Interventions	Outcomes
Yang (2007)	case-series (IV) China	N = 12 male %: 58% mean age 50 years (35-62)	mean F/U: 5.2 months (2-8) F/U %: NR	• cervical spondylotic myelopathy (n = 5) and cervical disc herniation (n = 7)	• Bryan cervical disc prosthesis • 14 replacements in 12 patients • Single level n = 10 • Two-level n = 2	• Japanese Orthopedic Association (JOA) scores • Odom's criteria: excellent, good, fair, poor • Radiographic and MRI evaluation for device stability and HO
Yoon (2006)	case-series (IV) Seoul, Korea	N = 46 male %: 52.2 mean age: 42.3 years (26-58)	mean F/U: 11.8 months (range, 2.9-19.5) F/U %: NR	• herniated cervical disc (n = 39) or cervical stenosis (n = 6) with radiculopathy or myelopathy • failed conservative treatment	• Bryan ADR following anterior cervical discectomy • number of levels monolevel (n = 34) bilevel (n = 12) • spinal segment C4-5: (n = 4) C5-6: (n = 32) C6-7: (n = 10)	• VAS pain • self-administered NDI • complications

NDI = Neck Disability Index.
NR = not reported.
ODI = Oswestry Disability Index.
ROM = range of motion.
SF-36 = Short Form 36.
VAS = Visual Analog Scale.

APPENDIX H. Evidence Tables: Results of Included Studies for ADR

Table H1. Efficacy and outcomes other than adverse events or complications for included RCTs for L-ADR

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion
Blumenthal (2005) McAfee (2005) Geisler (2004) Statistical Review for Expedited PMA (2004) Summary of Safety and Effectiveness (2004)	• four-point success measure using sponsor's ODI criterion* ADR: 57.1% (100/176) fusion: 46.5% (34/74) *P* < .0001 • four-point success measure using FDA's ODI criterion* ADR: 52.1% (92/176) fusion: 44.4% (33/74) *P* = NR FDA table	• ODI improved ≥ 25% from baseline ADR: 63.9% (112/176) fusion: 50.5% (37/74) *P* = 0.004 • ODI improved ≥ 15 points from baseline ADR: 57.1% (100/176) fusion: 47.5% (35/74) *P* = NR • mean % improvement in ODI compared to baseline† *6 weeks* ADR: 23.9% fusion: 12.7% *P* = .02 *3 months* ADR: 40.2% fusion: 25.7% *P* = .001 *6 months* ADR:46.2% fusion:30.8% *P* = .002 *12 months* ADR: 48.8% fusion: 37.9% *P* = .04	• mean improvement in VAS compared to baseline† *6 weeks* ADR:35.9 fusion:27.7 *P* = .02 *3 months* ADR:35.7 fusion:27.4 *P* = .02 *6 months* ADR:39.0 fusion:28.2 *P* = .004 *12 months* ADR:39.1 fusion:30.9 *P* = .04 *24 months* ADR:40.6 fusion:34.1 *P* = .1 • still using narcotics for pain‡ ADR: 64% (73) fusion: 80% (37) *P* = .04	• physical SF-36 improved ≥ 15% from baseline ADR: 72% (127/176) fusion: 63% (47/74) *P* = NR • mental SF-36 improved ≥ 15% from baseline ADR: 50% (88/176) fusion: 51% (38/74) *P* = NR • report they would have procedure again ADR: 69.9% fusion: 50.0% *P* = .006 • report they are "satisfied"§ ADR: 73.7% fusion: 53.1% *P* = .001	• employed *baseline* ADR: 53.2% fusion: 57.6% *P* = NR *24 months* ADR: 62.4% fusion: 65% *P* = .6	• mean flexion-extension: *Pre-op:* 6.6° *Post-op*: 7.5°

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion
		24 months ADR: 48.5% fusion: 42.4% *P* = .3				
Zigler (2007)	• ten-point success measure using sponsor's ODI criterion** ADR: 63.5% (94/148) fusion: 45.1% (32/71) *P* = .005 • ten-point success measure using FDA's ODI criterion** ADR: 53.4% (79/148) fusion: 40.8% (29/71) *P* = .04 *using FDA report demographics	• ODI ≥ 15% improved from baseline ADR: 77.2% fusion: 64.8% *P* = .04 • ODI ≥ 25% improved from baseline ADR: 69.1% (110/159) fusion: 54.9% (40/73) *P* = .04 • ODI improved ≥ 15 points from baseline ADR: 67.8% (108/159) fusion: 54.9% (40/73) *P* = .04 • any improvement in ODI ADR: 91.8% fusion: 84.5% *P* = NR • mean ODI†† *baseline* ADR: 63.4 fusion: 62.7 *P* = .6 *6 weeks* ADR: 42 fusion: 48 *P* ≤ .02	• mean reduction in VAS from baseline ADR: 39mm fusion: 32mm *P* = .08†† • narcotic use ADR: baseline: 84% successful: 39% unsuccessful: 79% fusion: baseline: 76% successful: 31% unsuccessful: 76% *P* = NR	• any improvement in composite SF-36 *6 weeks* ADR: 72.1% fusion: 56.4% *P* = .02 *3 months* ADR: 86.6% fusion: 70.0% *P* = .004 *6 months* ADR: 80.4% fusion: 75.0% *P* =.2 *12 months* ADR: 81.0% fusion: 76.7% *P* = .3 *18 months* ADR: 79.1% fusion: 74.5% *P* = .3 *24 months* ADR: 79.2% (126/159) fusion: 70.0% (51/73) *P* = .09	• employed *baseline* ADR: 83.5% fusion: 78.1% *P* = NS *24 months*†† ADR: 92.4% fusion: 83.5% *P* = .05 • participating in recreation *baseline* ADR: 42.4% fusion: 49.3% *P* = NS *24 months*†† ADR: 87.4% fusion: 77.3% *P* = .03	• mean flexion-extension: *Post-op:* 7.7° • restoration to normal flexion-extension at implanted level ADR: 93.7% • greater flexion-extension (than baseline) at implanted level ADR: 89.5%

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion
		3 months ADR: 37 fusion: 46 *P* ≤ .02 *6 months* ADR: 37 fusion: 42 *P* ≤ .02 *12 months* ADR: 40 fusion: 35 *P* = NR *24 months* ADR: 34.5 fusion: 39.8 *P* = .06		• would have again ADR: 81% fusion: 69%		

Outcomes are at final f/u and means and percentages are based on intent-to-treat analysis, unless otherwise noted.
NS = no statistically significant difference.
NA = not applicable.
NR = not reported.
ODI = Oswestry Disability Index.
*Clinical success was defined as 1) substantially improved function as measured by ODI, 2) no device failure, 3) no major complications, and 4) no neurologic deterioration. The sponsor considered function to be substantially improved if an individual had an ODI score ≥ 25% higher at 24 months than at baseline. The FDA considered function to be substantially improved if an individual had an ODI score ≥ 15 points higher at 24 months than at baseline. The authors did not report definitions for "major complications" or "neurologic deterioration".
†All intragroup comparisons between follow-up and baseline were significant at the level $P < .001$.
‡ Narcotic use is only reported for patients meeting the four criteria for clinical success.
§ Response options included "satisfied", "somewhat satisfied", "somewhat dissatisfied", and "dissatisfied". Only those responding "satisfied" are included here.
** Clinical success was defined as 1) substantial improvement in function as measured by ODI, 2) device success (no reoperation to modify or remove device nor supplemental fixation), 3) maintenance or improvement on all neurologic evaluations, 4) any improvement in composite SF-36 score, 5) no device migration, 6) no subsidence, 7) no radiolucency, 8) no loss of disc height, 9) fusion status (no spontaneous fusion in ADR subjects, successful union in fusion subjects), and 10) restoration of 6-20° flexion-extension at L3-4 or L4-5, or 5-20°at L5-S1. The sponsor considered function to be substantially improved if an individual had an ODI score ≥ 15% higher at 24 months than at baseline. The FDA considered function to be substantially improved if an individual had an ODI score ≥ 15 points higher at 24 months than at baseline.
††All intragroup comparisons of ODI, VAS pain, employment, and recreation relative to baseline are significant at the level $P < .0001$. Mean ODI scores are approximated from a graph for time-points other than baseline and 24 months.

Table H2. Efficacy and outcomes other than adverse events or complications for included nonrandomized studies for L-ADR

Author (year)	Range of motion	Occurrence of ASD
Bertagnoli (2006)	NR	NR
Bertagnoli (2006)	ROM at disc level: preoperative: 3° postoperative: 12° *P* = .004	adjacent level disc heights did not change
Cakir (2005)	NR	mean Cobb angle of global lumbar lordosis: preoperative: 53.7° postoperative: 55.9° P = .084 mean Cobb angle of segmental lumbar lordosis: preoperative: 17.9° postoperative: 26.3° P < .001 change in Cobb angle of global lumbar lordosis: decrease: 0 (0%) no change: 4 (13.8%) increase: 25 (86.2%) change in Cobb angle of segmental lordosis: decrease: 2 (6.9%) no change: 23 (79.3%) 4 (13.8%)
Caspi (2003)	average range of segmental motion: 3°-9°	NR
Chung (2006)	mean sagittal ROM per operative segment L5-S1: baseline: 7.1° ≥ 24 months: 11.2° *P* = .008 L4-5: baseline: 11.4° ≥ 24 months: 14.6° *P* = .006	NR

Author (year)	Range of motion	Occurrence of ASD
Chung (2006)	mean ROM preoperatively: 9.7° 1 year: 13.0° 2 years: 12.7° *P* = .001	NR
David (2007)	mean segmental flexion-extension : 10.1° L4-L5: 12.2° L5-S1: 9.4° mean segmental lateral bending: 4.4° L4-L5: 6.0° L5-S1: 3.9°	The adjacent-level reoperation rate was 2.8% (3/106). Two patients experienced a disc herniation above their index surgical level and were treated successfully with microdiscectomy at 4 and 5 years postsurgery, respectively. One patient developed spinal stenosis 5 years postsurgery and required a decompression and fusion procedure.
Fraser (2004)	NR	NR
Kim (2007)	flexion-extension at level of intervention ± sd: *baseline* L3-4: 4.23° ± 3.12° L4-5: 3.66° ± 2.47° L5-S1: 3.12° ± 1.56° *6 months* L3-4: 7.11° ± 2.53° L4-5: 6.45° ± 3.70° L5-S1: 3.23° ± 1.89° *24 months* all levels: 4.78° L3-4: 6.81° ± 3.76°, *P* = .04 L4-5: 6.09° ± 2.11°, *P* = .03 L5-S1: 2.86° ± 1.26°, *P* = .2 no patient or operative factors correlate with ROM except level of surgery high or low ROM doesn't correlate with ODI or VAS pain flexion-extension at adjacent segments:	NR

Author (year)	Range of motion	Occurrence of ASD
	no significant changes, although tendency toward progressive increase in segment above when ADR performed at L5-S1	
Le Huec (2005)	mean flexion-extension L3-4: 7.1° L4-5: 9.4° L4-5 with L5-S1 arthrodesis: 7.4° L5-S1: 7.9°	NR
Leivseth (2006)	rotational ROM 1 year f/u L1-2 (n = 1): 6.4° L2-3 (n = 3): 6.1° L3-4 (n = 7): 7.9° L4-5 (n = 20): 7.1° L5-S1 (n = 23): 3.0° 2 year f/u L1-2 (n = 1): 5.2° L2-3 (n = 3): 8.9° L3-4 (n = 7): 8.0° L4-5 (n = 20): 8.0° L5-S1 (n = 23): 3.5°	NR
Lemaire (2005)	mean ROM: all patients: • flexion-extension = 10.3° • lateral bending = 5.4° patients with a single L4-L5 replacement: • flexion-extension = 9.7° • lateral bending = 4.6° • axial rotation in was 1.3° asymptomatic volunteers: • flexion-extension = 8.2° • lateral bending = 3.4°	There were 2 (1.9%) cases of adjacent level degeneration. These two cases could be explained by an underlying functional overload compensating for a kyphosis of the dorsolumbar hinge joint of about 25°, concomitant in one case with the appearance of T12–L3 degenerative lumbar scoliosis after 10 years.

Author (year)	Range of motion	Occurrence of ASD
	• axial rotation in was 1.6°	
Putzier (2006)	preserved segmental motion with no ASD or spontaneous fusion or heterotopic ossification (HO) but were significantly less satisfied with their outcome compared with those with sponateous ankylosis or fused motion after implant failure 9/53 (17%)	radiographic ASD 9/53 (17%) ASD occurred only in those who had spontaneous fusion with or without heterotopic ossification (HO)
SariAli (2006)	mean vertebral rotation: 5.75° ± 1.8° mean right axial motion: healthy: 1.6°± 2° (0°-5°) ADR at L4-5: 4.3° ± 4.7° mean lateral bending: healthy: 8.2° (1.4°-13°) ADR at L4-5: 9.7° mean flexion: healthy: 2.5° (0°-6°) ADR at L4-5: 4.6° increased mobility healthy: none (definition) ADR: 6° (n = 17, 35%) monolevel: 0° (n = 5, 0%) bilevel: 6° (n = 12, 50%)	NR
Shim (2007)	Charite preoperatively mean ROM at L4-5: 9.3° (range, 1.7°-20.5°) mean ROM at L5-S1: 8.8° (range, 0.8°-19.5°) postoperatively mean ROM at L4-5: 11.7° (range, 2.6°-23.8°) mean ROM at L5-S1: 11.2° (range, 4.2°-20°) Prodisc preoperatively	Charite: (n = 6 of 31 segments, 19.4%) Prodisc (n = 6 of 21 segments, 28.6%)

Author (year)	Range of motion	Occurrence of ASD
	mean ROM at L4-5: 6.5° (range, 0°-18.4°) mean ROM at L5-S1: 7.7° (range, 0.4°-17.5°) postoperatively mean ROM at L4-5: 11.9° (range, 3.3°-21.8°) mean ROM at L5-S1: 5.6° (range, 0.3°-11.5°)	
Siepe (2007)	average flexion/extension all patients: preoperative: 5.9° (0°-19.3°) postoperative: 6.5° (0°-14.5°) L5/S1 replacement (n = 26): 5.9° (0°-14.5°) L4-5 replacement (n = 7): 7.2° (0°-13.2°) bilevel replacement (L4-5/S1, n = 3) mean 13.4° at L4-5, 9.9° at L5/S1 (n = 2); < 1° (n = 1)	NR
Tortolani (2007) Regan (2006)	*Tortolani* change in degrees flexion-extension ± sd early subjects: 1.26° ± 5.66° late subjects: 0.98° ± 6.24° final degrees flexion-extension early subjects: 7.28° ± 4.60° late subjects: 7.58° ± 5.35° postoperative range of motion exceeded the preoperative range in all of the patients with heterotopic ossification *Regan* mean flexion-extension: preoperative: nonrandomized: 6.02° (4.32°) randomized: 6.60° (5.02°) postoperative (24 months): nonrandomized: 7.28° (4.60°) randomized: 7.58° (5.35°) change: nonrandomized: 1.26° (5.66°) randomized: 0.98° (6.24°)	NR

Author (year)	Range of motion	Occurrence of ASD
Tropiano (2003)	average flexion-extension at ADR level (range): L4-5: 10° (8°-18°) L5-S1: 8° (2°-12°)	no degenerative changes were seen at the levels adjacent to the disc replacement or at the facet joints
Tropiano (2005) Huang (2006)	flexion-extension at ADR level ± sd (range): overall: 3.8°± 2.0° (0°-18°) in subjects with ASD: 1.6°± 1.3° (0°-4°) in subjects without ASD: 4.7°± 4.5° (0°-18°)	overall: 24% in subjects with ROM < 5°: 10 (n = 29, 34.5%) in subjects with ROM > 5°: 0 (n = 13, 0%)
Xu (2004)	†anterior flexion: 9.8° ± 1.7 †posterior extension: 5.1° ± 1.1	intervertebral space stenosis: intervertebral height ± sd‡: preoperative: 0.95 ± 0.10 postoperative: 1.14 ± 0.12 P < 0.01 foramen size ± sd‡: preoperative: 0.92 ± 0.08 postoperative: 1.16 ± 0.07

All outcomes are at final follow-up, unless otherwise noted.
*Mayer and Wiechart also report on a series of patients receiving fusion surgeries for other indications (spondylolisthesis, spinal stenosis, and more), but only DDD patients receiving ADR are included here.
†Measured only in those with ADR performed at L4-5 (n = 25).
‡Measured on in those with ADR performed at L4-5 who had grade I-II spinal stenosis (n = 15).

Table H3. Adverse events and complications from RCTs of L-ADR

Author (year)	Patient Characteristics	Intervention	Complications
Blumenthal (2005) McAfee (2005) Geisler (2004) Statistical Review for Expedited PMA (2004)	• age 18-60 years • symptomatic DDD confirmed by discogram • single level L4-5 (n = 61) or L5-S1 (n = 144) • ODI ≥ 30 • VAS pain ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive list of medications and diagnoses • able to comply informed consent	• Charite artificial disc via the anterior retroperitoneal approach • ALIF with BAK cages at 1 or 2 contiguous levels	• death ADR: 1 (0.5%) fusion: 0 (0%) P = NR • approach-related* ADR: 20 (9.8%) fusion: 10 (10.1%) NS P = .7 • infection† ADR: 26 (12.7%) fusion: 8 (8.1%)

Summary of Safety and Effectiveness (2004)			P = NR • nonunion or graft site pain ADR: NA fusion: 27 (27.3%) P = NA • device collapse, subsidence or displacement ADR: 8 (3.9%) fusion: 1 (1.0%) P = NR • additional surgery at index level ADR = 11 (5.4%) fusion = 9 (9.1%) P = 0.4 • catastrophic device failure ADR = 0 (0%) fusion = 0 (0%) P = NA • neurological complications ADR: NR fusion: NR P = .32 • ossification or calcification ADR: 2 (1.0%) fusion: NA P = NA
Zigler (2007)	• age 18-60 years • symptomatic DDD confirmed by any of several radiographic confirmations • single level L3-S1 • ODI ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive list of diagnoses • able to comply • informed consent	• Prodisc-L total disc replacement per IDE No. G010133 • circumferential fusion	• death ADR: 0 (0%) fusion: 0 (0%) *P* = NA • clinically significant blood loss (1500cc) ADR: 0 (0%) fusion: 2 (2.7%) *P* = NR • major vessel injury ADR: 0 (0%) fusion: 0 (0%) *P* = NA • retrograde ejaculation

			ADR: 2 (1.2%) fusion: 0 (0%) *P* = NR • DVT ADR: 2 (1.2%) fusion: 1 (1.3%) *P* = NR • infection ADR: 0 (0%) fusion: 2 (2.7%) *P* = NR • nonunion ADR: NA fusion: 2 (2.7%) *P* = NA • device migration or subsidence ADR:4 (2.5%) fusion:1 (1.3%) *P* = 1 • loss of disc height or radiolucency ADR: 0 (0%) fusion: 6 (8.0%) *P* = .003 • neurologic damage ADR: 0 (0%) fusion: 0 (0%) *P* = NA • nerve root injury ADR: 0 (0%) fusion: 0 (0%) *P* = NA • spontaneous fusion ADR: 0 (0%) fusion: NA *P* = NA

*Approach-related = venous injury, retrograde ejaculation, ileus, perioperative vein thrombosis, clinically significant blood loss (> 1500cc), incisional hernia, epidural hematoma, dural tear, deep vein thrombosis, arterial thrombosis.
†Infection = superficial wound with incision site pain, other nonwound related, UTI, wound swelling, pulmonary, peritonitis, graft site.

Table H4. Adverse events and complications from nonrandomized trials of L-ADR

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
Caspi (2003)	N = 20 male %: 55 age range: 24–50 years	duration of F/U: 48 months F/U %: NR	• low back pain with or without radicular pain • mean duration of disease = 5 years	• Charite SB III • number of levels: monolevel: n = 17 bilevel: n = 3	• prosthesis migration, n = 2 (10.0%) • laceration of the ureter & arterial thrombosis, n = 1 (5.0%) • spontaneous ossification of the intervertebral anterior ligament, n = 2 (10.0%) • secondary fusion, n = 1 (5.0%)
Cinotti (1996)	N = 46 male%: 46% age: 36 years (27-44)	mean F/U: 3.2 years (2-5) F/U%: NR	• disc degeneration (n = 22) and failed disc excision (n = 24) • Degenerated disc at one or two levels • Exclusion criteria included degenerative changes of the facet joints, disc degeneration adjacent to a fused area, spondylolisthesis	• Charite SB III • single level n = 36 L5-S1 n = 20 L4-L5 n = 14 L3-L4 n = 2 • two levels n = 10 L4-L5, L5-S1 n = 8 • L3-L4, L4-L5 n = 2	•back pain or leg symptoms requiring medication n = 16/46 (35%) •fusion n = 8 (out of 17 with unsatisfactory results) •bilateral radicular pain after surgery n = 1/46 (2%) •anterior dislocation of implant 6 days after surgery n = 1/46 (2%) •perianular ossifications n = 7/46 (15%) •malposition of prosthesis in the sagittal plane n = 3/46 (7%) •collapse into the vertebral bodies of the undersized prosthesis n = 4/46 (9%) •no degenerative changes at adjacent levels in 10 patients with MRI at f/u
David (2007)	N = 108 male %: 41.7 mean age: 36.4 years (23-50)	mean F/U: 13.2 years (10.0-16.8) F/U%: 98.1	• single level DDD with (n = 68) or without (n = 44) radiculopathy • failed ≥ 6 months conservative treatment	• Charite SB III • spinal segments L3-4: n = 1 L4-5: n = 25 L5-S1: n = 82	• index-level with secondary fusion procedure, n = 8/106 (7.5%) • symptomatic facet arthrosis with posterior fusion 5 (4.7%) • continued axial low back pain (nonfacet) with posterior fusion, n = 1 (1.0%) • subsidence with posterior fusion, n = 1 (1.0%) • sciatica with drop foot with prosthesis removal and 360° fusion, n = 1 (1.0%) • index-level with prosthesis replacement, n = 3/106 (2.8%) • early core subluxation with prosthesis replacement, n = 2 (1.9%) • late core failure with prosthesis replacement, n = 1 (1.0%) • index-level without reoperation, n = 8/106 (7.5%) • partial device ossification, n = 4 (3.8%) • complete ossification, spontaneous fusion, n = 2 (1.9%) • subsidence with spontaneous fusion, n = 1 (1.0%) • subsidence with no spontaneous fusion, n = 1 (1.0%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
Lemaire (2005)	N = 107 †male %: 41 †mean age: 39.6 years (24-51)	mean F/U: 11.3 years (10.0-13.4) F/U %: 93.4 (100/107)	• DDD with intractable low back pain • failed nonsurgical treatment • mean duration of disease = 6 years	• Charité SB III • number of levels: monolevel: n = 54 bilevel: n = 45 trilevel: n = 1 • spinal segment: L3-4: n = 6 L4-5: n = 69 L5-S1: n = 72	• vessel laceration, n = 2 (1.9%) • retrograde ejaculation in males, n = 1 (n = 44, 2.3%) • acute leg ischemia, n = 1 (0.9%) • subsidence, n = 2 (1.9%) • loss of disc height, n = 1 (0.9%) • additional surgery at index level, n = 5 (4.7%) • neurologic damage, n = 1 (0.9%) • ossification, n = 3 (2.8%) • arthritis, n = 4 (3.7%)
Punt (2008)	N = 75 male %: 45% age: 42 years (30-51)	F/U: at least 1 year F/U %: NR	• serious and constant back and leg pain in DDD	• Charite SB III L2-L3 n = 1 L3-L4 n = 3 L4-L5 n = 22 L5-S1 n = 30 L3-L4, L5-S1 n = 1 L4-L5, L5-S1 n = 16 L3-L4, L4-L5, L5-S1 n = 1 L2-L3, L4-L5, L5-S1 n = 1	late complications : • subsidence n = 39/75 (52%) • disc prosthesis too small n = 24/75 (32%) • adjacent disc degeneration n = 36/75 (48%) • degenerative scoliosis n = 11/75 (15%) • facet joint degeneration on CT scan n = 25/75 (33%) • anterior migration n = 6/75 (8%) • posterior migration n = 2/75 (3%) • breakage metal wire n = 10/75 (13%) • wear n = 5/75 (7%) • severe osteolysis n = 1/75 (1%) • subluxation PE core n = 1/75 (1%)
Putzier (2006)	N = 71 (84 segments) male %: 38 (after loss to f/u) age 44 years (30-59) (after loss to f/u)	mean F/U: 17.3 years (14.5-19.2) F/U%: patients 74.6% (53/71) segments 75.0% (63/84)	• DDD at 1 or 2 levels • moderate to severe osteochondrosis • some with previous disc surgery or history of spondylolisthesis	• Charite Type I, II or III • Type I: n = 15 Type II: n = 22 Type III: n = 16 • number of levels monolevel: n = 43 bilevel: n = 10 • spinal segments L3-4: n = 2 L4-5: n = 25 L5-S1: n = 16 L4-S1: n = 10	• spontaneous fusion radiographically, n = 4 (8.3%) • fusion secondary to implant failure (n = 7) or pain (n = 5) n = 12 (23%) • implant failure requiring secondary operation with instrumentation , n = 5 (9.4%) subsidence 2 implant fracture 1 implant dislocation 1 pain with progressive degeneration 1
Xu (2004)	N = 34 male %: 59 mean age: 41.1 years (21-65)	mean F/U: 18.6 months (3-28) F/U %: 100	• DDD	• Charite SB III • number of levels: monolevel: n = 27 bilevel: n = 7 • spinal segment: L3-5: n = 2	• laceration in iliac vein, n = 1 (2.9%) • anterior subluxation of the inferior endplate, n = 1 (2.9%) • mild low back pain after operation n = 2 (5.9%) • depression and sensation of heat and pain in waist, n = 1 (2.9%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
				L4-5: n = 18 L5-S1: n = 7 L3-4, L4-5: n = 1 L4-5, L5-S1: n = 6	
Zeegers (1999)	N = 50 male %: 40% age: 43 years (24-59)	Mean F/U: 2 years F/U%: 92% (n = 46/50)	• medically refractory lumbar discopathies • exclusion criteria included predominant symptoms or deficits in the legs related to the involvement of the nerve roots • failed conservative management	• Link SB Charite • 75 disc prostheses in 50 patients One level n = 29 Two levels n = 18 Three levels n = 3 • operated level include: L5-S1 n = 8 L4-L5 n = 16 L4-S1 n = 12 L3-S1 n = 5 L3-L5 n = 5 • L5-S1 and L3-L4 n = 1	•52 complications reported in 30/46 patients at 2 year F/U including: •dysaesthesia of legs n = 7 (3 permanent) •paresis/muscle weakness n = 1 •cramps in legs n = 2 •painful/numb scar n = 5 •haematoma n = 12 •retroperitoneal haematoma n = 1 •visceral dysfunction n = 1 •abdominal pain n = 1 •low back or leg pain n = 5 •sympathectomy effect n = 7 (4 permanent) •disturbance of miction n = 1 •aortal lesion at removal of prosthesis n = 1 •infection of urinary tract n = 4 •impotence, retrograde ejaculation n = 1 •deep venous thrombosis n = 1 •malposition of prosthesis n = 2 (1 permanent) •reoperations for complications: 7 surgeries in 3/50 patients • all reoperations: 24 reoperations in 12/50 patients
Bertagnoli (2002)	N = 108 male%: 54 age: 41.5 years (34-65)	duration of F/U: range of 3 months to 2 years F/U%: NR	• disc degeneration (n = 67), failed disc surgery syndrome (n = 35), transition zone syndrome (TZS, n = 6) • exclusion criteria included severe osteoporosis, physiological dysfunction, hisotry of previous disc infection, severe posterior element pathologies, fracture of the vertebra, tumor	• Prodisc II • 134 prosthetic discs replaced in 108 patients L5/S1 n = 61 L5/L6 n = 3 L4/L5 n = 31 L3/L4 n = 7 L2/L3 n = 3 L4/L5 and L5/S1 n = 10 L2/L3 and L4/L5 n = 1 L3/L4, L4/L5 and L5/S1 n = 2	• residual leg pain or back pain including facet joint pain n = 9/108 (8%) • analgesics required more than 2 weeks n = 45/108 (42%); of whom 12 required regular analgesics 6 months-1 year, and 33 only occasionally • systemic septicemia n = 1/108 (1%)
Bertagnoli (2005)	N = 29 male%: 60% (15/25) age: 49 years (30-60) smokers: 24%	median F/U: 31 months (25-41) F/U%: 86% (n = 25/29)	• average duration of pain 70 months (9-210) • prior posterior surgery in 68% (laminoforminotomies, laminectomies) • age 18-60 years	• Prodisc • triple segmental L3-L4, L4-L5, L5-S1 n = 10 • double segmental: L4-L5, L5-S1 n = 8 L3-L4, L4-L5 n = 5	• partial implant subsidence n = 1/25 (4%) • anterior extrusion of a polyethylene component n = 1/25 (4%) • no other loosenings, migration, metallic or polyethylene failure, allergic rejection/reaction, visceral or neurologic injuries (0%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
			• disabling and recalcitrant discogenic low back pain • minimal radicular pain secondary to multilevel lumbar disc disease from L1 to S1 • complete 2 year follow-up data included • exclusion criteria included spinal stenosis, osteoporosis, prior fusion surgery, chronic infections, metal allergies, pregnancy, facet arthrosis, inadequate vertebral endplate size, neuromuscular disease, pregnancy, Workers' Compensation, spinal litigation, body mass index > 35, and/or any isthmic or degenerative spondylolisthesis > Grade 1 • failed conservative treatment for a minimum of 9 months	L2-L3, L4-L5 n = 1 L3-L4, L5-S1 n = 1	• subcutaneous sterile inflammatory suture reaction n = 1/25 (4%) • temporary retrograde ejaculation n = 1/25 (4%) • no cases of vascular injury, ureteral injury, or other neurologic injury (0%)
Bertagnoli (2005)	N = 118 male%: 45 (n = 47/104) median age: 47.5 years smokers: 31%	median F/U: 31 months (24-45) F/U%: 88% (n = 104/118)	• age 18-60 years • average duration of pain 104 monhts (6-400) • prior posterior surgery in 57% • disabling discognic low back pain • with or without radicular symptoms • complete 2 year follow-up data included • DDD • Exlusion criteria included: spinal stenosis, osteoporosis, prior fusion surgery, chronic infections, metal allergies, pregnancy, facet arthrosis, inadequate vertebral endplate size, more than one level of spondylosis, neuromuscular disease, pregnancy, Worker's Compensation, spinal litigation, body mass index > 35, and/or any isthmic or degenerative spondylolisthesis > Grade 1 • Failed conservation treatment for a minimum of 9 months	• Prodisc • Level of surgery L5-S1 n = 80 L4-L5 n = 17 L3-L4 n = 7	• no device-related complications: no loosening, subsidence, migration, metallic or polyethylene failure, allergic rejection/reaction, visceral or neurologic injuries • retroperitoneal hematomas n = 2/104 (2%) • single subcutaneous hematoma n = 1/104 (1%) • temporary retrograde ejaculation n = 1/104 (1%) • no vascular injury, ureteral injury or neurologic injury (0%) • persistent leg pain following application of an L5-S1 implant n = 1/80 (13%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
Cakir (2005)	N = 29 male %: 34 mean age ± sd: 40.8 years ± 6.4 (29-56)	mean F/U: 15.3 months (12-35) F/U%: 100	• symptomatic DDD (n = 21) or postdiscectomy syndrome (n = 8) • low back pain ≥ 12 months • failed ≥ 6 months conservative treatment	• Prodisc • number of levels: monosegmental: all	• loosening, subsidence, migration or spontaneous fusion, n = 0 (0%)
Chung (2006)	N = 38 †male %: 44.4 †mean age: 43 years (25-58)	mean F/U: 37 months (25-42) F/U %: 94.7	• 18-60 years of age • symptomatic DDD at 1 or 2 levels • primary complaint of back pain • disc height ≥ 4mm • ODI ≥ 40 • failed ≥ 6 months conservative treatment	• Prodisc II • number of levels monolevel: n = 25 bilevel: n = 11 • spinal segments L3-4: n = 2 L4-5: n = 24 L5-S1: n = 25	• major vein injury, n = 2/36 (5.6%) • increased radicular pain (resolved by 6 weeks), n = 3/36 (8.3%)
Hannibal (2007)	N = 59 male %: 64% mean age: 39 years	F/U: 2 years F/U %: 92% (n = 45/59)	• minimum 2 years follow-up • age 18-60 years • failed conservative treatment for at least 6 months • minimum ODI score of 40 • no more than 1 or 2 levels of lumbar DDD • exclusion criteria included severe facet arthropathy, compromised vertebral bodies, fusion patients, others not specified	• Prodisc II • 1 level replacement (n = 25/27 at F/U) L5-S1 n = 17 L4-L5 n = 10 • 2 level replacement (n = 29/32 at F/U) L4-L5, L5-S1 n = 29 L3-L4, L4-L5 n = 3	• complications not reported
Kim (2007)	N = 32 male%: 40% age: 39 years (24-60)	mean F/U: 30 months (24-41) F/U %: 94% (n = 30/32)	• intractable discogenic pain • DDD from L3 to S1 • age range 18-60 years • inadequate conservative treatment for minimum of 6 months • exclusion criteria included spinal stenosis, advanced facet arthrosis, osteoporosis, prior fusion, obesity, instability, deformity, chronic infection, pregnancy, improvement in back pain after facet block	• Prodisc II • 1 level replacement n = 19 • 2 level replacement n = 11	• no radioluent or sclerotic lines • no disc narrowing, instability, or change in facet configuration at adjacent levels • other complications not reported
Mayer, (2002)‡	N = 26 ADR male %: 42	average F/U: 6 months (3-18)	• DDD with discogenic lower back pain	• Prodisc II • spinal segment L5-S1: n = 24	• L5 root irritation, n =1 (3.8%) • extrusion of the polyethylene inlay, n =1 (3.8%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
	mean age (range): 44 years (25.2-65)	F/U%: NR		L5-6: n = 2	
Siepe (2006) population may overlap with Siepe 2007	N = 192 male%: 33% for n = 92 age: 43 years (22-66) for n = 92	mean F/U: 34.2 months (24-62) F/U %: 48% (n = 92/192)	• DDD with or without modic changes • Exclusion criteria included central or lateral spinal stenosis, facet joint arthrosis, symptomatic facet joint problems, spondylolysis, spondylolisthesis, spinal instability, major deformity/curvature deviations, metabolic bone disease, previous operation with severe scarring and radiculopathy, compromised vertebral body, previous/latent infection, metal allergy, spinal tumor, post-traumatic segments	• Prodisc II • number of levels monolevel n = 77 bilevel n = 14 three levels n = 1 • spinal segment L5-S1 n = 57 L5-L6 n = 5 L4-L5 n = 12 L4-L5-S1 n = 13 L2-L3 n = 1 L5-L6-S1 n = 1 L4-S1 n = 2 L3-L4-L5-S1 n = 1	• overall complications : n = 18/92 (20%) • retrograde ejaculation n = 2 (2%) • sympathectomy related dysesthesia n = 1 (1%) • DVT + LAE + lysis n = 1 (1%) • superficial wound healing impaired n = 1 (1%) • extraforaminal disc protrusion following TDR n = 1 (1%) • neuropathy L5 n = 1 (1%) • heterotopic ossification n = 1 (1%) • primary suboptimal implantation n = 1 (1%) • inlay dislocation n = 1 (1%) • implant subsidence n = 2 (2%) • segmental hyperlordosis persisting n = 1 (1%) • persisting facet joint problems n = 2 (2%) • secondary spinal canal stenosis n = 1 (1%) • adjacent segment disc herniations leading to reop n = 2 (2%) • reoperations required at index level n = 8 (9%)
Siepe (2007) population may overlap with Siepe 2006	N = 99 male %: NR mean age: NR	F/U: ≥ 12 months F/U %: NR	• DDD without accompanying pathologies or transitional vertebrae • low back pain > sciatica • failed conservative treatment	• Prodisc II • number of levels monolevel: n = 79 bilevel: n = 20 • spinal segment L4-5: n = 42 L5-S1: n = 77	• overall : n = 17/99 (17%) • sympathectomy related dysesthesia n = 1 (1%) • L5 neuropathy n = 2 (2%) • hematoma of the abdominal wall n = 1 (1%) • superior hypogastric plexus lesion n = 2 (2%) • heterotopic ossification n = 1 (1%) • inlay dislocation n = 1 (1%) • persisting facet joint problems n = 2 (2%) • primary suboptimal implantation n = 1 (1%) • segmental hyperlordosis with persisting problems n = 1 (1%) • adjacent segment disc herniation n = 2 (2%) • secondary spinal canal stenosis (same segment) n = 1 (1%) • superficial wound healing imipaired n = 1 (1%) • seroma, retroperitoneal n = 1 (1%) • overall reoperations n = 8 (8%)
Tropiano (2003)	N = 53 male %: 34 mean age: 45 years (28-67)	F/U: 1.4 years (1-2) F/U %: 100	• DDD (n = 33) or failed spine surgery (n = 20) • 6 months severe back pain • failed conservative treatment	• Prodisc II • number of levels monolevel: n = 40 bilevel: n = 11 trilevel: n = 2 • spinal segment	• postoperative vertebral body fracture n = 1 (1.9%) • implant malposition n = 2 (3.8%) • persistent radicular pain without evident neural compression n = 2 (3.8%) • reoperation n = 3 (5.7%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
				L3-4: n = 4 L4-5: n = 26 L5-S1: n = 38	
Tropiano (2005)§ Huang (2006)§	N = 64 †male %: 54.5% †mean age: 46 years (25-65)	mean F/U ± sd (range): 8.7 years ± 1 (6.9 – 10.7) F/U %: overall: 85.9% with complete ASD and ROM data: 65.6%	• symptomatic DDD confirmed by any of several radiographic criteria • discogenic back pain • failed ≥ 6 months conservative treatment • no facet arthrosis, central or lateral recess stenosis, osteoporosis, sagittal or coronal plane deformity, absence of posterior elements, sequestrated herniated nucleus	• Prodisc I • number of levels monolevel: n = 35 bilevel: n = 17 trilevel: n = 3 • spinal segment L3-4: n = 8 L4-5: n = 43 L5-S1: n = 28	surgical complications, n = 5 (7.8%) including: • DVT, n = 1 (1.6%) • iliac vein laceration, n = 1 (1.6%) • transient retrograde ejaculation, n = 1 (1.6%) • incisional hernias, n = 2 (3.1%) other complications included: • migration, n = 0 • transiently increased radicular pain, n = 5 (7.8%) • mechanical failures, n = 0 (0%) • radiolucency or substantial loss of disc height 0 (0%) • end-plate penetration ≤ 2mm, n = 15 (23.4%) > 2mm, n = 2 (3.1%)
Shim (2007)	N = 61 Charite: n = 33 Prodisc: n = 24 (data available on 57 patients followed) male %: 52.6 Charite: 51.5 Prodisc: 54.2 mean age Charite: 44.4 years (31-63) Prodisc: 44 years (31-66)	mean F/U Charite: 41 months (36-48) Prodisc: 38 months (36-40) clinical F/U %: 93 (57/61) radiographic F/U %: 91.2 (52/57)	• DDD • low back pain • failed conservative treatment ≥ 6 months • disc herniation and significant space narrowing	• Charite or Prodisc • number of levels monolevel: n = 50 bilevel: n = 7 • spinal segment L4-5: n = 36 L5-S1: n = 14 L4-5/L5-S1: n = 7	• tear of the great vein during surgical approach Charite: n = 1 (3%) Prodisc: n = 1 (3.7%) • subsidence Charite: n = 1 (3%) Prodisc: n = 2 (7.4%) • incisional hernia Charite: n = 1 (3%) Prodisc: none
Fraser (2004)	N = 28 AcroFlex I: n = 11 AcroFlex II: n = 17 male%: 50 mean age: 41years (30-54)	duration of F/U: 24 months F/U %: NR	• 30-55 years of age • symptomatic DDD, with or without leg symptoms, confirmed by discography • failed ≥ 6 months conservative treatment • consenting, able to f/u • no previous lumbar surgery • lumbosacral angle not too steep • no significant lateral or recess spinal stenosis	• AcroFlex • number of levels monolevel: n = 24 bilevel: n = 4 • spinal segments L4-5: n = 9 L5-S1: n = 23	• pulmonary embolism, n = 1 (3.6%) • retrograde ejaculation, n = 1 (3.6%) • nerve root irritation, n = 2 (7.4%) • autofusion, n = 1 (3.6%) • partial anterior disc expulsion, n = 1 (3.6%) • minor anterior polyolefin tear, n = 7 (25.0%) • large anterior polyolefin tear, n = 3 (10.7%) • revision surgery, n = 8 (28.6%)

Author (year)	Demographics*	Follow-up	Patient Characteristics	Type of ADR	Complications
			• no spondylolisthesis, systemic disease that would limit ability to assess in f/u, morbid obesity, EtOH or drug abuse, structural scoliosis • < 3 positive Waddell signs • no major psych disorder or other condition limiting ability to comply • no current litigation		
Le Huec (2005)	N = 64 male %: 39 mean age: 44 years (20-60)	mean F/U: 18 months (12-26) F/U%: 100	• chronic back pain • failed ≥ 12 months conservative treatment • received medical and rheumatologic follow-up and rehabilitation physiotherapy	• Maverick • number of levels monolevel: all • spinal segment: L5-S1 (n = 35) L4-5 (n = 27) L3-4 (n = 2)	• visceral lesion, n = 1 (1.6%) • superficial infection, n = 1 (1.6%) • spinal pain in other than the lumbar region 3 (4.7%) • postoperative root pain, n = 4 (6.3%) • posterior facet infiltration, n = 17 (26.6%) • minor intraoperative complications due to surgical approach, n = 11 (17.2%) • device migration axially 3–5 mm, n = 5 (7.8%) • subsidence stable at 1 year, n = 3 (4.7%) • heterotopic ossification, n = 3 (4.7%)

*Demographics are before loss to follow-up, unless otherwise noted.
†Demographics reported in this study are after loss to follow-up.
‡ Mayer and Wiechart also report on a series of patients receiving fusion surgeries for other indications (spondylolisthesis, spinal stenosis, and more), but only DDD patients receiving ADR are included here.
§Tropiano et al and Huang et al studied the same patients. Tropiano et al evaluated whether gender, age, previous surgery or multiple levels were associated with clinical and radiographic outcomes. Huang et al reported the frequency of ASD and whether it was associated with ROM or clinical outcome. Not all patients in the entire series reported by Tropiano et al had complete ASD and ROM data to be included in Huang et al's analysis, but distribution of age, gender, number of levels and segment treated were similar in both reports.

Table H5. Efficacy and outcomes other than adverse events or complications for included RCTs for C-ADR

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
Bryan Panel meeting 2007 (24 month assessments)	• Over success at 24 months: ADR n = 129/160 (80.6%); ACDF n = 99/140 (70.7%) • Subsequent surgical interventions: ADR n = 6/242 (2.5%); ACDF n = 9/221 (4.1%) • Physician global assessment excellent/good: ADR 93.8%; ACDF 89.3%	Neurological improvement: Successes: ADR n = 150/160 (93.7%); ACDF n = 128/140 (91.4%) Failures: ADR n = 10/160 (6.3%); ACDF n = 12/140 (8.6%) NDI score successes: ADR n = 134/160 (83.7%); ACDF n = 106/140 (75.7%)	Neck or arm pain n = 115/242 (47.5%); n = 96/221 (43.4%) Arm pain score (mean): ADR 19.3 (n = 159); ACDF 22.5 (n = 140)	• SF-36 PCS mean improvement from baseline: ADR 14.4; ACDF 14.5 • SF-36 MCS mean improvement from baseline: ADR 8.1; ACDF 7.3 • SF-36 PCS success rate: ADR 90.6%; ACDF 85.5% • SF-36 MCS success rate: ADR 72.5%; ACDF 69.8% • Patient global assessment (completely recovered or much improved): ADR 92.4%; ACDF 86.4%	• Median time to return to work: ADR 48 days; ACDF 61 days	Angular motion above treated segment: ADR 9.1°; ACDF 8.9° Angular motion below treated segment: ADR 6.4°; ACDF 6.2°	•
Mummaneni (2007)	• neurological status: motor function, sensory function, and deep tendon reflexes; maintenance or improvement in all three indicators is success ADR: 92.8% (207/223) at 24 months ACDF: 84.3% (167/198) at 24 months *P* = .005 failures ADR: 223-207 = 16 ACDF: 198-167 = 31 • overall success (from NDI score, no serious implant associated or implantation procedure adverse event, no second	**NDI** *preoperative* ADR: 55.7 ACDF: 56.4 *6 weeks* ADR: 27.1 ACDF: 32.1 *P* = .0014 *3 months* ADR: 20.7 ACDF: 26.8 *P* = .0004 *6 months* ADR: 21.7 ACDF: 24.5 *P* = .0835 *12 months* ADR: 20.6 ACDF: 23.4 *P* = .0897	**Neck pain (VAS)** † *preoperative* ADR: 68 ACDF: 69 *6 weeks* ADR: 16 ACDF: 20 *P* = .0395 *3 months* ADR: 13 ACDF: 16 *P* = .0148 *6 months* ADR: 16 ACDF: 17 *P* = .3058 *12 months* ADR: 15 ACDF: 19 *P* = .0350 *24 months*	• NR	• work status *Preoperative* ADR: 66% ACDF: 63% *24 months* ADR: 75.4% ACDF: 74.7% • time to return to work (median): ADR: 45 days ACDF: 61 days *P* = 0.094 (log-rank test) *P* = 0.022 (Wilcoxon test)	data not included; NR	• reoperations for adjacent-segment disease disc: n = 3 (2 with symptoms at adjacent level above and 1 with symptoms at adjacent level below the arthroplasty site) ACDF: n = 11 (3 with symptoms at adjacent level above, 7 with symptoms at adjacent level below, 1 with symptoms both above and below the fusion)

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
	surgery classified as a failure) 12 months ADR: 77.6% (206/265) ACDF: 66.4% (151/228) *P* = .0040 24 months ADR: 79.3% (177/223) ACDF: 67.8% (134/198) *P* = .0053 • NDI success only = ≥ 15 point improvement 12 months ADR: 82.4% (218/265) ACDF: 79.4% (181/228) *P* = .215 24 months ADR: 83.0% (185/223) ACDF: 80.1% (159/198) *P* = .282	*24 months* ADR: 19.3 ACDF: 22.4 *P* = .0827 **SF-36 PCS** † *preoperative* ADR: 34 ACDF: 35 *6 months* ADR: 44 ACDF: 43 *P* = .0797 *12 months* ADR: 44 ACDF: 43 *P* = .0788 *24 months* ADR: 45 ACDF: 44 *P* = .1744 **SF-36 MCS**† *preoperative* ADR: 42 ACDF: 42 *6 months* ADR: 49 ACDF: 49 *P* = .5480 *12 months* ADR: 50 ACDF: 48 *P* = .0529 *24 months* ADR: 49 ACDF: 50	ADR: 15 ACDF: 16 *P* = .3781 **Arm pain (VAS)** † *preoperative* ADR: 59 ACDF: 63 *6 weeks* ADR: 13 ACDF: 13 *P* = .5990 *3 months* ADR: 11 ACDF: 12 *P* = .3191 *6 months* ADR: 15 ACDF: 13 *P* = .6752 *12 months* ADR: 16 ACDF: 17 *P* = .2485 *24 months* ADR: 13 ACDF: 14 *P* = .4812 (composite score from multiplying intensity and duration scores, 0-100)				

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
		P = .5621					
Nabhan (2007)	• NR	• NR	**neck pain (VAS)** *preoperative* disc: 6.0 +/- 1.2 ACDF: 6.2 +/- 0.9 *1 weeks* disc: 3.5 +/- 0.9 ACDF: 2.9 +/- 0.7 *3 weeks* disc: 3.4 +/- 0.6 ACDF: 2.2 +/- 0.7 *6 weeks* disc: 2.8 +/- 0.4 ACDF: 2.0 +/- 0.5 *12 weeks* disc: 2.4 +/- 0.5 ACDF: 1.8 +/- 0.6 *24 weeks* disc: 2.3 +/- 0.6 ACDF: 1.7 +/- 0.5 *52 weeks* disc: 1.8 +/- 0.3 ACDF: 2.0 +/- 0.3 *52 weeks change from preop* disc: *P* = .001 ACDF: *P* = .001 **arm pain (VAS)** *preoperative*	• NR	• NR	[mean (sd) for disc (n = 19) and ACDF (n = 21)] **mediolateral translation (mm)** *Postoperative 1 week* disc: 0.70 (0.9) ACDF: 0.25 (0.30) *3 weeks* disc: 0.40 (0.16) ACDF: 0.12 (0.06) disc: *P* = .001 compared to 1 week ACDF: *P* = .03 compared to 1 weeks *6 weeks* disc: 0.30 (0.13) ACDF: 0.07 (0.018) *12 weeks* disc: 0.40 (0.18) ACDF: 0.06 (0.05) *24 weeks* disc: 0.33 (0.17) ACDF: 0.06 (0.09) *52 weeks* disc: 0.39 (0.17) ACDF: 0.06 (0.05) *from 6 to 52 weeks:*	• None at one year follow-up

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
			disc: 7.3 +/- 1.0 ACDF 7.2 +/- 1.5 *1 weeks* disc: 1.4 +/- 0.4 ACDF: 1.4 +/- 0.3 *3 weeks* disc: 1.5 +/- 0.4 ACDF: 1.7 +/- 0.4 *6 weeks* disc: 1.4 +/- 0.2 ACDF 1.7 +/- 0.3 *12 weeks* disc: 1.3 +/- 0.3 ACDF: 1.5 +/- 0.3 *24 weeks* disc: 1.5 +/- 0.3 ACDF 1.7 +/- 0.3 *52 weeks* disc: 1.0 +/- 0.2 ACDF: 1.2 +/- 0.3 *change from 0 to 52 weeks* disc: *P* = .00 ACDF: *P* = .00			disc: *P* = .07 *from 3 to 52 weeks:* ACDF: *P* = .35 **Craniocaudal translation (mm)** *Postoperative 1 week* disc: 0.50 (0.15) ACDF: 0.30 (0.14) *3 weeks* disc: 0.27 (0.10) ACDF: 0.16 (0.05) disc *P* = .001 ACDF *P* = .04 *6 weeks* disc: 0.23 (.012) ACDF: 0.13 (0.1) *12 weeks* disc: 0.30 (0.1) ACDF: 0.06 (0.06) *24 weeks* disc: 0.27 (0.13) ACDF: 0.06 (0.03) *52 weeks* disc: 0.26 (0.13) ACDF: 0.06 (0.06) *from 6 to 52 weeks:* disc *P* = .44 *from 3 to 52 weeks:* ACDF *P* = .95 **Anteroposterior translation (mm)** *Postoperative 1 week* disc: 1.7 (0.73)	

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
						ACDF: 0.42 (0.35) *3 weeks* disc: 1.1 (0.4) ACDF: 0.13 (0.05) disc *P* = .001 ACDF *P* = .01 *6 weeks* disc: 0.70 (0.38) ACDF: 0.2 (0.05) *12 weeks* disc: 0.58 (0.3) ACDF: 0.11 (0.09) *24 weeks* disc: 0.56 (.042) ACDF: 0.07 (0.05) *52 weeks* disc: 0.66 (0.42) ACDF: 0.07 (0.05) *from 6 to 52 weeks* disc: *P* = .37 *from 3 to 52 weeks* ACDF: *P* = .25 **XYZ vector (segmental motion) translation (mm)** *Postoperative 1 week* disc: 2.3 (1.1) ACDF: 0.60 (0.2) *3 weeks* disc: 1.2 (0.37) ACDF: 0.25 (0.4) *6 weeks*	

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
						disc: 1.1 (0.32) ACDF: 0.22 (0.30) *12 weeks* disc: 0.74 (0.30) ACDF: 0.14 (0.27) *24 weeks* disc: 0.8 (0.41) ACDF: 0.13 (0.42) *52 weeks* disc: 0.8 (0.41) ACDF: 0.1 (0.3)	
Sun Peng-Fei (2008)	• NR	**JOA** *preoperative* ADR: 8.6 ACDF: 9 *postoperative* ADR: 15.8 ACDF: 16.2 *rate of improvement (ns)* ADR: 70% (8/12?) ACDF: 72% (9/12?) **Odom criteria** ADR*:* excellent, n = 6 good, n = 3 fair, n = 3 rate of excellent and good, 75% ACDF: excellent, n = 7 good, n = 3 fair, n = 2	• NR	• NR	• NR	average in degrees (sd) *preoperative* ADR: 12.8 (5.7) ACDF: 11.9 (5.8) *postoperative* ADR: 11.2 (3.9) ACDF: 11.4 (4.9) *P* > .05	• NR

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
		rate of excellent and good, 83% *P* > .05					
Prodisc-C FDA report (2007)	4 point success measure using sponsor's NDI criteria: • NDI ≥ 20% improvement • Neurological success, i.e. motor, sensory and reflexes are maintained or improved • No revisions, removals, reoperations, or supplemental fixation at the index level • No adverse events related to the implant or implantation ADR, n = 78, 77.2% (78/101) ‡ ACDF, n = 75, 74.3% (75/101) ‡ 4 point success measure using FDA's NDI criteria: • NDI ≥ 15 point improvement • Neurological success, i.e. motor, sensory and reflexes are maintained or improved • No revisions, removals, reoperations, or	**NDI** (table 13) NDI ≥ 20% improvement at 24 months ADR, n = 84/99 (84.9%) ACDF, n = 79/92 (85.9%) P = .6561 NDI ≥ 15 points improvement at 24 months ADR, n = 79/99 (79.8%) ACDF, n = 72/92 (78.3%) P = .4665 **SF-36** (table 23) improvement ≥ 15 points at 24 months *PCS* ADR, n = 51/99 (51.5%) ACDF, n = 31/90 (34.4%) *MCS* ADR, n = 36/99 (36.4%) ACDF, n = 38/90 (42.2%)	**VAS** (tables 25, 26, 27, 28) > 20mm improvement in pain intensity at 24 months *neck* ADR, n = 77 (78.6%) ACDF, n = 68 (75.6%) *arm* ADR, n = 70 (71.4%) ACDF, n = 69 (76.7%) >20 mm improvement in pain frequency at 24 months *neck* ADR, n = 75 (76.5%) ACDF, n = 71 (78.9%) *arm* ADR, n = 70 (71.4%) ACDF, n = 68 (76.4%)	**VAS** (table 29) patient satisfaction scores 80-100 mm at 24 months ADR, n = 67 (70.5%) ACDF, n = 60 (68.2%) Patients asked whether they would have same surgery again (figure 3): ADR, 86% ACDF, 81% ns	Employed currently (figure 4): ADR, 83% ACDF, 80% ns	ROM successes (≥ 4° of flexion/extension or maintenance of motion relative to baseline) in ADR patients: n = 81/96 (84.4%)	• NR

Author (year)	Overall success	Functional outcome	Pain relief	Patient satisfaction and QoL	Employment	Range of motion	Rate of ASD
	supplemental fixation at the index level • No adverse events related to the implant or implantation ADR: n = 73, 72.3% (73/101) ‡ ACDF: n = 69, 68.3% (69/101) ‡						

ACDF = anterior cervical decompression and fusion.
HO = heterotopic ossification.
NDI = Neck Disability Index.
NR = not reported.
SF-36 = Short Form 36.
VAS = visual analog scale.
*In the Bryan device study, the data reported is interim data for that portion of the study population with 24 months of follow-up at the time of the report. Of the original group, 160 of 168 ADR and 140 of 165 ACDF patients had passed the 24 month point in the course of their treatment.
†In the Mummaneni study, SF-36 PCS and MCS, neck pain and arm pain (VAS) scores are estimated from graphs.
‡The denominator used for outcomes reflects all those patients with known outcomes at month 24.

Table H6. Efficacy and outcomes other than adverse events or complications for included nonrandomized studies for C-ADR

Author (year)	Range of motion	Occurrence of ASD
Amit (2007)	mean Cobb angle (C2-7): 14.6° (range, 6°-22°) mean ROM in flexion-extension: 8.4° (range, 3°-21°)	NR
Bertagnoli (2005)	ROM = 11.5° at 12 month f/u	no spontaneous fusions occurred at the affected or adjacent levels height of adjacent discs were not significantly changed
Bertagnoli (2005)	ROM = 10° at 12 month f/u showed a 240% improvement from preoperative condition	no spontaneous fusions occurred at the affected or adjacent levels
Bryan (2002)	with 1 year f/u (n = 43): =/> 2° in 38 patients, 88%; = 1° in 4 patients; not interpretable in 1 patient; average 8° ± 5° with 2 years f/u (n = 10): =/> 2° in 10 patients, 100%; average 11° ± 5°	no evidence of spondylotic bridging
Duggal (2004)	measured in a subset of 16 patients: mean sagittal ROM = 7.8°	symptomatic disc herniation adjacent to prior fusion (not related to ARD) 11.5% (n = 3)
Fong (2006)	data available for 9 patients mean ROM = 8° mean flexion = 4° mean extension = 4°	NR
Goffin (2003)	single level study: 6 month: average 8.3° ± 4.5° 12 month: average 7.9° ± 5.3° 24 month: average 9.0° ± 4.9° bilevel study: 6 month: average 7.3° ± 4.1° 12 month: average 7.4° ± 5.1°	single level study: 1 disc herniation at adjacent level causing radiculopathy – symptomatic ASD bilevel study: 1 residual foraminal stenosis

Author (year)	Range of motion	Occurrence of ASD
Goffin (2002)	with 6 months f/u (n = 57): =/> 2° in 53 patients, 93%; not interpretable in 4 patients; average 9° ± 4° with 12 months f/u (n = 24): =/> 2° in 21 patients, 88%; = 1° in 2 patients; not interpretable in 1 patient; average 9° ± 6°	NR
Jollenbeck (2004)	3 month f/u (n = 32): mean ROM = 7.8° (range, 2-11°) 6 month f/u (n = 21): mean ROM = 7.3° (range, 2-10°) 12 months f/u (n = 13): mean ROM = 8.1° (range, 2-11°)	no evidence for the formation of new osteophytes of the treated or adjacent segments
Kim (2007)	at 6 month f/u: mean C2-7 ROM = 52.56° mean FSU ROM = 14.55° mean shell ROM = 10.31°	ROM of upper adjacent vertebra showed hypermobility at 3 months and returned to preoperative ROM at 6 months
Lafuente (2005)	mean 7.72° (SD 4.5°)	bony ankylosis 4.3% (n = 2)
Leung (2005)	disc movement of < 2° on flexion-extension x-rays 11% (10/90) at 12 months - 4/10 of these pts with HO of grade 3 or 4	NR
Liu (2007)	average ROM normal: 80.56° ± 6.40° ACDF: 46.53° ± 14.55° CADR: 76.72° ± 17.46° average intersegmental ROM at the adjacent C6-7 and C4-5 levels during neck rotation from 20° flexion to 15° extension normal: 3.7° and 4.8° ACDF: 13.4° and 8.8° CADR: 5.8° and 3.2°	NR
Mehren (2006)	NR	NR
Pickett (2006)	mean ROM = 8.13	NR

Author (year)	Range of motion	Occurrence of ASD
Rabin 2007	early f/u Bryan: 6.7° ± 3.0° ACDF: 1.0° ± 1.4° late f/u: Bryan: 8.6° ± 3.5° ACDF: 0.89° ± 0.92°	NR
Robertson (2004)	mean ROM = 5.7° (range, 1-15°) at 48 months f/u (n = 12)	no evidence of ASD or radiological disc disease
Robertson (2005)	NR	*Bryan* new osteophytes formation: 10.8% (n = 8) osteophytes enlargement: 0% DDD increase: 1.3% (n = 1) new: 1.3% (n = 1) ALL calcification increase: 1.3% (n = 1) *Affinity cage* new osteophytes formation: 17.9% (n = 28) osteophytes enlargement: 8.9% (n = 14) DDD increase: 3.8% (n = 6) new: 1.9% (n = 3) ALL calcification increase: 1.9% (n = 3)
Sekhon (2004)	NR	NR
Shim (2006)	mean ROM = 8.5°	NR
Wigfield (2002)	mean ROM = 6.5° (range, 3-12°, SD, 3.8°) at 24 month f/u (n = 14)	brachialgia and removal of osteophytes at adjacent level 7.1% (1/14) – symptomatic ASD
Yoon (2006)	ROM of whole cervical spine 36.5° ± 11.0° at 1 month 55.1° ± 18.5° at 1 year ROM of treated segment 9.3° ± 3.7° at 1 month 14.4° ± 4.5° at 1 year ROM of adjacent segments 9.0° ± 3.2° at 1 month	NR

Author (year)	Range of motion	Occurrence of ASD
	15.7° ± 4.3° at 1 year	

ACDF = anterior cervical decompression and fusion.
CADR = cervical artificial disc replacement.
DDD = degenerative disc disease.
HO = heterotopic ossification.
NR = not reported.
ROM = range of motion.

Table H7. Adverse events and complications from RCTs of C-ADR

Author (year)	Patient Characteristics	Intervention	Complications
Bryan Panel meeting Executive Summary 2007	• DDD at single level between C3 and C7 • Disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy • 6 weeks minimum unsuccessful conservative unless myelopathy requiring immediate treatment • CT, myelography and CT, and/or MRI demonstration of need for surgical treatment • ≥21 years old • Preopearative NDI ≥ 30 and minimum one clinical sign associated with level to be treated • Willing to sign informed consent and comply with protocol	• ADR: BRYAN Cervical Disc • Standard anterior cervical discectomy and fusion (ACDF) using allograft and MEDTRONIC Sofamor Danek ATLANTIS Cervical Plate system • Treatment levels: C3-4 n = 3 C4-5 n = 29 C5-6 n = 250 C6-7 n = 181	**Total patients with any adverse event:** ADR n = 202/242 (83.5%); ACDF n = 174/221 (78.7%) • anatomical/technical difficulty: ADR n = 0/242; ACDF n = 1/ 221 (0.5%) • cancer: ADR 2 (0.8%); ACDF 0 • cardiovascular: ADR 4 (1.7%); ACDF 2 (0.9%) • carpal tunnel syndrome: ADR 12 (5%); ACDF 4 (1.8%) • death: ADR 0; ACDF 1 (0.5%) • dysphagia/dysphonia: ADR 26 (11%); ACDF 19 (8.6%) • gastrointestinal: ADR 9 (3.7%); ACDF 6 (2.7%) • infection: ADR 17 (7%); ACDF 10 (4.5%) • malpositioned implant: ADR 2 (0.8%); ACDF 0 • neurological: ADR 48 (20%); ACDF 46 (21%) • nonunion: ADR 0; ACDF 5 (2.3%) • other: ADR 59 (24%); ACDF 39 (18%) • other pain: ADR 29 (20%); ACDF 44 (20%) • pending nonunion: ADR 0; ACDF 5 (2.3%) • respiratory: ADR 4 (1.7%); ACDF 6 (2.7%) • spinal event: ADR 21 (8.7%); ACDF 20 (9%) • trauma: ADR 34 (14%); ACDF 22 (10%) • urogenital: ADR 6 (2.5%); ACDF 3 (1.4%) • vascular intra-op: ADR 2 (0.8%); ACDF 3 (1.4%) • neck or arm pain: ADR n = 115/242 (47.5%); ACDF n = 96/221 (43.4%) • potential HO (osteophytes or bone demineralization observed): ADR n = 42 (17%); ACDF n = 154 (70%) • subsequent surgical interventions: ADR n = 6/242 (2.5%); ACDF n = 9/221 (4.1%)
Mummaneni (2007)	• adults >18 years of age • single level symptomatic DDD between C3-7 • intractable radiculopathy, myelopathy or both • NDI scores ≥ 30 • VAS neck pain scores ≥ 20 • preserved motion at the symptomatic level found in all included patients • unresponsive to ≥ 6 weeks conservative treatment or progressive neurological worsening despite conservative treatment • no previous procedures at the operative level • negative for several radiographic findings, medications, and diagnoses	• Prestige ST Cervical Disc System prosthesis • interbody fusion with cortical ring allograft spacers and Atlantis Cervical Plate System	• revisions ADR: n = 0/276 (0%) ACDF: n = 5/265 (1.9%) *P* = .0277 • hardware removals ADR: n = 5/276 (1.8%) ACDF: n = 9/265 (3.4%) *P* = .2870 • supplemental fixations due to hardware fracture or migration ADR: n = 0/276 (0%) ACDF: n = 8/265 (9 events) (3.4%) *P* = .0031 • reoperations for adjacent-segment disease

Author (year)	Patient Characteristics	Intervention	Complications
			ADR: n = 3 (1.1%) including 2 with symptoms at adjacent level above and 1 with symptoms at adjacent level below the arthroplasty site ACDF: n = 11 (4.2%) including 3 with symptoms at adjacent level above, 7 with symptoms at adjacent level below, 1 with symptoms both above and below the fusion Reasons for hardware removals included: ACDF: suspected nonunion n = 7 graft fractures n = 5 migration of fusion construct n = 3 *P* = .0492 **perioperative adverse events total:** ADR: 6.2% (n = 17/276) ACDF: 4.2% (n = 11/265) **ADR adverse events:** • neurological (numbness, paresthesia, back and leg, paresthesia/pain (arm), Lhermitte phenomenon) n = 4 • infections (UTI and sinusitis) n = 2 • pain (bursitis, headaches, neck and/or arm pain) n = 3 • respiratory (sleep apnea) n = 1 • dysphagia/ dysphonia n = 2 • anatomical/technical (screw fixation) difficulty n = 1 • hematoma n = 2 • low bone density n = 1 • spinal fluid leak n = 1 **ACDF adverse events:** • venous bleeding n = 1 • neurological (lt arm numbness) n = 1 • pain (headaches) n = 2 • dysphagia/ dysphonia n = 3 • nausea n = 1 • vomiting n = 1 • CSF leaks n = 2
Nabhan (2007)	• monosegmental cervical DDD between C3-C7	• ADR: disc prosthesis implant: metal polyethylene ball-in-socket design with 2 metal fins; interface UHMW	• mortality during surgery disc: n = 1 ACDF: n = 0

Author (year)	Patient Characteristics	Intervention	Complications
	• unresponsive to conservative treatment or presence of signs of nerve root compression with paresis • soft disc herniation • no myelopathy • age between 20-60 years • negative for specific radiographic findings, medications, and diagnoses • signed informed consent	polyethylene inlay, and cobalt-chrome alloy with titanium surface superior and inferior plate (Synthes) • ACDF: with "Solis" cage (PEEK) and nonconstrained plate for anterior osteosynthesis	• no calcifications around disc prosthesis or in ACDF • no loosening of bone around disc prosthesis • no deformity in ACDF
Sun Peng-Fei (2008)	• single C5-6 intervertebral disc hernia • failed conservative treatment w/ worsening symptoms	• cervical ADR • interbody ACDF	• no neurological or vascular • no prosthesis subsidence or extrusion
Prodisc-C FDA report (2007)	• Symptomatic cervical disc disease (SCDD) in one level between C3-C7 • Age 18-60 years • Unresponsive to nonop treatment for six weeks or progressive symptoms • NDI ≥ 15/50 (30%) • Able to comply with protocol • Informed consent	• Prodisc-C ADR • ACDF • Treatment levels: C3-C4 n = 4 C4-C5 n = 16 C5-C6 n = 119 C6-C7 n = 70	• device failure (table 6) ADR n = 2/103 (1.9%) ACDF n = 12/106 (11.3%) calculated by subtracting those who had no device failure (ADR n = 101/103; ACDF n = 97/106) from total at study start (ADR n = 103; ACDF n = 106) • neurological failure (table 13) ADR n = 13/103 (12.6%) ACDF n = 25/106 (23.6%) calculated by subtracting those who had neurological success (ADR n = 90/99, 91%; ACDF n = 81/92, 88%) from total at study start (ADR n = 103; ACDF n = 106) • Bridging bone present on radiograph in n = 3/98 (3.0%) ADR patients • Bridging bone not present on radiograph in n = 8/92 (8.7%) of ACDF patients **All adverse events (patients) (Table 3):** ‡ ADR n = 84/103 (81.6%); ACDF n = 86/106 (81.1%); *P* = 1.000 • Adjacent level DDD or DJD: ADR n = 0 (0%); ACDF 4 (3.8%) • Burning or dysesthetic pain: ADR n = 1 (1.0%); ACDF 0 (0%) • Cancer: ADR n = 1 (1.0%); ACDF 0 (0%) • Cardiovascular: ADR n = 5 (4.9%); ACDF n = 7 (6.6%) • DDD progression (noncervical): ADR n = 1 (1.0%); ACDF n = 1 (0.9%) • Dermatological: ADR n = 1 (1.0%); ACDF n = 1 (0.9%) • Dizziness: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Dural tear: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Dysphagia: ADR n = 6 (5.8%); ACDF n = 9 (8.5%) • Dysphonia: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Edema: ADR n = 2 (1.9%); ACDF n = 1 (0.9%)

Author (year)	Patient Characteristics	Intervention	Complications
			• Fatigue: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Fracture (vertebral): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Gastrointestinal: ADR n = 16 (15.5%); ACDF n = 15 (14.2%) • Genitourinary: ADR n = 5 (4.9%); ACDF n = 3 (2.8%) • Headache: ADR n = 18 (17.5%); ACDF n = 12 (11.3%) • Infection (non-wound): ADR n = 2 (1.9%); ACDF n = 6 (5.7%) • Infection (superficial wound): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Insomnia: ADR n = 6 (5.8%); ACDF n = 3 (2.8%) • Musculoskeletal: ADR n = 18 (17.5%); ACDF n = 16 (15.1%) • Musculoskeletal (back spasms): ADR n = 1 (1.0%); ACDF n = 1 (0.9%) • Musculoskeletal (neck spasms): ADR n = 3 (2.9%); ACDF n = 5 (4.7%) • Musculoskeletal (nonspecific spasms): ADR n = 3 (2.9%); ACDF n = 4 (3.8%) • Narcotics use: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Neurological: ADR n = 4 (3.9%); ACDF n = 1 (0.9%) • Numbness index level: ADR n = 0 (0%); ACDF n = 2 (1.9%) • Numbness nonindex level: ADR n = 11 (10.7%); ACDF n = 7 (6.6%) • Ossification: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Other: ADR n = 4 (3.9%); ACDF n = 6 (5.7%) • Pain (back): ADR n = 11 (10.7%); ACDF n = 8 (7.5%) • Pain (lower extremities): ADR n = 4 (3.9%); ACDF n = 2 (1.9%) • Pain (incision site): ADR n = 1 (1.0%); ACDF n = 1 (0.9%) • Pain (neck): ADR n = 16 (15.5%); ACDF n = 22 (20.8%) • Pain (neck and other): ADR n = 1 (1.0%); ACDF n = 0 (0%) • Pain (neck and shoulder): ADR n = 7 (6.8%); ACDF n = 6 (5.7%) • Pain (neck and upper extremities): ADR n = 3 (2.9%); ACDF n = 6 (5.7%) • Pain (neck and upper extremities with numbness): ADR n = 6 (5.8%); ACDF n = 6 (5.7%) • Pain (other): ADR n = 5 (4.9%); ACDF n = 7 (6.6%) • Pain (shoulder): ADR n = 9 (8.7%); ACDF n = 9 (8.5%) • Pain (upper extremities): ADR n = 8 (7.8%); ACDF n = 5 (4.7%) • Pain (upper extremities with numbness): ADR n = 4 (3.9%); ACDF n = 5 (4.7%) • Pseudoarthrosis: ADR n = 0 (0%); ACDF n = 2 (1.9%) • Psychological: ADR n = 4 (3.9%); ACDF n = 5 (4.7%) • Pulmonary infection: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Puritis: ADR n = 0 (0%); ACDF n = 2 (1.9%) • Reflex change: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Respiratory: ADR n = 4 (3.9%); ACDF n = 3 (2.8%) • Seizures: ADR n = 0 (0%); ACDF n = 2 (1.9%) • Sore throat: ADR n = 1 (1.0%); ACDF n = 1 (0.9%) • Surgery (index level): ADR n = 2 (1.9%); ACDF n = 10 (9.4%) • Surgery (other): ADR n = 12 (11.7%); ACDF n = 21 (19.8%) • Wound issues (other): ADR n = 3 (2.9%); ACDF n = 2 (1.9%)

Author (year)	Patient Characteristics	Intervention	Complications
			• No device migration, subsidence, or disc height decrease in either group at 24 months **Implant related adverse events (table 16):** ‡ All: ADR n = 2/103 (1.9%); ACDF n = 7/106 (6.6%); *P* = 0.1708 • Dysphagia: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Infection (superficial wound): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Musculoskeletal: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Pain (neck): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Surgery (index level): ADR n = 2 (1.9%); ACDF n = 5 (4.7%) **Surgery related adverse events (table 17):** ‡ All: ADR n = 11/103 (10.7%); ACDF n = 16/106 (15.1%); *P* = 0.411 • DDD progression, other cervical: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Dural tear: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Dysphagia: ADR n = 2 (1.9%); ACDF n = 4 (3.8%) • Edema: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Gastrointestinal: ADR n = 6 (5.8%); ACDF n = 4 (3.8%) • Genitourinary: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Pain (back): ADR n = 1 (1.0%); ACDF n = 0 (0%) • Pain (neck): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Pain (neck and upper extremities): ADR n = 0 (0%); ACDF n = 2 (1.9%) • Pain (upper extremities): ADR n = 2 (1.9%); ACDF n = 0 (0%) • Pseudoarthrosis: ADR n = 0 (0%); ACDF n = 2 (1.9%) • Surgery (index level): ADR n = 0 (0%); ACDF n = 2 (1.9%) • Wound issues (other): ADR n = 0 (0%); ACDF n = 2 (1.9%) **Severe or life-threatening adverse events (Table 17) :** ‡ All: ADR n = 16/103 (15.5%); ACDF n = 32/106 (30.2%); *P* = 0.0137 • Cardiovascular: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Dermatological: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Dural tear: ADR n = 1 (1.0%); ACDF n = 0 (0%) • Gastrointestinal: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Infection (non-wound): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Infection (superficial wound): ADR n = 0 (0%); ACDF n = 1 (0.9%) • Other: ADR n = 0 (0%); ACDF n = 1 (0.9%) • Surgery (index level): ADR n = 2 (1.9%); ACDF n = 10 (9.4%) • Surgery (other): ADR n = 13 (12.6%); ACDF n = 21 (19.8%)

*Patients included are those with 24 months of follow-up at time of paper preparation; of the original group, 160 of 168 ADR and 140 of 165 ACDF patients had passed the 24 month point in the course of their treatment.

†Follow-up values for n are from table 13 of the FDA report (based on number of patients who have completed 24 months of follow-up); percentages are calculated from those values.

‡Adverse events are listed by numbers of patients having events in each category. Patients may have more than one adverse event. Severe or life-threatening adverse events may also be events that were implant related or surgery related.

Table H8. Adverse events and complications from nonrandomized trials of C-ADR

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
Amit (2007)	N = 22 male %: 59.1 mean age: 51 years (39-79)	mean F/U: 15 months (range, 12-20 months) F/U %: NR	• cervical spondylosis with myelopathy (n = 4) or radiculopathy (n = 18)	• single level anterior decompression and Bryan ADR	• osteolysis n = 0 • heterotopic calcification n = 0 • subsidence n = 0
Bertagnoli (2005)	N = 16 male %: 50 mean male age: 45.6 years (33-60) mean female age: 51 years (32-59) overall median age: 50.5 years	median F/U: 12.7 months (12-14 months, range) F/U%: 100	• one or two level cervical spondylosis with: 1) severe axial neck pain of greater than 6 months' duration and secondary to intervertebral DDD without radicular and/or myelopathic symptoms (n = 4); and 2) with persistent radicular symptoms of greater than 2 months' duration with axial neck pain and absent or minimal clinical signs of myelopathy (n = 12) • overall median duration of pain: 50 months (6 weeks to 400 months, range) • previous anterior cervical ADR with Bryan disc experiencing ASD (n = 2)	• Prodisc C ADR via anterior approach • spinal segment: C4-5 (n = 3) C5-6 (n = 7) C6-7 (n = 6)	• no device related complications were observed (ie, loosening, subsidence, and migration of the implant as well as metallic or polyethylene failure, allergic rejection/reaction, visceral or neurological injuries caused by the implant components, and/or infection) • no approach-related complications were observed (ie, fractures, hematomas, dural tears/leaks, postoperative airway compromise, esophageal or tracheal disruption, laryngeal nerve injury, and/or • sympathetic nerve dysfunction)
Bertagnoli (2005)	N = 27 male %: 48 mean age: 49 years (31-66)	F/U: 12 months F/U %: NR	• single level cervical DDD	• Prodisc-C ADR • spinal segment C4-5 (n = 2) C5-6 (n = 16) C6-7 (n = 9)	• No device-related or approach- related complications were observed (ie, loosening, subsidence, migration, metallic or polyethylene failure, allergic rejection/reaction, visceral or neurologic injuries; intraoperative fractures, hematomas, dural tears/leaks, postoperative airway compromise, esophageal or racheal disruption, laryngeal nerve injury, or sympathetic nerve dysfunctions, or spontaneous fusions)
Bryan (2002) population same as Goffin 2002	N = 97 male %: 42 age range: 26-79 years	number of eligible and lost to follow-up not reported at time of publication 49 patients had reached 1 year f/u and 10 had reached 2 year f/u	• single level cervical DDD • disc herniation (n = 75) or spondylosis (n = 33) with radiculopathy (n = 90) and/or myelopathy (n = 13)* • failing conservative treatment • duration of symptoms (range) = 6 weeks to 24 months • several patients presented with multiple diagnoses and/or cause	• Bryan cervical ADR via anterior cervical discectomy • spinal segment: C4-5 (n = 11) C5-6 (n = 42) C6-7 (n = 44)	• wrong level operated on requiring second operation for unresolved pain after which temporary dysphonia occurred n = 1 • posterior foraminotomy due to pain as a result of insufficient far lateral decompression n = 1 • pain in the right shoulder, right arm, and sternum n = 1 • unresolved nonspecific left shoulder pain n = 1

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
					• surgical intervention due to a drainage catheter that had loosened and ceased draining; a hematoma was seen n = 1 • device failures or explants n = 0
Duggal (2004)	N = 26 male %: 62 mean age (SD): 43.3 (7.9) years (30-67)	mean F/U: 12.3 months (1.5-27 months, range) F/U%: 100	• cervical DDD with radiculopathy and/or myelopathy whose main symptom was arm pain and NOT neck pain • mean duration of symptoms for radiculopathy = 12.5 months (2.5- 60 months, range) • mean duration of symptoms for myelopathy = 6.2 months (1-14 months, range) • failed nonsurgical medical therapy: activity modification, nonsteroidal anti-inflammatory medications, physiotherapy, massage • preoperative motion at the symptomatic level • previous anterior cervical discectomy and fusion (n = 4)	• Bryan cervical ADR via anterior approach and a transverse skin incision made on the right side of the neck • number of levels: monolevel at C5-6 or C6-7: (n = 22) bilevel at C5-6 & C6-7: (n = 4) • spinal segment C4-5 (n = 1) C5-6 (n = 13) C6-7 (n = 16)	• increased radicular pain 3.8% (n = 1/26) • transient unilateral vocal cord paralysis 3.8% (n = 1/26) • persistent dysphagia 3.8% (n = 1/26) • possible device migration 3.8% (n = 1/26) • symptomatic disc herniation adjacent to a pervious surgical fusion 11.5% (n = 3/26)
Fong (2006)	N = 10 male %: 60 mean age: 44 years (36-52) subpopulation from larger, ongoing, prospective study	median F/U: 4 months (3-12 months, range) F/U %: 100	• single level disease with cervical radiculopathy and/or myelopathy • duration of symptoms ranged from 6-36 months • disc herniation was the cause of foraminal or central canal stenosis, or both, in all patients • previous anterior discectomy and fusion (n = 1)	• Bryan ADR via a standard right-sided cervical exposure through a transverse incision • spinal segment: C5-6 (n = 7) C6-7 (n = 3)	• no prosthetic migration or subsidence associated with shell angulation • kyphosis (mean 8° ± 4, range 3-13°) through the prosthesis seen at latest follow-up, 90% (n = 9/10) • average segmental height loss of 1.7 mm
Goffin (2003) population same as Goffin 2002 and Bryan 2002 with the addition of 6 single level patients and all bilevel patients	single level study: N = 103 male %: 41 age range: 26-79 years bilevel study: N = 43 male %: 58 age range: 28-62 years	F/U: 24 months single level study:† 12 month F/U%: 97.1 24 month F/U%: 49.5 bilevel study:† 12 month F/U%: 67.4 24 month F/U%: 2.3 % F/U based on author's report of patients who had reached 12 & 24 month F/U at time of publication	• disc herniation or spondylosis with radiculopathy and or myelopathy • failed conservative treatment during at least 6 weeks	• Bryan ADR	• Single level study group: • device migration n = 1 (suspected in a second patient) • prevertebral hematoma n = 1 • posterior foraminotomy without device involvement to treat residual symptoms n = 1 • posterior decompression to treat residual myelopathic symptoms n = 1 • wrong level operated on; temporary dysphonia occurred after follow-up surgery n = 1 • pain in right shoulder, arm, and the sternum region n = 1 • unresolved unspecific left shoulder pain n = 1

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
					• second device implanted at an adjacent level because of radiculopathy caused by disc herniation; severe dysphonia occurred following this surgery n = 1 • Bilevel study group: • cerebral spinal fluid leak n = 1 • epidural hematoma n = 1 • prevertebral hematoma n = 1 • pharyngeal tear/esophageal wound n = 1 • nerve root compression requiring anterior decompression n = 1 • device failures or explants n = 0
Goffin (2002) population same as Bryan 2002	N = 97 male %: 42.2 age range: 26-79 years	number of eligible and lost to follow-up not reported at time of publication 60 patients had reached 6 month f/u and 10 had reached 12 month f/u	• single level cervical DDD • disc herniation (n = 75) or spondylosis (n = 33) with radiculopathy (n = 90) and/or myelopathy (n = 13)* • failing conservative treatment • duration of symptoms (range) = 6 weeks to 24 months *several patients presented with multiple diagnoses and/or cause	• Bryan cervical ADR via anterior cervical discectomy • spinal segment: C4-5 (n = 11) C5-6 (n = 42) C6-7 (n = 44)	• wrong level operated on requiring second operation for unresolved pain after which temporary dysphonia occurred n = 1 • posterior foraminotomy due to pain as a result of insufficient far lateral decompression n = 1 • pain in the right shoulder, right arm, and sternum n = 1 • unresolved nonspecific left shoulder pain n = 1 • surgical intervention due to a drainage catheter that had loosened and ceased draining; a hematoma was seen n = 1 • device failures or explants n = 0
Heidecke (2008)	N = 54 male %: 41% mean age: 47 years (26-58)	F/U: 2 years F/U %: NR	• disc herniation and/or spondylosis with preserved mobility in the affected segment • cervical radiculopathy and/or myelopathy with or without neck pain • exclusion criteria included: advanced kyphotic deformity, spondylolisthesis, translational instability of the cervical spine, insulin-dependent diabetes, advanced osteopororsis, ankylosing spondylitis, rheumatoid arthritis, age > 60 years	• Bryan cervical disc prosthesis in standard anterior cervical discectomy • number of levels treated single level (n = 49) two levels (n = 5) • 59 total spinal segments replaced: C4-5 n = 18 discs C5-6 n = 33 discs C6-7 n = 8 discs	• no migration or dislocation lduring the follow-up • heterotopic ossification (grade 3 and 4) in n = 5 patients • heterotopic ossification (grade 1 and 2) in n = 12 levels of the remaining 52 segments • no intraoperative or early postoperative complications related to disc • early postoperative retropharyngeal haematoma n = 1 • radicular neurological symptoms at one year n = 1

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
Jollenbeck (2004)	N = 50 male%: 52 mean age: 46.2 years (32-65)	number of eligible patients not reported F/U: range, 1-14 months 6 month F/U%: 82 12 month F/U%: 26	• prolapse or protruding degenerative cervical disc with local neck pain and radicular pain (n = 13), sensory loss and some motor deficits (n = 38), and myelopathy with gait ataxia and increased tendon reflexes (n = 7)	• unspecified cervical disc used for ADR via anterior approach (? Bryan) • number of levels: monolevel (n = 49) bilevel (n = 1) • spinal segments C3-4 (n = 2) C4-5 (n = 2) C5-6 (n = 35) C6-7 (n = 10) C5-6 & C6-7 (n = 1)	• hemorrhage causing breathing difficulties requiring surgical removal of the hematoma n = 2 • minor difficulties in swallowing in all patients • no prosthesis dislocation was noted
Kim (2007)	N = 23 male %: 70 mean age: 43 years (31-62)	mean F/U: 6 months F/U %: NR	• cervical DDD with axial pain, radiculopathy, or myelopathy (n = 8) • mean symptom duration: 7.5 months (2 weeks to 36 months, range) • previous anterior cervical fusion (n = 2)	• Mobi-C cervical ADR via anterior approach, with anterior cervical interbody fusion also in different levels (n = 6) • number of levels: monolevel (n = 22) bilevel (n = 1) • spinal segment: C3-4 (n = 2) C4-5 (n = 4) C5-6 (n = 11) C6-7 (n = 6)	• no complications or neurological deterioration including postoperative dysphasia, dysphonia, or hoarseness occurred • kyphotic FSU angle (mean -4.2° at 6 months) 11
Lafuente (2005)	N = 46 male %: 61 mean age (SD): 47.6 (10.5) years (33-70)	mean F/U: 14 months F/U%: 100	• single level disease with either radiculopathy or myelopathy • failing nonsurgical treatment • mean (SD) duration of symptoms = 13.8 (11.9) months (1-6 months, range) • previous lumbar discectomy (n = 2) and cervical fusion at one level (n = 3)	• Bryan ADR via anterior cervical discectomy • number of levels: all between C3-5 and C6-7	• worsening of muscle spasms 2.2% (n = 1/46) • mild postoperative dysphonia 6.5% (n = 3/46) • removal of prosthesis following a fall 2.2% (n = 1/46) • bony ankylosis at implanted disc level 4.3% (n = 2/46)
Leung (2005)	N = 103 male%: 43 mean age (SD): 45 (9.8) years (26-79)	F/U: 12 months x-ray F/U%: 87.3 clinical F/U%: 86.4	• disc herniation or spondylosis with radiculopathy and/or myelopathy • failed conservative treatment: relative rest, soft collar, physiotherapy, and medication for at least 6 weeks	• Bryan cervical ADR	• heterotopic ossification 17.8% (n = 16/90) • grade 1 and 2 11.1% (n = 10/90) • grade 3 and 4 6.7% (n = 6/90)
Liu (2007)	N = 30 male: NR age: NR	NR	• normal subjects (n = 10) • patients treated with an anterior cervical decompression and fusion (ACDF) (C5–C6) (n = 10) • patients having cervical artificial disc replacement (CADR) (C5–C6) (n = 10)	• full flexion to extension motions under fluoroscopic surveillance in the sagittal plane • kinematic data were obtained from the fluoroscopic images	• NR

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
				• kinetic data were derived based on an inverse dynamic model of the entire cervical spine.	
Mehren (2006)	N = 54 male%: NR mean age: NR	F/U: 12 months F/U%: NR	• disc herniation or other degenerative changes leading to neurological deficits, and/or arm and/or neck pain	• Prodisc C ADR via anterior approach • number of levels: monolevel (n = 34) bilevel (n = 17) trilevel (n = 3) • spinal segment: C3-4 (n = 3) C4-5 (n = 9) C5-6 (n = 36) C6-7 (n = 29)	• heterotopic ossification: • grade 1 in 6 segments (7.8%, n = 1 monosegmental, n = 5 multisegmental) • grade 2 in 30 segments (39%, n = 13 mono, n = 17 multi) • leading to restricted range of motion in 8 segments (10.4%, n = 3 mono, n = 5 multi) • spontaneous fusion of the treated segment in 7 (9.1%, n = 5 multi)
Pickett (2006)	N = 74 male %: 50 mean age: 44 years	mean F/U: 12 months (maximum 39 months) F/U%: NR	• cervical disc herniation or spondylosis with radiculopathy and/or myelopathy or neck pain • 12 patients had prior neck surgery, 11 of whom had ACDF	• Bryan ADR	• venous bleeding requiring transfusion n = 2 • retropharyngeal hematoma n = 1 • neurological worsening n = 3 • intraoperative prosthesis migration n = 1 • delayed prosthesis migration n = 1 • heterotopic ossification (class 4) and spontaneous fusion n = 2 • partial dislocation of the prosthesis n = 1 • posterior migration of the prosthesis n = 1 • persistent neck and/or shoulder pain n = 19 • reoperation due to marked segmental kyphosis n = 1 • reoperation due to recurrent arm pain n = 2
Pimenta (2004)	N = 53 male %: 40% mean age: 45 years (28-68)	F/U: 12 months F/U %: NR	• DDD (n = 43), degenerative adjacent segment disease (n = 10) • Radicular or medullary compression symptoms • Age 20-70 years • Neurological compression of one, two or three levels from C3-C4 to C7-T1 • Herniation of the nucleus pulposus • Cervical spondylosis • Nontraumatic segmental instability	• PCM (Cervitech) discs implanted by PRESS FIT Model or Flange Fixed Model • 81 discs in 53 patients One level in n = 28 Two level in n = 22 Three level in n = 3 • Levels receiving implants: C3-C4 n = 28 C4-C5 n = 15	• Anterior displacement by 4 mm of prosthesis n = 1/53 • Grade 1 heterotopic ossification n = 1/53

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
			• Exclusion criteria included metabolic and bone diseases, terminal phase of chronic disease, pyogenic infection or active granulomatosis, neoplasty or traumatic disease of the cervical column, biomechanical instability of traumatic origin	C5-C6 n = 34 C6-C7 n = 22 C7-T1 n = 2	
Pointillart (2001)	N = 10 male %: 50% mean age: 36 years (25-49)	F/U: 1 year F/U %: NR	• Cervicobrachial pain for over 3 months • Soft disc herniation by MRI • Exclusion criteria included intervertebral instability	• Prototype prosthesis (not otherwise specified) • Levels receiving implants: C5-C6 n = 6 C6-C6 n = 4	• Disc removal and fusion 6 months later for intractable cervical pain and referred pain in trapezius muscles n = 1/10 • Postoperative neck pain n = 1/10
Rabin (2007)	N = 20 male: 80% age: 34.8 (ACDF) 35.8 (AD)	ACDF: 24.8 months ADR: 15 months	• single-level Bryan cervical disc (n = 10) • single-level ACDF matched based on age and sex (n = 10)	• lateral neutral, flexion and extension cervical x-rays were obtained preoperatively and at regular intervals up to 24 months postoperatively.	• NR
Robertson (2005)	ADR N = 310 male: 41% age: 55.9 years (28-79) fusion: N = 202 male: 49% age: 44.5 years	24 months F/U %: 75	• symptomatic single level disc herniation or spondylosis (C2-3 to C7-T1) with radiculopathy and/or myelopathy	• Bryan ADR (n = 74) or fusion using an Affinity Anterior Cervical Cage System (n = 158) • anteroposterior, neutral, and lateral flexion-extension x-rays were collected pre-, peri-, and postoperatively at 6 weeks, and 3, 6, 12, and 24 months	• Adjacent herniation cervical disc: ADR n = 1 with further surgery in n = 1; affinity n = 11 with further surgery in n = 3 • Further treatment for neck, shoulder, and/or arm pain: Bryan 1.3%; affinity 33% • Surgery at incorrect level: Bryan n = 1 • Surgery for explantation and fusion: Bryan n = 1 • Postoperative hematoma: Bryan n = 1 • No mortality or neurological deterioration due to procedure
Robertson (2004) pilot study and extension of the Wigfield 2002 study, 2 additional patients enrolled	N = 17 male %: 59 mean age (SD): 50.1 (11.4) years (31.9-74.5)	F/U: 36 and 48 months x-ray F/U% at 36 months: 64.7 x-ray F/U% at 48 months: 70.5 clinical F/U% at 48 months: 82.4	• radiculopathy or myelopathy with cervical disc herniation or posterior vertebral body osteophytes AND have either a previous adjacent-level surgical or congenital spinal fusion or radiologic evidence of ASD • previous surgical fusions (n = 9)	• Prestige I ADR • discs inserted between C3-4 and C6-7	• prosthesis removal at 12 months n = 1 • progression of myelopathy n = 1 • no adverse events reported on questionnaires or neurological exam during extended f/u period

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
Sekhon (2004)	N = 11 male %: 64 mean age: 43.7 years (31-55) 7 patients presented in a previous report with shorter f/u	mean F/U: 18.4 months (10-32 months, range) F/U%: 100	• spinal cord compression and/or clinically confirmed cervical myelopathy • mean duration of symptoms = 15.2 months (.75-72 months, range)	• Bryan ADR via left-sided transverse cervical incision or an oblique left-sided paramedian incision for a bilevel disease • number of levels: single level (n = 7) bilevel (n = 4) • spinal segment: C3-4 (n = 1) C4-5 (n = 1) C5-6 (n = 2) C6-7 (n = 3) C4-5, C5-6 (n = 2) C5-6, C6-7 (n = 2)	• worsening of preoperative hand and gait dysfunction 9.1% (n = 1/11) • persistent neck and arm pain with loss of motion at operated segment due to spondylotic bridging 9.1% (n = 1/11) • myelopathic deterioration 9.1% (n = 1/11) • worsened alignment 27.3% (n = 3/11)
Shim (2006)	N = 61 male %: 70 mean age: 45.6 years (32-64) (% male and mean age available for only 47 patients with 3 months f/u)	mean F/U: 6 months F/U%: 77	• cervical radiculopathy or myelopathy with (n = 41) or without (n = 6) soft disc herniation	• Bryan cervical ADR (n = 43) in combination with ACDF (n = 4) • number of levels: monolevel (n = 39) bilevel (n = 8)	• continued neck or arm/shoulder pain 7 • persistent arm pain due to incomplete decompression requiring revision 1 • persistent neck pain due to inadvertent joint destruction 1 • device migration or subsidence 0
Wigfield (2002)	N = 15 male %: 67 mean age (SD): 47.6 (18.1) years	F/U: 24 months F/U%: 93.3	• radiculopathy or myelopathy with cervical disc herniation or posterior vertebral body osteophytes AND have either a previous adjacent-level surgical or congenital spinal fusion or radiologic evidence of ASD • previous surgical fusions (n = 9) • mean (SD) duration of symptoms = 5 (5.4) years	• Frenchay ADR via a standard anterolateral approach using the Smith and Robinson technique • discs inserted between C3-4 and C6-7	• 9 patients experienced significant interventions and adverse events: • persistence of preoperative radicular pain 2 • progression of myelopathy 2 • device removal for joint loosening, had been causing neck pain 1 • screw breakage, developed neck pain 2 years later 1 • brachialgia and removal of osteophytes at adjacent level 1 • hoarse voice (resolved) 2
Yang (2007)	N = 12 male %: 58% mean age 50 years (35-62)	mean F/U: 5.2 months (2-8) F/U %: NR	• cervical spondylotic myelopathy (n = 5) and cervical disc herniation (n = 7)	• Bryan cervical disc prosthesis • 14 replacements in 12 patients • Single level n = 10 • Two-level n = 2	• no device subsidence or excursion, no ossification in replaced levelsa

Author (year)	Demographics*	Follow-up	Characteristics	Interventions	Complications
Yoon (2006)	N = 46 male %: 52.2 mean age: 42.3 years (26-58)	mean F/U: 11.8 months (range, 2.9-19.5) F/U %: NR	• herniated cervical disc (n = 39) or cervical stenosis (n = 6) with radiculopathy or myelopathy • failed conservative treatment	• Bryan ADR following anterior cervical discectomy • number of levels monolevel (n = 34) bilevel (n = 12) • spinal segment C4-5: (n = 4) C5-6: (n = 32) C6-7: (n = 10)	• acute subdural hematoma 1

NDI = Neck Disability Index.
NR = not reported.
ODI = Oswestry Disability Index.
ROM = range of motion.
SF-36 = Short Form 36.
VAS = Visual Analog Scale.
*Demographics are before loss to follow-up, unless otherwise noted.
†Study design is determined relative to the exposures being compared.

Table H9. Detailed Evidence Tables For Economic Analysis Studies-Overview of studies

Author (year)	Study Design	Population	Alternatives Compared	Benefits Measured & Weighting	Cost Data Sources and discounting	Summary of Primary Results (including sensitivity analyses)
Levin (2007) Authors indicate no funding received for study	Hospital charge analysis of prospectively selected participants of one site in multi-site RCT evaluating Prodisc-L ADR compared with fusion for one- and two-level DDD	N = 53 Severe, disabling back pain Female 38%; Age 39 years (22-55) BMI overall mean 26.9 Patient inclusion/exclusion criteria for patients per Prodisc IDE trial	1-One-level L-ADR; n = 22 2-One-level fusion; n = 9 3-Two-level L-ADR; n = 14 4-Two-level fusion; n = 8	None- alluded to the idea that outcomes are equivalent	OR charges; inpatient charges; implant charges (adjusted to USD 2006) [Source: hospital records] Surgeon and anesthesiologist fees [source: Medicare reimbursement schedule]	Primary Results: *One-level disease:* Total charge L-ADR $35592 vs. fusion $46280 (p<0.0018) *Two-level disease:* Total charge L-ADR $55524 vs. fusion $56823 (p=0.55) Sensitivity Analyses: not reported
Guyer (2007) Authors acknowledge financial relationship with DePuy and use of DePuy consultant for the study	Direct cost models (a) hospital perspective (time = index hospitalization) (b) payer perspective (time = index hospitalization + two year followup) For each: DRG payment and per diem arms	214 claims for L-ADR 1145 claims for fusion (total), but no break down with respect to numbers of claims for each type of fusion Population characteristics not reported	1-ADR with Charite Artificial Disc 2-ALIF with iliac crest bone graft 3-ALIF with LT-Cages and INFUSE 4-Posterior lumbar interbody fusion with adjunct posterolateral fusion and transpedicular fixation (IPLIF)	None—benefits assumed equivalent	Peer-reviewed medical literature; pre-marketing approval materials; commercial payer claims data; clinical expert opinion Costs adjusted to USD 2006 No discounting reported	Primary Results: (a) Hospital perspective: Charite lowest cost $16601 vs. $18596 (2) vs. $22668 (3) vs. $22662 (4) (b) Payer perspective (DRG arm): Charite lowest cost $17614 vs. $32960 (2) vs. $32196 (3) vs. $35052 (4) Payer perspective (per diem arm): Charite $24885 vs. $23778 (2) vs. $28892 (3) vs. $31620 (4) Sensitivity Analyses: none reported

ADR = Artificial Disc Replacement.
ALIF = anterior lumbar interbody fusion.
DDD = degenerative disc disease.
DRG = diagnostic-related group.
OR = operating room.

Results and Detailed Cost Data Tables:

Table H10. Mean costs in 2006 USD comparing L-ADR with various fusion procedures from a hospital perspective - Details of Data form Levin (Prodisc) and Guyer (Charité)

Author (Year)	Charge Category	Comparitors				Comments
		ADR -1 level	**Fusion 1-level**	**ADR-2-level**	**Fusion 2-level**	
Levin (2007)	Implant charge*	13,800	13,990	23,000	18,460	CPT codes (1-level fusion): 22558, 22612, 22840, 20937 CPT Codes (2-level fusions): 22585, 22614, 22842 CPT Code (L-ADR): 22857
	Operating room†	12,000	18,950	15,340	20,560	
	Inpatient hospital‡	NR	NR	9427	11,430	
	Post-op charges§	7500	7000	16,000	10,000	
	Surgeon (Medicare Schedule)	1413	4917	2826	5857	
	Anesthesiologist (Medicare Schedule)	253	473	331	525	
	Total Costs per patient	35,592	46,280	55,524	56,823	
Guyer (2007)		**ADR**	**ALIF w/ICBG**	**ALIF w/ INFUSE**	**Instrumented PLIF**	Commercial payer claims Data for fusion from Milliman Data base; For L-ADR, commercial payer claims data for post-FDA approval from 71 hospitals
	Facility**	4632	7756	6589	6444	
	Therapy (Physical/Occupational)	177	267	256	201	
	Medical devices, supplies, pharmacy, anesthesia	10,914	9058	14,444	14,768	
	Diagnostic tests (CT, MRI, X-ray)	750	1393	1240	1067	
	Other (blood, cardiac, respiratory services)	127	121	138	186	
	Total Costs per patient	16,601	18,596	22,668	22,662	

ADR = Artificial Disc Replacement.
ALIF = anterior lumbar interbody fusion.
CPT = Current Procedural Terminology.
ICBG = iliac crest bone graft.
NR = not reported.
PLIF = posterior lumbar interbody fusion.
*ADR cost $10,000 each x institution's fusion cost -charge ratio of 1.38; Implants for fusion included: femoral ring allograft, 6.5 mm AO screw and washer, bone graft substitute such as Grafton Putty (anterior procedure) and pedicle screws, rods, caps (posterior procedure).
†Operating room charges included: gowns, gloves, drapes, disposable items, prep kits, medications, cell saver, and a fixed charge per unit time of operating room use.
‡Inpatient hospital charges included: room charges, medications, blood draws, physical therapy, and incidentals.
§Estimated from author figures 1 and 2. Unclear what this includes and how it factors into the total cost per patient.
**Facility costs included: operating room time, recovery room time, accommodation.

Table H11. Mean costs in 2006 USD comparing Charite ADR with various fusion procedures[68] from two different payer perspectives

	Payer perspective: DRG arm				Payer perspective: Per diem payment			
Cost Category	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**
Index Procedure	9611	22,338	22,165	24,663	16,822	13,156	18,861	21,231
Successful Surgery care	6000	6824	6010	6010	6000	6824	6010	6010
Unsuccessful Surgery care	590	1023	1214	1214	590	1023	6824	6010
Revision surgery (rate)*	1218 (5.4%)	2053 (9.1%)	2437 (10.8%)	2437 (10.8%)	1218 (5.4%)	2053 (9.1%)	2437 (10.8%)	2437 (10.8%)
Complications	194	721	370	728	194	721	370	728
Total per patient cost	17,614	32,960	32,196	35,052	24, 885	23,778	18,892	31,620
Compared with Charité (%)	-	87.0	82.8	99.0	-	-.4.4	16.1	27.1

ALIF = anterior lumbar interbody fusion.
ICBG = iliac crest bone graft.
PLIF = posterior lumbar interbody fusion.
*****Revision rates provided by Guyer are based on the following references: Blumenthal et al[28] (ADR) and Brantigan et al[29], Burkus et al[32] (Fusion).

APPENDIX I. Excluded Studies for ADR

STUDIES EXCLUDED for L-ADR

Subset of clinical sites reporting preliminary data from a multicenter trial

Sasso RC, Foulk DM, Hahn M. Prospective, randomized trial of metal-on-metal artificial lumbar disc replacement: initial results for treatment of discogenic pain. *Spine.* Jan 15 2008;33(2):123-131.

Auerbach JD, Wills BPD, McIntosh TC, Balderston RA. Lumbar disc arthroplasty versus fusion for single-level degenerative disc disease: Two-year results from a randomized prospective study. *Seminars in Spine Surgery.* Dec 2005;17(4):310-318.

Delamarter RB, Fribourg DM, Kanim LE, Bae H. Prodisc artificial total lumbar disc replacement: introduction and early results from the United States clinical trial. *Spine.* Oct 15 2003;28(20):S167-175.

Guyer RD, McAfee PC, Hochschuler SH, et al. Prospective randomized study of the Charite artificial disc: data from two investigational centers. *Spine J.* Nov-Dec 2004;4(6 Suppl):252S-259S.

McAfee PC, Fedder IL, Saiedy S, Shucosky EM, Cunningham BW. Experimental design of total disk replacement-experience with a prospective randomized study of the SB Charite. *Spine.* Oct 15 2003;28(20):S153-162.

McAfee PC, Fedder IL, Saiedy S, Shucosky EM, Cunningham BW. SB Charite disc replacement: report of 60 prospective randomized cases in a US center. *J Spinal Disord Tech.* Aug 2003;16(4):424-433.

Zigler JE. Lumbar spine arthroplasty using the Prodisc II. *Spine J.* Nov-Dec 2004;4(6 Suppl):260S-267S.

Zigler JE, Burd TA, Vialle EN, Sachs BL, Rashbaum RF, Ohnmeiss DD. Lumbar spine arthroplasty: early results using the Prodisc II: a prospective randomized trial of arthroplasty versus fusion. *J Spinal Disord Tech.* Aug 2003;16(4):352-361.

Did not answer key questions

Geisler FH, Guyer RD, Blumenthal SL, et al. Patient selection for lumbar arthroplasty and arthrodesis: the effect of revision surgery in a controlled, multicenter, randomized study. *J Neurosurg Spine.* Jan 2008;8(1):13-16.

Yaszay B, Bendo JA, Goldstein JA, Quirno M, Spivak JM, Errico TJ. Effect of intervertebral disc height on postoperative motion and outcomes after Prodisc-L lumbar disc replacement. *Spine.* Mar 1 2008;33(5):508-512; discussion 513.

Regan JJ, McAfee PC, Blumenthal SL, et al. Evaluation of surgical volume and the early experience with lumbar total disc replacement as part of the investigational device exemption study of the Charite Artificial Disc. *Spine.* Sep1 2006;31(19):2270-2276.

STUDIES EXCLUDED for L-ADR

Biomechanical study

Moumene M, Geisler FH. Comparison of biomechanical function at ideal and varied surgical placement for two lumbar artificial disc implant designs: mobile-core versus fixed-core. *Spine.* Aug 1 2007;32(17):1840-1851.

Denoziere G, Ku DN. Biomechanical comparison between fusion of two vertebrae and implantation of an artificial intervertebral disc. *J Biomech.* 2006;39(4):766-775.

Did not report on primary outcome

Auerbach JD, Wills BP, McIntosh TC, Balderston RA. Evaluation of spinal kinematics following lumbar total disc replacement and circumferential fusion using in vivo fluoroscopy. *Spine.* Mar 1 2007;32(5):527-536.

Chin KR. Epidemiology of indications and contraindications to total disc replacement in an academic practice. *Spine J.* Jul-Aug 2007;7(4):392-398.

SariAli el H, Lemaire JP, Pascal-Mousselard H, Carrier H, Skalli W. In vivo study of the kinematics in axial rotation of the lumbar spine after total intervertebral disc replacement: long-term results: a 10-14 years follow up evaluation. *Eur Spine J.* Oct 2006;15(10):1501-1510.

Tournier C, Aunoble S, Le Huec JC, et al. Total disc arthroplasty: consequences for sagittal balance and lumbar spine movement. *Eur Spine J.* Mar 2007;16(3):411-421.

No relevant comparison group

Shim CS, Lee SH, Shin HD, et al. CHARITI versus Prodisc: A comparative study of a minimum 3-year follow-up. *Spine.* Apr 2007;32(9):1012-1018.

STUDIES EXCLUDED for C-ADR

Subset of clinical sites reporting preliminary data from a multicenter trial

Coric D, Finger F, Boltes P. Prospective randomized controlled study of the Bryan Cervical Disc: early clinical results from a single investigational site. *J Neurosurg Spine.* Jan 2006;4(1):31-35.

Hacker RJ. Cervical disc arthroplasty: a controlled randomized prospective study with intermediate follow-up results. Invited submission from the joint section meeting on disorders of the spine and peripheral nerves, March 2005. *J Neurosurg Spine.* Dec 2005;3(6):424-428.

Sasso RC, Smucker JD, Hacker RJ, Heller JG. Clinical outcomes of BRYAN cervical disc arthroplasty: a prospective, randomized, controlled, multicenter trial with 24-month follow-up. *J Spinal Disord Tech.* Oct 2007;20(7):481-491.

Sasso RC, Smucker JD, Hacker RJ, Heller JG. Artificial disc versus fusion: A prospective, randomized study with 2-year follow-up on 99 patients. *Spine.* Dec 2007;32(26):2933-2940.

Did not answer key questions

Bartels RH, Donk R, van der Wilt GJ, Grotenhuis JA, Venderink D. Design of the PROCON trial: a prospective, randomized multi-center study comparing cervical anterior discectomy without fusion, with fusion or with arthroplasty. *BMC Musculoskelet Disord.* 2006;7:85.

Biomechanical study

Chang UK, Kim DH, Lee MC, Willenberg R, Kim SH, Lim J. Changes in adjacent-level disc pressure and facet joint force after cervical arthroplasty compared with cervical discectomy and fusion. *J Neurosurg Spine.* Jul 2007;7(1):33-39.

Chang UK, Kim DH, Lee MC, Willenberg R, Kim SH, Lim J. Range of motion change after cervical arthroplasty with Prodisc-C and prestige artificial discs compared with anterior cervical discectomy and fusion. *J Neurosurg Spine.* Jul 2007;7(1):40-46.

Liu F, Cheng J, Komistek RD, Mahfouz MR, Sharma A. In vivo evaluation of dynamic characteristics of the normal, fused, and disc replacement cervical spines. *Spine.* Nov 1 2007;32(23):2578-2584.

Pickett GE, Rouleau JP, Duggal N. Kinematic analysis of the cervical spine following implantation of an artificial cervical disc. *Spine.* Sep 1 2005;30(17):1949-1954.

STUDIES EXCLUDED for C-ADR

Did not report on primary outcome

Sekhon LH, Duggal N, Lynch JJ, et al. Magnetic resonance imaging clarity of the Bryan, Prodisc-C, Prestige LP, and PCM cervical arthroplasty devices. *Spine.* Mar 15 2007;32(6):673-680.

No relevant comparison group

Johnson JP, Lauryssen C, Cambron HO, et al. Sagittal alignment and the Bryan cervical artificial disc. *Neurosurg Focus.* Dec 15 2004;17(6):E14.

Thome C, Leheta O, Krauss JK, Zevgaridis D. A prospective randomized comparison of rectangular titanium cage fusion and iliac crest autograft fusion in patients undergoing anterior cervical discectomy. *J Neurosurg Spine.* Jan 2006;4(1):1-9.

Duplicate report

Nabhan A, Ahlhelm F, Pitzen T, et al. Disc replacement using Pro-Disc C versus fusion: a prospective randomised and controlled radiographic and clinical study. *Eur Spine J.* Mar 2007;16(3):423-430.

Preliminary data with minimal follow-up

Porchet F, Metcalf NH. Clinical outcomes with the Prestige II cervical disc: preliminary results from a prospective randomized clinical trial. *Neurosurg Focus.* Sep 15 2004;17(3):E6.

APPENDIX J. Overview of Outcomes Measures

Oswestry Disability Index (ODI): Also called the Oswestry Low Back Pain Disability Questionnaire, is a standardized and validated patient-reported measure of disability. The ODI is a 10-item instrument; each item has 6 accompanying statements, which correspond to degrees of disability, and the respondent is asked to choose the statement that best describes his or her pain or discomfort. The 10 items are: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. Scores range from 0-100; higher scores indicate greater disability.

Neck Disability Index (NDI): A validated patient-reported outcome questionnaire used to evaluate neck pain and its impact on disability in daily living tasks. The ten categories of recreation, sleeping, driving, work, concentration, pain intensity, self care, lifting, reading and headaches are scored on a 0 to 5 point scale. The total score is divided by the total number possible (50), and multiplied by 100%, to report a percentage of 0-100%, with a score of 10-28% representing mild disability, 30-48% moderate disability, 50-68% severe disability, and 72% or more complete disability.

***Visual Analog Scale (VAS)*:** Used to assess pain; patient asked to allocate his/her pain on a horizontal graphic rating scale (0-100), with the descriptions severe, moderate, and mild at equal intervals along a line that started with "pain as bad as it could be" and ended with "no pain". This was calculated as a percentage with 0% equivalent to "no pain" and 100% equivalent to "pain as bad as it could be".

***Short Form-36 (SF-36)*:** Standardized and validated questionnaire used to determine patients' healthcare-related quality of life (HRQOL). The SF-36 is composed of 36 items, with 8 domains that measure physical functioning, limitations in usual role of activities resulting from physical health problems, bodily pain, general health perceptions, vitality, social functioning, limitations in usual role activities because of emotional problems, and mental health; scored 0-100 (high score indicates positive health status). The eight domains are:

- Physical function
- Role-physical
- Bodily pain
- General health
- Vitality
- Social functioning
- Role-emotional
- Mental health

The Physical Component Summary (PCS) is a composite score which indicates physical status. Higher scores indicate better physical health status. Similarly, the Mental Component Summary (MCS) is a composite score which indicates mental status. Higher scores indicate better mental health status.

Japanese Orthopaedic Association score

	Grade
I. Motor function - arms	
Unable to feed oneself with chopsticks or a spoon	0
Able to feed oneself with a spoon but not with chopsticks	1
Able to use chopsticks	2
Slightly clumsy in using chopsticks	3
Normal	4
II. Motor function - legs	
Unable to walk by any means	0
Unable to walk without a cane or others support on the level	1
Able to walk independently on the level but needs support on stairs	2
Slightly clumsy in walking	3
Normal	4
III. Sensation	
Arms: definitely impaired	0
slightly impaired or subjectively numb	1
normal	2
Trunk: 0-2 as above	
Legs: 0-2 as above	
IV. Bladder function	
Incontinent	0
Great difficulty	1
Slight difficulty	2
Normal	3
Total for normal patient	17

REFERENCE: Chapman JR, Hanson BP, Dettori JR, et a**l** (2007) *Spine Outcomes Measures and Instruments.* 1st ed. Stuttgart New York: Thieme. pp. 81-89, 249

Appendix K. Clinical and Peer Reviewers

Reviewer	Areas of expertise
Brian M. Drew, MD Assistant Clinical Professor Medical Director of Spine Unit Hamilton General Hospital (Ontario, Canada)	• Evidence-based practice • Spine fracture care • Adult spinal surgery • Spinal cord injury and clearance
Michael J. Lee, MD Assistant Professor, Orthopaedics & Sports Medicine University of Washington	• Orthopedic surgeon • Cadaveric/pathology correlation • Risk factor/complication evaluation
Jens Chapman MD Professor, Dept of Orthopedic Surgery, University of Washington School of Medicine	• Surgical treatment of spinal disorders • Disease severity • Spinal outcomes
Jennifer Mayfield, MD, MPH Primary Care and Preventative Medicine	• Clinical diabetes care • Quality assessment and improvement • Chronic disease registries • Electronic medical records • Primary care • Health Services Research
Ann Derleth, PhD, MSPH Health Services Researcher, Health Economics	• Quantitative methods for outcomes and economic analysis • Statistical methods for health services research including outcomes measures, disease severity and risk adjustment • Use of administrative data related to reimbursement policy
Sean D. Sullivan, PhD Director, Pharmaceutical Outcomes Research and Policy Program at University of Washington	• Research in pharmacy, health economics and outcomes and related areas

References

1. Food and Drug Administration (FDA). Clinical review for PMA (P040006) Charité artificial disc, DePuy Spine Inc (report on the Internet). Edited, United States Department of Health & Human Services, 2004.
2. Food and Drug Administration (FDA). In-depth statistical review for expedited PMA (P040006) Charite artificial disc, DePuy Spine Inc (report on the Internet). Edited, United States Department of Health & Human Services, 2004.
3. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED). Prosthesis intervertebral disc (report on the Internet). Edited, 2004.
4. Food and Drug Administration (FDA). New device approval: PRESTIGE cervical disc system - P060018 [report on the Internet]. Edited, 2007.
5. Food and Drug Administration (FDA). New device approval: ProDisc-C total disc replacement - P070001 [report on the Internet]. Edited, 2007.
6. Food and Drug Adminstration (FDA) Executive Summary, Bryan Cervical Disc. Edited, 2007.
7. NIH consensus conference: Total hip replacement. NIH Consensus Development Panel on Total Hip Replacement. Jama, 273(24): 1950-6, 1995.
8. NIH Consensus Statement on total knee replacement. NIH Consens State Sci Statements, 20(1): 1-34, 2003.
9. U.S. Artificial Disc Replacement Market to Reach $440 Million by 2013. In Business Wire. Edited, 2008.
10. Washington State Department of Health, Center for Health Statistics, Comprehensive Hospitalization Abstract Reporting System (2005-2007). Edited.
11. Abd-Alrahman, N.; Dokmak, A. S.; and Abou-Madawi, A.: Anterior cervical discectomy (ACD) versus anterior cervical fusion (ACF), clinical and radiological outcome study. Acta Neurochir (Wien), 141(10): 1089-92, 1999.
12. Amit, A., and Dorward, N.: Bryan cervical disc prosthesis: 12-Month clinical outcome. British Journal of Neurosurgery, 21(5): 478-484, 2007.
13. An, H. S. et al.: Introduction: disc degeneration: summary. Spine, 29(23): 2677-8, 2004.
14. Anderson, P. A., and Rouleau, J. P.: Intervertebral disc arthroplasty. Spine, 29(23): 2779-86, 2004.
15. Andersson, G. B.: The epidemiology of spinal disorders. In The Adult Spine: Principles and Practice, pp. 93-141. Edited by JW, F., 93-141, Philadelphia, Lippincott-Raven, 1997.
16. Atkins, D. et al.: Grading quality of evidence and strength of recommendations. Bmj, 328(7454): 1490, 2004.
17. Badley, E. M.; Webster, G. K.; and Rasooly, I.: The impact of musculoskeletal disorders in the population: are they just aches and pains? Findings from the 1990 Ontario Health Survey. J Rheumatol, 22(4): 733-9, 1995.
18. Bartels, R. H.; Donk, R.; van der Wilt, G. J.; Grotenhuis, J. A.; and Venderink, D.: Design of the PROCON trial: a prospective, randomized multi-center study comparing ervical anterior discectomy without fusion, with fusion or with arthroplasty. BMC Musculoskelet Disord, 7: 85, 2006.

19. Bertagnoli, R.; Duggal, N.; Pickett, G. E.; Wigfield, C. C.; Gill, S. S.; Karg, A.; and Voigt, S.: Cervical total disc replacement, part two: clinical results. Orthop Clin North Am, 36(3): 355-62, 2005.
20. Bertagnoli, R., and Kumar, S.: Indications for full prosthetic disc arthroplasty: a correlation of clinical outcome against a variety of indications. Eur Spine J, 11 Suppl 2: S131-6, 2002.
21. Bertagnoli, R. et al.: Lumbar total disc arthroplasty utilizing the ProDisc prosthesis in smokers versus nonsmokers: a prospective study with 2-year minimum follow-up. Spine, 31(9): 992-7, 2006.
22. Bertagnoli, R.; Yue, J. J.; Nanieva, R.; Fenk-Mayer, A.; Husted, D. S.; Shah, R. V.; and Emerson, J. W.: Lumbar total disc arthroplasty in patients older than 60 years of age: a prospective study of the ProDisc prosthesis with 2-year minimum follow-up period. J Neurosurg Spine, 4(2): 85-90, 2006.
23. Bertagnoli, R.; Yue, J. J.; Pfeiffer, F.; Fenk-Mayer, A.; Lawrence, J. P.; Kershaw, T.; and Nanieva, R.: Early results after ProDisc-C cervical disc replacement. J Neurosurg Spine, 2(4): 403-10, 2005.
24. Bertagnoli, R.; Yue, J. J.; Shah, R. V.; Nanieva, R.; Pfeiffer, F.; Fenk-Mayer, A.; Kershaw, T.; and Husted, D. S.: The treatment of disabling multilevel lumbar discogenic low back pain with total disc arthroplasty utilizing the ProDisc prosthesis: a prospective study with 2-year minimum follow-up. Spine, 30(19): 2192-9, 2005.
25. Bertagnoli, R.; Yue, J. J.; Shah, R. V.; Nanieva, R.; Pfeiffer, F.; Fenk-Mayer, A.; Kershaw, T.; and Husted, D. S.: The treatment of disabling single-level lumbar discogenic low back pain with total disc arthroplasty utilizing the Prodisc prosthesis: a prospective study with 2-year minimum follow-up. Spine, 30(19): 2230-6, 2005.
26. Blue Cross Blue Shield Association: Artificial Intervertebral Disc Arthroplasty for Treatment of Degenerative Disc Disease of the Cervical Spine [report on the Internet]. Edited, Technology Evaluation Center Assessment Program, 2007.
27. Blue Cross Blue Shield Association: Artificial vertebral disc replacement [report on the Internet]. Edited, Technology Evaluation Center Assessment Program, 2005.
28. Blumenthal, S.; McAfee, P. C.; Guyer, R. D.; Hochschuler, S. H.; Geisler, F. H.; Holt, R. T.; Garcia, R., Jr.; Regan, J. J.; and Ohnmeiss, D. D.: A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes. Spine, 30(14): 1565-75; discussion E387-91, 2005.
29. Brantigan, J. W.; Steffee, A. D.; Lewis, M. L.; Quinn, L. M.; and Persenaire, J. M.: Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. Spine, 25(11): 1437-46, 2000.
30. Brox, J. I. et al.: Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. Pain, 122(1-2): 145-55, 2006.
31. Brox, J. I. et al.: Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine, 28(17): 1913-21, 2003.

32. Burkus, J. K.; Heim, S. E.; Gornet, M. F.; and Zdeblick, T. A.: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech, 16(2): 113-22, 2003.
33. Cabanela, M. E.; Campbell, D. C., 2nd; and Henderson, E. D.: Total joint arthroplasty. The hip. Mayo Clin Proc, 54(9): 559-63, 1979.
34. Carragee, E. J. et al.: Treatment of neck pain: injections and surgical interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine, 33(4 Suppl): S153-69, 2008.
35. Caspi, I.; Levinkopf, M.; and Nerubay, J.: Results of lumbar disk prosthesis after a follow-up period of 48 months. Isr Med Assoc J, 5(1): 9-11, 2003.
36. Chiou, C. F. et al.: Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care, 41(1): 32-44, 2003.
37. Cho, K. J.; Suk, S. I.; Park, S. R.; Kim, J. H.; Kim, S. S.; Choi, W. K.; Lee, K. Y.; and Lee, S. R.: Complications in posterior fusion and instrumentation for degenerative lumbar scoliosis. Spine, 32(20): 2232-7, 2007.
38. Chou, W. Y.; Hsu, C. J.; Chang, W. N.; and Wong, C. Y.: Adjacent segment degeneration after lumbar spinal posterolateral fusion with instrumentation in elderly patients. Arch Orthop Trauma Surg, 122(1): 39-43, 2002.
39. Chung, S. S.; Lee, C. S.; and Kang, C. S.: Lumbar total disc replacement using ProDisc II: a prospective study with a 2-year minimum follow-up. J Spinal Disord Tech, 19(6): 411-5, 2006.
40. Chung, S. S.; Lee, C. S.; Kang, C. S.; and Kim, S. H.: The effect of lumbar total disc replacement on the spinopelvic alignment and range of motion of the lumbar spine. J Spinal Disord Tech, 19(5): 307-11, 2006.
41. Cihangiroglu, M.; Yildirim, H.; Bozgeyik, Z.; Senol, U.; Ozdemir, H.; Topsakal, C.; and Yilmaz, S.: Observer variability based on the strength of MR scanners in the assessment of lumbar degenerative disc disease. Eur J Radiol, 51(3): 202-8, 2004.
42. Cinotti, G.; David, T.; and Postacchini, F.: Results of disc prosthesis after a minimum follow-up period of 2 years. Spine, 21(8): 995-1000, 1996.
43. Coric, D.; Finger, F.; and Boltes, P.: Prospective randomized controlled study of the Bryan Cervical Disc: early clinical results from a single investigational site. J Neurosurg Spine, 4(1): 31-5, 2006.
44. Cunningham, B. W. et al.: Distribution of in vivo and in vitro range of motion following 1-level arthroplasty with the CHARITE artificial disc compared with fusion. J Neurosurg Spine, 8(1): 7-12, 2008.
45. David, T.: Long-term results of one-level lumbar arthroplasty: minimum 10-year follow-up of the CHARITE artificial disc in 106 patients. Spine, 32(6): 661-6, 2007.
46. de Kleuver, M.; Oner, F. C.; and Jacobs, W. C.: Total disc replacement for chronic low back pain: background and a systematic review of the literature. Eur Spine J, 12(2): 108-16, 2003.
47. Deyo, R. A.; Gray, D. T.; Kreuter, W.; Mirza, S.; and Martin, B. I.: United States trends in lumbar fusion surgery for degenerative conditions. Spine, 30(12): 1441-5; discussion 1446-7, 2005.

48. Dowd, G. C., and Wirth, F. P.: Anterior cervical discectomy: is fusion necessary? J Neurosurg, 90(1 Suppl): 8-12, 1999.
49. Drummond MF: Methods for the economic evaluation of health care programmes. Edited, Oxford; New York, Oxford University Press, 2005.
50. Duggal, N.; Pickett, G. E.; Mitsis, D. K.; and Keller, J. L.: Early clinical and biomechanical results following cervical arthroplasty. Neurosurg Focus, 17(3): E9, 2004.
51. Errico, T. J.: Lumbar disc arthroplasty. Clin Orthop Relat Res, (435): 106-17, 2005.
52. Etebar, S., and Cahill, D. W.: Risk factors for adjacent-segment failure following lumbar fixation with rigid instrumentation for degenerative instability. J Neurosurg, 90(2 Suppl): 163-9, 1999.
53. Fairbank, J.; Frost, H.; Wilson-MacDonald, J.; Yu, L. M.; Barker, K.; and Collins, R.: Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. BMJ, 330(7502): 1233, 2005.
54. Fernstrom, U.: Arthroplasty with intercorporal endoprosthesis in herniated disc and in painful disc. Acta Chir Scand Suppl, 357: 154-9, 1966.
55. Fong, S. Y.; DuPlessis, S. J.; Casha, S.; and Hurlbert, R. J.: Design limitations of Bryan disc arthroplasty. Spine J, 6(3): 233-41, 2006.
56. Fraser, R. D.; Ross, E. R.; Lowery, G. L.; Freeman, B. J.; and Dolan, M.: AcroFlex design and results. Spine J, 4(6 Suppl): 245S-251S, 2004.
57. Frelinghuysen, P.; Huang, R. C.; Girardi, F. P.; and Cammisa, F. P., Jr.: Lumbar total disc replacement part I: rationale, biomechanics, and implant types. Orthop Clin North Am, 36(3): 293-9, 2005.
58. Fritzell, P.; Hagg, O.; and Nordwall, A.: Complications in lumbar fusion surgery for chronic low back pain: comparison of three surgical techniques used in a prospective randomized study. A report from the Swedish Lumbar Spine Study Group. Eur Spine J, 12(2): 178-89, 2003.
59. Fritzell, P.; Hagg, O.; Wessberg, P.; and Nordwall, A.: 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine, 26(23): 2521-32; discussion 2532-4, 2001.
60. Frymoyer, J. W.: The economics of spinal disorders. In The Adult Spine: Principles and Practice, pp. 143-150. Edited by JW, F., 143-150, Philadelphia, Lippincott-Raven, 1997.
61. Geisler, F. H.; Blumenthal, S. L.; Guyer, R. D.; McAfee, P. C.; Regan, J. J.; Johnson, J. P.; and Mullin, B.: Neurological complications of lumbar artificial disc replacement and comparison of clinical results with those related to lumbar arthrodesis in the literature: results of a multicenter, prospective, randomized investigational device exemption study of Charite intervertebral disc. Invited submission from the Joint Section Meeting on disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine, 1(2): 143-54, 2004.
62. Ghiselli, G.; Wang, J. C.; Bhatia, N. N.; Hsu, W. K.; and Dawson, E. G.: Adjacent segment degeneration in the lumbar spine. J Bone Joint Surg Am, 86-A(7): 1497-503, 2004.
63. Gibson, J. N., and Waddell, G.: Surgery for degenerative lumbar spondylosis

Surgery for degenerative lumbar spondylosis: updated Cochrane Review. Cochrane Database Syst Rev., 30(4): CD001352., 2005.

64. Goetz, C. G.: Textbook of Clinical Neurology. Edited, Philadelphia, PA, Saunders Elsevier, 2003.
65. Goffin, J.; Geusens, E.; Vantomme, N.; Quintens, E.; Waerzeggers, Y.; Depreitere, B.; Van Calenbergh, F.; and van Loon, J.: Long-term follow-up after interbody fusion of the cervical spine. J Spinal Disord Tech, 17(2): 79-85, 2004.
66. Goffin, J. et al.: Intermediate follow-up after treatment of degenerative disc disease with the Bryan Cervical Disc Prosthesis: single-level and bi-level. Spine, 28(24): 2673-8, 2003.
67. Guyer, R. D.; Geisler, F. H.; Blumenthal, S. L.; McAfee, P. C.; and Mullin, B. B.: Effect of age on clinical and radiographic outcomes and adverse events following 1-level lumbar arthroplasty after a minimum 2-year follow-up. J Neurosurg Spine, 8(2): 101-7, 2008.
68. Guyer RD, T. S., Regan JJ: An economic model of one-level lumbar arthoplasty versus fusion. Spine Journal, 7(5): 558-562, 2007.
69. Hallab, N.; Link, H. D.; and McAfee, P. C.: Biomaterial optimization in total disc arthroplasty. Spine, 28(20): S139-52, 2003.
70. Hambly, M. F.; Wiltse, L. L.; Raghavan, N.; Schneiderman, G.; and Koenig, C.: The transition zone above a lumbosacral fusion. Spine, 23(16): 1785-92, 1998.
71. Harris, W. H., and Sledge, C. B.: Total hip and total knee replacement (1). N Engl J Med, 323(11): 725-31, 1990.
72. Harris, W. H., and Sledge, C. B.: Total hip and total knee replacement (2). N Engl J Med, 323(12): 801-7, 1990.
73. Hartvigsen, J.; Christensen, K.; and Frederiksen, H.: Back and neck pain exhibit many common features in old age: a population-based study of 4,486 Danish twins 70-102 years of age. Spine, 29(5): 576-80, 2004.
74. Heidecke, V.; Burkert, W.; Brucke, M.; and Rainov, N. G.: Intervertebral disc replacement for cervical degenerative disease--clinical results and functional outcome at two years in patients implanted with the Bryan cervical disc prosthesis. Acta Neurochir (Wien), 150(5): 453-9; discussion 459, 2008.
75. Herkowitz, H. N.; Kurz, L. T.; and Overholt, D. P.: Surgical management of cervical soft disc herniation. A comparison between the anterior and posterior approach. Spine, 15(10): 1026-30, 1990.
76. Hermsmeyer, J. T.: Outcomes Measures and Instruments. In Spine Outcomes Measures and Instruments, pp. 114-115, 249. Edited by Chapman, J. R.; Hanson, B. P.; Dettori, J. R.; and Norvell, D. C., 114-115, 249, Stuttgart, New York, Thieme, 2007.
77. Higgins, J. P., and Thompson, S. G.: Quantifying heterogeneity in a meta-analysis. Stat Med, 21(11): 1539-58, 2002.
78. Higgins, J. P.; Thompson, S. G.; Deeks, J. J.; and Altman, D. G.: Measuring inconsistency in meta-analyses. Bmj, 327(7414): 557-60, 2003.
79. Hilibrand, A. S.; Carlson, G. D.; Palumbo, M. A.; Jones, P. K.; and Bohlman, H. H.: Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. J Bone Joint Surg Am, 81(4): 519-28, 1999.

80. Hoang, L.; Thongtrangan, I.; and Kim, D.: Historical review of cervical arthroplasty. Edited, 2004.
81. Huang, R. C.; Lim, M. R.; Girardi, F. P.; and Cammisa, F. P., Jr.: The prevalence of contraindications to total disc replacement in a cohort of lumbar surgical patients. Spine, 29(22): 2538-41, 2004.
82. Huang, R. C.; Tropiano, P.; Marnay, T.; Girardi, F. P.; Lim, M. R.; and Cammisa, F. P., Jr.: Range of motion and adjacent level degeneration after lumbar total disc replacement. Spine J, 6(3): 242-7, 2006.
83. Ishihara, H.; Kanamori, M.; Kawaguchi, Y.; Nakamura, H.; and Kimura, T.: Adjacent segment disease after anterior cervical interbody fusion. Spine J, 4(6): 624-8, 2004.
84. Jollenbeck, B.; Hahne, R.; Schubert, A.; and Firsching, R.: Early experiences with cervical disc prostheses. Zentralbl Neurochir, 65(3): 123-7, 2004.
85. Jones, C. A.; Voaklander, D. C.; Johnston, D. W.; and Suarez-Almazor, M. E.: Health related quality of life outcomes after total hip and knee arthroplasties in a community based population. J Rheumatol, 27(7): 1745-52, 2000.
86. Kanayama, M.; Hashimoto, T.; Shigenobu, K.; Harada, M.; Oha, F.; Ohkoshi, Y.; Tada, H.; Yamamoto, K.; and Yamane, S.: Adjacent-segment morbidity after Graft ligamentoplasty compared with posterolateral lumbar fusion. J Neurosurg, 95(1 Suppl): 5-10, 2001.
87. Katsuura, A.; Hukuda, S.; Saruhashi, Y.; and Mori, K.: Kyphotic malalignment after anterior cervical fusion is one of the factors promoting the degenerative process in adjacent intervertebral levels. Eur Spine J, 10(4): 320-4, 2001.
88. Katz, J. N. et al.: Association of hospital and surgeon volume of total hip replacement with functional status and satisfaction three years following surgery. Arthritis Rheum, 48(2): 560-8, 2003.
89. Kim, D. H.; Ryu, K. S.; Kim, M. K.; and Park, C. K.: Factors influencing segmental range of motion after lumbar total disc replacement using the ProDisc II prosthesis. J Neurosurg Spine, 7(2): 131-8, 2007.
90. Kim, S. H.; Shin, H. C.; Shin, D. A.; Kim, K. N.; and Yoon do, H.: Early clinical experience with the mobi-C disc prosthesis. Yonsei Med J, 48(3): 457-64, 2007.
91. Kulkarni, V.; Rajshekhar, V.; and Raghuram, L.: Accelerated spondylotic changes adjacent to the fused segment following central cervical corpectomy: magnetic resonance imaging study evidence. J Neurosurg, 100(1 Suppl Spine): 2-6, 2004.
92. Kumar, M. N.; Jacquot, F.; and Hall, H.: Long-term follow-up of functional outcomes and radiographic changes at adjacent levels following lumbar spine fusion for degenerative disc disease. Eur Spine J, 10(4): 309-13, 2001.
93. Lafuente, J.; Casey, A. T.; Petzold, A.; and Brew, S.: The Bryan cervical disc prosthesis as an alternative to arthrodesis in the treatment of cervical spondylosis: 46 consecutive cases. J Bone Joint Surg Br, 87(4): 508-12, 2005.
94. Laupacis, A.; Bourne, R.; Rorabeck, C.; Feeny, D.; Wong, C.; Tugwell, P.; Leslie, K.; and Bullas, R.: The effect of elective total hip replacement on health-related quality of life. J Bone Joint Surg Am, 75(11): 1619-26, 1993.

95. Le Huec, J. C.; Mathews, H.; Basso, Y.; Aunoble, S.; Hoste, D.; Bley, B.; and Friesem, T.: Clinical results of Maverick lumbar total disc replacement: two-year prospective follow-up. Orthop Clin North Am, 36(3): 315-22, 2005.
96. Leivseth, G.; Braaten, S.; Frobin, W.; and Brinckmann, P.: Mobility of lumbar segments instrumented with a ProDisc II prosthesis: A two-year follow-up study. Spine, 31(15): 1726-1733, 2006.
97. Lemaire, J. P.; Carrier, H.; Sariali el, H.; Skalli, W.; and Lavaste, F.: Clinical and radiological outcomes with the Charite artificial disc: a 10-year minimum follow-up. J Spinal Disord Tech, 18(4): 353-9, 2005.
98. Leung, C.; Casey, A. T.; Goffin, J.; Kehr, P.; Liebig, K.; Lind, B.; Logroscino, C.; and Pointillart, V.: Clinical significance of heterotopic ossification in cervical disc replacement: a prospective multicenter clinical trial. Neurosurgery, 57(4): 759-63; discussion 759-63, 2005.
99. Levin, D. A.; Bendo, J. A.; Quirno, M.; Errico, T.; Goldstein, J.; and Spivak, J.: Comparative charge analysis of one- and two-level lumbar total disc arthroplasty versus circumferential lumbar fusion. Spine, 32(25): 2905-9, 2007.
100. Levin DA, B. J., Quirno M, Errico T, Goldstein J, Spivak J: Comparative charge analysis of one- and two-level lumbar total disc arthroplasty versus circumferential lumbar fusion. Spine 32(25): 2905-9, 2007.
101. Lin, E. L., and Wang, J. C.: Total disk arthroplasty. J Am Acad Orthop Surg, 14(13): 705-14, 2006.
102. Liu, F.; Cheng, J.; Komistek, R. D.; Mahfouz, M. R.; and Sharma, A.: In vivo evaluation of dynamic characteristics of the normal, fused, and disc replacement cervical spines. Spine, 32(23): 2578-84, 2007.
103. Lunsford, L. D.; Bissonette, D. J.; Jannetta, P. J.; Sheptak, P. E.; and Zorub, D. S.: Anterior surgery for cervical disc disease. Part 1: Treatment of lateral cervical disc herniation in 253 cases. J Neurosurg, 53(1): 1-11, 1980.
104. Martins, A. N.: Anterior cervical discectomy with and without interbody bone graft. J Neurosurg, 44(3): 290-5, 1976.
105. Mathers, C.: The burden of disease and injury in Australia. Edited, Canberra, Australian Institute of Health and Welfare, 1999.
106. Mayer, H. M.: Total lumbar disc replacement. J Bone Joint Surg Br, 87(8): 1029-37, 2005.
107. Mayer, H. M., and Wiechert, K.: Microsurgical anterior approaches to the lumbar spine for interbody fusion and total disc replacement. Neurosurgery, 51(5 Suppl): S159-65, 2002.
108. McAfee, P. C.: The indications for lumbar and cervical disc replacement. Spine J, 4(6 Suppl): 177S-181S, 2004.
109. McAfee, P. C. et al.: A prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part II: evaluation of radiographic outcomes and correlation of surgical technique accuracy with clinical outcomes. Spine, 30(14): 1576-83; discussion E388-90, 2005.

110. McAfee, P. C. et al.: Revisability of the CHARITE artificial disc replacement: analysis of 688 patients enrolled in the U.S. IDE study of the CHARITE Artificial Disc. Spine, 31(11): 1217-26, 2006.
111. McCullen, G. M., and Yuan, H. A.: Artificial disc: current developments in artificial disc replacement. Curr Opin Orthop, 14: 138-143, 2003.
112. Medical Services Advisory Committee (Australia): Artificial intervertebral disc replacement (Total disc arthroplasty). Edited, Canberra, Commonwealth of Australia, 2006.
113. Mehren, C.; Suchomel, P.; Grochulla, F.; Barsa, P.; Sourkova, P.; Hradil, J.; Korge, A.; and Mayer, H. M.: Heterotopic ossification in total cervical artificial disc replacement. Spine, 31(24): 2802-6, 2006.
114. Miyakoshi, N.; Abe, E.; Shimada, Y.; Okuyama, K.; Suzuki, T.; and Sato, K.: Outcome of one-level posterior lumbar interbody fusion for spondylolisthesis and postoperative intervertebral disc degeneration adjacent to the fusion. Spine, 25(14): 1837-42, 2000.
115. Mummaneni, P. V.; Burkus, J. K.; Haid, R. W.; Traynelis, V. C.; and Zdeblick, T. A.: Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: a randomized controlled clinical trial. J Neurosurg Spine, 6(3): 198-209, 2007.
116. Murphy, M. G., and Gado, M.: Anterior cervical discectomy without interbody bone graft. J Neurosurg, 37(1): 71-4, 1972.
117. Nabhan, A.; Ahlhelm, F.; Pitzen, T.; Steudel, W. I.; Jung, J.; Shariat, K.; Steimer, O.; Bachelier, F.; and Pape, D.: Disc replacement using Pro-Disc C versus fusion: a prospective randomised and controlled radiographic and clinical study. Eur Spine J, 16(3): 423-30, 2007.
118. Nabhan, A.; Ahlhelm, F.; Shariat, K.; Pitzen, T.; Steimer, O.; Steudel, W. I.; and Pape, D.: The ProDisc-C prosthesis: clinical and radiological experience 1 year after surgery. Spine, 32(18): 1935-41, 2007.
119. Ofman, J. J.; Sullivan, S. D.; Neumann, P. J.; Chiou, C. F.; Henning, J. M.; Wade, S. W.; and Hay, J. W.: Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm, 9(1): 53-61, 2003.
120. Patel, R. K., and Slipman, C. W.: Lumbar degenerative disk disease. Edited, Omaha, 2007.
121. Peng-Fei, S., and Yu-Hua, J.: Cervical disc prosthesis replacement and interbody fusion: a comparative study. Int Orthop, 32(1): 103-6, 2008.
122. Petersilge, C. A.: Lumbar disc replacement. Semin Musculoskelet Radiol, 10(1): 22-9, 2006.
123. Phillips, B.; Ball, C.; Sackett, D.; Badenoch, D.; Straus, S.; Haynes, B.; and Dawes, M.: Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp. Edited, 2001.
124. Piaggio, G.; Elbourne, D. R.; Altman, D. G.; Pocock, S. J.; and Evans, S. J.: Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. Jama, 295(10): 1152-60, 2006.
125. Pickett, G. E.; Sekhon, L. H.; Sears, W. R.; and Duggal, N.: Complications with cervical arthroplasty. J Neurosurg Spine, 4(2): 98-105, 2006.

126. Pickett, G. E.; Van Soelen, J.; and Duggal, N.: Controversies in cervical discectomy and fusion: practice patterns among Canadian surgeons. Can J Neurol Sci, 31(4): 478-83, 2004.
127. Pimenta, L.; McAfee, P. C.; Cappuccino, A.; Bellera, F. P.; and Link, H. D.: Clinical experience with the new artificial cervical PCM (Cervitech) disc. Spine J, 4(6 Suppl): 315S-321S, 2004.
128. Pointillart, V.: Cervical disc prosthesis in humans: first failure. Spine, 26(5): E90-2, 2001.
129. Porchet, F., and Metcalf, N. H.: Clinical outcomes with the Prestige II cervical disc: preliminary results from a prospective randomized clinical trial. Neurosurg Focus, 17(3): E6, 2004.
130. Punt, I. M.; Visser, V. M.; van Rhijn, L. W.; Kurtz, S. M.; Antonis, J.; Schurink, G. W.; and van Ooij, A.: Complications and reoperations of the SB Charite lumbar disc prosthesis: experience in 75 patients. Eur Spine J, 17(1): 36-43, 2008.
131. Putzier, M.; Funk, J. F.; Schneider, S. V.; Gross, C.; Tohtz, S. W.; Khodadadyan-Klostermann, C.; Perka, C.; and Kandziora, F.: Charite total disc replacement--clinical and radiographical results after an average follow-up of 17 years. Eur Spine J, 15(2): 183-95, 2006.
132. Rabin, D.; Pickett, G. E.; Bisnaire, L.; and Duggal, N.: The kinematics of anterior cervical discectomy and fusion versus artificial cervical disc: a pilot study. Neurosurgery, 61(3 Suppl): 100-4; discussion 104-5, 2007.
133. Rao, R. D.; Gourab, K.; and David, K. S.: Operative treatment of cervical spondylotic myelopathy. J Bone Joint Surg Am, 88(7): 1619-40, 2006.
134. Ratliff, J. K., and Cooper, P. R.: Cervical laminoplasty: a critical review. J Neurosurg, 98(3 Suppl): 230-8, 2003.
135. Regan, J. J.; McAfee, P. C.; Blumenthal, S. L.; Guyer, R. D.; Geisler, F. H.; Garcia, R., Jr.; and Maxwell, J. H.: Evaluation of surgical volume and the early experience with lumbar total disc replacement as part of the investigational device exemption study of the Charite Artificial Disc. Spine, 31(19): 2270-6, 2006.
136. Robertson, J. T., and Metcalf, N. H.: Long-term outcome after implantation of the Prestige I disc in an end-stage indication: 4-year results from a pilot study. Neurosurg Focus, 17(3): E10, 2004.
137. Robertson, J. T.; Papadopoulos, S. M.; and Traynelis, V. C.: Assessment of adjacent-segment disease in patients treated with cervical fusion or arthroplasty: a prospective 2-year study. J Neurosurg Spine, 3(6): 417-23, 2005.
138. Rodts, M. F.: Total disc replacement arthroplasty. Orthop Nurs, 23(3): 216-9, 2004.
139. Roh, J. S.; Teng, A. L.; Yoo, J. U.; Davis, J.; Furey, C.; and Bohlman, H. H.: Degenerative disorders of the lumbar and cervical spine. Orthop Clin North Am, 36(3): 255-62, 2005.
140. SariAli el, H.; Lemaire, J. P.; Pascal-Mousselard, H.; Carrier, H.; and Skalli, W.: In vivo study of the kinematics in axial rotation of the lumbar spine after total intervertebral disc replacement: long-term results: a 10-14 years follow up evaluation. Eur Spine J, 15(10): 1501-10, 2006.
141. Sasso, R. C.; Foulk, D. M.; and Hahn, M.: Prospective, randomized trial of metal-on-metal artificial lumbar disc replacement: initial results for treatment of discogenic pain. Spine, 33(2): 123-31, 2008.

142. Sasso, R. C.; Smucker, J. D.; Hacker, R. J.; and Heller, J. G.: Clinical outcomes of BRYAN cervical disc arthroplasty: a prospective, randomized, controlled, multicenter trial with 24-month follow-up. J Spinal Disord Tech, 20(7): 481-91, 2007.
143. Schwarzer, A. C.; Aprill, C. N.; Derby, R.; Fortin, J.; Kine, G.; and Bogduk, N.: The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine, 20(17): 1878-83, 1995.
144. Seitsalo, S.; Schlenzka, D.; Poussa, M.; and Osterman, K.: Disc degeneration in young patients with isthmic spondylolisthesis treated operatively or conservatively: a long-term follow-up. Eur Spine J, 6(6): 393-7, 1997.
145. Sekhon, L. H.: Cervical arthroplasty in the management of spondylotic myelopathy: 18-month results. Neurosurg Focus, 17(3): E8, 2004.
146. Sekhon, L. H., and Ball, J. R.: Artificial cervical disc replacement: principles, types and techniques. Neurol India, 53(4): 445-50, 2005.
147. Shim, C. S.; Lee, S. H.; Park, H. J.; Kang, H. S.; and Hwang, J. H.: Early clinical and radiologic outcomes of cervical arthroplasty with Bryan Cervical Disc prosthesis. J Spinal Disord Tech, 19(7): 465-70, 2006.
148. Shim, C. S. et al.: CHARITI versus ProDisc: A comparative study of a minimum 3-year follow-up. Spine, 32(9): 1012-1018, 2007.
149. Siepe, C. J.; Mayer, H. M.; Heinz-Leisenheimer, M.; and Korge, A.: Total lumbar disc replacement: different results for different levels. Spine, 32(7): 782-90, 2007.
150. Siepe, C. J.; Wiechert, K.; Khattab, M. F.; Korge, A.; and Mayer, H. M.: Total lumbar disc replacement in athletes: clinical results, return to sport and athletic performance. Eur Spine J, 16(7): 1001-13, 2007.
151. Singh K, V. A., Albert TJ: Assessing the potential impact of total disc arthroplasty on surgeon practice patterns in North America. Spine Journal, 4(6S): S195-201, 2004.
152. Snapinn, S. M.: Noninferiority trials. Curr Control Trials Cardiovasc Med, 1(1): 19-21, 2000.
153. Span, M. M.; TenVergert, E. M.; van der Hilst, C. S.; and Stolk, R. P.: Noninferiority testing in cost-minimization studies: Practical issues concerning power analysis. Int J Technol Assess Health Care, 22(2): 261-6, 2006.
154. Teramoto, T.; Ohmori, K.; Takatsu, T.; Inoue, H.; Ishida, Y.; and Suzuki, K.: Long-term results of the anterior cervical spondylodesis. Neurosurgery, 35(1): 64-8, 1994.
155. The Medical Advisory Secretariat: Artificial discs for lumbar and cervical degenerative disc disease - update. Edited, Toronto, Ministry of Health and Long Term Care, 2006.
156. Tortolani, P. J.; Cunningham, B. W.; Eng, M.; McAfee, P. C.; Holsapple, G. A.; and Adams, K. A.: Prevalence of heterotopic ossification following total disc replacement. A prospective, randomized study of two hundred and seventy-six patients. J Bone Joint Surg Am, 89(1): 82-8, 2007.
157. Tropiano, P.; Huang, R. C.; Girardi, F. P.; Cammisa, F. P., Jr.; and Marnay, T.: Lumbar total disc replacement. Seven to eleven-year follow-up. J Bone Joint Surg Am, 87(3): 490-6, 2005.

158. Tropiano, P.; Huang, R. C.; Girardi, F. P.; and Marnay, T.: Lumbar disc replacement: preliminary results with ProDisc II after a minimum follow-up period of 1 year. J Spinal Disord Tech, 16(4): 362-8, 2003.
159. Truumees, E., and Herkowitz, H. N.: Cervical spondylotic myelopathy and radiculopathy. Instr Course Lect, 49: 339-60, 2000.
160. West, S., King V, Carey TS, et.al.: Systems to Rate the Strength of Scientific Evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center, Contract No. 290-97-0011). Edited, Agency for Healthcare Research and Quality, Rockville, MD, 2002.
161. Wigfield, C.; Gill, S.; Nelson, R.; Langdon, I.; Metcalf, N.; and Robertson, J.: Influence of an artificial cervical joint compared with fusion on adjacent-level motion in the treatment of degenerative cervical disc disease. J Neurosurg, 96(1 Suppl): 17-21, 2002.
162. Wigfield, C. C.; Gill, S. S.; Nelson, R. J.; Metcalf, N. H.; and Robertson, J. T.: The new Frenchay artificial cervical joint: results from a two-year pilot study. Spine, 27(22): 2446-52, 2002.
163. Wright, J. G.; Swiontkowski, M. F.; and Heckman, J. D.: Introducing levels of evidence to the journal. J Bone Joint Surg Am, 85-A(1): 1-3, 2003.
164. Xu, Y. C.; Liu, S. L.; Huang, D. S.; Shen, H. Y.; Li, C. H.; and Ma, R. F.: Correlated evaluation on the spinal segment motion scope and the alteration of the corresponding parameters after artificial lumbar intervertebral disc replacement. Ch J of Clin Rehab, 8(32): 7294-96, 2004.
165. Yang, S.; Hu, Y.; Zhao, J.; He, X.; Liu, Y.; Xu, W.; Du, J.; and Fu, D.: Follow-up study on the motion range after treatment of degenerative disc disease with the Bryan cervical disc prosthesis. J Huazhong Univ Sci Technolog Med Sci, 27(2): 176-8, 2007.
166. Yoon, D. H.; Yi, S.; Shin, H. C.; Kim, K. N.; and Kim, S. H.: Clinical and radiological results following cervical arthroplasty. Acta Neurochirurgica, 148(9): 943-950, 2006.
167. Young, W. F.: Cervical spondylotic myelopathy: a common cause of spinal cord dysfunction in older persons. Am Fam Physician, 62(5): 1064-70, 1073, 2000.
168. Yue, W. M.; Brodner, W.; and Highland, T. R.: Long-term results after anterior cervical discectomy and fusion with allograft and plating: a 5- to 11-year radiologic and clinical follow-up study. Spine, 30(19): 2138-44, 2005.
169. Zdeblick, T. A.: The treatment of degenerative lumbar disorders. A critical review of the literature. Spine, 20(24 Suppl): 126S-137S, 1995.
170. Zeegers, W. S.; Bohnen, L. M.; Laaper, M.; and Verhaegen, M. J.: Artificial disc replacement with the modular type SB Charite III: 2-year results in 50 prospectively studied patients. Eur Spine J, 8(3): 210-7, 1999.
171. Zigler, J. et al.: Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine, 32(11): 1155-62; discussion 1163, 2007.