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Artificial Discs for Lumbar and Cervical Degenerative Disc Disease –Update

An Evidence-Based Analysis

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Medical Advisory Secretariat
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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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Abbreviations

ADR	Artificial disc replacement
ALIF	Anterior lumbar interbody fusion
BAK	Bagby & Kuslich
CI	Confidence interval
DDD	Degenerative disc disease
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDE	Investigational device exemption
ITT	Intent-to-treat
NDI	Neck disability index
ODI	Oswestry disability index
RCT	Randomized controlled trial
ROM	Range of motion
SB	Shellnack Buttner-Janz
SF-36	Short-form 36
VAS	Visual analog scale

Glossary

Arthrodesis	The surgical fixation of a joint by a procedure designed to accomplish fusion of the joint surfaces by promoting the proliferation of bone cells. Also called artificial ankylosis.
Arthroplasty	A surgical procedure to remove and replace a diseased or damaged joint with an artificial joint (a prosthesis).
Degenerative disc disease	Deterioration in disc structure and function, which commonly causes pain and loss of function.
Facet Joint	A joint between 2 adjacent vertebrae. Each vertebra is connected at the intervertebral disk in the front and the 2 facet joints in the back.
Intradiscal electrotherapy	Nonsurgical procedure used to treat low back pain which involves percutaneous introduction of a heated catheter into the disc under fluoroscopy.
Kyphosis	A condition where parts of the spinal column lose some or all of their lordotic profile (i.e., a convex curvature). When related to a single vertebra, describes the angle created between the superior and inferior endplates.
Laminectomy	Excision of 1 or more laminae of the vertebrae. Removal of the lamina, the bony element covering the posterior portion of the spinal canal
Laminotomy	An opening made in a lamina. Formation of a hole in the lamina without disrupting the continuity of the entire lamina to approach the intervertebral disc or neural structures.
Lordosis	The inward curvature of the spine at the lower back; while curvature of this sort is normal to a certain degree, it can become excessive due to medical conditions.
Myelopathy	Any of various functional disturbances or pathological changes in the spinal cord, often referring to nonspecific lesions in contrast to the inflammatory lesions of myelitis.
Neck Disability Index	A modified Oswestry Disability Index questionnaire, which can be used to rate disability and to track patient progress quantitatively.
Oswestry Disability Index	A measure used to indicate the extent to which a person's functional level is restricted by pain.
Polyethylene	Also called polyethene, this is one of the simplest and most inexpensive polymers. It is a waxy, chemically inert plastic.
Pseudoarthrosis	Failure to achieve a solid bone fusion.

Radicular pain	Pain radiating down the arm or leg in a specific pattern secondary to nerve root compression.
Radiculopathy	Disease of the nerve roots.
SF-36	A brief and comprehensive generic, quality of life questionnaire, or rating scale, which is able to distinguish between patients with a given disease or condition, and the general population.
Spondylosis	A general term for degenerative spinal changes due to osteoarthritis.
Spondylosyndesis	Spinal fusion.
Visual Analog Scale	A bipolar scale used to determine the degree of stimuli a patient is experiencing.

Executive Summary

Objective

To assess the safety and efficacy of artificial disc replacement (ADR) technology for degenerative disc disease (DDD).

Clinical Need

Degenerative disc disease is the term used to describe the deterioration of 1 or more intervertebral discs of the spine. The prevalence of DDD is roughly described in proportion to age such that 40% of people aged 40 years have DDD, increasing to 80% among those aged 80 years or older. Low back pain is a common symptom of lumbar DDD; neck and arm pain are common symptoms of cervical DDD. Nonsurgical treatments can be used to relieve pain and minimize disability associated with DDD. However, it is estimated that about 10% to 20% of people with lumbar DDD and up to 30% with cervical DDD will be unresponsive to nonsurgical treatments. In these cases, surgical treatment is considered. Spinal fusion (arthrodesis) is the process of fusing or joining 2 bones and is considered the surgical gold standard for DDD.

Artificial disc replacement is the replacement of the degenerated intervertebral disc with an artificial disc in people with DDD of the lumbar or cervical spine that has been unresponsive to nonsurgical treatments for at least 6 months. Unlike spinal fusion, ADR preserves movement of the spine, which is thought to reduce or prevent the development of adjacent segment degeneration. Additionally, a bone graft is not required for ADR, and this alleviates complications, including bone graft donor site pain and pseudoarthrosis. It is estimated that about 5% of patients who require surgery for DDD will be candidates for ADR.

Review Strategy

The Medical Advisory Secretariat conducted a computerized search of the literature published between 2003 and September 2005 to answer the following questions:

- What is the effectiveness of ADR in people with DDD of the lumbar or cervical regions of the spine compared with spinal fusion surgery?
- Does an artificial disc reduce the incidence of adjacent segment degeneration (ASD) compared with spinal fusion?
- What is the rate of major complications (device failure, reoperation) with artificial discs compared with surgical spinal fusion?

One reviewer evaluated the internal validity of the primary studies using the criteria outlined in the Cochrane Musculoskeletal Injuries Group Quality Assessment Tool. The quality of concealment allocation was rated as: A, clearly yes; B, unclear; or C, clearly no. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review. A random effects model meta-analysis was conducted when data were available from 2 or more randomized controlled trials (RCTs) and when there was no statistical and or clinical heterogeneity among studies. Bayesian analyses were undertaken to do the following:

- Examine the influence of missing data on clinical success rates;
- Compute the probability that artificial discs were superior to spinal fusion (on the basis of clinical success rates);
- Examine whether the results were sensitive to the choice of noninferiority margin.

Summary of Findings

The literature search yielded 140 citations. Of these, 1 Cochrane systematic review, 1 RCT, and 10 case series were included in this review. Unpublished data from an RCT reported in the grey literature were obtained from the manufacturer of the device. The search also yielded 8 health technology assessments evaluating ADR that are also included in this review.

Six of the 8 health technology assessments concluded that there is insufficient evidence to support the use of either lumbar or cervical ADR. The results of the remaining 2 assessments (one each for lumbar and cervical ADR) led to a National Institute for Clinical Excellence guidance document supporting the safety and effectiveness of lumbar and cervical ADR with the proviso that an ongoing audit of all clinical outcomes be undertaken owing to a lack of long-term outcome data from clinical trials.

Regarding lumbar ADR, data were available from 2 noninferiority RCTs to complete a meta-analysis. The following clinical, health systems, and adverse event outcome measures were synthesized: primary outcome of clinical success, Oswestry Disability Index (ODI) scores, pain VAS scores, patient satisfaction, duration of surgery, amount of blood loss, length of hospital stay, rate of device failure, and rate of reoperation.

The meta-analysis of overall clinical success supported the noninferiority of lumbar ADR compared with spinal fusion at 24-month follow-up. Of the remaining clinical outcome measures (ODI, pain VAS scores, SF-36 scores [mental and physical components], patient satisfaction, and return to work status), only patient satisfaction and scores on the physical component scale of the SF-36 questionnaire were significantly improved in favour of lumbar ADR compared with spinal fusion at 24 months follow-up. Blood loss and surgical time showed statistical heterogeneity; therefore, meta-analysis results are not interpretable. Length of hospital stay was significantly shorter in patients receiving the ADR compared with controls. Neither the number of device failures nor the number of neurological complications at 24 months was statistically significantly different between the ADR and fusion treatment groups. However, there was a trend towards fewer neurological complications at 24 months in the ADR treatment group compared with the spinal fusion treatment group.

Results of the Bayesian analyses indicated that the influence of missing data on the outcome measure of clinical success was minimal. The Bayesian model indicated that the probability for ADR being better than spinal fusion was 79%. The probability of ADR being noninferior to spinal fusion using a -10% noninferiority bound was 92%, and using a -15% noninferiority bound was 94%. The probability of artificial discs being superior to spinal fusion in a future trial was 73%.

Six case series were reviewed, mainly to characterize the rate of major complications for lumbar ADR. The Medical Advisory Secretariat defined a major complication as any reoperation; device failure necessitating a revision, removal or reoperation; or life-threatening event. The rates of major complications ranged from 0% to 13% per device implanted. Only 1 study reported the rate of ASD, which was detected in 2 (2%) of the 100 people 11 years after surgery.

There were no RCT data available for cervical ADR; therefore, data from 4 case series were reviewed for evidence of effectiveness and safety. Because data were sparse, the effectiveness of cervical ADR

compared with spinal fusion cannot be determined at this time.

The rate of major complications was assessed up to 2 years after surgery. It was found to range from 0% to 8.1% per device implanted. The rate of ASD is not reported in the clinical trial literature.

The total cost of a lumbar ADR procedure is $15,371 (Cdn; including costs related to the device, physician, and procedure). The total cost of a lumbar fusion surgery procedure is $11,311 (Cdn; including physicians' and procedural costs).

Conclusions

Lumbar Artificial Disc Replacement

- Since the 2004 Medical Advisory Secretariat health technology policy assessment, data from 2 RCTs and 6 case series assessing the effectiveness and adverse events profile of lumbar ADR to treat DDD has become available. The GRADE quality of this evidence is moderate for effectiveness and for short-term (2-year follow-up) complications; it is very low for ASD.
- The effectiveness of lumbar ADR is not inferior to that of spinal fusion for the treatment of lumbar DDD. The rates for device failure and neurological complications 2 years after surgery did not differ between ADR and fusion patients. Based on a Bayesian meta-analysis, lumbar ADR is 79% superior to lumbar spinal fusion.
- The rate of major complications after lumbar ADR is between 0% and 13% per device implanted. The rate of ASD in 1 case series was 2% over an 11-year follow-up period.
- Outcome data for lumbar ADR beyond a 2-year follow-up are not yet available.

Cervical Artificial Disc Replacement

- Since the 2004 Medical Advisory Secretariat health technology policy assessment, 4 case series have been added to the body of evidence assessing the effectiveness and adverse events profile of cervical ADR to treat DDD. The GRADE quality of this evidence is very low for effectiveness as well as for the adverse events profile. Sparse outcome data are available.
- Because data are sparse, the effectiveness of cervical ADR compared with spinal fusion cannot be determined at this time.
- The rate of major complications was assessed up to 2 years after surgery; it ranged from 0% to 8.1% per device implanted. The rate of ASD is not reported in the clinical trial literature.

Objective

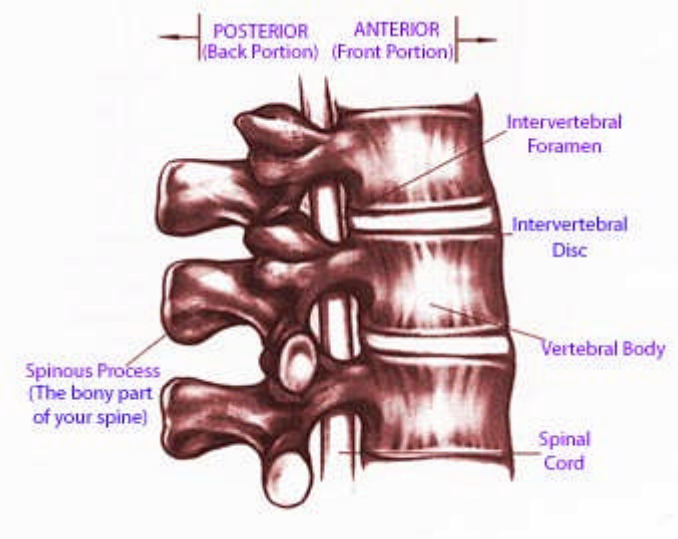
To assess the safety and efficacy of artificial disc replacement (ADR) technology for degenerative disc disease (DDD).

Background

Clinical Need: Target Population and Condition

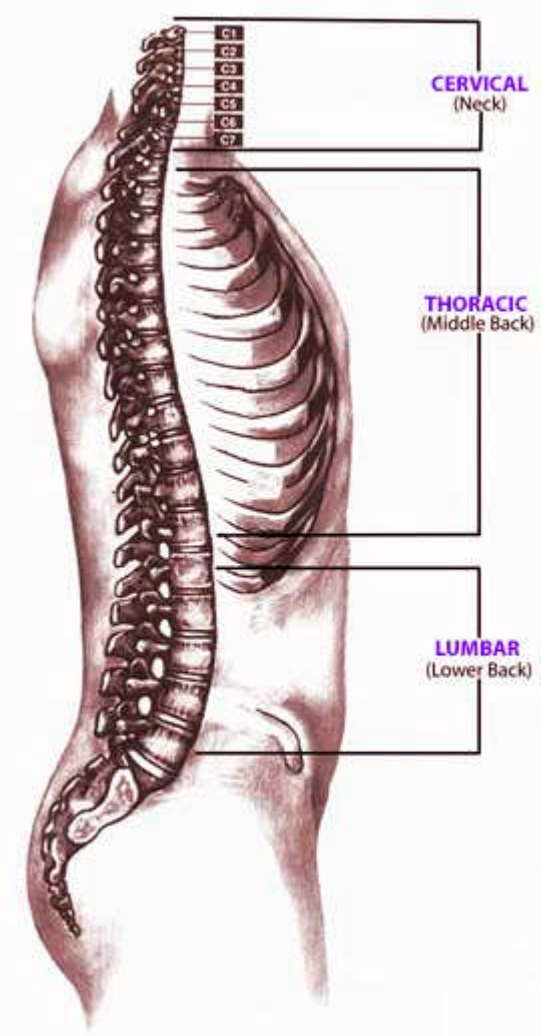
Degenerative disc disease is the term used to describe the deterioration of 1 or more intervertebral discs of the spine. Intervertebral discs are soft, round, spongy pads of tissue that are found between the bones of the spine (called vertebrae) and that act as shock absorbers for the spine (Figure 1). While all intervertebral discs of the spine are prone to deterioration, it is those of the lower back (lumbar spine) or neck (cervical spine) that are most often affected (Figure 2). (2;3) Although the exact cause of DDD is unknown, it is thought to be associated with the aging process during which the intervertebral discs become dry, lose elasticity, and collapse. (4) These changes ultimately affect the structure of the spine and result in abnormal spinal motion and, eventually, pain and disability. (5)

Figure 1: Intervertebral Discs of the Spine*



*Reproduced from York Neurosurgical Associates:
http://www.yna.org/New%20Pages/CervNormSpine.html

Figure 2: Intervertebral Discs of the Spine: Cervical, Thoracic and Lumbar*



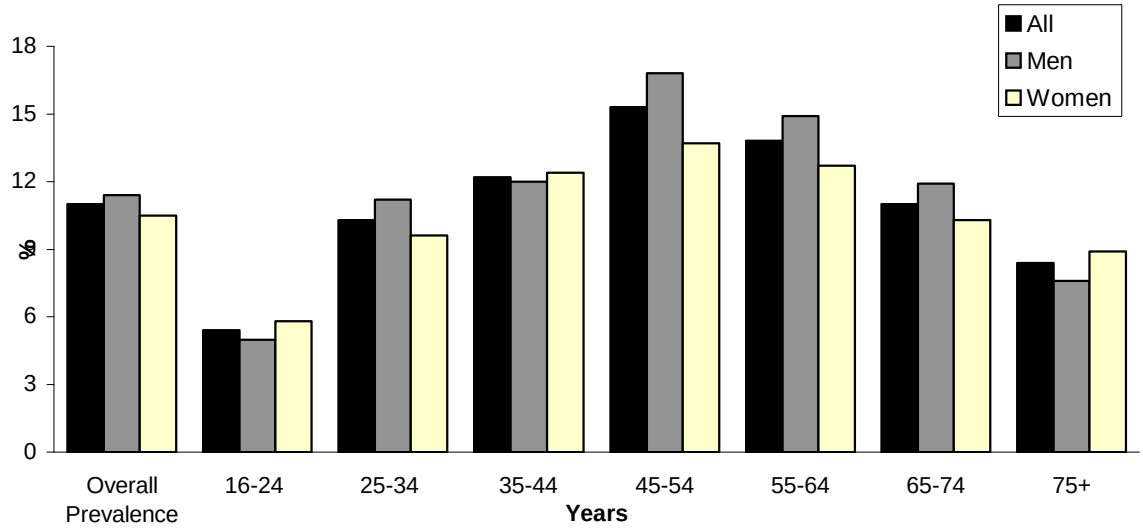
*Reproduced from York Neurosurgical Associates:
http://www.yna.org/New%20Pages/CervNormSpine.html

The prevalence of DDD is roughly described in proportion to age, such that 40% of people aged 40 years have DDD, increasing to 80% among those aged 80 years or older. (1) Lumbar DDD can affect people as young as 30 years of age with the peak incidence estimated to occur around 40 years. (4) Cervical DDD occurs mostly in the middle-aged or elderly and is known to be the most common cause of cervical spinal cord and nerve root dysfunction in people aged 55 years or older. (4) While most people aged over 50 years have some degree of DDD in the spine, only about one-third are symptomatic. (3)

Low back pain is a common symptom of lumbar DDD, while neck and arm pain are common symptoms of cervical DDD. (6) The estimated point prevalence of low back pain is reported to range between 4% and 33%, with a 1-year prevalence rate estimated at 73 %, and lifetime prevalence between 58% and 84%. (7;8) However, the prevalence of low back pain will vary according to the definition used and the population studied. (6) While the lifetime prevalence of low back pain is high, it is thought that 80% to 90% of all lower back pain resolves with some form of nonsurgical treatment. (9) In contrast, the pain of only about 30% to 50% of patients with cervical myelopathy and 75% with cervical radiculopathy (a disease of the nerve roots) resolves with nonsurgical treatment. (4)

Badley et al. (10) determined the prevalence of back and neck disorders (e.g., pain, stiffness), other than arthritis and rheumatism, in residents of Ontario aged 16 years or older using information from the 1990 Ontario Health Survey database. The overall prevalence of back and neck disorders was about 11%. It peaked between 45 and 54 years of age, with greater prevalence seen in men than women in that age group (Figure 3). Back and neck disorders ranked third as the most common chronic condition, and 75% of those affected reported visiting a health professional for treatment. Similarly, in a more recent survey, Lee et al. (11) estimated the prevalence of low back pain in a cohort of males working in an Ontario industrial setting to be 11.1%. The mean age of men surveyed was 36.9 years. Cassidy et al. (12) estimated the 1-year age- and sex-standardized incidence of low back pain episodes in a population-based cohort of Canadian adults aged 20 to 69 years at 18.6% (95% confidence interval [CI], 14.2–23.0). The incidence of intense lower back pain was 1.0% (95% CI, 0–2.2); of disabling pain, 0.4% (95% CI, 0–2.2).

Figure 3: Prevalence of Back and Neck Disorders in Ontario by Age and Gender



Low back and neck pain are considered major health and socioeconomic problems that contribute to lower quality of life and work-related absences. Moreover, the presence of Grade I (low disability-low intensity pain) neck or low back pain doubles the risk of developing depression. (12) Statistics on sickness-related work absences in Norway indicate that of those people absent 4 days or longer, 33% had low back pain and 20% had neck and shoulder disorders. (8)

Existing Treatments for Degenerative Disc Disease

Nonsurgical and surgical treatments can be used to relieve pain and minimize disability associated with DDD. (3) Nonsurgical treatments include physical therapy, facet joint injections, epidural steroids, acupuncture, back school cognitive therapy, behavior modification, ultrasound, anti-inflammatory medications, analgesic medications, muscle relaxants, lumbosacral stabilization therapy, and orthotic management. (13-15) Minimally invasive methods to relieve pain include periradicular therapy (injection of local anesthetic and/or glucocorticoids), percutaneous laser discectomy, and intradiscal electrothermal therapy. It is estimated that 10% to 20% of people with lumbar DDD and up to 30% with cervical DDD will be unresponsive to nonsurgical treatments. In these cases surgical treatment is considered. Spinal fusion (arthrodesis) is the process of fusing or joining 2 bones and is considered the surgical gold standard for DDD. (16)

The goals of spinal fusion are to relieve any existing pressure on the spinal nerves (decompression) and to restore the alignment and stability of the spine. (17) Fusion involves the removal of all or part of the degenerated intervertebral disc (discectomy) that is thought to be the source of pain. After the disc is removed, the surgeon can either leave the intervertebral space (space between the vertebrae where the disc was) empty, or fill it with a bone graft. The bone graft fills the space providing stability and promoting fusion. (18;19) It is estimated that spontaneous fusion (no bone graft used) will occur in 70% to 80% of cases. (17) Different surgical methods, types of instrumentation, and bone graft sources for spinal fusion have been developed over the last 20 years. Bone grafts are most often taken from the patient's hip bone (called an autograft) but also may be obtained from a donor (called an allograft). Synthetic bone grafting material such as bone morphogenic proteins may also be used. Surgical methods include posterior and posterolateral fusion; anterior or posterior interbody fusion; and the combined anterior interbody fusion and posterior or posterolateral fusion, called the circumferential approach. (20) Instrumentation implies the use of hardware such as screws or plates to add stability to the fused spinal segment and reduce the chance of pseudofusion (incomplete fusion). (21)

Disadvantages of surgical fusion include loss of movement in the spine, which is thought to promote ASD. Adjacent segment degeneration is the degeneration of the vertebrae above or below the fusion site. (22) It is thought that increased mobility of the adjacent vertebrae, as well as more pressure on the adjacent intervertebral discs as a result of motion transfer from the fused vertebrae may play a key role in the development of ASD. (22) However, it is unclear if ASD is solely related to the spinal fusion process or to the natural degeneration of the vertebrae. (22;23) Based on radiographic findings, ASD after spinal fusion is common and estimated to occur at rates ranging between 8% over 4 years to 100% over 6 years. The incidence of symptomatic ASD after spinal fusion is lower, ranging from 5.2% in 13 years to 18.5% in 5 years. (22) The broad ranges reflect the different definitions of ASD used, as well as the retrospective nature of the studies. The development of ASD is concerning because it can increase the need for additional surgery if it causes symptoms like pain and disability.

The surgical management of chronic low back pain due to DDD is still controversial, with inconsistent evidence from prospective RCTs to support its effectiveness. In a 2005 Cochrane systematic review on surgical interventions for lumbar DDD, Gibson and Waddell (24) were unable to determine the

superiority of any one fusion technique or combination of techniques when compared with other types of surgical and nonsurgical interventions.

Spinal fusion surgery is associated with complications such as pseudoarthrosis (15%), bone graft donor site (hip bone) pain and infection (11%), instrument failure (7%), and neural injuries (3%). (13;25) Fritzell et al. (26) reported a 12% 2-year incidence rate of major complications defined as potentially life-threatening or cause of considerable suffering in 211 people who had lumbar spinal fusion. The rate of reoperation was 14.6% (31 of the 211) over a 2-year period. Fritzell et al. also noted that complications increased significantly with increasing technicality of the surgical procedure.

Higher rates of gastrointestinal and vascular complications have been reported with anterior approach spinal fusion procedures, whereas dura- and neurology-related complications have been reported more often after a posterior approach. (21) Vascular injury has been reported to occur at a rate of 18% after anterior lumbar fusion surgery. The incidence of dural tears after spinal surgery has been reported to occur at a rate of 0.3% to 13%. (21)

Harvesting bone graft from the patient's iliac crest (hip bone) has been associated with persistent hip-bone pain. Sasso et al. (27) determined the prevalence of persistent donor site pain 2 years after anterior lumbar interbody fusion in 208 patients. Data was collected prospectively and included VAS scores of pain intensity and frequency. Results indicated that 44 (31%) of 141 people had persistent donor site pain with a mean VAS pain score of 1.8.

Fritzell et al. (26) reported a 25% complication rate in 211 people having lumbar spinal fusion (posterolateral fusion without internal fixation (n = 71), posterolateral fusion with variable screw placement (n = 68), or posterolateral fusion with variable screw placement and interbody fusion (circumferential fusion; n = 72). There were no deaths in the study. The investigators classified the complications as either major (Table 1) or minor (Table 2). Major was defined as potentially life-threatening or a cause of considerable suffering. Minor included a reversible relevant event and/or one that caused minor suffering. Thirty-one (14.7%) people had a reoperation within 2 years after surgery; 17 (8%) of these were unintended reinterventions, and 14 (6.6%) were for hardware removal. Hardware was removed before the 2-year follow-up time point either due to suspicion of a pain-generating mechanism, or because the patient wanted it removed.

Table 1: Major Complications in Patients Treated With Lumbar Spinal Fusion Surgery*

Complication	Number (%) of Patients N = 211	Number of Patients Needing a Reoperation Because of Complications
Injured nerve over anterior iliac crest causing severe persistent pain	1 (0.47)	1
Heart failure	1 (0.47)	0
Wrong level operated on	1 (0.47)	1
Major bleed during surgery	2 (0.95)	0
Deep wound infections of back	5 (2.40)	5
New nerve root pain	10 (4.70)	3
Pulmonary edema	1 (0.47)	0
Aspiration sepsis with respiratory distress syndrome	1 (0.47)	0
Refusion due to pseudoarthrosis	3 (1.40)	3
Thrombosis	1 (0.47)	0
Pulmonary embolism	1 (0.47)	0

*Fritzell et al. (26)

Table 2: Minor Complications in Patients Treated With Lumbar Spinal Fusion Surgery

Complication	Number (%) of Patients N = 211	Number of Patients Needing a Reoperation Because of Complication
Donor site pain	9 (4.30)	0
Dural tear	1 (0.47)	0
Gastrointestinal bleeding	3 (1.40)	0
Superficial wound infection (of back)	2 (0.95)	2
Sympathetic cord damage with symptoms	2 (0.95)	0
Laterally placed screws	2 (0.95)	0
Hematoma at donor site	2 (0.95)	2
Skin pressure wound postoperatively	2 (0.95)	0
Wing scapula and shoulder weakness after surgery due to intraoperative positioning	1 (0.47)	0
Pain in arm after surgery	1 (0.47)	0

*Fritzell et al. (26)

Brox et al. (28) reported a complication rate of 18% (6 of 33) in people who underwent posterolateral fusion with transpedicular screws of the L4-L5 segment and/or the L5-S1 segment, including 2 wound infections, 2 cases of bleeding, 1 dural tear, and 1 venous thrombosis.

Fairbank et al. (29) reported that of those patients treated with surgical spinal fusion, 19 (10.8%) had intraoperative complications as a result of surgery. Overall, there were 35 complications in these 19 patients (Table 3).

Table 3: Complications in Patients Treated With Surgical Spinal Fusion*

Complication	Number (%) of Patients† (N = 48)
Dural tear	5 (10.4)
Excessive bleeding	3 (6.3)
Implant Problems	5 (10.4)
Bone fracture	1 (2.2)
Vascular injury	1 (2.2)
Loss of purchase or fixation	3 (6.3)
Broken drain	1 (2.2)
Vascular injury	1 (2.2)
Loss of swab, peritoneal tear	3 (6.3)
Hemorrhage	1 (2.2)
Reoperation (within 2-year follow-up period)	11 (22.9)

* Fairbank et al. (29)
†Patients could have more than 1 complication.

In summary, the following rates of complications were reported from these 3 clinical trials: reoperation after spinal fusion surgery ranged between 4.3% and 23%; wound infection ranged between 3.3% and 6.1%; and donor site pain of 4.3% was reported in a single study

New Technology Being Reviewed

Artificial Disc Replacements

Artificial disc replacement is the replacement of the degenerated intervertebral disc with an artificial disc

in people with DDD of the lumbar or cervical spine that has been unresponsive to nonsurgical treatments for at least 6 months. In general, people with chronic disabling mechanical back pain without radiculopathy are eligible for lumbar ADR, whereas cervical ADR is best suited for those with radiculopathy or myelopathy. (15) The goals of ADR are similar to those of spinal fusion described earlier. However, unlike spinal fusion, ADR preserves movement of the spine, and this is thought to reduce or prevent the development of ASD. (2) Additionally, a bone graft is not required for ADR, and this alleviates complications including bone graft donor site pain and pseudoarthrosis. (30)

It is estimated by the president of the Spinal Arthroplasty Society (United States) that about 20,000 total disc implantations have been performed worldwide since the inception of artificial disc replacement. (31)

The surgical procedure for disc replacement involves an anterior approach for exposure of the spine, which predisposes the patient to vascular injury of the great vessels more so than does the posterior approach of spinal fusion. However, an anterior approach to fusion surgery is also an accepted method. Often a vascular surgeon is needed to carry out the anterior approach, while the actual disc replacement is completed by either an orthopedic surgeon or a neurosurgeon. Revision surgery for ADR is a complicated process because of the scarring around the great vessels from the initial surgery. Fluoroscopy (a type of x-ray) is used during either fusion or ADR surgery; however, because of the precision involved in inserting an artificial disc, the duration of fluoroscopy is slightly longer for ADR than it is for spinal fusion.

The primary reason for ADR is intervertebral disc pain (discogenic pain) from DDD. It is estimated that about 5% of patients who require surgery for DDD will be candidates for ADR. Patient selection criteria for lumbar or cervical ADR are predicated on the inclusion and exclusion criteria of the United States Food and Drug Administration (FDA) Investigational Device Exemption (IDE) studies and are summarized below. (32)

Lumbar ADR inclusion criteria:

- Male or female
- Aged 18–60 years, optimally aged under 50 years
- Symptomatic DDD or lumbar spondylosis
- Provocative discogram which demonstrates concordant pain reproduction
- 1 or 2 intervertebral level disc disease at L3-L4, L4-L5, or L5-S1
- Nonradicular leg or back pain in the absence of nerve root compression without lateral recess stenosis
- Post laminectomy syndrome
- Patients with prior lumbar discectomy
- Failed a minimum of 6 months of nonsurgical treatments

Lumbar artificial disc replacement exclusion criteria:

- Previous attempted fusion procedure anywhere in the thoracolumbar spine
- Osteopenia (reduced bone mass)
- Nerve root compression
- Spinal fracture
- Spondylolysis
- Spondylolisthesis
- Scoliosis
- Spinal tumor
- Severe facet joint arthrosis
- Obesity

Other contraindications to lumbar ADR include spinal stenosis, osteoporosis, arachnoiditis, degeneration of an adjacent segment, and metal allergies. (13;33)

Cervical artificial disc replacement inclusion criteria:

- Radiculopathy and/or myelopathy with or without axial neck pain
- Aged 18–65 years
- Failed conservative treatment lasting at least 6 weeks for any 1 or more of the following: disc herniation with radiculopathy or myelopathy, or spondylotic radiculopathy or myelopathy at 1 to 3 levels from C3 to T1.

Cervical ADR exclusion criteria:

- Ankylosing spondylitis
- Rheumatoid arthritis
- Ossification of the posterior longitudinal ligament or diffuse idiopathic skeletal hyperostosis
- Insulin dependent diabetes mellitus
- Previous cervical spinal infection
- Chronic steroid use
- Morbid obesity
- Pregnancy
- Axial neck pain as the solitary symptom

Other contraindications to cervical arthroplasty include significant segmental or global deformity, radiographic instability, and recent history of osteomyelitis, renal failure, osteoporosis, and/or corticosteroid medication.

Artificial Disc Devices

There are 5 types of artificial discs available for clinical use in Canada: The SB (Schellnack and Büttner-Janz) Charité, the ProDisc-L, the Maverick, the Activ L (Table 4), and the Bryan (Table 5). Those listed in Table 4 are indicated for lumbar DDD, and the Bryan artificial disc (Table 5) is indicated for cervical DDD. The Charité disc was developed in 1980 and has been used more extensively (in various prototypes) than any of the other 4 types. (13) More on these devices is found in the section on regulatory status. Information for the Activ L artificial disc was not available in the published literature. The devices can be classified based on the number of components (2 vs. 3), the articulating material used (metal-on-polymer vs. metal-on-metal) and the kinematic (motion) constraints of their articulation (more or less constrained).

Depending on the model, each artificial disc consists of 2 or 3 components including 2 endplates and an articulating mechanism. The metal endplates are affixed to the upper and lower vertebral bones and the articulating mechanism, which preserves motion in several planes, is inserted between these endplates. (13) To achieve primary stability and secure the disc in place, all models except the Bryan cervical disc have teeth-like structures on the upper and lower surfaces of the endplates that are driven into the vertebral bone for vertebral engagement. These teeth-like structures are called spikes or fins. The SB Charité and the Activ L each have spikes while the ProDisc-L and the Maverick both have fins (see diagram Appendix 1). Similarly, all artificial disc models have a porous coated surface on the endplates that promotes bony ingrowth around these spikes or fins for secondary stability. (2) The configuration of the articulating mechanism is unique to each model. Also unique to each model are the different kinematic designs, which will determine the movement conferred to the patient after surgery. All discs are supplied as modular devices so that the surgeon can get the correct fit. With all implants, postoperative

evaluation is done with either computed tomography or myelography.

It has been suggested that the artificial disc is unlikely to have the exact characteristics of the native vertebrae, and because of this different models can be expected to yield different long-term results. (25) After comparing their results of segmental lordosis with the ProDisc-L artificial disc to those reported for the Charité artificial disc, Cakir et al. (34) concluded that design-related changes in segmental lordosis may exist between different artificial disc models.

Table 4: Characteristics of Lumbar Artificial Disc Devices*

Type	Number of Components	Endplate Characteristics	Vertebral Engagement	Articulating Material	Articulation Geometry	Kinematic Design
Activ L	No data available in published literature					
SB Charité	1. Superior endplate 2. A biconvex sliding articulating insert 3. Inferior endplate	Metal, cobalt chromium alloy (CoCrMo) Surface coated with titanium calcium phosphate to promote bony ingrowth.	Spikes	Polymer* on metal	Mobile bearing	Unconstrained in flexion, extension, lateral bending and axial rotation. Provides 14 degrees of total flexion-extension
ProDisc-L (also called ProDisc II in European literature)	1. Superior endplate 2. Articulating Insert 3. Inferior endplate	Metal (CoCrMo) Titanium plasma coated endplate surface to promote bony ingrowth.	Fins (keels)	Polymer* on metal	Ball and socket	Semiconstrained in flexion, extension and lateral bending Unconstrained in axial rotation Designed to provide 13 degrees of flexion, 7 degrees of extension, 10 degrees of lateral bending.
Maverick Total Disc Replacement	1. superior endplate 2. inferior endplate	Metal (CoCrMo) Surfaces have hydroxyapatite coating to promote bony ingrowth	Fins (keels)	Metal on metal	Ball and socket design	Semiconstrained with in flexion, extension and lateral bending. Unconstrained in axial rotation. Provides 5 degrees of flexion, 3 degrees of extension, 3 degrees of lateral bending and 2 degrees of axial rotation.

*UHMWPE indicates ultra high molecular weight polyethylene.

Table 5: Characteristics of Cervical Artificial Disc Model Devices

Type	Number of Components	Endplate Characteristics	Vertebral Engagement	Articulating Mechanism	Articulation Geometry	Kinematic Design

Bryan Cervical Disc System	1. Upper concave shell 2. Polyurethane nucleus 3. Lower concave shell	Titanium alloy Surfaces have titanium porous coating to facilitate bony ingrowth	None Vertebral body hollowed out and the concave surface of the Bryan disc fits into place. The rim of the disc is captured inside a ridge of bone	Metal on polyurethane; The polyurethane nucleus is surrounded with a polyurethane sheath into which sterile saline is injected to function as a lubricant.	Data not available	Data not available

Possible Benefits of Artificial Disc Replacement

The benefits of ADR include preservation of movement at the affected spinal segment, and the possibility of preventing or delaying adjacent spinal segment degeneration.

Possible Harms of Artificial Disc Replacement

Various complications are possible, or have been reported in the literature. (3;33) A synopsis of each of these follows.

Injury to Other Structures

Vascular injury leading to hemorrhage can occur as a result of the anterior approach to the lumbar spine, given the proximity of the aorta and iliac vessels. Injury to neural structures such as the cauda equina, nerve roots or superior hypogastric plexus may also occur, causing severe pain, sensation loss, leg weakness, and bladder, bowel, and sexual dysfunction. It is possible that a malpositioned artificial disc could result in postoperative vascular and neural damage.

Infection

Postoperative wound infections are reported to occur in 1% to 12% of patients who undergo spinal surgery depending on the type and duration of the procedure, number of comorbid conditions, nutritional status, and other risk factors. Treatment of infection occurring after disc replacement is very complicated, because the artificial disc may act as a retained foreign body, and implant removal is difficult.

Loosening/Dislodgment

Implant loosening over time is possible and will vary depending on product design; however, a dislodged disc may have serious consequences and is extremely difficult to remove. Expulsion or retropulsion could cause pain, paralysis, vascular or neurological damage, or spinal cord impingement or damage.

Polyethylene Wear

Small fragments of polyethylene can cause a major histological reaction in synovial joints, and the long-term consequences of polyethylene debris in the retroperitoneal space are unknown. Granulomas could

result from chronic inflammation caused by foreign-body reactions requiring further surgical intervention. Neural structures are also at risk of injury from wear debris.

Metal Wear

Over time, metal-on-metal implants may have a deleterious effect on surrounding tissue.

Loss of Motion

The theoretical preservation of motion gained by ADR may be lost over time, resulting in autofusion, which could necessitate surgical decompression.

Impact on Adjacent Discs and Facet Joints

Treatment of 1 disc may cause pressure on other discs and vertebrae leading to problems elsewhere in the spine.

Subsidence

Total ADR requires removal of endplate bone which may weaken the vertebral body, making subsidence (settling of the artificial disc into the vertebra) more likely.

Implant Failure

The long-term durability of artificial intervertebral discs is unknown. Given that the target population requiring discs are aged 30 to 50 years, disc implants need to last up to 40 years to avoid the need for repeat procedures.

Potential adverse events, reported in the FDA Summary of Safety and Effectiveness Data (35) of the Charité artificial disc that might be expected to occur after the implantation of the disc, but were not observed in the FDA IDE clinical trial of the disc, include these:

- Mechanical failure of the device due to bending or breakage resulting in loss of disc height
- Expulsion or retropulsion, potentially causing pain, paralysis, vascular or neurological damage, spinal cord impingement or damage, or other conditions
- Implant breakage
- Reoperation due to mechanical breakdown of the device or if the implantation procedure fails to resolve the patient's syndrome
- Change in lordosis
- Injury to kidney(s) or ureter(s)
- Deterioration in neurological status
- Facet joint deterioration
- Spondylolysis
- Spondylolisthesis
- Nerve damage due to surgical trauma or presence of the device, neurological difficulties including bowel and/or bladder dysfunction, impotence, tethering of nerves in scar tissue, muscle weakness, or paresthesia.

Canadian Regulatory Status

As of September 2005, there were 5 artificial disc devices licensed by Health Canada (Table 6); 4 are indicated for lumbar DDD, 1 for cervical DDD. All have a Class III licence. (36)

Table 6: Artificial Disc Devices Licensed by Health Canada

Disc	Manufacturer (Location)	Licence Number	Indication
Activ L	Aesculap AG & Co. (Tuttlingen, Germany)	69012	Lumbar: Used for replacing intervertebral discs in the lumbar spine. They restore the disc height and the segmental mobility.
SB Charité Intervertebral Endoprosthesis	DePuy Spine (Raynham, MA, United States)	62847	Lumbar: Mono- and bi-segmental degenerative disc disease, long term chronic back pain, postnucleotomy syndrome, segmental instability with

Disc	Manufacturer (Location)	Licence Number	Indication
			degenerated disc, recurrent hernia, or unsuccessful conservative therapy.
ProDisc-L (Second-generation ProDisc. Also called ProDisc II in the literature)	Synthes (Canada) Ltd. (Mississauga, ON)	65063	Lumbar: A lumbar disc prosthesis for replacing a lumbar intervertebral disc and restoring disc height and segmental motion. The device is used when surgical intervention for the relief of the pain of degenerative disc disease in indicated.
Maverick Total Disc Replacement System	Medtronic Sofamor Danek (Memphis, TN, United States)	61915	Lumbar: A spinal arthroplasty system used to replace a damaged lumbar intervertebral disc.
Bryan Cervical Disc System	Medtronic Sofamor Danek (Memphis, TN, United States)	62403	Cervical: A cervical intervertebral disc prosthesis designed to permit motion similar to the normal cervical functional spinal unit. Used to treat stable cervical degenerative disc disease without fusion.

International Regulatory Status

United States

On October 26, 2004, the SB Charité artificial disc (DePuy Spine, Inc., Raynham, MA, United States) became the first artificial disc device to receive marketing approval from the FDA. The device is approved for use in people who have lumbar DDD at 1 level (L4-S1) and who have not had relief from lower back pain after at least 6 months of nonsurgical treatments. As a condition of postmarket approval, the sponsor is required to monitor those people who participated in the study for 5 years after treatment to assess the long-term safety and effectiveness of the artificial disc, including correlating range of motion data with disability and pain measures, and assessing the rate of ASD. (33)

A pivotal FDA IDE clinical trial with the ProDisc-L device was completed at the end of 2005. In January 2006, Synthes Spine, its manufacturer, announced that an initial approval letter had been issued to the company from the FDA in response to its postmarketing approval application. The company expects final approval for distribution and sale of the device in the United States by the second quarter of 2006. (3)

Currently, neither the Maverick lumbar nor Bryan cervical discs are approved for use in the United States. However, approval is pending review of FDA IDE clinical trial data for both devices.

The Activ L is not approved for use in the United States.

Europe

The Charité, ProDisc-L, Maverick, and Bryan artificial discs have European CE mark certification. The European CE (Conformité Européne) mark is a mandatory European marking to indicate that a product conforms to essential health and safety requirements set out in the European Directive. The SB Charité disc has been commercially available in markets outside North America since 1987. It is available in more than 25 countries throughout Europe, Asia, Latin America, Africa, and Australia. ProDisc-L has been available since 2000 in Europe. It is marketed throughout 26 countries in Europe, Asia Pacific, Latin America, and South Africa.

Information on the CE mark certification status of the Activ L artificial disc was not found.

Literature Review of Effectiveness

Objective

The aim of this assessment was to review the literature for evidence of effectiveness and safety published since March 2004 for the lumbar and cervical artificial discs approved by Health Canada.

Questions Asked

- What is the effectiveness of ADR in people with DDD of the lumbar or cervical regions of the spine compared with spinal fusion surgery?
- Does an artificial disc reduce the incidence of ASD compared with spinal fusion?
- What is the rate of major complications (device failure, reoperation) with artificial discs compared with surgical spinal fusion?

Methods

The Medical Advisory Secretariat conducted a computerized search of the literature in the following databases:

- OVID Medline
- Ovid In Process and Not-Yet-Indexed Citations
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)

The literature search for the previous Medical Advisory Secretariat health technology assessment published March 2004 ended November 2003. Therefore the literature search for this update was limited to English-language articles with human subjects published between 2003 and September 2005. Letters, editorial, comments, case reports, and nonsystematic reviews were excluded. The literature search strategy is available in Appendix 2.

In addition, the International Health Technology Assessment Agency database and the Web were searched for published guidelines, assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references that may have been missed in the computerized database search.

Inclusion Criteria

- Studies with at least 10 subjects
- Studies that evaluated at least 1 of the 5 devices licensed by Health Canada (Charité, ProDisc-L, Maverick, Activ L, and Bryan)
- Studies that reported on at least 1 of pain and/or disability outcomes
- Studies that reported at least 1 year of outcome data

Exclusion Criteria

- Non-English-language studies

- Case reports
- Animal and in vitro studies
- Duplicate publications (superseded by another publication by the same investigator group with the same objective)
- Studies that did not examine the outcome(s) of interest
- Single site reports from multicentre studies
- Greater than 20% loss to follow-up in study sample

Health Outcomes

- Physical functioning/disability
- Pain relief
- Quality of life
- Patient satisfaction
- Return to work

Health Systems Outcomes

- Duration of surgery
- Surgical blood loss
- Duration of hospitalization

Radiological Outcomes

- Rate of ASD

Complications

- Reoperation
- Device failure or removal
- Neurological complications
- Death

Study Eligibility

One reviewer who was not blinded to author, institution, and journal of publication evaluated the eligibility of the citations retrieved from the literature search. Articles were excluded based on information reported in the title and abstract, and the full document of potentially relevant articles was retrieved for further assessment. Characteristics of included studies are described in Appendix 6.

Data Extraction

One reviewer extracted data from the included studies. Information on the study population, study methods, study interventions, study outcomes, and adverse events were recorded. Where possible, the primary author of the study was contacted for missing data.

Assessment of Study Methodological Quality

One reviewer evaluated the internal validity of the primary studies using the criteria outlined in the Cochrane Musculoskeletal Injuries Group Quality Assessment Tool (37) (Appendix 3). The quality of concealment allocation was rated as: A, clearly yes – some form of centralized randomization scheme or

assignment system; B, unclear – evidence of possible randomization failure such as markedly unequal control and trial groups, or no description of study randomization; C, clearly no – allocation procedures that were transparent before assignment. (24)

Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (38) was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review. A description of the GRADE system is reported in Appendix 4.

Meta-Analysis

A random effects model meta-analysis was conducted when data was available from 2 or more RCT studies and when there was no statistical and or clinical heterogeneity among studies. Dichotomous data was reported using risk difference (RD), and continuous data using the weighted mean difference (WMD). Associated 95% confidence intervals are reported for all estimates.

Results of Literature Review

The literature search yielded 140 forty citations using the strategy in Appendix 2. From these, 2 level-1 citations (1 Cochrane systematic review (24) and 1 RCT (5) with 2 companion reports of outcome data) were retained and included. Data from a level-1 study evaluating the ProDisc-L artificial lumbar disc reported in the grey literature were obtained from the manufacturer of the device. Ten level-4C case series are also included in this review (Table 7). Details of the included studies are reported in Appendix 5.

The evidence available for the Medical Advisory Secretariat 2004 initial health technology assessment and for this 2006 update is presented in Table 8. Full results are now available for the Charité (5) and ProDisc-L FDA RCTs (unpublished data), whereas only preliminary results were available in 2004. Two of the lumbar ADR case series cited in the 2004 Medical Advisory Secretariat assessment described the results of the same patient population reported in the Blumenthal 2005 and ProDisc-L 2006 studies. Data from the case series by Tropiano et al. (39) and Ross et al. (40) included in the Medical Advisory Secretariat 2004 assessment are not included in this update.

However, both of the case series for cervical discs included in the 2004 Medical Advisory Secretariat assessment, Sekhon et al. (41) and Goffin et al., (9) have been updated to reflect longer durations of follow-up. They are included in this analysis.

Summary of Medical Advisory Secretariat Review

Table 7: Quality of Evidence of Included Studies

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT*, systematic reviews of RCT	1	2
Large RCT unpublished but reported to an international scientific meeting	1(g)†	1
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	10
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial.
†g indicates grey literature.

Table 8: Evidence Available: Health Technology Policy Assessments of 2004 and 2006

Medical Advisory Secretariat, 2004	Medical Advisory Secretariat, 2006
Lumbar artifical disk replacement	**Lumbar artifical disk replacement**
RCTs:	RCTs:
McAfee 2003(42) Zigler 2003 (43) Delamarter 2003 (44)	Blumenthal 2005 (5) (same patients as RCT by McAfee 2003, and case series by Blumenthal 2003 and Zeegers 2003) ProDisc –L 2006 (same patients as Zigler 2003 (43) and Delamarter 2003 (44))
Case series:	Case series:
Blumenthal 2003 (45) Zeegers 2003 (46) Tropiano 2003 (39) Ross 1997 (40)	Lemaire 2005s (47) Xu 2004 (48) Caspi 2003 (49) Su 2003 (50) Cakir 2005 (34) LeHuec 2005 (51)
Cervical artifical disk replacement	**Cervical artifical disk replacement**
Case series:	Case series:
Sekhon 2003 (41) Goffin 2003 (9)	Sekhon 2004 (52) (same patients as Sekhon 2003) Goffin 2004 (53) (same patients as Goffin 2003) Duggal 2004 (54) Lafuente 2005 (55)

Summary of Existing Health Technology Assessments

Table 9 summarizes the evidence and outcomes of 8 health technology assessments evaluating ADR. Details of the studies included in these health technology assessments are reported in Appendix 6.

Several RCT reports are included among the health technology assessments; however, these reports describe results from 2 FDA clinical trials, 1 for the SB Charité disc, the other for the ProDisc-L. Among the 8 health technology assessments there are 20 unique case series.

Six of the 8 health technology assessments concluded that there is insufficient evidence to support the use of either lumbar or cervical ADR. The remaining 2 health technology assessments, completed for or by NICE, also identified gaps in the evidence. However, the resulting NICE guidance produced for both lumbar (56) and cervical (56) disc replacement supports the safety and effectiveness for both applications. However, due to the paucity of long-term outcome data for either device, NICE has recommended an ongoing audit of all clinical outcomes in patients having either lumbar or cervical ADR.

Of interest, both ECRI (3) and NICE (57) reviewed data published from the Charité artificial lumbar disc FDA RCT (5;58) (SB Charité disc vs. anterior lumbar interbody fusion [ALIF]). While NICE concluded in their guidance document that the evidence for safety was adequate to support the use of the artificial lumbar disc, ECRI (3) was hesitant, stating that limited data suggested that ADR may offer some advantages over spinal fusion, and the short-term adverse event rate may be similar to that of spinal fusion. However, ECRI noted that the true rate of complications and their clinical impact cannot be determined as yet, and the available 2-year safety data is inadequate to draw any conclusions regarding the long-term safety of artificial discs compared with spinal fusion.

The health technology assessment completed by Blue Cross Blue/Shield (BCBS) (13) did not support the use of the lumbar ADR citing 4 methodological flaws in the Charité lumbar artificial disc FDA RCT that they felt made the study results difficult to interpret. First, they suggested that a noninferiority threshold is acceptable only if there is a trade-off between efficacy outcomes and some other advantage of the new technology (e.g., morbidity, invasiveness). However, they felt that no such advantage was demonstrated for the Charité artificial disc, making noninferiority unacceptable. Second, that noted that there was no prespecified plan for the statistical analysis outlined in the FDA study application. Third, there was an unexplained closure of the database before all patients reached study completion. Finally, there was no intention-to treat analysis. Blue Cross Blue/Shield also noted that there is doubt regarding the effectiveness of fusion to manage DDD. Because of this, the appropriateness of the comparator used in the Charité FDA RCT (fusion surgery using a Bagby & Kuslich [BAK] interbody cage) was questioned.

The Cochrane review, (17) the Washington State Department of Labor and Industry (WSDLI) health technology assessment, (59) the MAS (1) and the ECRI (3;33) reports each reported that preliminary or limited data precluded drawing any conclusions about ADR.

In summary, only NICE, through its guidance statements, supports the safety and effectiveness of the lumbar and cervical artificial discs, while acknowledging the deficit of long-term outcomes and the need for continued data collection in patients receiving these devices.

Table 9: Summary of Existing Health Technology Assessments

Study	Year	Spine	Type of Disc	Total Receiving Artificial Disc	Mean Follow-Up, Range (Months)	Favours ADR?	Reason
ECRI (3)	2006	*L	Charité ProDisc II	250	6–24	No	Limited evidence
Cochrane Review (17)	2005	L	Charité ProDisc	268	6–24	No	Preliminary data from clinical trials of disc ADR did not permit any firm conclusions
WCB Evidence-Based Practice Group (60)	2005	L And C	Charité Bryan	615	6–24	No	Lack of published comparative data and long term follow-up greater than 10; artificial intervertebral discs should still be considered at an experimental stage.
Blue Cross/Blue Shield (13)	2005	L	Charité	531	12–51	No	Insufficient evidence
NICE (61)	2005	C	Bryan †Prestige II †Prestige I	165	6–24	Yes (through guidance document)	There are few data available concerning the use of two-level prostheses; Few long-term data are available particularly in relation to potential reduction in adjacent level degeneration compared with fusion. Issues for consideration included: variability of efficacy and safety between devices and controversy regarding the role of prostheses for patients with neck pain but no nerve root or spinal cord compression. NICE Guidance 2005: Current evidence suggests that there are no major safety concerns about the use of prosthetic intervertebral disc replacement in the cervical spine and

Study	Year	Spine	Type of Disc	Total Receiving Artificial Disc	Mean Follow-Up, Range (Months)	Favours ADR?	Reason
							there is evidence of short-term efficacy.
Washington State (59)	2004	L	Charité ProDisc II	633	3–48	No	Insufficient evidence
(ASERNIP-S) for NICE (57)	2003	L	Charité	642	11.5–52	Yes (through guidance document)	The benefits of prosthetic discs in patients over 45 years of age remain unresolved in the literature. NICE guidance 2004 stated that current evidence on safety and efficacy appears adequate to support use of this procedure.
Medical Advisory Secretariat (1)	2004	L And *C	Charité ProDisc II Bryan Cervical	302 (L) 71 (C)	6–36 (L) 6–18 (C)	No (L) No (C)	Insufficient evidence for lumbar and cervical

* L indicates lumbar; C, cervical.
† Discs are not available in Canada.

Quality of Level-1 Evidence

Two RCTs are included in this review (Table 10). The ProDisc-L RCT is reported in the grey literature; therefore, a full assessment of the methodological quality is not possible for that study. Both studies were FDA investigational device exemption clinical trials.

Table 10: Table of FDA Investigational Device Exemption Randomized Controlled Trials*

Trial	N	Artificial Disk Group, n	Spinal Fusion Group, n	Age, Years Mean (SD)	Primary Outcome	Follow-Up, Months
Blumenthal 2005 (5) (Charité lumbar disc)	304	205	99	AD: 39.6 (8.16) Fusion: 39.6 (9.07)	Composite score of clinical success	24
ProDisc (Lumbar disc)	236	161	75	AD: 38.7 (8.0) Fusion: 40.4 (7.6)	Composite score of clinical success	24

*All studies are United States Food and Drug Administration investigational device exemption trials. Studies used a 2:1 randomization scheme.

Blumenthal et al. 2005

Blumenthal et al. (5) published the complete results of the FDA RCT comparing the safety and effectiveness of lumbar ADR using the Charité artificial disc (DePuy Spine, Raynham, MA) with ALIF,

using threaded BAK cages (Zimmer Spine, Minneapolis, MN) filled with hip bone autograft for the treatment of single-level degenerative disc disease at L4-S1, unresponsive to conventional treatments. This was a multicentre noninferiority RCT using a 2:1 randomization scheme. The noninferiority margin was set at -15% (the FDA requested that a -10% noninferiority margin be used in the analysis as well). The ADR group would be considered noninferior to the control group (fusion surgery) if the difference in the overall success rates was no greater than 15%. (35;62) The sample size was determined using a one-sided alpha.

The primary outcome measure was a composite score of clinical success defined using 4 criteria: greater than or equal to 25% improvement in Oswestry Disability Index (ODI) score at 24 months compared with the preoperative score (FDA requested a 15-point increase in ODI be used as well); no device failure; no major complications; and no neurological deterioration compared with preoperative status. The clinical endpoint was binary (success /failure), and all 4 criteria had to be met for clinical success.

The primary outcome was analyzed for the total population (intention to treat, [ITT]) and for the cohort that completed the study (completers). All losses to follow-up were categorized as failures for the ITT analysis (Table 11).

Table 11: Lost to Follow-Up at 24 Months

Reason	Treatment n = 205	Control n = 99
Deaths*	1	0
Incomplete data†	4	1
Early discontinuation	16	17
Failures‡	12	8
Completers evaluated at 24 months‡§	184	81
Noncompleters at 24 months	21	18

*Death from overdose of recreational drugs.
†Confirmation of data from DePuy (December 21, 2005).
‡Failures include device removals, revisions, and supplemental fixations.
§A completer is defined as a patient who has both 24-month ODI and neurological exam.

Study Quality Assessment

Results of a quality assessment of the Blumenthal et al. study using the Cochrane Musculoskeletal Injuries Group Quality Assessment Tool (63) are reported in Table 12. A detailed explanation of these results can be found in Appendix 7. Of the criteria used in the assessment tool, only blinding procedures were lacking in the study. Based on the published report, the randomization scheme appeared to be concealed in this study. Baseline characteristics were equivocal, except that patients in the control group had a statistically significant higher mean weight at the time of surgery ($P < .0349$). This was not deemed as an important source of confounding, as the average baseline body mass index was not different between treatment and control groups**.**

The authors of the study acknowledged that blinding of the study subject, treatment provider, and outcome assessors was not carried out. The authors state that difficulty in blinding patient charts, x-rays, computed tomography images, and side effects (i.e., iliac crest (hip bone) donor site pain) precluded blinding the outcome assessors, which included the patients themselves for the self-assessment outcome measures (ODI, VAS scores), and treatment providers for the objective assessment measures (neurological exam, eligible for discharge). There is a small chance that a performance bias may exist because of the lack of treatment provider blinding. This may account for the statistically significantly shorter length of hospital stay in the artificial disc treatment group compared with the controls and

because there were no protocol-defined criteria for this outcome. Finally, because assessor blinding was not undertaken and impossible according to the authors, a detection bias is possible.

Table 12: Methodological Assessment of Blumenthal et al.*

*Criteria	Blumenthal 2005 (5)
Concealment	2
Intention-to-treat analysis	2
Blinding of outcome assessors	0
Baseline comparability	2
Study subject blinding	0
Treatment provider blinding	0
Care programs	1
Inclusion and exclusion criteria	2
Clearly defined interventions	2
Clearly defined outcomes	2
Clinical useful diagnostic test	2
Duration of follow-up	2

*All criteria are scored from 0 to 2. A score of 2 equals full compliance with the criterion. See Appendix 3 for the definition of each score for each criterion.

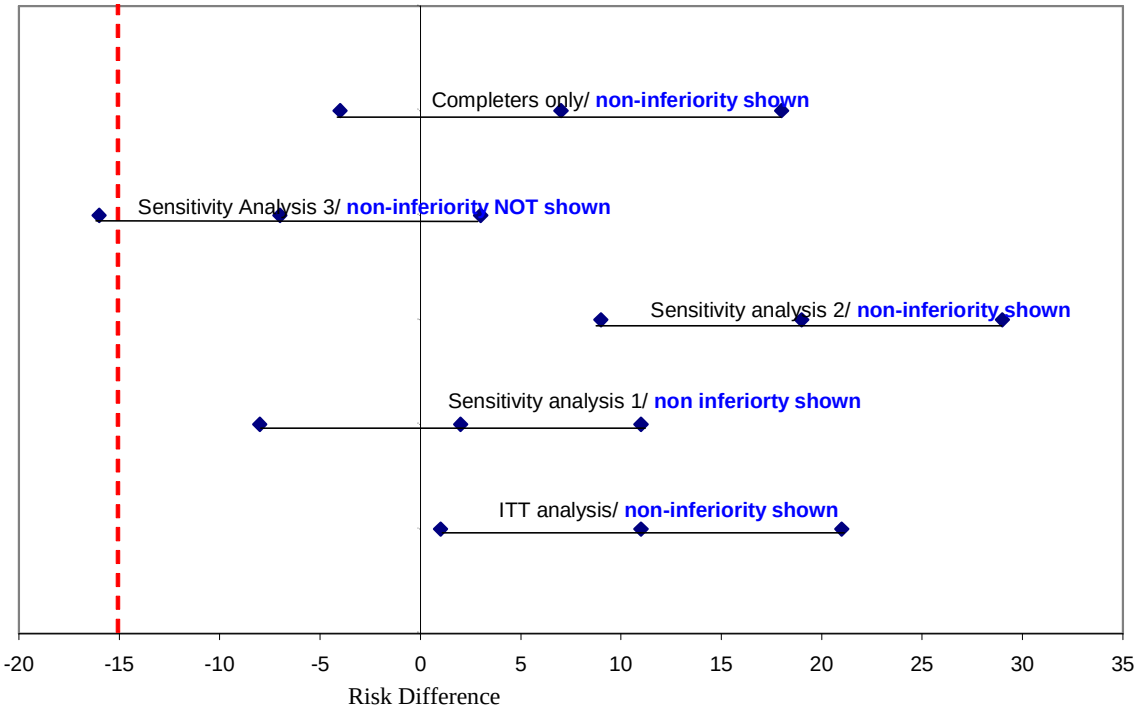
It should be mentioned that an FDA summary and statistical report (35) of the study was available on-line before the 2005 Blumenthal (5) publication and in which several shortcomings of the study were noted. These are outlined below.

The sponsor did not prespecify the statistical analysis for the trial in the original FDA protocol submission. Only after an FDA request did the sponsor provide a statistical analysis plan to the FDA, which appeared to be finalized after most trial data were probably available. The FDA suggested that the unblinded development of a statistical analysis plan would generally introduce bias and that the sponsor should clarify if the developers of the statistical plan were blinded to the outcome data before developing the plan.

The data were analyzed before the completion of the study despite the lack of an interim statistical analysis plan.

Regarding the sensitivity analysis, the FDA in-depth statistical analysis noted that if data scenarios are examined to impute missing data, one finds that in a worst-case scenario (sensitivity analysis 3, Figure 4, next page), where the missing data in the control group were thought to be all successes and those in the artificial disc group were thought to be failures, noninferiority criteria for ADR were not met.

Figure 4: Sensitivity Analyses for Blumenthal et al. Study*



* Blumenthal et al. (5)

Sensitivity analysis 1: all missing data considered success either group
Sensitivity analysis 2: missing data in artificial disc group =success, control group = failure
Sensitivity analysis 3: missing data in artificial disc group =failure, control group =success

There was a comparable proportion of protocol deviations (Charité n = 13 (6.3%), control n = 7, (7.1%) with the violation of inclusion/exclusion criteria as the only reason. None of the patients with protocol deviations were excluded from the intent-to-treat (ITT) analysis for the primary effectiveness analysis.

Likewise, the FDA has presented several analyses of the data. The in-depth statistical review (64) dated April 13, 2004 stated that 23 (11%) Charité patients and 14 (14%) control patients were excluded from the ITT analysis because they were overdue for their 24 months follow-up or had not reached the 24-month follow-up. However, the final report by Blumenthal et al. (5) includes all randomized subjects in the ITT analysis with those who died, discontinued study participation early or did not complete the study treated as failures.

The Blumenthal publication (5) reports a statistically significant difference in weight between treatment groups, while the FDA in-depth clinical report (35) states that as well as weight, the age (by category greater or at least 45 years of age), and body mass index were statistically significantly different between groups. The artificial disc group had more patients younger than 45 years of age (77% artificial disc vs. 67% control, $P = .07$), and a lower weight ($P = .01$) and mean body mass index ($P = .01$) than the control group. The discrepancy may involve the sample size used for the analysis. In the FDA document, the analysis included 182 artificial disc patients and 85 control patients, whereas in the Blumenthal et al. publication, the analysis included all subjects (205 artificial disc patients and 99 control subjects).

Comment on Blumenthal et al. Study

The Blumenthal et al. (5) study was designed as a noninferiority trial with the difference between groups to be no more than 15%. Large differences (deltas) between treatment groups in noninferiority trials are accepted by regulatory agencies to reduce the required sample size and therefore the required number of people exposed to the potentially inferior experimental treatment. It has been said to be a tradeoff between ethics and precision. However, in doing so, there is a risk of allowing treatments with greater inferiority to be accepted as non-inferior.

With regard to a noninferiority design, Pocock (62) has suggested that more weight be attached to a per protocol analysis, which focuses on patient outcomes among compliers instead of an ITT analysis. Unlike superiority trials, an ITT analysis could artificially enhance the claim of noninferiority. This is shown in figure 4 (ITT analysis vs. completers-only analysis). However, he also notes that compliers are a select group of patients whose data taken alone may also bias the interpretation. Therefore, he suggests that where noninferiority is concerned, results of both a per protocol and an ITT analysis should be considered. Blumenthal et al. have reported the results of both types of analyses.

ProDisc 2006

This is an FDA RCT with a 2:1 randomization scheme designed as a noninferiority trial comparing the ProDisc-L artificial lumbar discs to lumbosacral spinal circumferential fusion with an autograft, femoral ring, and posterior or anterior screws. The primary outcome was a composite measure of clinical success. Results of this study were obtained from the manufacturer and have been reported in abstract format.

It is conceivable that because the ProDisc-L lumbar artificial disc clinical trial is an FDA RCT similar to that reported by Blumenthal et al., (5) it may have at least the same methodological quality as the Blumenthal et al. RCT. However, without a published report of the entire study, methodological quality cannot be assessed in it entirety.

Level 1 Evidence of Effectiveness

Blumenthal et al. 2005

Primary Outcome

Using either an ITT or a per protocol analysis (study completers only defined as a patient with both 24 months ODI index scores and a neurological exam completed), the primary outcome of clinical success was noninferior in the ADR group compared with the control group (spinal fusion surgery). In the ITT analysis, 57.1% of people in the artificial disc group and 46.5% in the control group were considered clinically successful by protocol definition ($P < .0001$) (Table 13). These rates improved when only protocol completers (per protocol analysis) were analyzed (63.6% vs. 56.8%, $P < .004$) (Table 14).

Table 13: Clinical Success: Intention-to-Treat Analysis*

	Treatment Group n = 205	Control Group (Fusion) n = 99	*P*
Success, n (%)	117 (57.1)	46 (46.5)	< .0001
Failure, n (%)	88 (42.9)	53 (53.5)	

* Blumenthal et al. (5)

Table 14: Clinical Success: Completers*

	Treatment Group n = 184	Control (Fusion) n = 81	*P*
Success, n (%)	117 (63.6)	46 (56.8)	.0004
Failure, n (%)	67 (36.4)	35 (43.2)	

* Blumenthal et al. (5)

Likewise, the FDA summary report (35) on clinical effectiveness and safety states that in those considered completers, the two-sided 90% CI indicates that the overall clinical success rate for the artificial disc group is no worse than the control rate by more than 10%, regardless of whether clinical success was defined using a 25% improvement in ODI (sponsor's definition) or a 15-point improvement in ODI (FDA definition) (Table 15).

Table 15: Results of Different Outcome Measure Cut Points

Variable	25% Improvement in *ODI		15-Point Improvement in ODI	
	Artificial Disc n (%)	Fusion n (%)	Artificial Disc n (%)	Fusion n (%)
Number of subjects (completers)	184	81	184	81
Overall clinical success	117 (63.6)	46 (56.8)	107 (58)	44 (54)
ODI from baseline Success	130 (71.0)	50 (62.0)	117 (64)	47 (58)
†No device failure	175 (95.0)	74 (91.0)	175 (95)	74 (91)
‡No Major complications	182 (99.0)	80 (99.0)	182 (99)	80 (99)
§ No neurological deterioration	167 (91.0)	77 (95.0)	167 (91)	77 (95)

* ODI indicates Oswestry Disability Index.
†Device failure included revisions, reoperation, or removal of device;
‡ Major complications were defined as major vessel injury, neurological damage, nerve root injury, or death.
§ Neurological deterioration was defined as slight deterioration, significant deterioration, or mixed response at 24 months.

Secondary Outcomes

Disability

The mean percent change from baseline in ODI scores was significantly greater in the artificial disc group compared with the fusion group at 6 weeks (*P* = .02), 3 months, (*P* = .001), 6 months (*P* = .002), and 12 months (*P* = .04) after surgery, but not at 24 months (*P* = .27).

Pain

The mean score change from baseline in pain VAS scores was significantly greater in the artificial disc group compared with the fusion group at 6 weeks (*P* = .02), 3 months, (*P* = .02), 6 months (*P* = .004), and 12 months (*P* = .04) after surgery, but not at 24 months (*P* = .11).

Quality of Life: SF-36

At 24 months, 72% of people in the ADR group compared with 63% in the control group had a 15%

improvement from baseline in the physical component score of the SF-36 questionnaire, and 50% of the 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. No statistical analysis was reported for these results.

Narcotic Use

In the subgroup demonstrating clinical success, 73 (64%) of 114 people treated with the artificial disc reported using narcotics at 24 months to control pain compared with 37 (80.4%) of 46 controls.

Return to Work

At 24 months, there was no statistical difference in the proportion of patients that were employed (full-time or part-time) in either the treatment or control group (62.4% vs. 65%, $P = .6329$).

Patient Satisfaction

At 24 months, 69.9% of patients in the artificial disc group said they would have the same treatment again compared with 50% in the fusion group ($P < .0062$).

Radiological Outcomes

The artificial disc group had statistically significantly better restoration of disc height ($P < .05$) and less subsidence ($P < .05$) than did the fusion control group.

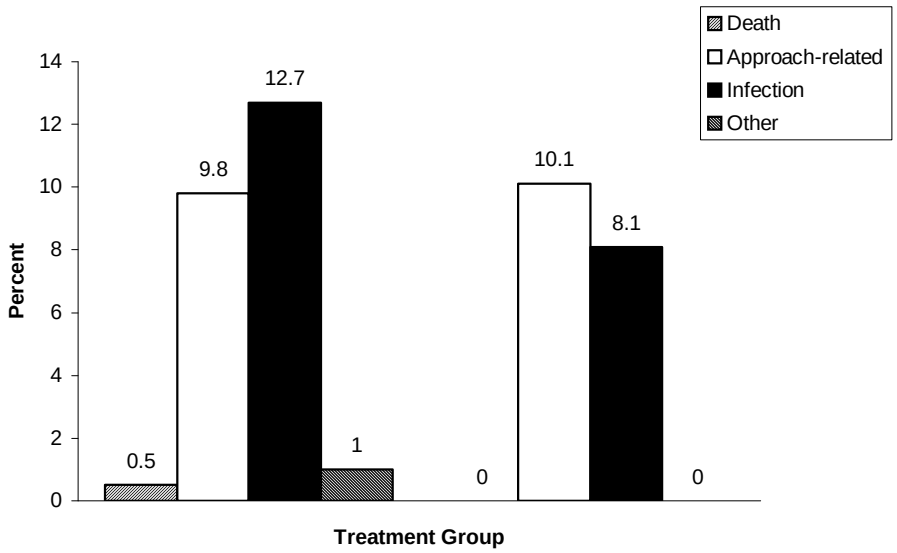
Health Systems Outcomes

Duration of surgery and blood loss did not differ statistically between groups. Mean duration of hospitalization was significantly lower in the artificial disc group compared with the control group (3.7 days versus 4.2 days, $P < .0039$). However, discharge from the hospital was not standardized within the protocol; therefore, this result may be biased.

Complication Rate: Reoperations, Device Failures, Neurological, Death, Other

The overall complication rate was not statistically significant between treatment groups. Deaths, approach-related complications, infection, and other types of complications not otherwise categorized are presented in Figure 5 on the following page. An itemized list of complications is reported in Appendix 8.

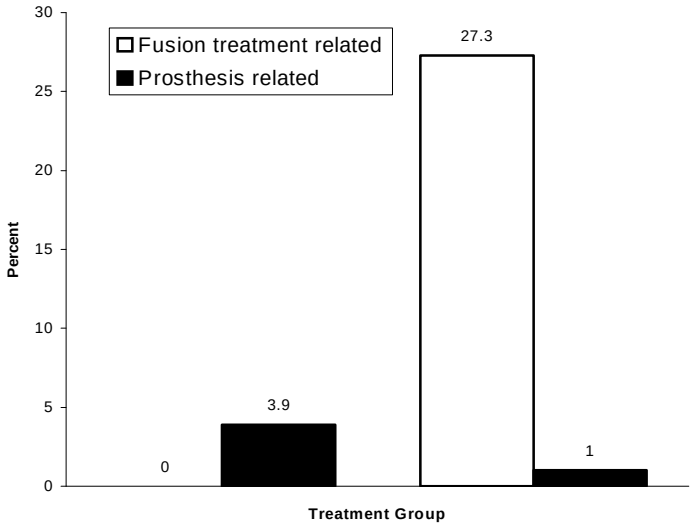
Figure 5: Complication Rates



Treatment-Related Complications

Treatment-related complications occurred more frequently in the fusion group compared with the artificial disc group (27.3% vs. 0%) (Figure 6). Fusion treatment-related complications included nonunion, pseudoarthrosis, and bone graft donor site pain. The rate of device-related complications was 1% in the control group compared with 3.9% in the ADR group.

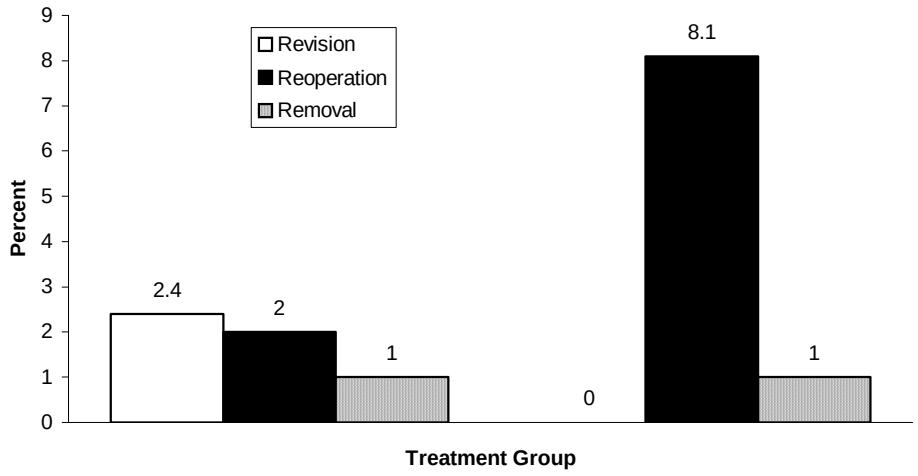
Figure 6: Treatment-Related Complications



Device Failures

Device failures requiring reoperation, revision, or removal occurred in 11 (5.4%) patients in the ADR group, and 9 (9.1%) patients in the control group (P = .45) (Figure 7). Supplemental fixation was required in 9 (4.4%) of the 205 patients in the ADR group and in 6 of the 99 (6.1%) control patients.

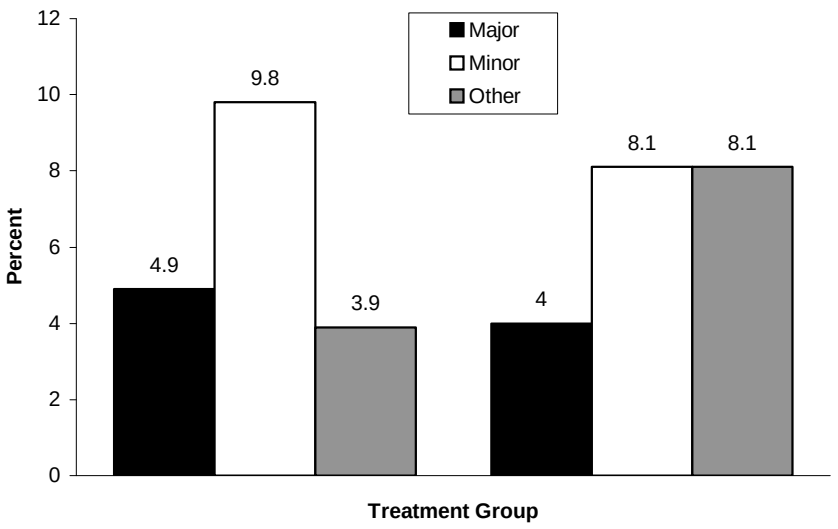
Figure 7: Device Failures



Neurological Outcomes

There was no statistically significant difference in neurological status between groups at 6, 12, or 24 months compared with their respective baseline neurological status. (58) Adverse neurological events were classified as major, minor, or other, and as related or unrelated to the device. Figure 8 shows the major, minor, and other neurological adverse events in both groups. Major events were burning or dysesthetic leg pain, motor deficit in index level, and nerve root injury. Minor events were numbness in index level and sacral nerve distribution. Neurological events classified as other were numbness in peripheral nerve or nonindex level, positive Waddell signs, reflex change, and mechanical signs (straight leg-raising test).

Figure 8: Adverse Neurological Events



ProDisc 2006

Data on clinical effectiveness is reported as aggregated values in the meta-analysis.

Medical Advisory Secretariat Meta-Analysis

Data were available from the Blumenthal 2005 RCT involving the Charité artificial lumbar disc and the ProDisc-L 2006 RCT to complete a meta-analysis. The following clinical, health systems, and adverse event outcome measures were synthesized: primary outcome of clinical success; ODI; pain VAS; patient satisfaction; duration of surgery; amount of blood loss; length of hospital stay; rate of device failure; and reoperation rate. The overall risk difference (RD) for dichotomous data, or weighted mean difference (WMD) for continuous data as determined from the meta-analysis of each outcome measure, are presented in Table 16.

The analysis for the primary outcome measure of overall clinical success was interpreted using a -10% noninferiority boundary as per the FDA analyses of the Blumenthal et al. (5) study. The remaining outcome measures were interpreted for superiority. The 95% CIs are also reported for the primary outcome.

Table 16: Results of the Medical Advisory Secretariat's Meta-Analysis*

Outcome Measure	Risk Difference (95% Confidence Interval)	Weighted Mean Difference (95% Confidence Interval)
Overall clinical success at 24 months (yes/no), intention-to-treat analysis	0.09 (0.00–0.18)	
Overall clinical success at 24 months (yes/no), completers (using ≥15 point improvement as part of composite score)	0.08 (-0.02– 0.17)	
≥ 15 point improvement from baseline in	0.09 (0.00– 0.18)	

Outcome Measure	Risk Difference (95% Confidence Interval)	Weighted Mean Difference (95% Confidence Interval)
Oswestry Disability Index scores at 24 months		
≥ 20mm decrease from baseline on Visual Analogue Scale pain scores at 24 months	0.06 (- 0.03–0.15)	
15% increase from baseline in SF-36 scores at 24 months - physical component scale - mental component scale	 0.12 (0.03–0.22) 0.01 (-0.09–0.11)	
Patient satisfaction at 24 months (yes/no) Would you have this procedure again?	0.16 (0.07–0.25)	
Employed at 24 months	0.03 (-0.07, 0.12)	
Duration of surgery, minutes		-55.4 (-158.11– 47.30)
Blood Loss, ml		-128.80 (-380.66–123.05)
Length of hospital stay, days		0.71 (0.32–1.10)
No device failures at 24 months (yes/no)	0.01 (-0.04–0.06)	
Neurological complications at 24 months (yes/no)	0.06 (-0.02–0.14)	

Clinical Outcome Measures

The meta-analysis of overall clinical success supported the noninferiority at the -10% noninferiority margin of lumbar ADR compared with spinal fusion at 24 months (Table 16; Figures 9 and 10). Clinical success was defined by a composite outcome measure in both studies. To minimize heterogeneity in the meta-analysis, data using the definition of clinical success, which employed the FDA criterion of at least a 15-point improvement from baseline ODI scores, were used for both studies. Given this, the definition of clinical success was similar in both studies, with the exception of the ProDisc-L study definition of improvement in the SF-36 scores and radiological success. It was thought that the addition of these 2 variables to the composite definition of clinical success would make it harder to achieve clinical success and therefore not bias the result in favour of clinical success. Because of this, synthesizing the data from these slightly different definitions was thought to be acceptable. The minimal clinically important difference (MCID) in the ODI score remains a contentious issue. Published research indicates the MCID ranges from 4 to 17, and that the value may differ depending on whether the assessment is for an individual or a group. Currently, the FDA accepts 15 points as the MCID.

Figure 9: Clinical Success (Intention-To-Treat Analysis)

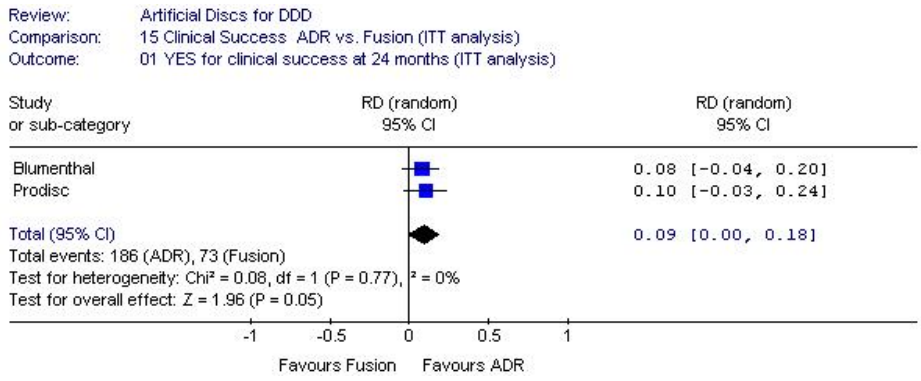
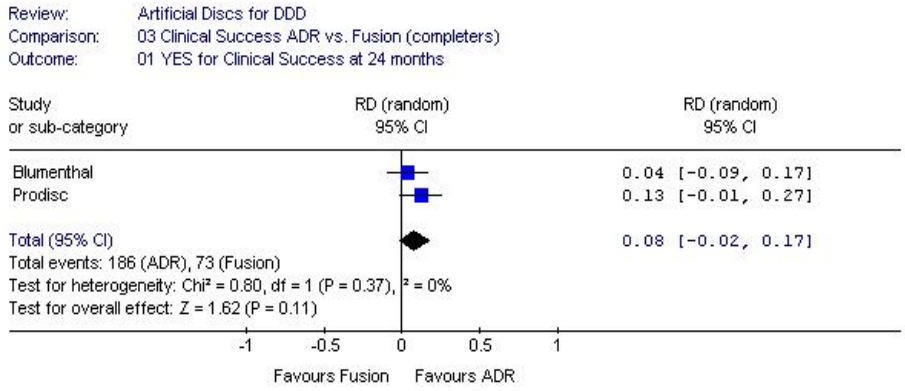


Figure 10: Clinical Success (Completers)



Of the remaining clinical outcome measures (ODI, pain VAS scores, SF-36 scores [mental and physical components], patient satisfaction, and return to work status) only patient satisfaction and scores on the physical component scale of the SF-36 questionnaire were significantly improved in favour of lumbar ADR compared with spinal fusion (Figures 11 and 12). However, there was a trend towards favouring ADR in the ODI scores and pain VAS scores (Figures 13 and 14), but not in work status and SF-36 mental component scores (Figures 15 and 16).

Figure 11: Patient Satisfaction

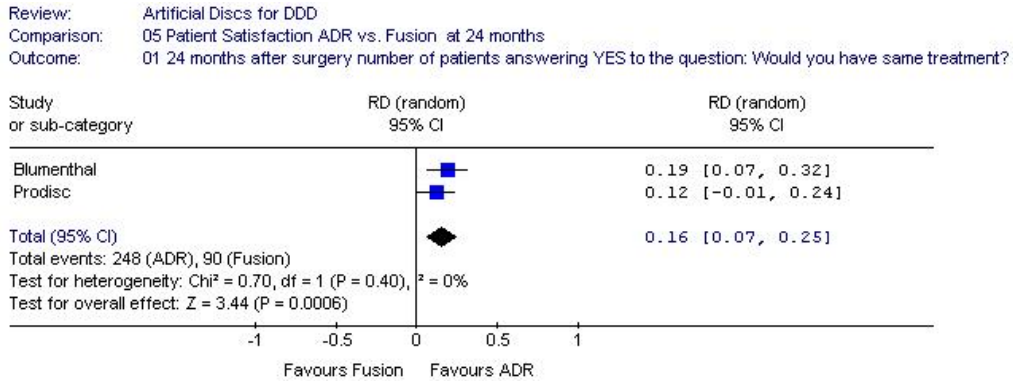


Figure 12: SF-36 Physical Component Score

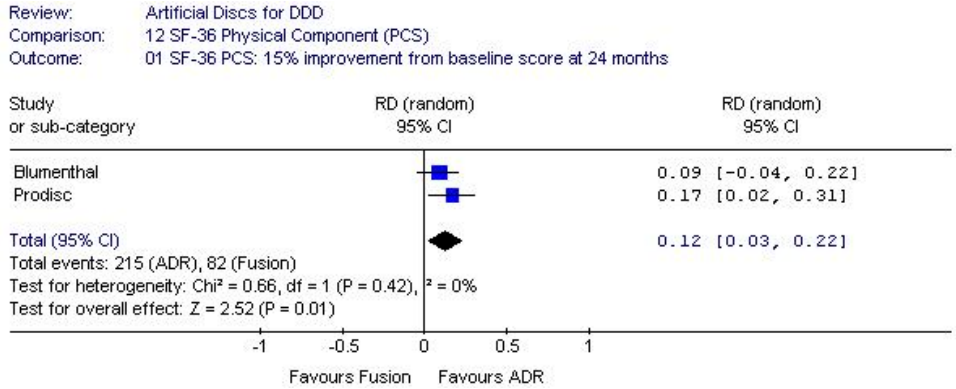


Figure 13: Oswestry Disability Index Scores

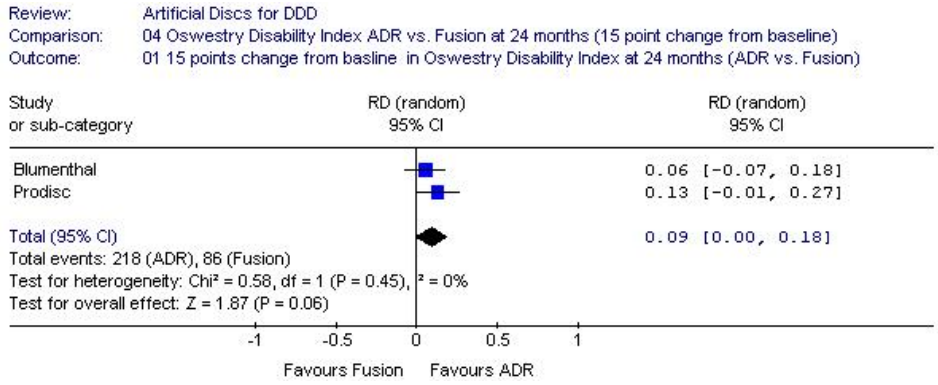


Figure 14: Visual Analogue Score (VAS) of Pain

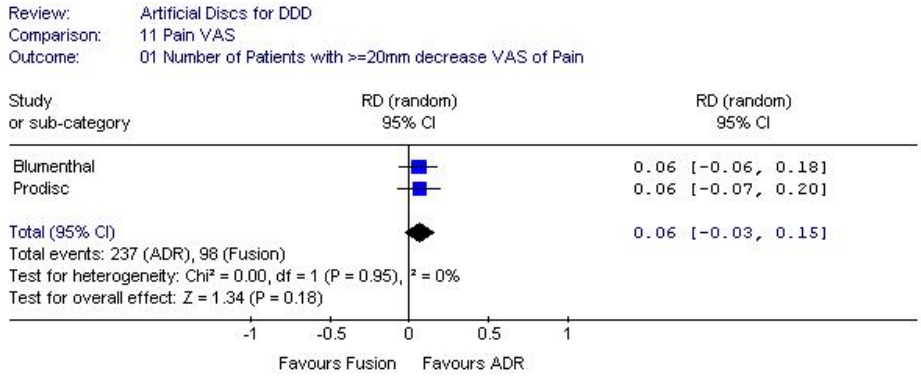


Figure 15: Total Employed at 24 Months

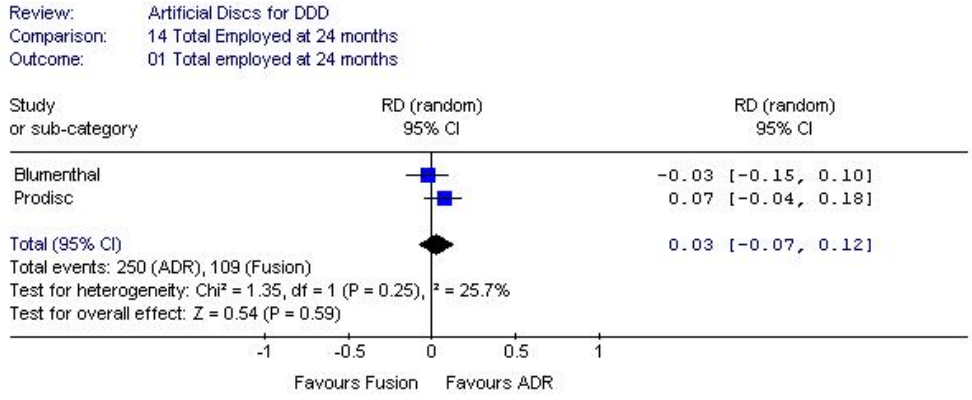
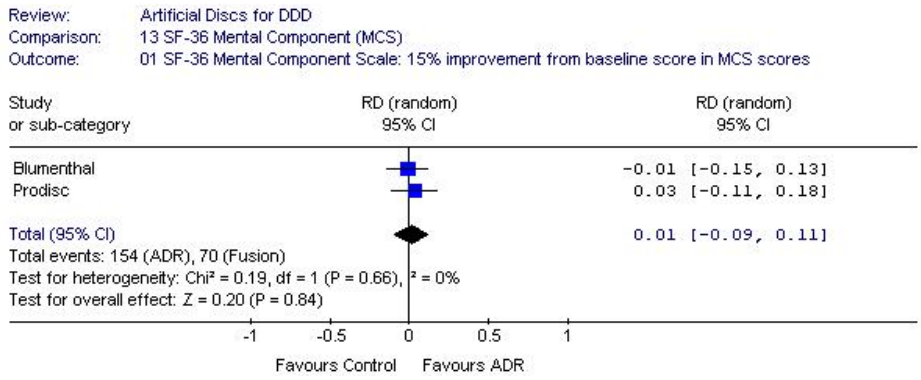


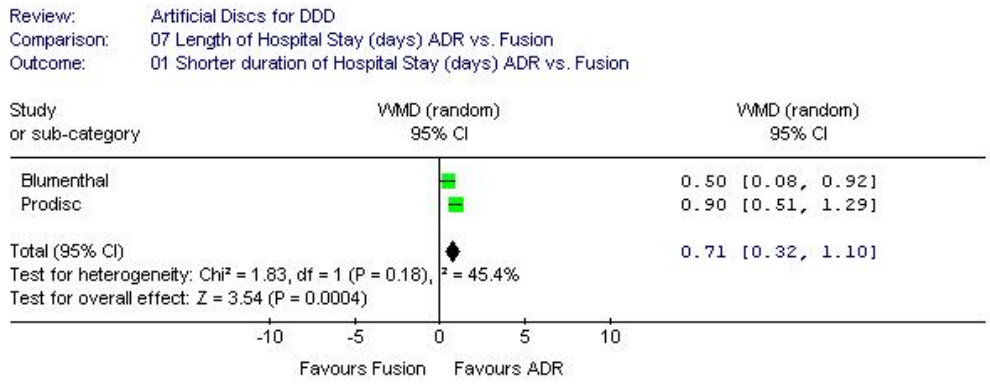
Figure 16: SF-36 Mental Component Score



Health Systems Outcomes

Blood loss and surgical time showed statistical heterogeneity; therefore, the meta-analysis results are not interpretable. Length of hospital stay was significantly shorter in patients receiving the ADR compared with controls (Figure 17). However, discharge criteria were not standardized in the Blumenthal et al. study. It is unknown if the discharge criteria were standardized in the ProDisc study.

Figure 17: Length of Hospital Stay



Adverse Events

Neither the number of device failures (Figure 18) nor the number of neurological complications (Figure 19) at 24 months was statistically significantly different between the ADR and fusion groups. However, there was a trend toward fewer neurological complications at 24 months in the ADR group compared with spinal fusion. A detailed description of the overall complications reported by Blumenthal et al. for the Charité disc and control group are reported in Appendix 8.

Figure 18: Device Failure (Defined as Reoperation, Revision, or Removal Required)

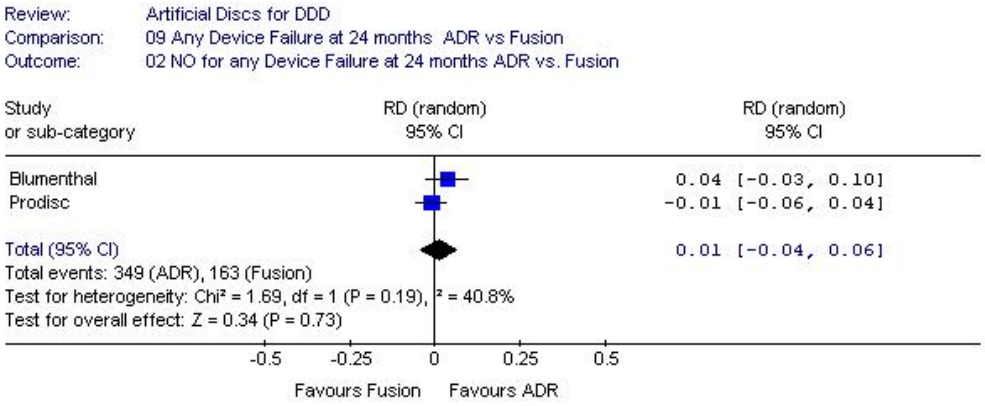
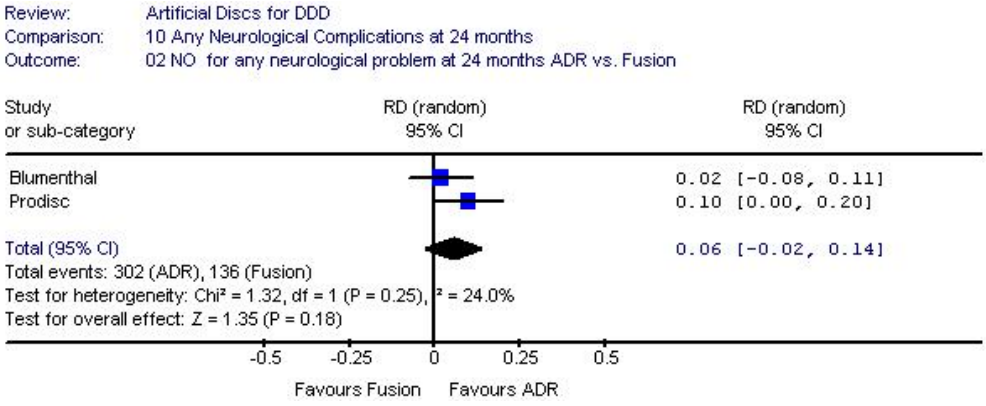


Figure 19: Neurological Complications



Bayesian Analyses

The objectives of these analyses were as follows:

- To examine the influence of missing data on clinical success rates
- To compute the probability that artificial discs are superior to spinal fusion (on the basis of clinical success rates)
- To examine whether the results were sensitive to the choice of noninferiority margin

Methods

The Medical Advisory Secretariat performed a sensitivity analysis once by assuming a 50% failure rate and the second time by assuming a 100% failure rate in missing observations. This was to examine the influence of missing data on clinical success. If the conclusions did not change, then we could ignore the influence of missing data, and use data on study completers.

The Medical Advisory Secretariat then used a Bayesian random-effects model to compute the difference in success rates and 95% credible region (CR) (CRs are analogous to confidence intervals) using the clinical success rates reported in Blumenthal et al. (5) and the FDA IDE ProDisc (unpublished data)

clinical trial. Using noninformative priors and success rates of the 2 interventions in the 2 trials, we generated the posterior distribution of the difference in success rates. From the posterior distribution, we computed the probabilities that the success rate of ADR was better than the success rate of spinal fusion. In addition, using 2 noninferiority margins of -10% and -15%, we computed the probabilities that the success rate of ADR was not inferior to the success rate of fusion. Finally, using the posterior distribution we computed the same probabilities for a new trial (Prediction).

Results

The sensitivity analyses revealed that the influence of missing data on the outcome measure of clinical success was minimal.

The Bayesian model that used data on completers indicated that the probability for ADR being better than spinal fusion was 79% (Table 17). The probability of ADR being noninferior to spinal fusion using a -10% noninferiority bound was 92%; using a -15% noninferiority bound, it was 94%. The probability of artificial discs being superior to spinal fusion in a future trial was 73%.

Table 17: Results of Bayesian Model Analyses

	*SR[d] – SR[f] (d; 95% CR)	†P: d > 0, %	P: d > -0.10, %	P: d > -0.15, %
Blumenthal 2005	0.07 (-0.013–0.19)	91	99	100
ProDisc	0.08 (-0.03–0.19)	91	99	100
Pooled estimate	0.08 (-0.26–0.41)	79	92	94
Prediction	0.08 (-0.50–0.64)	73	86	89

*SR[d] indicates success rate [disc];SR[f], success rate [fusion]; d, difference in success rates; P, probability.

Level 4: Case Series Evidence

Lumbar Artificial Disc Replacement

Because level-1 data for the effectiveness of lumbar ADR existed, observational data were reviewed mainly to characterize the rate of major complications. Six case series have been added to the literature since the 2004 Medical Advisory Secretariat health technology policy assessment describing adverse events in 278 patients receiving the Charité, ProDisc, or Maverick lumbar artificial disc. There were 341 artificial discs implanted. Mean duration of follow ranged from 15.3 months to 11.3 years. The type of disc, study sample size, mean age, duration of follow-up, and major complication rate are shown in Table 18. A description of each adverse event is detailed in Table 19. A major complication was defined as any reoperation, device failure necessitating a revision, removal or reoperation, or any life-threatening event. The major complication rate ranged from 0% to 13% per device implanted. Only 1 study reported the rate of ASD, which was detected in 2 (2%) of the 100 people 11 years after surgery.

Table 18: Major Complications of Lumbar Artificial Disk Replacement*

Study	Type of Disc	Sample Size	No. of Prostheses	Mean Age, Years (Range)	Mean Follow-Up, Months	No. (%) of Major Complications Per Device†	No. (%) of ASD
Capsi (49)	Charité	20	23	*NR (24.0–50.0)	48.0	3 (13.0)	Not assessed
Su (50)	Charité	31	37	43.5 (32.0–55.0)	26.0	0 (0.0)	Not assessed
Xu (48)	Charité	34	41	41.1 (21.0–65.0)	18.6	1 (2.4)	Not assessed
Lemaire (47)	Charité	100	147	39.6 (23.9–50.8)	11.3 years	7 (4.8)	2 (2)
Cakir (34)	ProDisc	29	29	40.8 (29.0–56.0)	15.3	NR	No data
LeHuec (51)	Maverick	64	64	44 (20.0–60.0)	24.0	1 (1.6)	Not assessed

* ASD indicates adjacent segment degeneration; NR, not reported.
† Reoperation, device failure requiring reoperation, revision, removal, or life-threatening adverse event.

Table 19: Complications of Lumbar Artificial Disk Replacement

Study	Type of Disc	Sample Size	No. of Prostheses	Mean Follow-Up, Months	Number and Type of Complication
Capsi (49)	Charité	20	23	48.0	- 2 migrations of prosthesis requiring surgical revision 2 days after surgery in 1 patient due to incomplete severing of the post longitudinal ligament and 2 weeks postoperatively due to a small fracture of the lower end plate. - 1 intraoperative laceration of the ureter and thrombosis of the iliac artery immediately treated. - 1 spontaneous ossification of the intervertebral anterior ligament but progress halted with intensive physiotherapy.
Su (50)	Charité	31	37	26.0	- 1 displacement of sliding core, but no clinical symptoms
Xu (48)	Charité	34	41	18.6	- 1 anterior subluxation of the inferior endplate on S1 in patient with 2 level replacement at L4-5 and L5-S1 at 3 months postoperatively, but patient did not have symptoms. No management required. - 1 mild laceration iliac vein during operation, repaired with no adverse event.
Lemaire (47)	Charité	100	147	11.3 yrs	- 5 patients required secondary arthrodesis - 4 symptomatic articular arthritis (facet arthrosis/poor placement) - 2 periprosthetic ossification affecting prosthesis mobility - 2 adjacent level degeneration

Study	Type of Disc	Sample Size	No. of Prostheses	Mean Follow-Up, Months	Number and Type of Complication
					- 2 neurological complications - 2 minor subsidence (secondary to trauma) - 2 perioperative vascular laceration - 1 sexual dysfunction - 1 acute leg ischemia
Cakir (34)	ProDisc	29	29	15.3	None reported
LeHuec (51)	Maverick	64	64	24.0	- 4 postoperative root pain - 2 sequelae from previous discectomy surgery - 17 required posterior facet infiltration - 3 spinal pain other than lumbar region - 1 superficial infection requiring local debridement - 1 laceration of the ureter during surgery, repaired - 11 minor intraoperative complications due to surgical approach - 3 heterotrophic ossification (type I and 3 McAfee Classification.) - 5 migration of device axially 3–5 mm in the region of the superior end plate. Stable at 1-year follow-up.

Adverse Events Reported in the Manufacturer and User Facility Device Experience Database

The FDA analyzed the medical device reports (MDRs) that were entered into the Manufacturer and User Facility Device Experience (MAUDE) database between August 11, 2003 (data of first report) and November 16, 2005. (31) One hundred and one MDRs were analyzed for 96 patients. One MDR was for the ProDisc; the others were for the Charité disc. Fifty-four (56%) of 96 patients experienced device migration from the implanted location. Seventy-six (79%) patients required a reoperation to remove all or part of the implant to correct problems with the device or to correct problems produced during the initial implant surgery. Removal of all or part of the artificial disc followed by spinal fusion of the implanted motion segment was the most common reason for a second surgery. Most adverse events resulting in reoperation occurred in the first 2 months after implantation. Twelve patients each had 2 artificial discs replacements. Of the 96 patients, 2 deaths were attributed to pulmonary emboli.

Cervical Artificial Disc Replacement

Due to the lack of published level-1 data for effectiveness of cervical ADR, observational data were reviewed to ascertain effectiveness as well as to characterize the adverse events profile of the procedure. Four case series (9;52;54;55) have been added to the literature since the 2004 Medical Advisory Secretariat health technology policy assessment which describe clinical outcomes and adverse events in 229 patients of which data for 158 people are reported. There were 280 artificial discs implanted and data on 192 implants are reported. Mean duration of follow-up was 12 to 24 months. The study sample size, mean age, duration of follow-up, clinical outcome, and complications are shown in Table 20. A description of each adverse event is given in Table 21.

Three studies reported clinical effectiveness using Odom's criteria (65) which classifies the outcome of the surgery as either excellent (person has no discomfort due to cervical disease and can carry out daily work without impairment), good (intermittent discomfort related to cervical disease which does not significantly interfere with work), satisfactory (subjective improvement but physical activities are significantly limited) or poor (no improvement or worse as compared with pre-operative condition).

Lafuente et al. (55) reported that at 14 months follow-up, 70% (32 of the 46) of patients had a good to excellent clinical outcome. Sekhon et al. (52) reported 90% (10 of the 11) of patients had a good to excellent clinical outcome at 18 months follow-up. Finally, Goffin (9) reported that at 24 months follow-up 69% (34 of the 49) of people in the single-level implant group had a good to excellent outcome, as did 81% (21 of the 26) in the bilevel implant group at 12 months follow-up. However, there was variation in the definition of Odom's criteria used among the studies.

Duggal et al. (54)($P < .05$) and Lafuente et al. (55)($P < .001$) reported that postoperative neck disability index scores were statistically significantly better compared with preoperative scores at about 1 year, as did Sekhon et al. (52) at 18 months postoperatively ($P < .001$). Sekhon et al. also reported a statistically significant improvement in neck and arm pain postoperatively compared with preoperatively ($P < .001$) (Table 20).

The rate of major complications, defined as any reoperation, device failure requiring reoperation, revision, or removal, or a life-threatening event ranged from 0% to 8.1% in up to 24 months (Table 21). Adjacent segment degeneration was not reported in any study.

Table 20: Clinical Outcomes and Major Complication Rates for Cervical Artificial Disk Replacement

Study, Year	Type of Disc	Sample Size	No. of Prostheses	Mean Age, Years (Range)	Mean Follow-Up, Months	No. (%) Clinical Outcomes	No. (% per Device) Major Complications
Duggal, 2004 (54)	Bryan	26	30	43.3 (30–67)	12.3	Neck Disability Index scores significantly improved after surgery compared with values before surgery ($P < .05$)	0 (0)
Lafuente, 2005 (55)	Bryan	46	46	47.6 (33–70)	14.0	Odom's criteria: Poor 6 (13) Fair 8 (17) Good 5 (11) Excellent 27 (59) SF-36 mental and physical components ($P <$ .0001 postop. vs. baseline values) Neck Disability Index ($P < .0001$ postop. vs. baseline values)	1 (2.2)
Sekhon, 2004 (52)	Bryan	11	15	43.7 (31–55)	18.4	Odom's criteria: Poor 0 (0) Fair 1 (9) Good 2 (18) Excellent 8 (72) Nurick Grade, neck pain, arm pain, and neck disability Index ($P < .001$ post op. vs. baseline)	0 (0)
Goffin, 2003 (9)	Bryan	146 (data reported for n =	189 data reported for n = 101)	NR (26–79)	24 (single level)	Odom's criteria Single level: Excellent 32 (65)	4 (8.1)

Study, Year	Type of Disc	Sample Size	No. of Prostheses	Mean Age, Years (Range)	Mean Follow-Up, Months	No. (%) Clinical Outcomes	No. (% per Device) Major Complications
		75) single level n = 49 bilevel n = 26	n = 49 n = 52		12 (bilevel)	Good 2 (4) Fair 10 (21) Poor 5 (10) Bilevel: Excellent 20(77) Good 1 (4) Fair 4(15) Poor 1(4)	4 (7.7)

Table 21: Complications of Cervical Artificial Disk Replacement

Study, Year	Type of Disc	Sample Size	No. of Prostheses	Mean Follow-Up, Months	Number and Description of Complication
Duggal, 2004 (54)	Bryan	26	30	12.3	- No reoperations or prosthesis subsidence occurred - 1 increased radicular pain (arm pain) in the recovery room after surgery. Improved over several weeks. - 1 transient unilateral vocal cord paralysis resolving completely in 6 weeks. - 1 dysphagia lasting 6 weeks postoperatively. - 1 possible device migration at 2 years follow-up (superior endplate of disc moved anteriorly 2 mm at 2 years postoperatively) - 3 symptomatic disc herniation adjacent to earlier fused segments
Lafuente, 2005 (55)	Bryan	46	46	14.0	- 1 worsening of muscle spasms which improved by discharge postoperatively. - 3 mild postoperative dysphonia resolved by first clinic visit. - 1 removal of prosthesis after fall which dislodged inferior endplate - 2 bony ankylosis at implanted disc level
Sekhon, 2004 (52)	Bryan	11	15	18.4	- 1 readmission for worsening of preoperative hand and gait dysfunction symptoms resolved in 72 hours with Dexamethasone - 1 Spondylotic bridging behind the prosthesis creating an interbody fusion at 17months after surgery. Arm and neck pain persisted to some degree but device not removed. - 1 myelopathic deterioration possibly attributable to swelling - 3 cases in which the preoperative alignment worsened.
Goffin, 2003 (9)	Bryan	49 Single Level	49 (Single level)	24.0 (Single level)	**Single-level study group:** - 1 evacuation of a prevertebral hematoma - 1 posterior foraminotomy without device involvement to treat residual symptoms - 1 posterior decompression to treat residual myelopathic symptoms - 1 wrong level operated on and second surgery needed after which patient developed temporary dysphonia
		26 Bi level	52 (bi-level)	12.0 (bi level)	- 1 pain in right shoulder, arm and in the sternum region about 6 months after surgery - 1 unresolved non specific left shoulder pain - 1 patient required a second device implanted at an adjacent level 21 months after the initial surgery because of radiculopathy caused by disc herniation. After surgery patient experienced severe dysphonia caused by bilateral vocal cord paralysis due to bilateral recurrent nerve compression from excessive retraction during surgery. - 1 evidence of temporary/anterior/posterior device migration in 1 patient and suspected in another both < 3.5 mm) **Bilevel study group**:

Study, Year	Type of Disc	Sample Size	No. of Prostheses	Mean Follow-Up, Months	Number and Description of Complication
					- 1 Cerebral spinal fluid leak during posterior decompression - 1 evacuation of hematoma - 1 evacuation of a prevertebral hematoma - 1 repair of a pharyngeal tear/esophageal wound caused during intubation - 1 anterior decompression required because of ongoing nerve root compression which required surgical revision for decompression of residual foraminal stenosis during which the device was repositioned. - 1 evidence of device migration < 3.5 mm detected

Quality of the Body of Evidence on Lumbar Artificial Disc Replacement

Based on the evidence reviewed, the following GRADE profiles, which summarize the quality of the body of evidence for lumbar ADR, have been determined (Tables 22–25). The GRADE quality of evidence is moderate for effectiveness outcome measures up to 2 years after surgery. Moderate indicates that further research is likely to have an impact on confidence in the estimate of effect and may change the estimate.

The GRADE quality of evidence is low for ASD. Low indicates an estimate of effect is uncertain.

Table 22: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative (95% CI)	Quality	Out-come
Outcome Measure: Clinical Success at 24 months (measured with composite score: ODI > 15 points, no device failure, no major complications, no neurological deterioration, ‡radiographic success, and improvement in SF-36 scores from baseline)										
Blumenthal et al.	Level-1 RCT	Serious limitation*	No important inconsistency	Direct	None	366	174	RD .09 (0.00–0.18) †	Moderate	Critical
Pro-Disc IDE FDA trial‡	Level-1 RCT									

* Blumenthal 2005, unblinded outcome assessors, unable to fully assess quality of ProDisc study reported in grey literature.
† RD for noninferiority using -10 % noninferiority margin (ITT analysis, 95% CI).
‡ ProDisc required all 5 criteria to be satisfied for clinical success; IDE indicates investigational device exemption; FDA, United States Food and Drug Administration.

Table 23: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative (95% CI)	Quality	Out-come
Complication: No Device Failure at 24 months (device failure defined as requiring reoperation, revision, or removal)										
Blumenthal et al.	Level-1 RCT	Serious limitation*	No inconsistency (see forest plot)	Direct	None	366	174	RD .01 (-0.04–0.06)	Moderate	Critical
ProDisc IDE FDA trial†	Level-1 RCT									

* Blumenthal 2005, unblinded outcome assessors, unable to fully assess quality of ProDisc study reported in grey literature.
† IDE indicates investigational device exemption; FDA, United States Food and Drug Administration

Table 24: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative (95% CI)	Quality	Out-come
Complication: No Neurological Problem at 24 months										
Blumenthal et al.	Level-1 RCT	Serious limitation*	No inconsistency (see forest plot)	Direct	None	353	169	RD .06 (-0.02–0.14)	Moderate	Critical
ProDisc IDE FDA trial†	Level-1 RCT									

*Blumenthal 2005, unblinded outcome assessors, unable to fully assess quality of ProDisc study reported in grey literature.
† IDE indicates investigational device exemption; FDA, United States Food and Drug Administration

Table 25: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile*

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative (95% CI)	Quality	Out-come
Complication: Adjacent Segment Degeneration										
Lemaire 2005		Level 4C Case series	Not applicable	Direct	Sparse data*	100	N/A	2% incidence over 11 years	Very Low	Critical

* Only 1 study reported ASD.

Quality of the Body of Evidence of Cervical Artificial Disc Replacement

Based on the evidence reviewed, the following GRADE profiles have been determined which summarize the quality of the body of evidence for cervical ADR (Table 26-28).

Table 26: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile*

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative	Quality	Out-come
Outcome: Odom's Criteria- excellent, good, fair, poor outcome										
Duggal 2004 Lafuente 2004 Goffin 2003	Level 4 Case series	N/A*	Variation in estimate†	Some indirectness ‡	Sparse data	112	N/a	Minimum 69% and Maximum 90% had good or excellent outcome at up to 2 years after surgery	Very low	Import-ant

* Refers to case series.
† Good/excellent ranged between 69% and 90%.
‡ Refers to variation in definition of Odom's criteria.

Table 27: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile*

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative	Quality	Out-come
Outcome : Disability measured using the Neck Disability Index										
Duggal 2004 Sekhon 2004 Sekhon 2004	Level 4 Case series	N/A*	None†	Direct	Sparse data	83	N/A	N/A	Very low	Critical

* Refers to case series.
†All studies report statistically significant different pre vs. post scores.

Table 28: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Profile*

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Artificial Disc	Fusion	Relative	Quality	Out-come
Disability: Major Complications (any reoperation, device removal, revision, or reoperation required for device failure)										
Duggal 2004 Sekhon 2004 Sekhon 2004	Level 4 Case series	N/A*	N/A	direct	Sparse data	83	N/A	8.1%/ up to 24 months follow-up	Very low	Critical

* This refers to case series.

Economic Analysis

Notes and Disclaimer:

The Medical Advisory Secretariat uses a standardized costing methods for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Ontario-Based Economic Analysis

Diffusion

The delivery of artificial discs is controlled by hospitals from within the global hospital budgets. The average cost of an artificial disc is $6,763 (Cdn). (Costs are from 3 separate manufacturers of lumbar artificial discs.)

Table 29 illustrates the total number of lumbar fusion surgeries and lumbar artificial disk replacements performed in Ontario in fiscal year 2003 and fiscal year 2004. The total number of lumbar fusion surgeries, reported below, are ones in which patients would also have been candidates for a lumbar ADR. Both the total number of fusion surgeries as well as the total number of lumbar ADR procedures remained fairly constant from fiscal year 2003 to fiscal year 2004.

Table 29: Number of Lumbar Fusion and Lumbar ADR Procedures in Ontario*

Fiscal Year	Number of Fusions	Number of Artificial Disks
2002	303	Not applicable
2003	300	8
2004	311	8

*ADR indicates artificial disk replacement.

Demographics

The prevalence of neck and back pain in Ontario was estimated at 11%. (10) About 10% to 20% of people with back pain would be unresponsive to nonsurgical treatment, with an estimated 50% of these proceeding to surgery. Of those patients proceeding to surgery, it is estimated that 50% would have fusion surgery. Finally, about 5% of people having spinal fusion may be eligible for lumbar ADR instead.

Total Ontario target population: People aged 35 to69 years = 5,358,265.

Population with neck or back pain = 589,409 (= 11%*5,358,265).

Potential candidates for surgical treatment = 58,940 to 117,881 (= 10%–20% *589,409).

Patients proceeding to surgery = 29,470 to 58,940 (50%*58,940 -50%*117,881).

Patients receiving fusion surgery = 14,735 to 29,470 (50%*29,470-50%*58,940).

Patients who are candidates for artificial discs = 736 to 1473 (5%*29,470-50%*29,470).

According to data from the United Kingdom and Sweden, the annual incidence rate for lower back pain is estimated at 2.8% of the total population (28 episodes/1000 people per year). (6)

Costs

All costs are in Canadian currency unless otherwise noted.

Professional Costs

Total professional costs (including anesthetist and assistant costs) for a lumbar fusion surgery was estimated at $2,636.56[1] compared with $ 2,537.37 for a lumbar ADR procedure (Ontario Schedule of Benefits Physician Claims, 2005).

Hospital Costs

Based on data from the Ontario Case Costing Initiative (OCCI) for 148 cases of lumbar fusion surgeries performed in Ontario, the median hospital cost of a lumbar fusion surgery procedure was estimated at $8,774. Similarly, based on OCCI data for 5 cases of lumbar artificial disk replacements in Ontario, the average procedural cost for a lumbar artificial disc replacement procedure was estimated at $5,971.

[1] Average of the posterior lumbar interbody fusion (PLIF) procedure, anterior lumbar interbody fusion (ALIF) procedure and ALIF procedure with an approach by a separate surgeon

Total Costs

The total cost of a lumbar ADR is $15,371 (including costs related to the device, physician, and procedure), while the total cost of a lumbar fusion surgery procedure is $11,311 (including physician costs and procedural costs).

Budget Impact Analysis

In fiscal year 2004, the total budget for the 311 lumbar fusion surgeries and 8 lumbar ADR procedures was estimated at $3,640,689. The total number of lumbar fusion surgeries and lumbar ADRs did not vary considerable from fiscal year 2003 to fiscal year 2004 in Ontario. Table 30 summarizes the increase in the current budget, depending on various estimates of the total percentage of lumbar fusion surgeries that might be replaced by lumbar ADR procedures in the future.

Table 30: Budget Impact with Various Estimates of the Percentage of Lumbar Fusions Surgeries Captured by Lumbar Artificial Discs

Lumbar Fusions Replaced by Artificial Discs, %	Total Number of Lumbar Fusions	Total Number of Lumbar Artificial Disc Replacements	Budget (Cdn) $
2.5	311	8	3,640,689
25.0	231	80	3,842,521
50.0	159	160	4,257,809
75.0	72	239	4,488,061
100.0	0	319	4,903,349

Unmeasured Costs

It is important to consider downstream cost savings that were not quantifiable in the economic analysis. These include savings that would result from a decrease in adjacent disk degeneration cases that occur in fusion surgery patients but not in patients receiving an ADR. There would also be a decrease in physician and hospital visits due to no apparent graft site pain in patients receiving artificial disks. This, in turn, would lead to decreased costs. In addition, there would be high cost avoidance due to a decrease in osteogenic protein-1 (OP-1) usage, a synthetic protein used in long bone non-union during fusion surgery, if fusion surgeries were indeed replaced with ADR procedures.

Existing Guidelines for Use of Technology

Centers for Medicare and Medicaid Services (United States)

As of August 16, 2005, the Centers for Medicare and Medicaid Services (CMS) (31) have opened a national coverage determination request to review the coverage of the lumbar artificial intervertebral disc. In the meantime, there is no national coverage policy, and coverage is left to the discretion of local carriers.

More recently, on February 15, 2006, CMS issued the following Proposed Coverage Decision

Memorandum for Lumbar Artificial Disc Replacement (31):

> "The Centers for Medicare and Medicaid Services (CMS) is seeking public comment on the proposed determination that the evidence is not adequate to conclude that lumbar artificial disc replacement with the Charité lumbar artificial disc is reasonable and necessary. Therefore, we propose to issue a national noncoverage determination.
>
> We are requesting public comments on this proposed determination pursuant to Section 731 of the Medicare Modernization Act. We are particularly interested in comments that include evidence we did not review or that assess how we evaluated the evidence included. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum."

AETNA (United States)

In a Clinical Policy Bulletin dated August 2005, AETNA (66) stated that the available evidence was adequate to support the efficacy and safety of prosthetic disc replacement in the lumbar spine.

> "Aetna considers the Charité artificial disc medically necessary for spinal arthroplasty in skeletally mature persons with degenerative disc disease at 1 level from L4 to S1 who have failed at least 6 months of conservative management. Prosthetic intervertebral disc replacement is considered experimental and investigational for use in the cervical spine and for all other indications."

The Regence Group (United States)

The Regence Group (67) published medical policy on Charité disc replacement in June 2005. They concluded that the Charité artificial disc was investigational, given a lack of evidence of efficacy, insufficient long-term follow-up, and inconclusive evidence regarding safety and complications.

Cigna Healthcare (United States)

Cigna Healthcare (68) delivered the following coverage position for intervertebral disc prostheses in February, 2005:

> "Cigna HealthCare does NOT cover the intervertebral disc (IVD) prosthesis for any indication, because it is considered experimental, investigational, or unproven."

CIGNA states that early data suggest that the artificial disc may be effective in a subset of patients; however, they are concerned with a lack of evidence demonstrating efficacy and safety of the devices. Of particular concern is a lack of long-term follow-up data. CIGNA investigators await long-term information on the durability of the device, the patients' systemic response to the implanted prosthesis, long-term complication and revision rates, and maintenance of any restored gains in range of motion.

National Institute for Clinical Excellence (United Kingdom)

The National Institute for Clinical Excellence issued guidance on the use of lumbar (56) and cervical (61) artificial discs in November 2004. They concluded that the evidence of efficacy and safety appeared adequate to support the use of either ADR procedure.

Regarding lumbar artificial discs, NICE stated that there was a lack of evidence beyond a 2 to 3 year

follow-up period, and stressed the importance of the collection of long-term data. Specifically, they stated that patients receiving an artificial disc should be audited. NICE also advised that the surgical procedure itself required skill in the anterior approach to the spine. They also noted that the potential for serious complications existed. They also indicated that different prostheses varied considerably, and that different outcomes could be expected from newer devices. Moreover, NICE investigators voiced concerns as to the life expectancy of the prosthetic disc, especially as compared with fusion instrumentation.

Regarding the cervical artificial disc, NICE stated that there was evidence of short-term efficacy and no major safety concerns about with the use of the device. Theoretical adverse events included nerve root compression and/or airway obstruction due to device migration. They also noted that device failure may cause spinal cord damage.

Policy Development

Policy Considerations

Patient Outcomes

Important patient outcomes include measurement of pain, disability, and complications including neurological complications and device failure requiring reoperation, revision, or removal. Radiographic evaluation of ASD has not occurred in any of the published RCTs and is in part the reason for the 5-year follow-up extension of the Charité FDA IDE RCT.

Demographics

Once DDD is diagnosed, surgery is considered after at least a 6-month course of nonsurgical treatments have been tried with no improvement in pain or disability. Based on data from the 2 RCTs reviewed in this report, the mean age of the target population needing a lumbar artificial disc is 40 years. Based on data from the case series reports, the mean age of the target population receiving a cervical artificial disc ranged from 43 to 48 years.

Diffusion

Surgeons interested in ADR must attend a training session offered by the manufacturers of the devices. Specialized training is required, as the procedure for artificial disc insertion is technically demanding Representatives of the Charité, ProDisc-L, Maverick, and Bryan cervical discs stated devices are not made available to untrained surgeons (Personal communication April 11 and 12, 2006).

Ontario Profile

Table 31 lists the number of health care facilities in Ontario that have a surgeon trained to perform ADR. Ontario has 6 surgeons trained to perform lumbar ADR, 5 trained to perform either lumbar or cervical ADR, and 3 trained to perform only cervical ADR. Two more physicians will be trained to insert the Charité artificial disc in 2006. Artificial disc replacement became part of the schedule of benefits on October 1, 2005. Before this, physicians billed under an R990 code, which is defined as “independent consideration will be given (under R990) to claims for other unusual but generally accepted surgical procedures which are not listed specially in the schedule.”

Table 31: Health Care Facilities with Surgeons Trained To Perform Artificial Disk Replacement

Type of Artificial Disc	Health Care Facility
Lumbar	- London Health Sciences Centre, London - Trillium Health Centre, Mississauga - St. Joseph's Healthcare Hamilton, Hamilton - Scarborough General Hospital, Scarborough - York Central Hospital, North York - Toronto Western Hospital, Toronto
Cervical	- London Health Sciences Centre, London - Trillium Health Centre, Mississauga - St. Joseph's Healthcare Hamilton, Hamilton - Toronto Western Hospital, Toronto

Using the Provincial Health Planning Database (69) and based on the Canadian Classification of Interventions (CCI) (70) and the International Classification of Disease-10 codes (ICD-10), (71) it is estimated that 300 fusion surgeries annually may be eligible for ADR instead of fusion. Based on CCI codes, 16 lumbar artificial discs have been inserted in Ontario since 2003. Based on CCI and ICD-10 codes data, and data from the Ontario Case Costing Initiative (OCCI), 9 cervical artificial discs procedures were completed in 2004.

National Diffusion

The availability of ADR in Canada is shown in Table 32. To date, ADR is done in Nova Scotia, Alberta, and Manitoba.

Table 32: Diffusion of Artificial Disk Replacement Procedures in Canada

Province	Service Offered?	Comment
Newfoundland and Labrador	No	
New Brunswick	No	No fee code for intervertebral disc prostheses and there is no request to negotiate a fee code. Service not being offered.
Prince Edward Island	No data obtained	
Nova Scotia	Yes	2006: 2 2005: none 2004: 3 artificial disc implants
Quebec	Not sure	No fee code specific to procedure. If done, would get billed as intervertebral fusion. Therefore it is not tracked. Information from manufacturer of artificial disc confirms disc arthroplasty is being done in Quebec.
Ontario	Yes	Fee code for ADR as of October 1, 2005
Manitoba	Yes	1 case done in province
Saskatchewan	No data obtained	
Alberta	Yes	2004-05:19 cervical replacements and 14 lumbar replacements 2003-04:none 2002-03:none
British Columbia	No	Service not offered because procedure considered experimental

International Diffusion

Lumbar and cervical disc replacements have been available in Europe for over 10 years.

System Pressures

A clinical expert (Personal communication, April 4, 2006) indicated that a lack of resources, including operating room time, operating room nurses, and anesthetists, would limit the diffusion of artificial disc device technology in Ontario.

Another clinical expert (Personal communication, April 7, 2006) indicated that the cost of the artificial device limits patient access to this technology. Some hospitals pay for the device, while others do not; because of this, there is unequal access to this treatment throughout Ontario. Data from an ICES report (72) published in June 2005 indicated that the following:

- There are limitations in access to important technology in Ontario to neurosurgical services.
- Five years after graduation, it is estimated that about 50% of Ontario neurosurgery graduates leave to practice in the United States or other provinces.

Emerging Research

Study Title:	Five-Year Follow-Up of the Charité Artificial Disc Compared with Anterior Lumbar Interbody Fusion With the BAK Cage. Web site for information: (73)
Purpose:	This study is an extension out to 5-year follow-up of a randomized comparative IDE trial of the Charité artificial disc versus ALIF with the BAK cage for treatment of degenerative disc disease. This extension will continue to follow-up the original outcome measures and will also examine adjacent segment progression
Study start:	March 2005
Study Title:	Clinical Study Protocol for the Investigation of the Kineflex Spinal System - a Pivotal Study Web site for information: (74)
Purpose:	The Kineflex Spinal System is no worse than the Charité Spinal System in patients with single level degenerative disc disease at L4/5 or L5/S1.
Study start:	January 2005; expected completion: January 2009

Conclusion: Lumbar Artificial Discs

Since the 2004 Medical Advisory Secretariat health technology policy assessment, data from 2 RCTs and 6 case series have become available that assesses the effectiveness and adverse events profile of lumbar ADR to treat DDD. The GRADE quality of this evidence is moderate for effectiveness and short-term (2-year follow-up) for complications, but very low for ASD.

With respect to effectiveness, lumbar ADR is no worse than spinal fusion. The rates for device failure and neurological complications 2 years after surgery did not differ between ADR and fusion patients. Based on a Bayesian meta-analysis, lumbar ADR is 79% superior to lumbar spinal fusion.

The rate of major complications associated with lumbar ADR is estimated to range from 0% to 13% per device implanted. The rate of ASD estimated in 1 case series was 2% over an 11-year follow-up period.

Outcome data beyond a 2-year follow-up are not yet available. Five-year outcome data will be available

from the Charité RCT in 2007, at which time data on ASD rates between the lumbar artificial disc-treated patients and the spinal fusion control group will be available.

Conclusion: Cervical Artificial Disks

Since the 2004 Medical Advisory Secretariat health technology policy assessment, data from 4 case series have become available that assess the effectiveness and adverse events profile of cervical ADR to treat DDD. The GRADE quality of this evidence is very low for effectiveness and for the adverse events profile. Moreover, not much data on outcomes is available.

Because data are sparse, the effectiveness of cervical ADR compared with spinal fusion cannot be determined at this time.

With respect to complications, the rate of major complications associated with cervical ADR was assessed up to 2 years after surgery and estimated to range between 0% and 8.1% per device implanted. The rate of ASD is not reported in the clinical trial literature.

Results of the FDA RCT comparing the Bryan cervical disc with spinal fusion will be available within 12 to 24 months.

Appendices

Appendix 1: Photographs of Artificial Discs

The Bryan Cervical Disc Prosthesis
Reproduced from Spine Universe: http://www.spinemd.com/artificialdisc.htm (last accessed June 16, 2006)

The Maverick Total Disc System
Reproduced from The Virginia Spine Institute: http://www.spinemd.com/artificialdisc.htm (last accessed June 16, 2006)

The SB Charité III
Reproduced from The Virginia Spine Institute: http://www.spinemd.com/artificialdisc.htm (last accessed June 16, 2006)

The ProDisc-L
Reproduced from Spine Service: http://www.spine-service.org/dr.html (last accessed June 16, 2006)

The Activ L
Reproduced from Yale Orthopaedics and Rehabilitation: http://info.med.yale.edu/ortho/clinical/yue-research.html#active (last accessed June 16, 2006)

Appendix 2: Literature Search Strategy

Database: Ovid MEDLINE(R) <1999 to August Week 5 2005>
Search Strategy:

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1 exp Spinal Diseases/ (12764)
2 exp Spinal Fusion/ (3103)
3 exp Lumbar Vertebrae/ (7199)
4 exp Intervertebral Disk Displacement/ or degenerative disc disease.mp. (2025)
5 exp Cervical Vertebrae/ (5166)
6 exp Intervertebral Disk/ (1370)
7 exp Back Pain/ (5542)
8 exp Diskectomy/ (813)
9 or/1-8 (25072)
10 (dis$ adj1 (artificial or prosthe$ or arthrodesis or arthroplasty or replacement)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (898)
11 Arthroplasty, Replacement/ (1116)
12 Joint Prosthesis/ (857)
13 exp prosthesis failure/ (4421)
14 or/10-13 (6468)
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] (66)
16 15 or (9 and 14) (258)
17 limit 16 to (humans and english language and yr="2003 - 2005") (133)
18 limit 17 to (case reports or comment or editorial or letter) (18)
19 17 not 18 (115)

Database: EMBASE <1996 to 2005 Week 37>
Search Strategy:

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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] (1423)
2 exp Spine Fusion/ (3713)
3 exp intervertebral disk/ or exp lumbar disk/ or exp lumbar vertebra/ or exp vertebra/ (4375)
4 exp Spine Disease/ (26524)
5 exp Lumbar Spine/ or exp Cervical Spine/ (12151)
6 exp Backache/ (14148)
7 exp intervertebral diskectomy/ (1400)
8 or/1-7 (47448)
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] (2871)
10 exp joint prosthesis/ (9963)
11 exp bone prosthesis/ (1231)
12 exp arthroplasty/ (15841)
13 or/9-12 (19766)
14 8 and 13 (799)
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] (77)

16 14 or 15 (802)
17 limit 16 to (human and english language and yr="2003 - 2006") (332)
18 limit 17 to (editorial or letter or note) (51)
19 Case Report/ (367941)
20 17 not (18 or 19) (226)

Appendix 3: Cochrane Musculoskeletal Injuries Group Methodological Assessment Tool

This assessment tool has been developed by the Cochrane Collaboration Musculoskeletal Injuries Group. (37) It includes aspects of internal and external validity. Individual scores for each item are derived and a total score is optional and may be obtained by summing the scores of individual items. The scores for the last 3 items used in the total score are those for the primary measure of the systematic review. The scoring sheet indicates items that need further review. In cases where the items remain unknown, all items are designated the lowest score except for allocation concealment where the middle score is given. The scoring criteria are detailed below:

A. Was the assigned treatment adequately concealed prior to allocation?
   2 = method did not allow disclosure of assignment.
   1 = small but possible chance of disclosure of assignment or unclear.
   0 = quasi-randomized or open list/tables.
   Cochrane code: clearly yes, A; not sure, B; clearly no, C

B. Were the outcomes of patients/participants who withdrew described and included in the analysis (intention-to-treat)?
   2 = withdrawals well described and accounted for in analysis.
   1 = withdrawals described and analysis not possible.
   0 = not mentioned or not possible.

C. Were the outcome assessors blinded to treatment status?
   2 = effective action taken to blind assessors.
   1 = small or moderate chance of unblinding of assessors.
   0 = not mentioned or not possible.

D. Were the treatment and control group comparable at entry?
   2 = good comparability of groups, or confounding adjusted for in analysis.
   1 = confounding small; mentioned but not adjusted for.
   0 = large potential for confounding, or not discussed.

E. Were the participants blind to assignment status after allocation?
   2 = effective action taken to blind participants.
   1 = small or moderate chance of unblinding of participants.
   0 = not possible, or not mentioned (unless double-blinded), or possible but not done.

F. Were the treatment providers blind to assignment status?
   2 = effective action taken to blind treatment providers.
   1 = small or moderate chance of unblinding of treatment providers.
   0 = not possible, or not mentioned (unless double-blinded), or possible but not done.

G. Were care programs, other than the trial options, identical?
   2 = care programs clearly identical.
   1 = clear but trivial differences.
   0 = not defined.

H. Were the inclusion and exclusion criteria clearly defined?
   2 = clearly defined.
   1 = inadequately defined.
   0 = not defined.

I. Were the interventions clearly defined? (This item was optional.)
   2 = clearly defined interventions are applied with a standardized protocol.
   1 = clearly defined interventions are applied but the application protocol is not standardized.
   0 = intervention and/or application protocol are poorly or not defined.

J. Were the outcome measures used clearly defined (by outcome)?
   2 = clearly defined.
   1 = inadequately defined.
   0 = not defined.

K. Were diagnostic tests used in outcome assessment clinically useful (by outcome)?
   2 = optimal.
   1 = adequate.
   0 = not defined, not adequate.

L. Was the surveillance active and clinically appropriate duration (by outcome)?
   2 = active surveillance and appropriate duration.
   1 = active surveillance but inadequate duration.
   0 = surveillance not active or not defined.

Appendix 4: GRADE System

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (38) system has 4 levels: very low, low, moderate, and high. The criteria for assigning the GRADE level are outlined below.

Type of evidence

- Randomized controlled trial (RCT): given a high GRADE level to start
- Observational study: given a low GRADE level to start
- Any other evidence: given a very low GRADE level to start

Decrease GRADE level if:

- Serious limitation to study quality (-1, reduce GRADE level by 1 so a high GRADE level will become a moderate GRADE level) or very serious limitation to study quality (-2, reduce GRADE level by 2 so a high GRADE level will become a low GRADE level)
- Important inconsistency (-1, reduce GRADE level by 1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

Increase GRADE level if:

- Strong evidence of association-significant relative risk of > 2 (< 0.5) based on consistent evidence from 2 or more observation studies, with no plausible confounders (+1, increase GRADE level by 1, so a moderate GRADE level will become high. However a high GRADE level will remain high)
- Very strong evidence of association-significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2, increase GRADE level by 2, so a low GRADE level will become a high GRADE level)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

Overall GRADE Level definitions

High:	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low:	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low:	Any estimate of effect is very uncertain.

Appendix 5: Characteristics of Included Studies

Study	*Blumenthal et al., 2005; (5) *Geisler et al., 2004; (58) †McAfee et al., 2005 (32)
Web site	http://clinicaltrials.gov/ct/search;jsessionid=A909FDA9320441F70759139FF8668FB9?term=degenerative+disc+disease&submit=Search
Methods	Study design: randomized controlled trial Method of randomization: computer-generated using SAS software by contract research organization monitoring study. 2:1 allocation ratio (Charité vs. Anterior Lumbar Interbody Fusion (ALIF)) Assessor blinding: no Intent-to-treat analysis: yes
Participants	Multicentre study, 14 centres in the United States N = 304; 71 additional cases of total disc replacement done before randomization (5 per site) as a run in. Inclusion criteria: 18 to 60 years, symptomatic DDD confirmed by discography, single-level DDD at L4-L5 or L5-S1, Oswestry score ≥ 30, VAS score ≥ 40 (out of 100), failed ≥ 6 months of appropriate nonoperative care, back and/or leg pain with no nerve root compression, able to tolerate anterior approach, able and willing to comply with follow up schedule, willing to give written informed consent. Exclusion criteria: previous thoracic or lumbar fusion, current or prior fracture at L4, L5, or S1, symptomatic multilevel degeneration, noncontained herniated nucleus pulposus, spondylosis, spondylolisthesis > 3mm, scoliosis >11 degrees, midsagittal stenosis < 8mm, positive straight leg raise, spinal tumor, osteoporosis, osteopenia, or metabolic bone disease, infection , facet joint arthrosis, psychosocial disorder, morbid obesity, metal allergy, use of a bone growth stimulator, participation in another study, arachnoiditis, chronic steroid use, autoimmune disorder, pregnancy, other spinal surgery at affected level. Sex (total sample): 51.6% male Age: mean (SD), years: treatment: 39.6 (8.16); control: 39.6 (9.07) Assigned: 205/99 (treatment/control) Assessed for primary outcome(completers) :184/81(at 24 months)
Interventions	Treatment group received a discectomy in the L4-L5 or L5-S1 region and implantation of the Charité artificial disc through an anterior retroperitoneal approach. Control patients received an ALIF at 1 or 2 contiguous levels with autogenous bone grafting from the iliac crest and stabilization with the a threaded Bagby & Kuslich (BAK) cage (Zimmer Spine, Minneapolis, MN) filled with hip bone autograft. All patients underwent surgical treatment through an open anterior. Postoperatively, all patients were required to wear a thoracolumbar spinal orthosis (a type of brace) for 6 weeks. Patients in both groups were started on activities as tolerated as per a standardized rehabilitation protocol.
Outcomes	Duration of follow-up: 24 months postoperatively Outcomes measured at baseline before surgery, 6 weeks, 3, 6, 12, 24 months after surgery including: Pain using Visual Analogue Scale (VAS; 0–100)

Study	*Blumenthal et al., 2005; (5) *Geisler et al., 2004; (58) †McAfee et al., 2005 (32)
	Function using ODI Quality of life using Short-Form 36 (SF-36) Health Survey Neurological status questionnaire Radiological evaluation Patient satisfaction questionnaires Primary outcome was a composite measure of clinically successful defined as: 1. ≥ 25% improvement in ODI score at 24 months compared with preoperative score; 2. no device failure; 3. no major complications; 4. no neurological deterioration compared with preoperative status. †Radiographic assessments including (32): 1. to determine if range of motion (ROM) in flexion/extension was restored to preoperative levels and maintained to 24 months; 2. to determine if there was a difference regarding disc space height restoration and subsidence between the 2 groups; 3. to determine if clinical outcome success correlated with Charité artificial disc placement (radiographic success); 4. to determine how individual surgical technical accuracy of prosthesis placement influenced the flexion/extension ROM at the 24-month follow-up. Neurological outcomes included reporting of neurological adverse events/complications at 6, 12, and 24 months. Neurological adverse events were categorized by major, minor, and other, and by device-related complications. Events were also stratified by postoperative time frame: 0–2 days, > 2–42 days, > 42–210 days, and > 210 days (58).
Notes	Noninferiority study One-sided alpha used for sample size and statistical analysis. Fixed block randomization using 6 assignments per block. Randomization occurred 1 day before surgery A noninferiority trial with a noninferiority margin set at 15%. Statistical analysis is on polled population and a sensitivity analysis was performed to evaluate the potential impact of losses to follow-up. Run in period: each investigational site could perform up to 5 nonrandomized cases with the Charité artificial disc at the outset of the study to insure technical competence with the treatment procedure. Discharge from the hospital was not based on standardized criteria within the study protocol but instead was based on the investigator's standard discharge criteria and the respective participating site.
Funding	Blumenthal: corporate/industry funds were received to support this work. One or more of the authors has received or will receive benefits from a commercial party related directly or indirectly to the subject of this manuscript. Benefits will be directed to a research fund, foundation, educational institution, or other nonprofit organization with which the authors have been associated. One or more of the authors has also received or will receive benefits in the form of honoraria, gifts, or consultancies from a commercial party related directly or indirectly to the subject of this manuscript.
Allocation concealment	Sequentially numbered sealed envelopes containing treatment assignments for the site.

Study	ProDisc-L, 2005 (75)
Methods	Study design: randomized controlled trial Method of randomization: 2:1 allocation ratio (method unknown) (ProDisc-L vs. lumbosacral spinal fusion with autograft, femoral ring and posterior or anterior screws) Assessor blinding: unknown; patients were blinded to treatment until after surgery. Intent-to-treat analysis: Unknown
Participants	Multicentre study, 17 centres in the United States N = 236 Inclusion criteria: ▪ Age between 18 and 60 years ▪ Failed at least 6 months of conservative treatment ▪ ODI score of at least 20/50 (40%), DDD in 1 vertebral level between L3 and S1. ▪ Diagnosis of DDD requires: back and/or leg pain (radicular pain), radiographic confirmation by CT, MRI, discography, plain film, myelography and/or flexion/extension films of any 1 of the following: instability (≥ 3mm translation or ≥ 5 degrees angulation, decreased disc height > 2mm, scarring/thickening of annulus fibrosis, herniated nucleus pulposus, or vacuum phenomenon) ▪ Psychologically, mentally, or physically able to comply with this protocol, including adhering to the follow-up schedule and requirements and filling-out of forms. Exclusion criteria: ▪ 2 degeneration levels ▪ Endplate dimensions < 34.5 mm in the coronal plane and/or < 27 mm in the sagittal plane ▪ Known allergy to titanium, polyethylene, cobalt, chromium, or molybdenum ▪ Prior lumbar fusion, post-traumatic vertebral body compromise/deformity, facet degeneration, lytic spondylolisthesis or spinal stenosis, degenerative spondylisthesis [AU: Do you mean spondylolisthesis?] of grade > 1, back or leg pain of unknown etiology, osteoporosis, metabolic bone disease (excluding osteoporosis, e.g., Paget's disease), ▪ Morbid obesity (body mass index > 40 or weight > 100 pounds over ideal weight) ▪ Pregnant or interested in becoming pregnant in the next 3 years ▪ Active systemic/local infection ▪ Medications or drugs known to have the potential to interfere with bone/soft tissue healing ▪ Smoking, rheumatoid arthritis or other autoimmune spondyloarthropathies (diseases of the joints of the spine), systemic disease including but limited to [AU: Do you mean including but NOT limited to?] AIDS, HIV, hepatitis, active malignancy. Sex (total sample): 49.1% male Age: mean (SD), years: treatment: 38.7 (8.0); control: 40.4(7.6) Assigned: 161/75 (treatment/control) Assessed for primary outcome (completers): 148/71 (at 24 months)
Interventions	Treatment group received the ProDisc-L via anterior insertion Control received lumbosacral spinal circumferential fusion with an autograft, femoral ring, and posterior or anterior screws.
Outcomes	Duration of follow-up: 24 months postoperatively Outcomes measured at baseline before surgery, 6 weeks, 3, 6, 12, 18 and 24 months after

Study	ProDisc-L, 2005 (75)
	surgery including: Pain using VAS (0–100) Function using ODI Quality of life using SF-36 Health Survey Neurological status questionnaire Radiological evaluation Range of motion Primary outcome was a composite score of clinical success defined as ≥ 15% improvement in ODI score at 24 months compared with preoperative score, no reoperation required to remove or modify the ProDisc-L implant, improved or maintained neurological status, radiographic success, and improvement in SF-36 relative to baseline. Radiographic success was a composite score defined as: no device migration or subsidence, no extensive radiolucency around the implant, no loosening of the implant, and no loss of disc height. In the control group: no motion and evidence of fusion. In the ProDisc-L group: normal motion. FDA-defined motion success as ROM at 24 months being ≥ preoperative (baseline) ROM.
Notes	Noninferiority study Study is not yet published; therefore, study details are lacking.
Funding	Unknown
Allocation concealment	Unknown

Study	Caspi 2003 (49)
Methods	Study design: case series Follow-up: 48 months Lost to follow-up: none
Participants	Country: Israel N = 20 Number of artificial disks implanted: 23 Population: All patients had low back pain with/without radicular pain for 5 years. Sex: 55% males Age: 24–50 years
Interventions	All patients received the Charité SB III artificial disc Surgical approach: anterior retroperitoneal surgical approach Levels of arthroplasty: monolevel (17 patients), bilevel (L4-5, L5-S1, 3 patients)
Outcomes	Clinical results rated as poor, fair, good, or excellent. Return to work Radiological assessment Study does not describe who did assessments
Complications	There were 2 cases of prosthesis migration, 1 due to incomplete severing of the postlongitudinal ligament, and 1 due to a small fracture of the lower endplate; 1 intraoperative laceration of the ureter and thrombosis of the iliac artery; in 2 patients spontaneous ossification of the intervertebral anterior ligament was observed, but

	progression was halted by physiotherapy; of the 4 patients with poor results, 1 underwent secondary fusion, and the other is waiting for surgery

Study	**Su, 2003 (50)**
Methods	Study design: case series Follow-up: mean, 26 months, range 17–41 months Lost to follow-up: none
Participants	Country: China N = 31 Number of artificial disks implanted: 37 Population: Patients with degeneration of lumbar intervertebral disc, or recurrent degeneration of lumbar intervertebral disc, or complicated with severe significant narrowing of intervertebral space. Duration of disease ranged from 6 months to 10 years with a mean of 1.7 years. All had failed nonsurgical treatments. Sex: not reported Age: mean, 43.5 years; range, 32–55 years
Interventions	All patients received the Charité SB III artificial disc Surgical approach: anterior Levels of arthroplasty: not reported
Outcomes	Clinical results were rated as poor, fair, good, or excellent Radiological outcomes lumbar, anteflexion and posterior flexion X-ray and magnetic resonance imaging Position of prosthesis, intervertebral space height, motion of lumbar segment. Study does not describe who did assessments
Complications	1 case of asymptomatic slight displacement of core

Study	**Xu, 2004 (48)**
Methods	Study design: case series Follow-up: 18.6 months (mean); 3–38 months (range) Lost to follow-up: none
Participants	Country: China N = 34 Number of artificial disks implanted: 41 Population: All patients had intervertebral disc degenerative disease treated with ADR Sex: 20 males, 14 females Age: mean, 41.1 years; range, 21–65
Interventions	All patients received the Charité SB III artificial disc Surgical approach: anterior extra-peritoneal approach Levels of arthroplasty: monolevel (L3-5, n = 2), (L4-5, n = 18), (L5-S1 (n = 7); bilevel (L3-4 & L4-5, n = 1), (L4-5, L5-S1, n = 6)
Outcomes	Radiological evaluation including: ▪ Lumbar spine stability ▪ Angle between superior and inferior endplates in flexion and extension ▪ Intervertebral space height ▪ Intervertebral foramen size

	Follow-up by telephone using the lower lumbar pain criteria of Japanese Orthopaedic Association.
Complications	One person had asymptomatic anterior subluxation of the inferior endplate; 1 had mild laceration in iliac vein; of 3 rated "fair," 1 patient had mild depression and felt heat and pain in waist, and 2 still had mild back pain.

Study	**Lemaire, 2005 (47)**
Methods	Study design: case series Follow-up: 11.3 years (mean); 10–13.4 years (range) Lost to follow-up: 6 (5 moved, and 1 died of lung cancer)
Participants	Country: France N = 107 Number of artificial disks implanted: 147 (of 100 cases) Population: DDD with intractable low back pain of discogenic origin at 1 or 2 levels with 1 case at 3 levels. All failed nonsurgical treatment. Mean duration of disease was 6 years. Sex: 41 males, 59 females Age: mean, 39.6 years;, range, 23.9–50.8 years
Interventions	All patients received the Charité SB III artificial disc Surgical approach: Left side anterior retroperitoneal approach Levels of arthroplasty: monolevel (n = 54); bilevel (n = 45); trilevel (n = 1) Spinal segment: L3-L4 (n = 6), L4-L5(n = 69), L5-S1(N = 72)
Outcomes	Radiological evaluation for gain in intervertebral disc space height, sagittal alignment, plain flexion/extension and lateral bending radiographs for kinematic assessment. Clinical evaluation using a modified Stauffer Coventry scoring system.
Complications	Level of reported complications = 9%. There were 2 cases of subsidence of the caudal plate observed but these did not require further surgery; both were secondary to trauma. There was 1 case of a disc height loss of 1 mm. Five patients required a secondary posterior arthrodesis. There were 3 cases of periprosthetic ossification, 1 without affecting mobility of the prosthesis. One case of paralysis at L5 was corrected with a ligamentoplasty (still a poor clinical result); 1 patient with sexual dysfunction recovered spontaneously at 1 year; and 2 perioperative vascular lacerations were repaired without sequelae. There was 1 acute leg ischemia subsequent to atheromatous plaque mobilization that required endarterectomy and had a good result. There were 2 cases of adjacent-level degeneration and 4 of symptomatic articular arthritis.

Study	**Cakir et al., 2005 (34)**
Methods	Study design: case series Follow-up: 15.3 months (mean); 12–35 (range) Lost to follow-up: none
Participants	Country: Germany N = 29 Number of artificial disks implanted: 29 Population: Patients had symptomatic degeneration disc disease (n = 12) or postdiscectomy syndrome (n = 8). Low back pain was present for at least 12 months and all patients had a minimum course of 6 months conservative therapy. Sex: 10 males, 190 females Age: mean (SD): 40.8 (6.4) years; range, 29–years

Interventions	All patients received the ProDisc artificial disc Surgical approach: retroperitoneal approach using a pararectal incision for level L3-L4 and L4-L5 or a horizontal incision for level L5-S1. Levels of arthroplasty: all monosegmental
Outcomes	Evaluation of the segmental lordosis at the operated level and the total lumbar lordosis using the standard Cobb measurements before and after surgery. Segmental/lumbar lordosis was classified as: insufficient (< 16º/< 41º); normative (16º-30º/41º-75º); excessive (> 30º/> 75º). VAS for pain Oswestry Low Back Pain Disability Questionnaire S-F 36 Health Survey
Complications	No signs of loosening, subsidence, migration or spontaneous fusion detected by 2 independent observers.

Study	**Le Huec, 2005 (51)**
Methods	Study design: case series Follow-up: 18 months (mean), 12–26 months (range) Lost to follow-up: none
Participants	Country: France N = 64 Number of artificial disks implanted: 64 Population: chronic back pain resistant to conservative treatment for at least 1 year and had also received medical and rheumatologic follow-up and rehabilitation physiotherapy. Sex: 25 males, 39 females Age: 44 years (mean); range, 20–60 years
Interventions	All patients received the Maverick artificial disc Surgical approach: mini-invasive anterior approach Levels of arthroplasty: all monolevel at either L5-S1, L4-L5, or L3-L4
Outcomes	VAS for pain Neurological function Oswestry Disability Index scores SF-36 Health Survey Clinical success was defined as 25% improvement on the Oswestry score Patient satisfaction Use of analgesics
Complications	There were 4 cases of postoperative root pain and 2 cases with sequelae from previous discectomies. Seventeen patients received posterior facet infiltration (11 with a good result). Three patients had spinal pain in other than the lumbar region; 1 patient had a superficial infection treated by debridement; and 1 visceral lesion was successfully repaired. There were minor intraoperative complications due to surgical approach in 11 cases; device migration axially 3–5 mm in 5 patients., subsidence stable at 1 year; 3 patients with heterotopic ossification

Study	**Duggal et al., 2004 (54)**
Methods	Study design: case series Follow-up: 12.3 months (mean); 1.5–27 months (range) Lost to follow-up: none

Study	Duggal et al., 2004 (54)
Participants	Country: Canada N = 26 Number of artificial disks implanted: 30 Population: Patients with cervical degenerative disc disease with radiculopathy and/or myelopathy whose main symptom was arm pain and NOT neck pain. Duration of symptoms for persons with radiculopathy was 2.5–60 months (mean, 12.5 months) People with myelopathy were symptomatic for 1–14 months (mean, 6.2 months). Four patients had a previous anterior cervical discectomy and fusion. All patients failed nonsurgical medical therapy including activity modification, nonsteroidal anti-inflammatory medications, physiotherapy, and massage. Preoperative motion at the symptomatic level was a prerequisite to being in the study. Sex: 16 males, 10 females Age: mean, 43.3 (SD, 7.93) years; range, 30–67 years
Interventions	All patients received the Bryan cervical disc (Medtronic Sofamor Danek, Memphis, TN) artificial disc Surgical approach: anterior cervical discectomy with insertion of the Bryan artificial cervical disc. All procedures were done with a transverse skin incision made on the right side of the neck. Levels of arthroplasty: monolevel at C5-6 or C 6-7 (n = 22), bilevel at C5-6 & C6-7 (n = 4)
Outcomes	Neurological examination Oswestry Neck Disability Index (self-administered) SF-36 (self-administered) Static and dynamic cervical X-rays Duration of surgery Blood loss Complications
Complications	There was 1 patient with increased radicular pain that improved over several weeks; 1 patient with transient unilateral vocal cord paralysis which resolved at 6 weeks; 1 case of persistent dysphagia for almost 6 weeks after surgery; 1 case of possible device migration at 2 years follow-up; and 3 of the 4 patients with previous surgical fusion had a symptomatic disc herniation that occurred adjacent to the earlier surgical fusion.
Notes	Segmental sagittal rotation measured in a sub group of patients.

Study	Lafuente, 2005 (55)
Methods	Study Design: case series Follow-up: 14 months (mean) Losses to follow-up: none
Participants	Country: United Kingdom N = 46 Number of artificial disks implanted: 46 Population: Patients with single level disease between C3-4 and C6-7 with either radiculopathy or myelopathy not responding to nonsurgical treatment. Mean duration of symptoms was 13.8 (SD, 11.9) months with a range of 1–6 months. Five patients had previous spinal surgery (2 lumbar discectomies and 3 cervical fusions at one level) Sex: 28 males, 18 females Age: mean (SD), 47.6 (10.5) years; range, 33–70 years
Interventions	All patients received the artificial Bryan artificial disc Surgical approach: anterior cervical discectomy

	Levels of arthroplasty: between C3-5 and C 6-7
Outcomes	Neurological examination Radiological evaluation to assess movement, stability, and subsidence or the prosthesis VAS for pain SF-36 for general health Oswestry Neck Disability Index (NDI) for functionality Results were categorized as excellent, good, fair, or poor according to modified Odom's criteria.
Complications	One patient had worsening of muscle spasms which improved by discharge; 3 patients (7%) had mild postoperative dysphonia resolving completely by the first clinic appointment; 1 patient required the prosthesis to be removed after he/she fell 7 months postoperatively, dislodging the inferior endplate; 2 patients had evidence of bony ankylosis at implanted disc level.

Study	**Sekhon, 2004 (52)**
Methods	Study Design: case series Follow-up: 18.4 months (mean), 10–32 months (range) Lost to follow-up: none
Participants	Country: Australia N = 11 Number of artificial disks implanted: 15 Population: All patients had spinal cord compression and/or clinically confirmed cervical myelopathy. Duration of symptoms was between .75 and 72 months. Sex: 7 males, 4 females Age: mean, 43.7; range, 31–55 years
Interventions	All patients received the Bryan artificial disc Surgical approach: left-sided transverse cervical incision was used. Alternatively, for a bilevel disease an oblique left-sided paramedian incision was also used. Levels of arthroplasty: single level: C3-4 (n = 1), C4-5 (n = 1) C5-6 (n = 2), C6-7 (n = 3), bilevel: C4-5, C5-6 (n = 2), C5-6, C6-7 (n = 2)
Outcomes	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
Complications	One patient was readmitted with worsening of preoperative hand and gait dysfunction. No compression was found on computed tomography myelogram. The patient was treated with dexamethasone and symptoms resolved within 72 hours. There was 1 patient with persistent neck and arm pain after surgery with loss of motion at the operated segment. Spondylotic bridging had occurred behind the prosthesis creating an interbody fusion 17 months after surgery. There was 1 case of myelopathic deterioration possibly attributable to swelling and 3 cases in which the preoperative alignment had worsened.

Study	**Goffin et al., 2003 (9)**
Methods	Study Design: case series Follow-up: 24 months
Participants	Country: Belgium

Study	Goffin et al., 2003 (9)
	N = 103 in single-level study and 43 in bilevel study. Inclusion criteria: Disc herniation or spondylosis with radiculopathy and or myelopathy, which had not responded to conservative treatment during at least 6 weeks. Patients with previous cervical spine surgery involving the use of any other device, axial neck pain as the solitary symptom, significant cervical anatomic deformity or radiographic signs of instability or active infection were also excluded. Sex: Single-level study, 41% male; bilevel study, 58% male Age: Single-level study, 26–79 years (range); bilevel study, 28–62 years (range) Sample size at follow-up: 24-month follow-up for single-level study (n = 51) 12-month follow-up for single-level study (n = 100) 24-month follow-up for bilevel study (n = 1) 12-month follow-up for bilevel study (n = 29)
Interventions	All patients received the Bryan artificial disc
Outcomes	Primary outcome was 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. Surgeons assessments included: ▪ 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. A success rate of 85% (excellent, good, fair) was established for the study.
Complications	Single-level study group: ▪ 1 evaluation of a prevertebral hematoma ▪ 1 posterior foraminotomy without device involvement to treat residual symptoms ▪ 1 posterior decompression to treat residual myelopathic symptoms. ▪ 1 wrong level operated on ▪ 1 temporary dysphonia ▪ 1 pain in right shoulder, arm, and the sternum region about 6 months after surgery. ▪ 1 unresolved unspecific left shoulder pain ▪ 1 patient required a second device implanted at an adjacent level 21 months after the initial surgery because of radiculopathy caused by disc herniation.

Study	Goffin et al., 2003 (9)
	▪ 1 severe dysphonia caused by bilateral vocal cord paralysis due to bilateral recurrent nerve compression from excessive retraction during surgery. Bilevel study group: ▪ Cerebral spinal fluid leak during posterior decompression ▪ 1 evacuation of a prevertebral hematoma ▪ 1 repair of a pharyngeal tear/esophageal wound caused ruing intubation ▪ 1 anterior decompression required because of ongoing nerve root compression ▪ 1 revision surgery for decompression of residual foraminal stenosis. No device failures or explants.

Appendix 6: Characteristics of Health Technology Assessments

Systematic Review	Literature Search Dates	Type of Disc	Study, Year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
Gibson and Wadell 2005 (most substantive update February 1, 2005) (24)	Up to March 31, 2004	SB Charité	Geisler, 2004	RCT N = 304 2 years	Preliminary data from clinical trials of disc arthroplasty did not permit any firm conclusions.
		SB Charité	McAfee, 2003	RCT Single-centre preliminary results of DePuy Spine FDA IDE clinical trial, 2004 N = 60 12–36 months (mean not reported)	
		ProDisc-L	Zigler, 2003	RCT Single-centre preliminary data from multicentre USA FDA IDE study N = 36 6 months	
		ProDisc-L	Delamarter, 2003	RCT (preliminary data from a single centre involved in same multicentre US FDA clinical trial reported in Zigler 2003) N = 53 6 months	

Health Technology Assessment Agency	Literature Search Dates	Type of Disc Evaluated in Study	Study, Year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
NICE February 2005	Up to February 23, 2005	Bryan	Goffin, 2003	Case series N = 146 (103 single level, 43 bilevel) Single level to 24 months (n = 49) Bilevel to 12 months (n = 26)	There are few data available concerning the use of bilevel prostheses; few long-term data are available, particularly in relation to potential reduction in adjacent level degeneration compared with fusion. Issues for consideration include variability of efficacy and safety between devices, and controversy regarding the role of prostheses for patients with neck pain but no nerve root or spinal cord compression. NICE GUIDANCE 2005: Evidence suggests there are no major safety concerns about the use of prosthetic intervertebral disc replacement devices in the cervical spine, and there is evidence of short-term efficacy.
		Bryan	Sekhon, 2003	Case series N = 7 6 months	
		Bryan	Sasso, 2004	RCT N = 13 (5 Bryan, 7 fusion) Preliminary report from single centre 6 months	
		Prestige 1	Wigfield, 2002	Case series N = 15 24 months	
		Prestige II	Porchet, 2004	RCT N = 55 (27 Prestige II, 28 fusion with autograft) 2 months	

Health Technology Assessment Agency	Literature Search Dates	Type of Disc	Study, Year	Study Design Sample Size (n) Mean Duration of Follow-Up	Conclusion(s)
Blue Cross/Blue Shield Association Technology Evaluation Center April 2005 (13)	1980 to March 2005.	Charité III	DePuy Spine/FDA unpublished report, (Web report) 2004*	RCT N = 304 2 years	Evidence is insufficient to support the effectiveness of disc arthroplasty or that it improves net health outcome or is beneficial as an alternative therapy. The only RCT that shows the Charité artificial disc is not inferior to Bagby & Kuslich fusion surgery has severe methodological issues that make study results difficult to interpret.
		Charité III	Sott, 2000	Case series N = 14 48 months	
		Charité III	Zeegers, 1999	Case series N = 46 24 months	
		Charité III	Lemaire, 1997	Case series N = 105 51 months	
		Charité III	Cinotti, 1996	Case series N = 46 38 months	
		Charité III	Griffith, 1994	Case series N = 93 12 months	
		Charité III	David, 1993	Case series N = 22 12 months	

*FDA documents used in Blue Cross/Blue Shield health technology assessment included:
Premarket approval letter (76)
Summary of safety and effectiveness data (35)
Clinical review (77)
In-depth statistical review (64)

Health Technology Assessment Agency	Literature Search	Type of Disc	Study, year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
WSDLI November 1, 2004 (59)	Through to July 2004	SB Charité	McAfee, 2003	RCT* Single-centre preliminary results of DePuy Spine FDA IDE clinical trial, 2004 N = 60 12–36 months (mean not reported)	It is not possible to draw any conclusion concerning the affect of disc replacements on improving patient outcomes. Disc replacement is, therefore, considered investigational and controversial.
		SB Charité	DePuy Spine/FDA IDE Web report, 2004	Case series N = 304 2 years	
		SB Charité	Blumenthal, 2003	Case series Single-centre data, preliminary results of DePuy Spine FDA IDE clinical trial, 2004) N = 57 12 months	
		SB Charité	Kim, 2003	Case series N = 5 6 months	
		SB Charité	Sott, 2000	Case series N = 14 48 months	
		SB Charité	Zeegers, 1999	Case series N = 50 24 months	
		ProDisc II	Delamarter, 2003	RCT (single-centre preliminary data from the multicentre US FDA IDE study N = 53 6 months	
WSDLI		ProDisc II	Zigler, 2003	RCT	

Health Technology Assessment Agency	Literature Search	Type of Disc	Study, year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
continued				Single-centre preliminary data from multicentre US FDA IDE study N = 36 6 months	
		ProDisc II	Tropiano, 2003	Case series N = 53 17 months	
		ProDisc II	Mayer, 2002	Case series N = 34 6 months	
		ProDisc II	Bertagnoli, 2002	Case series N = 108 3 months – 2 years	

*http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01320.html

Health Technology Assessment Agency	Literature Search Dates	Type of Disc	Study, Year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
Medical Advisory Secretariat, 2004 (1)	1966 to November 2003	Charité	Blumenthal, 2003	Case series N = 57 12 months	Comparative efficacy data for intervertebral prostheses and spinal fusion are sparse, but are expected within 12–24 months for SB Charité, ProDisc II lumbar, and Bryan cervical artificial discs
		Charité	McAfee, 2003	RCT Single-centre preliminary results of DePuy Spine FDA IDE clinical trial, 2004 n = 60 12–36 months (mean not reported)	
		Charité	Zeegers, 1999	Case series N = 50 24 months	
		Charité	Ross, 1997	Case series N = 41 3 years (11-72 months range)	
		ProDisc II	Zigler, 2003	RCT Single-centre preliminary data from multicentre US FDA IDE study 6 months	
		ProDisc II	Delamarter, 2003	RCT Single-centre preliminary data from multicentre US FDA IDE study N = 53 6 months	
		ProDisc II	Tropiano, 2003	Case series N = 53 17 months	
		Bryan	Sekhon, 2003	Case series N = 11 18 months	
		Bryan	Goffin, 2002	Case series N = 60 6 months – 1 year	

Health Technology Assessment Agency	Literature Search Dates	Type of Disc	Study, Year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
AESERNIP-S for NICE 2003	From inception of databases – October 2002	Charité III	Geisler, 2004	RCT N = 304 2 years	Issues for consideration include: The benefits of prosthetic discs in patients over 45 years of age remain unresolved in the literature. The exact positioning of the artificial disc is crucial for proper functioning of the disc NICE GUIDANCE 2004: The evidence of efficacy and safety appeared to be adequate to support artificial disc replacement. There is a lack of evidence beyond a 2–3-year follow-up period
		Charité III	Buttner-Janz, 2002	Nonrandomized comparative study Compared unisegmental vs. bisegmental disc arthroplasty) N = 20 Follow-up not reported	
		Charité III	Hopf, 2002	Case series N = 35 14.7 months	
		Charité III	Sott, 2000	Case series N = 14 48 months	
		Charité III	Zeegers, 1999	Case series N = 50 24 months	
		Charité III	LeMaire, 1997	Case series N = 105 51 months	
		Charité III	Ross, 1997	Case series N = 41 36 months	
		Charité III	Cinotti, 1996	Case series N = 46 38 months	
		SB Charité III	Griffith, 1994	Case series N = 93 11.5 months	
		SB Charité III	David, 1993	Case series N = 22 12 months	
		SB Charité III	Enker, 1993	Case series N = 6 41 months	

Health Technology Assessment Agency	Literature Search Dates	Type of Disc	Study, Year	Study Design, Sample Size, and Duration of Follow-Up	Conclusion(s)
ECRI, Published March 2004 (33) Updated February 2006 (3)	Not reported	SB Charité III	Blumenthal, 2005	RCT, N = 375 (205 Charité/ 99 lumbar fusion, 71 nonrandomized training cases) 2 years	Limited data from studies to suggest that disc arthroplasty may offer some advantages over spinal fusion and that the short-term adverse event rate may be similar to spinal fusion. The true rate of complications and clinical impact of disc arthroplasty cannot be determined because of the small number of patients studied and limited datasets. 2-year safety data is inadequate to draw conclusion about long-term safety compared with spinal fusion.
		ProDisc II	Delamarter, 2005	RCT (single-centre preliminary data from the multicentre USA FDA IDE study N = 78 (56 ProDsic II/ 22 spinal fusion) 18 months	
		ProDisc II	Zigler 2004	RCT Single-centre preliminary data from multicentre US FDA IDE study N = 78 (55 ProDisc II / 23 lumbar spinal fusion) 6 months	

Appendix 7: Methodological Quality Assessment

Table 1: Methodological Assessment*

Study	Criteria*											
Blumenthal et al. (2002)	A	B	C	D	E	F	G	H	I	J	K	L
	2	2	0	2	0	0	1	2	2	2	1	2

*All criteria are scored from 0 to 2. A score of 2 equals full compliance with the criterion.

A. Was the assigned treatment adequately concealed prior to allocation? **B.** Were withdrawals adequately described and included in the analysis (intention-to-treat)? **C.** Were the outcome assessors blinded to treatment status? **D.** Were the treatment and control groups comparable at entry? **E.** Were the participants blind to assignment status after allocation? **F.** Were the treatment providers blind to assignment status? **G.** Were care programs, other than the trial options, identical? **H.** Were the inclusion and exclusion criteria clearly defined? **I.** Were the interventions clearly defined? **J.** Were the outcome measures clearly defined? **K.** Were diagnostic tests used in outcome assessment clinically useful? **L.** Was the surveillance active and of a clinically appropriate duration?

A. Concealment: The contract research organization managing the study generated the random allocation sequence which was provided to the sites in sequentially numbered sealed envelopes opened the day before surgery and only after the patient had consented to study participation. Compliance with the sequential assignment of treatments was monitored throughout the study.
B. Intention-to-treat analysis: The primary outcome measure was that upon which the sample size was predicated which was the number of patients determined to have a clinically successful outcome (definition given in section K). This outcome was analyzed for the total population (intention to treat) and for the cohort that completed the study (completers). All losses to follow-up were categorized as failures for this analysis.
C. Blinding of outcome assessors: The outcome assessors were not blinded to the study treatment intervention. The authors stated that difficulty in blinding patient charts, x-rays, computed tomography images and side effects (iliac crease donor site pain) precluded blinding the outcome assessors, which included the patients for self-assessment outcome measures (ODI, VAS scores) and the treatment providers.
D. Baseline comparability: characteristics were equivocal except for patients in the control group having a slightly higher mean weight at the time of surgery ($P < .0349$). We did not deem this an important or even small source of confounding, as the average baseline body mass index was not different between treatment and control groups.
E. Study subject blinding: Participants were kept blinded to their randomized study treatment until immediately postoperatively (after waking up in the recovery room). The authors state that difficulty in masking the bone-graft donor site (iliac crest) pain precluded blinding the study participants.
F. Treatment provider blinding: The treatment providers were not blinded to the study assignment. The authors state that difficulty in blinding patient charts including x-ray and computed tomography images precluded blinding the treatment providers.
G. Care programs: Some clear but trivial differences in the care programs of the study groups including that there was no standardized hospital discharge criteria in the protocol and therefore discharge was left to the discretion of the investigator (who was not blinded to treatment allocation).
H. Inclusion and exclusion criteria: The study describes clearly defined inclusion and exclusion criteria
I. Clearly defined interventions: The interventions for this study were clearly defined with a standardized protocol.
J. Clearly defined outcomes: The study report described clear defined outcome measures.

K. Clinical useful diagnostic test: The outcome tools were appropriate, reliable, and valid. The primary outcome measure was a composite score of 4 variables: $\geq$ 25% improvement in Oswestry Disability Index score at 24 months compared with the preoperative score; no device failure; no major complications; and no neurological deterioration compared with preoperative status. The clinical endpoint was binary (success /failure), and all 4 criteria had to be met to be deemed a clinical success. The clinical utility of this composite score is unknown; however, the variables included seem reasonable to allow adequate clinical interpretation. The FDA also requested that the data be analyzed and reported using an improvement in the ODI $\geq$ 15 points at 24 months compared with the baseline score and a noninferiority margin of 10% instead of 15%.

L. Duration of follow-up: Follow-up was completed prospectively to 24 months after surgery.

Appendix 8: Complications Reported by Blumenthal et al.

Approach-Related Complications*

Complication	Charité, N = 205, n (%)	Control N = 99, n (%)
Venous injury	9 (4.4)	2 (2.0)
Retrograde ejaculation	3 (3.3)	3 (5.5)
Ileus	2 (1.0)	1 (1.0)
Perioperative vein thrombosis	2 (1.0)	0
Clinically significant blood loss > 1500 cc	1 (0.5)	2 (2.0)
Incisional hernia	1 (0.5)	2 (2.0)
Epidural hematoma	1 (0.5)	0
Dural tear	1 (0.5)	0
Deep vein thrombosis	0	0
Arterial thrombosis	0	0

*Blumenthal et al. (5)

Infections*

Complication	Charité N = 205, n (%)	Control N = 99, n (%)
Superficial wound with incision site pain	13 (6.3)	2 (2)
Other non wound related	5 (2.4)	1(1)
Urinary tract infection	5 (2.4)	1(1)
Wound swelling	2 (1.0)	0
Pulmonary	1 (0.5)	0
Peritonitis	0	1 (1)
Graft site	0	3 (3)

*Blumenthal et al. (5)

Treatment-Related Complications: Fusion*

Complication	Charité N = 205, n (%)	Control N = 99, n (%)
Nonunion/pseudoarthrosis	0	9 (9.1)
Bone graft donor site	0	18 (18.2)

*Blumenthal et al. (5)

Treatment-Related Complications: Artificial Disc*

Complication	Charité N = 205, n (%)	Control N = 99, n (%)
Collapse or subsidence of implant into adjacent vertebrae	7 (3.4)	1 (1)
Implant displacement	1 (0.5)	0

*Blumenthal et al. (5)

Other Complications*

Complications	Charité N = 205, n (%)	Fusion N = 99, n (%)
Annulus ossification	1 (0.5)	0
Calcification resulting in bridging trabecular bone	1 (0.5)	0

*Blumenthal et al. (5)

Adverse Events as Reported in Food and Drug Administration PM Memorandum Clinical Review 2004*

Adverse Events	Charité N = 205, n (%)	Bagby & Kuslich Cage N = 99, n (%)
Patients with severe or life-threatening adverse events	30 (15.0)	9 (9.0)
Device-related adverse events	15 (7.3)	4 (4.0)
Device failures	10 (4.9)	8 (8.1)

*Food and Drug Administration (35)

References

1. Medical Advisory Secretariat. Artificial discs: applications to cervical and lumbar spinal surgery for degenerative disc disease. Health technology literature review [report on the Internet]. March, 2004. Ministry of Health and Long-Term Care. [cited 2005 Oct. 9]. Available at: http://www.health.gov.on.ca/english/providers/program/mas/reviews/docs/art_disc_0304.pdf

2. Mayer HM. Total lumbar disc replacement. J Bone Joint Surg Br 2005; 87(8): 1029-1037

3. ECRI. Artificial intervertebral disc replacement for lumbar degenerative disc disease. Target report #852. February 2006. Emergency Care Research Institute (ECRI).

4. McCormack BM, Weinstein PR. Cervical spondylosis. An update. West J Med 1996; 165(1-2): 43-51

5. Blumenthal S, McAfee PC, Guyer RD, Hochschuler SH, Geisler FH, Holt RT et al. 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 2005; 30(14): 1565-1575

6. van Tulder M, Koes B, Bombardier C. Low back pain. Best Pract Res Clin Rheumatol 2002; 16(5): 761-775

7. Carragee EJ. Clinical practice. Persistent low back pain. N Engl J Med 2005; 352(18): 1891-1898

8. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003; 81(9): 646-656

9. Goffin J, Van Calenbergh F, van Loon J, Casey A, Kehr P, Liebig K et al. Intermediate follow-up after treatment of degenerative disc disease with the Bryan Cervical Disc Prosthesis: single-level and bi-level. Spine 2003; 28(24): 2673-2678

10. Badley EM, Webster GK, 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 1995; 22(4): 733-739

11. Lee P, Helewa A, Goldsmith CH, Smythe HA, Stitt LW. Low back pain: prevalence and risk factors in an industrial setting. J Rheumatol 2001; 28(2): 346-351

12. Cassidy JD, Cote P, Carroll LJ, Kristman V. Incidence and course of low back pain episodes in the general population. Spine 2006; 30(24): 2817-2823

13. Blue Cross Blue Shield Association. Artificial vertebral disc replacement [report on the Internet]. April, 2005. Technology Evaluation Center Assessment Program. [cited 2006 May 5]. Available at: http://www.bcbs.com/tec/Vol20/20_01.pdf

14. Rodts MF. Total disc replacement arthroplasty. Orthopaedic Nursing 2004; 23(3): 216-219

15. McAfee PC. The indications for lumbar and cervical disc replacement. Spine J 2004; 4(6 Suppl): 177S-181S

16. de Kleuver M, Oner FC, Jacobs WC. Total disc replacement for chronic low back pain: background and a systematic review of the literature. Eur Spine J 2003; 12(2): 108-116

17. Jacobs WC, Anderson PG, Limbeek J, Willems PC, Pavlov P. Single or double-level anterior interbody fusion techniques for cervical degenerative disc disease. Cochrane Database Syst Rev 2004; Issue 4(Art. No.: CD004958. DOI: 10.1002/14651858.CD004958.)

18. Sudhakar N, Laing RJ, Redfern RM. Assessment of fusion after anterior cervical discectomy. Br J Neurosurg 2003; 17(1): 54-59

19. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. Spine 2004; 29(4): 455-463

20. Lee CK, Langrana NA. A review of spinal fusion for degenerative disc disease: need for alternative treatment approach of disc arthroplasty? Spine J 2004; 4(6 Suppl): 173S-176S

21. Scaduto AA, Gamradt SC, Yu WD, Huang J, Delamarter RB, Wang JC. Perioperative complications of threaded cylindrical lumbar interbody fusion devices: anterior versus posterior approach. J Spinal Disord Tech 2003; 16(6): 502-507

22. Park P, Garton HJ, Gala VC, Hoff JT, McGillicuddy JE. Adjacent segment disease after lumbar or lumbosacral fusion: review of the literature. Spine 2004; 29(17): 1938-1944

23. Hilibrand AS, Robbins M. Adjacent segment degeneration and adjacent segment disease: the consequences of spinal fusion? Spine J 2004; 4(6 Suppl): 190S-194S

24. Gibson J, Waddell G. Surgery for degenerative lumbar spondylosis. Cochrane Database Syst Rev 2005; Issue 4(Art. No.: CD001352. DOI: 10.1002/14651858.CD001352)

25. Frelinghuysen P, Huang RC, Girardi FP, Cammisa FP, Jr. Lumbar total disc replacement part I: rationale, biomechanics, and implant types. Orthop Clin North Am 2005; 36(3): 293-299

26. Fritzell P, Hagg O, Nordwall A, Swedish Lumbar Spine Study Group. 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 2003; 12(2): 178-189

27. Sasso RC, LeHuec JC, Shaffrey C, and the Spine Interbody Research Group. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion. J Spinal Disord Tech 2005; 18(Supplement 1):S77-S81.

28. Brox JI, Sorensen R, Friis A, Nygaard O, Indahl A, Keller A 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 2003; 28(17): 1913-1921

29. Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R et al. 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 [serial on the Internet] 2005;[cited 2006 May 10] 330(7502): 1233

30. German JW, Foley KT. Disc arthroplasty in the management of the painful lumbar motion segment. Spine 2005; 30(16 Suppl): S60-S67

31. Centers for Medicare and Medicaid Services. Decision memo for lumbar artificial disc replacement (CAG-00292N). 2006. Centers for Medicare and Medicaid Services (CMS). [cited 2006 Mar. 3]. Available at: https://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=170

32. McAfee PC, Cunningham B, Holsapple G, Adams K, Blumenthal S, Guyer RD 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 2005; 30(14): 1576-1583

33. ECRI. Artificial intervertebral disc replacement for lumbar degenerative disc disease. Target Report # 852. March, 2004. Emergency Care Research Institute (ECRI).

34. Cakir B, Richter M, Kafer W, Puhl W, Schmidt R. The impact of total lumbar disc replacement on segmental and total lumbar lordosis. Clin Biomech 2005; 20(4): 357-364

35. Food and Drug Administration. Summary of safety and effectiveness data. Prosthesis intervertebral disc [report on the Internet]. Oct./2004. [cited 2005 Sept. 20]. Available at: http://www.fda.gov/ohrms/dockets/dockets/05m0092/05m-0092-aav0001-03-SSED-vol1.pdf

36. Government of Canada. Food and Drugs Act. Medical Devices Regulations. Canada Gazette [serial on the Internet] 1998;[cited 2005 Oct 3] 132(11)

37. Madhok R, Shaw LJ, Gillespie LD, (formerly the Musculoskeletal Injuries Group). About the Cochrane Collaboration (Cochrane Review Groups (CRGs)) [report on the Internet]. Issue 4[Art. No.: MUSKINJ]. 2005. [cited 2005 Nov. 10]. Available at: www.mrw.interscience.wiley.com/cochrane/clabout/articles/MUSKINJ/frame.html

38. GRADE Working Group. Grading quality of evidence and strength of recommendations. Br Med J 2004; 328: 1490-1494

39. Tropiano P, Huang RC, Girardi FP, Marnay T. Lumbar disc replacement: preliminary results with ProDisc II after a minimum follow-up period of 1 year. J Spinal Disord Tech 2003; 16(4): 362-368

40. Ross ERS, Tandon V. A pilot study of intervertebral disc replacement. J Back Musculoskeletal Rehabil 1997; 9(1): 69

41. Sekhon LH. Cervical arthroplasty in the management of spondylotic myelopathy. J Spinal Disord Tech 2003; 16(4): 307-313

42. 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 2003; 16(4): 424-433

43. 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 2003; 16(4): 352-361

44. 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 2003; 28(20): S167-S175

45. Blumenthal SL, Ohnmeiss DD, Guyer RD, Hochschuler SH. Prospective study evaluating total disc replacement: preliminary results. J Spinal Disord Tech 2003; 16(5): 450-454

46. Zeegers WS. Artificial disc replacement with the modular type SB Charite III: 2-year results in 50 prospectively studies patients. Eur Spine J 1999; 8(210): 217

47. Lemaire JP, Carrier H, Ali e, Skalli W, Lavaste F. Clinical and radiological outcomes with the Charitetrade mark artificial disc: a 10-year minimum follow-up. J Spinal Disord Tech 2005; 18(4): 353-359

48. Xu Y-C, Liu S-L, Huang D-S, Shen H-Y, Li C-H, Ma R-F. Correlated evaluation on the spinal segment motion scope and the alteration of the corresponding parameters after artificial lumbar intervertebral disc replacement. Zhongguo Linchuang Kangfu 2004; 8(32): 7294-7296

49. Caspi I, Levinkopf M, Nerubay J. Results of lumbar disk prosthesis after a follow-up period of 48 months. Isr Med Assoc J 2003; 5(1): 9-11

50. Su P-Q, Huang D-S, Li C-H, Ma R-F, Peng Y, Liu S-L. Significance of recovering spinal motion and carrying ability by artificial lumbar intervertebral disc replacement. Zhongguo Linchuang Kangfu 2003; 7(20): 2828-2829

51. Le Huec JC, Mathews H, Basso Y, Aunoble S, Hoste D, Bley B et al. Clinical results of Maverick lumbar total disc replacement: two-year prospective follow-up. Orthop Clin North Am 2005; 36(3): 315-322

52. Sekhon LH. Cervical arthroplasty in the management of spondylotic myelopathy: 18-month results. Neurosurg Focus 2004; 17:55-61.

53. Goffin J, Geusens E, Vantomme N, Quintens E, Waerzeggers Y, Depreitere B et al. Long-term follow-up after interbody fusion of the cervical spine. J Spinal Disord Tech 2004; 17(2): 79-85

54. Duggal N, Pickett GE, Mitsis DK, Keller JL. Early clinical and biomechanical results following cervical arthroplasty. Neurosurg Focus 2004; 17(3): E9

55. Lafuente J, Casey AT, Petzold A, Brew S. The Bryan cervical disc prosthesis as an alternative to arthrodesis in the treatment of cervical spondylosis. J Bone Joint Surg Br 2005; 87(4): 508-512

56. National Institute for Clinical Excellence (NICE). Prosthetic intervertebral disc replacement [report on the Internet]. Interventional Procedure Guidance 100. November 2004. National Health Service (NHS). [cited 2005 Sept. 17]. Available at: http://www.nice.org.uk/page.aspx?o=ip126overview

57. Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). Interventional Procedures Programme. Prosthetic intervertebral disc replacement [report on

the Internet]. Available at: .Accessed September 15, 2005 . September, 2003. National Institute for Clinical Excellence (NICE). [cited 2005 Sept. 15]. Available at: http://www.nice.org.uk/pdf/ip/ip126overview.pdf

58. Geisler FH, Blumenthal SL, Guyer RD, McAfee PC, Regan JJ, Johnson JP et al. 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 2004; 1(2): 143-154

59. Wang G. Artificial disc replacement. Health technology assessment [report on the Internet]. Washington State Department of Labor and Industries (WSDLI), Office of the Medical Director. 2004. [cited 2006 Sept. 9]. Available at: http://www.lni.wa.gov/ClaimsIns/Files/OMD/ArtificialDiscReplacement20041101.pdf

60. WCB Evidence Based Practice Group, Martin CW. Artificial cervical and lumbar disc implants: a review of the literature [report on the Internet]. April 2003. Workers' Compensation Board of BC. Worksafe Program Design Division. [cited 2006 Mar. 26]. Available at: http://www.worksafebc.com/health_care_providers/Assets/PDF/artificial_cervical_lumbar_disc.pdf

61. National Institute for Clinical Excellence (NICE). Prosthetic intervertebral disc replacement in the cervical spine - guidance [report on the Internet]. Interventional Procedure Guidance 143. November 2005. National Health Service (NHS). Quality Improvement Scotland. [cited 2006 Feb. 2]. Available at: http://www.nice.org.uk/page.aspx?o=114209

62. Pocock SJ. The pros and cons of noninferiority trials. Fundam Clin Pharmacol 2003; 17(4): 483-490

63. Ontario Medical Advisory Secretariat. Physiotherapy rehabilitation after total knee or hip replacement. 2006. Ontario Ministry of Health and Long Term Care. [cited 2006 Mar. 26]. Available at: http://www.health.gov.on.ca/english/providers/program/mas/tech/recommend/rec_rehabtkr_061705.pdf

64. Food and Drug Administration. In-depth statistical review for expedited PMA (P040006) Charite artificial disc, DePuy Spine Inc. [report on the Internet]. 2004. [cited 2006 Mar. 24]. Available at: http://www.fda.gov/ohrms/dockets/ac/04/briefing/4049b1_04_statistical%20Review%20Memo%20JCC.pdf

65. Odom G.L., Finney W., Woodhall B. Cervical disk lesions. J Am Med Assoc 1958; 166: 23-28

66. AETNA. Aetna Clinical Policy Bulletins. Intervertebral disc prostheses [report on the Internet]. AETNA. 2005. [cited 2005 Sept. 18]. Available at: http://www.aetna.com/cpb/data/CPBA0591.html

67. Regence. The Regence Group Medical Policy. Artificial intervertebral disc [report on the Internet]. 2005. [cited 2005 Sept. 14]. Available at: http://www.regence.com/trgmedpol/surgery/sur127.html

68. CIGNA. Intervertebral disc (IVD) prosthesis [report on the Internet]. February 15, 2005. CIGNA. [cited 2005 Sept. 19]. Available at: http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0104_coveragepositioncriteria_intervebral_disc_prosthesis.pdf

69. Canadian Institute for Health Information (CIHI). Provincial Health Planning Database (PHPDB). 2006. Ministry of Health and Long-Term Care.

70. Canadian Institute for Health Information (CIHI). Canadian Classification of Health Interventions [report on the Internet]. CCICD-10. 2006. Ministry of Health and Long Term Care. [cited 2006 Mar. 3]. Available at: http://www.cihi.ca/cihiweb/en/downloads/CCI_Vol3_2006.pdf

71. World Health Organizaton. International Statistical Classification of Diseases and Related Health Problems [monograph on the Internet]. 10th revision. 2006. World Health Organization (WHO). [cited 2006 May 4]. Available at: http://www3.who.int/icd/currentversion/fr-icd.htm

72. Tepper J, Jaigobin C , Wang C. Human health resources for neurosurgical services in Ontario. [report on the Internet]. June 2005. Institute for Clnical Evaluative Services (ICES). [cited 2006 Mar. 16]. Available at: http://www.ices.on.ca/file/HHR_Neurosurgical_Services_Final2.pdf

73. United States National Institutes of Health. CHARITE™ vs. ALIF 5-year follow-up [Web page]. 2006. [cited 2006 Mar. 28]. Available at: http://clinicaltrials.gov/ct/show/NCT00215332?order=2

74. United States National Institutes of Health. Kineflex Artificial Disc System to treat DDD [Web page]. 2006. [cited 2006 Mar. 26]. Available at: http://clinicaltrials.gov/ct/show/NCT00292292?order=1

75. Food and Drug Administration. Summary of Safety and Effectiveness Data. August 14 2006. Available at: www.fda.gov/cdrh/pdf5/p050010.html

76. Food and Drug Administration (FDA. Premarket approval application (PMA) approval letter [Web page]. 2004. United States Department of Health & Human Services. [cited 2006 Mar. 24]. Available at: http://www.fda.gov/cdrh/pdf4/p040006a.pdf

77. Food and Drug Administration (FDA). Clinical review [report on the Internet]. 2004. United States Department of Health & Human Services. [cited 2006 Mar. 24]. Available at: http://www.fda.gov/ohrms/dockets/ac/04/briefing/4049b1_03_Clinical%20Review%20Memo%20MAY.pdf