ARTIFICIAL DISC ARTHROPLASTY (ACDA)

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# Table of Contents

Abbreviations ........................................................................................................................................ 8

Glossary................................................................................................................................................ 9

Executive Summary ............................................................................................................................. 11

1. Introduction ........................................................................................................................................ 14
   1.1. Purpose of Assessment ............................................................................................................. 14
   1.2 Research Questions ................................................................................................................... 14

2. Background ......................................................................................................................................... 15
   2.1. Technology Definition ........................................................................................................... 15
   2.2. Condition Definition ............................................................................................................... 15

3. Methodology ..................................................................................................................................... 16
   3.1. Literature..................................................................................................................................... 16
      3.1.1. Literature Search .............................................................................................................. 16
      3.1.2. Selection of Literature .................................................................................................... 16
      3.1.3 Results of Literature Search ............................................................................................. 18
      3.1.4 Data Extraction ................................................................................................................ 18
   3.2 Social Systems and Demographics (S) Approach to Analysis ........................................ ... 19
   3.3 Technology Effects and Effectiveness (T) Approach to Analysis ........................................... 19
   3.4 Economic (E) Approach to Analysis .......................................................................................... 21

4. Social Systems and Demographics ................................................................................................. 21
   4.1 Patterns of Illness ..................................................................................................................... 21
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.1 Burden of Illness/Description of Condition(s)</td>
<td>21</td>
</tr>
<tr>
<td>4.1.2 Population Dynamics</td>
<td>26</td>
</tr>
<tr>
<td>4.2 Patterns of Care</td>
<td>28</td>
</tr>
<tr>
<td>4.2.1 History</td>
<td>28</td>
</tr>
<tr>
<td>4.2.2 Procedures Overview and Trends</td>
<td>30</td>
</tr>
<tr>
<td>4.2.3 Access to Technology in Alberta</td>
<td>31</td>
</tr>
<tr>
<td>4.3 Health System Capacity</td>
<td>32</td>
</tr>
<tr>
<td>4.3.1 Workforce Capacity</td>
<td>32</td>
</tr>
<tr>
<td>5. Technology Effects and Effectiveness</td>
<td>34</td>
</tr>
<tr>
<td>5.1 Current Context</td>
<td>34</td>
</tr>
<tr>
<td>5.1.1 Technology</td>
<td>34</td>
</tr>
<tr>
<td>5.1.2 Procedural Comparison</td>
<td>37</td>
</tr>
<tr>
<td>5.1.3 Health Canada Approval</td>
<td>39</td>
</tr>
<tr>
<td>5.2 Condition(s) and Limitations</td>
<td>39</td>
</tr>
<tr>
<td>5.2.1 Best Practice</td>
<td>39</td>
</tr>
<tr>
<td>5.2.2 Other Jurisdictional Guidelines</td>
<td>41</td>
</tr>
<tr>
<td>5.3 Effects/Effectiveness</td>
<td>43</td>
</tr>
<tr>
<td>5.3.1 Safety</td>
<td>43</td>
</tr>
<tr>
<td>5.3.2 Effectiveness in case series</td>
<td>44</td>
</tr>
<tr>
<td>5.3.3 Comparative Benefits and Risks</td>
<td>45</td>
</tr>
<tr>
<td>5.4 Delivery Context</td>
<td>57</td>
</tr>
<tr>
<td>5.4.1 Delivery Considerations</td>
<td>57</td>
</tr>
</tbody>
</table>
Table 7a. SF-36 Physical Component Score. (mean differences) ......................92
Table 7b. SF-36 Physical Component Score (summary estimate) ......................92
Table 8a. SF-36 Mental Component Score (mean differences) ..........................92
Table 8b. SF-36 Mental Component Score (summary estimate) .......................92
Table 9a. Arm Pain (mean differences) ..............................................................92
Table 9b. Arm Pain (summary estimate) .............................................................93
Table 10a. Neck Pain (mean differences) ..........................................................93
Table 10b. Neck Pain (summary estimate) .........................................................93
Table 11a. Neck Disability Index (mean differences) .........................................93
Table 11b. Neck Disability Index (summary estimate) ........................................93
Table 12. HTA reports .........................................................................................94
Table 13. Hospital costs ......................................................................................95
Table 14. Physician costs ...................................................................................95
Table 15. Costs to Alberta based on percentage of ACDA/cervical fusion .......95
Table 16. Proportions, in 2006/2007, of interventions, by age and procedure, per
100,000 individuals ...........................................................................................96
Table 17. Number of cervical fusions and ACDA procedures in 4-year study
period by region ..................................................................................................96
Table 18. Number of interventions (cervical fusion and ACDA) by delivery region
and fiscal year .......................................................................................................96
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACDA</td>
<td>Artificial cervical disc arthroplasty</td>
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<tr>
<td>AHW</td>
<td>Alberta Health and Wellness</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DDD</td>
<td>Degenerative disc disease</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<td>IDE</td>
<td>Investigational device exemption</td>
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<td>ITT</td>
<td>Intent-to-treat</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NDI</td>
<td>Neck disability index</td>
</tr>
<tr>
<td>OHTAC</td>
<td>Ontario Health Technology Advisory Committee</td>
</tr>
<tr>
<td>ODI</td>
<td>Oswestry disability index</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short-form 36 Health Survey</td>
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<tr>
<td>VAS</td>
<td>Visual analog scale</td>
</tr>
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</table>
Glossary

**Allograft** = the transplant of an organ or tissue from one individual to another of the same species with a different genotype; allografts account for many human transplants, including those from cadaveric, living related, and living unrelated donors.

**Autograft** = tissue transplanted from one part of the body to another in the same individual.

**Der Simonian-Laird method** = a random effects model used in meta-analysis in which two variances occur. One contribution of variation is coming from the individual studies involved in the meta-analysis. The other contribution of variation is due to the heterogeneity of the effect sizes. The DerSimonian-Laird estimator is known to behave well conditionally that the studyspecific variances are known.

**Efficacy** = the degree of beneficial effect under ideal circumstances

**Effectiveness** = the degree of beneficial effect under routine clinical settings.

**Myelopathy** = the gradual loss of nerve function caused by disorders of the spine.

**Non-inferiority trials** = these trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin. These trials have a number of inherent weaknesses that superiority trials do not: no internal demonstration of assay sensitivity, no single conservative analysis approach, lack of protection from bias by blinding, and difficulty in specifying the noninferiority margin.

**Radiculopathy** = term used to describe conditions which have caused damage to the nerve roots which connect the spine to the rest of the nervous system.

**Short-form Health Survey (SF-36)** = a survey of patient health. The SF-36 consists of eight scaled scores, which are the sums of the questions in their section. Each scale is directly
transformed into a 0-100 scale on the assumption that each question carries equal weight.

The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health.
Executive Summary

Introduction

The aim of this Report is to review the literature for evidence of effectiveness and safety of the cervical artificial disks approved by Health Canada.

Degenerative disc disease (DDD) of the spine includes a wide spectrum of degenerative abnormalities, either age-related or pathologic. The prevalence of DDD increases with age. An estimated 60% of individuals older than 40 years have radiographic evidence of cervical DDD. By age 65, some 95% of men and 70% of women have at least one degenerative change evident at radiographic examination.

Artificial cervical disc arthroplasty (ACDA) is a surgical procedure that may replace cervical fusion in selected patients suffering from cervical DDD. The main outcome of ACDA that sets it apart from fusion is the preservation of the spine mobility. Fusion alters the normal biomechanics of the spine, which may result in the acceleration of the adjacent-level disease and subsequent reoperation. Preserving the range of spinal motion rather than fusing the degenerating spine may limit the progression of the disease to the adjacent level.

Methods

We searched several databases and the grey literature, and included in our review of efficacy and effectiveness 5 RCTs comparing clinical outcomes of single level ACDA to single level fusion, one non-randomized comparative study and fourteen case series. Using published data from one RCT and unpublished data received from two companies producing the cervical artificial discs reviewed, we conducted a meta-analysis of clinical outcomes.
Results

The literature reviewed showed that both ACDA and cervical fusion have similar complication and reintervention rates. Therefore, we may conclude that there is no difference between ACDA and fusion in terms of short term safety. The results of our meta-analysis showed that ACDA is not inferior to fusion in terms of short term clinical outcomes (neck and arm pain, SF-36).

The surgical techniques used for both ACDA and cervical fusion are similar up to the point of interbody fusion/arthroplasty. None of the authors of the articles reviewed noted the need for new equipment for performing ACDA, except for the cervical disc itself.

Implications

The number of cervical fusion and ACDA procedures performed in Alberta during the last four years shows an increasing utilization for these procedures, trend that is expected to continue in the following years.

Conclusions

In the absence of adequate data (economic and long-term clinical data), performing a cost-effectiveness analysis of ACDA compared to fusion was not possible. Therefore, we cannot determine at this time if ACDA is more cost-effective than cervical fusion.

There are several completed and ongoing trials that have proved that one level ACDA is at least as effective and safe as one level cervical fusion in short term. There is no data regarding the comparative effectiveness of ACDA and cervical fusion at more than one cervical levels. Hence, ACDA at one cervical level cannot be considered an experimental procedure, but more data regarding the long term effectiveness and cost-effectiveness are
needed to decide if it will replace the cervical fusion for the treatment of cervical DDD in the near future.
1. Introduction

1.1 Purpose of Assessment

The purpose of this report was to determine what is the potential role of ACDA in the treatment of degenerative disc disease (DDD) of the cervical spine.

1.2 Research Questions

1. In comparison to discectomy/cervical fusion, how safe is ACDA at one, two and/or more cervical levels for the treatment of DDD?
2. In comparison to discectomy/cervical fusion, how efficacious is ACDA at one, two and/or more cervical levels for the treatment of DDD?
3. In comparison to discectomy/cervical fusion, how effective is ACDA at one, two and/or more cervical levels for the treatment of DDD?
4. What are the factors that might lead to the consideration of ACDA as an experimental method of treatment for cervical DDD?
2. Background

2.1. Technology Definition

The development of ACDA was possible in 1989, when the first artificial cervical disc (the Cummins-Bristol artificial cervical joint) was tested in a human trial. Since then, several artificial cervical discs have been developed and new generations of artificial discs are expected to be marketed in the near future. The devices reviewed in this report were: Bryan Cervical Disc, Porous Coated Motion (PCM) implant, ProDiscTM-C Total Disc Replacement, and Prestige Cervical Disc system. Table 1 presents the characteristics of these devices. Further details on the making of the implants are reported in Chapter 5.1.1.

Fusion alters the normal biomechanics of the spine, which may result in the acceleration of the adjacent-level disease and subsequent reoperation. Preserving the range of spinal motion rather than fusing the degenerating spine may limit the segmental progression of disease that affects some patients. Consequently, the clinical trials initiated to compare ACDA to cervical fusion were designed as non-inferiority trials, because the most clinical outcomes (neck pain, quality of life) are expected to be similar between the two treatment groups. The actual benefit of preserving the spinal mobility is expected to be observed in long term follow-up trials, which are currently under way in Europe and the United States.

2.2. Condition Definition

The focus of this report is the cervical DDD. Symptoms of cervical DDD include neck and arm pain associated with radiculopathy or myelopathy, respectively. Untreated, the signs...
and symptoms of cervical DDD may decrease, stabilize, or worsen. Initial conservative, noninvasive therapies aim to relieve pain and prevent permanent injury to the spinal cord and nerve roots. Typically, if at least 2 to 6 months of conservative treatment is ineffective, or the patient becomes unable to perform activities of daily living, surgical intervention is indicated.\(^1\)

### 3. Methodology

#### 3.1. Literature

##### 3.1.1. Literature Search

We searched the following databases: MEDLINE (OVID), Cochrane CENTRAL Register of Controlled Trials (OVID 4th Quarter), Cochrane Database of Systematic Reviews (OVID 4th Quarter), Health Technology Assessment Database (OVID 4th Quarter), DARE Database of Reviews of Effects (OVID 4th Quarter), NHS Economic Evaluation Database and EconLit (EBSCO) database. The search strategies used for each of these databases are presented in Appendix 1. Our searches were limited to the last 10 years (1998 – 2008), English language and human studies and they were completed in September 2008.

##### 3.1.2. Selection of Literature

We developed inclusion/exclusion criteria based on the inclusion/exclusion criteria used in the OHTA report (April, 2006)\(^2\). Unlike the OHTA team, we decided to include in our review relevant studies on all devices available, as Health Canada may consider licensing new artificial cervical discs in the future. Also, we included single-site reports from multi-center studies that met the inclusion criteria listed below and reported data that was not included in a
multi-center study publication in an effort to summarize all the data on ACDA reported in the
literature. The inclusion and exclusion criteria are presented below.

**Inclusion criteria:**

1. studies with at least 10 subjects;
2. studies that evaluated any of the artificial cervical discs on the market in America, even if the device was not licensed by Health Canada;
3. studies that reported on at least one of pain and/or disability outcomes; and
4. studies that reported at least 1 year of outcome data.

**Exclusion criteria:**

1. non-English language studies;
2. case reports;
3. animal and in vitro studies;
4. duplicate publications;
5. studies that did not examine the outcomes of interest;
6. single-site reports of data included in a multi-center study publication; and
7. studies with greater than 20% loss to follow-up in study sample.

The decision to include/exclude papers in the review was made independently by two reviewers (MC and LS) and conflicts were resolved by consensus.

The quality of the studies included in our review of efficacy and effectiveness was assessed by two independent reviewers (MC and EP). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Appendix 2) to evaluate the overall quality of the studies included in the review. The internal validity of the RCTs included in our review was assessed using the Cochrane Musculoskeletal Injuries Group Quality Assessment Tool (Appendix 3).
3.1.3 Results of Literature Search

Our literature search yielded 622 titles. After the title and abstract review we excluded 175 studies of other surgical treatment of cervical DDD than ACDA (fusion, laminoplasty etc); 33 records of in vitro, animal or cadaveric studies of cervical discs; 8 case reports; 9 studies published in other language than English; and 262 records of editorials, comments, anatomic studies, and studies of other diseases than cervical DDD. After a full text review of the remaining records, we excluded 96 studies that did not report any clinical data on ACDA, 10 case series with less than 12 months of follow-up,\(^5,6,7,8,9,10,11,12,13,14\), 5 case-series with greater than 20% of the sample loss to follow-up,\(^15,16,17,18,19\) and 1 single-site report of an RCT (multisite data that may have included the single-site were reported in another study).\(^20\) Four studies that included data reported in another published study were excluded.\(^21,22,23,24\)

We found 4 RCTs comparing clinical outcomes of single level ACDA to single level fusion. We also included in our review one in press RCT report obtain from the company producing the device under study. Data abstracted from these reports is presented in Table 3. One non-randomized comparative study was also included in our review (Table 4).

Fourteen case series met our criteria and were included in the review. The data abstracted from these studies are summarized in Table 5.

3.1.4 Data Extraction

Data were abstracted using a data abstraction form designed by our team by two members of our team (MC and EP). We abstracted information on study population, methods, interventions, outcomes, and complications. Where needed, the primary authors of the studies...
and the manufacturer of the device were contacted to obtain data not reported in the articles reviewed. The clinical outcomes of interest were arm and neck pain scores, NDI scores and SF-36 scores.

3.2 Social Systems and Demographics (S) Approach to Analysis

We included in this section information from published articles retrieved through our literature search, medical specialty books and experts that were consulted for this report. To estimate the burden of cervical DDD in the population of Alberta, we reviewed the ICD 9 diagnoses that may indicate the presence of DDD or DDD symptoms and selected three diagnostic codes: 723.1 (cervicalgia), 721.1 (cervical spondylosis with myelopathy) and 722.4 (degeneration of the cervical intervertebral disc). We assumed that cervicalgia (neck pain) is caused only by cervical DDD. We received from AHW data on the frequency of these codes in medical billing in four fiscal years (from 2004 to 2008) and used the population statistics data from Statistics Canada to estimate the one year prevalence of each diagnosis code for the four fiscal years.

3.3 Technology Effects and Effectiveness (T) Approach to Analysis

The clinical studies evaluating the efficacy and effectiveness of ACDA, either alone or in comparison to cervical fusion, were analyzed qualitatively. Where needed, the primary authors of the studies and the manufacturer of the device were contacted to obtain data not reported in the articles reviewed. We received unpublished clinical data from Medtronic (Prestige cervical disc) and Synthes (ProDisc-C). We signed a confidentiality agreement with one of the
representatives of the above mentioned manufacturers, which allows us to use the data
provided for our meta-analysis, but not to include them in our report.

The clinical outcomes of interest were Short Form (SF-36) scores, neck and arm pain
scores and Neck Disability Index (NDI) scores. These clinical scales are widely used to
evaluate the overall function and quality of life (SF-36) and the cervical spine function in
patients undergoing surgery for cervical DDD.

A meta-analysis was performed using published (one RCT) and unpublished data
obtained through the manufacturers of the devices. We were not able to include all the
published RCT's reviewed in the report because the data reported (ie, means and mean
differences of the clinical outcomes of interest) were insufficient. Our attempts to contact the
primary authors of the publications reviewed for more information were met with failure. We
further contacted the companies producing the devices under review (Medtronic and Synthes
Spine) and we received the additional clinical data (published and unpublished) we needed to
complete our meta-analysis. We included these data, but did not seek an opinion about the
conclusions of our report. Therefore we consider that no reporting bias was introduced in our
analysis.

Because different devices were used for each trial, we chose to use a random effects
model for each outcome, even if there was no statistical evidence of heterogeneity. A
DerSimonian-Laird approach for continuous outcomes was used for calculating weights for
the random effects models. We calculated a weighted mean difference and its 95% confidence
interval for each clinical outcome. The meta-analysis was performed using the /meta/
package in R version 7.0.25
3.4 Economic (E) Approach to Analysis

This economic evaluation is a cost evaluation. The comparison is between ACDA with the current standard of cervical fusion. A cost evaluation, in which costs are analyzed in conjunction with current demand, is done due to the lack of QALY data and the lack of long-term pain measurement scores in the literature.

The economic evaluation included calculations of costs and patient demand for both one-level cervical fusion and single cervical disc replacement. Data regarding the two level and 3+ level cervical fusion were summarized and included in our report. The economic analysis was performed using STATA version 9.26

4 Social Systems and Demographics

4.1 Patterns of Illness

4.1.1 Burden of Illness/Description of Condition(s)

Degenerative disc disease (DDD) of the spine includes a wide spectrum of degenerative abnormalities, either age-related or pathologic. Degeneration involves bony structures and the intervertebral disc, the main pathogenic factor being chronic overload. The distribution of axial load is responsible for the typical localization of spine degeneration. C5-6 and C6-7 levels are involved in most cases, because they are the sites of lordosis inversion.1

The progressive deterioration in the cervical spine may lead to radiculopathy and myelopathy. Radiculopathy may occur from posterolateral soft disc herniation. In addition, foraminal stenosis may also lead to compression of the existing nerve root.27 The decreased
disc height and degenerative changes of the uncovertebral joints anteriorly and zygapophyseal joint posteriorly determine the foraminal encroachment of the spinal nerve. In contrast to disorders of the lumbar spine, herniation of the nucleus pulposus is responsible for only one quarter of the cases.\textsuperscript{28}

Myelopathy of the cervical spine may be due to the stenosis of the spinal canal or cord compression secondary to ossification of the posterior longitudinal ligament. The stenotic spinal canal may lead to neurologic dysfunction via compression of the anterior spinal artery with cord ischemia or mechanical deformation of the spinal cord from direct pressure, and/or dynamic compression (hyperextension or flexion). Occasionally, a midline soft disc herniation may cause cord compression and myelopathy combined with a degree of nerve root compression, leading to a myeloradiculopathy.\textsuperscript{27}

The causes of age-related and pathologic spine degenerative changes are multiple: traumatic, metabolic, toxic, genetic, vascular, and infectious. Trauma is the main pathologic factor, however, including chronic overload, chronic multiple traumatisms, and sequelae of acute trauma.\textsuperscript{1}

Degenerative disc changes observed on image studies may reflect simple aging and do not necessarily indicate a symptomatic process. The disc begins to degenerate in the second decade of life. Circumferential tears form in the posterolateral annulus after repetitive use. Several circumferential tears coalesce into radial tears, which progress into radial fissures. The
disc then disrupts with tears passing throughout the disc. Loss of disc height occurs with subsequent peripheral annular bulging. Proteoglycans and water escape through fissures formed from nuclear degradation, resulting in further thinning of the disc space. Vertebral sclerosis and osteophytic formation ultimately follow.29

The clinical diagnosis of cervical DDD involves performance of imaging studies and evaluation of symptoms.

Imaging studies play an important role in the evaluation of degenerative spine. Plain X-ray films (upright flexion-extension and lateral bending) offer direct information about bony structures, misalignment and vertebral stability.1 MRI is the approach of choice when imaging is pursued in patients with cervical radiculopathy. CT may be performed when bony abnormalities are suspected, but CT alone is of limited value in assessing cervical radiculopathy.1,28 Myelography and discography are reserved for selected patients (patients with a contraindication for MRI or in whom subtle instability is suspected but not confirmed by other examinations).1 More advance imaging studies include weight-bearing CT or MRI and MRI with the patient in upright position, which also allows cervical dynamic flexion-extension evaluations.

Symptoms depend on the type of pathologic process affecting the cervical spine. Neck pain is the most frequent symptom of cervical radiculopathy, and is usually accompanied by paresthesia, muscle weakness, and diminished neuromuscular reflexes. The location of these symptoms varies with the level of radiculopathy.27 Discogenic pain without nerve root involvement may be vague, diffuse and distributed axially. When a motor or sensory involvement is present, radicular pain may be deep, dull, and achy or sharp, burning, and electric.29 A summary of symptoms, by cervical level involved, is presented below (adapted from Carette et al.28, with permission).
The natural history of neck pain has been evaluated through a retrospective review, which showed that nearly one third of the study group reported persistent moderate to severe pain after more than 10 years of follow-up. Notably, the outcome could not be correlated with radiographic or clinical findings, making neck pain prognosis difficult in these patients. Still, little is known about the natural history of cervical radiculopathy. In the population based study from Minnesota, one quarter of the patients diagnosed with cervical radiculopathy underwent surgery within three months of the diagnosis, whereas the remainder three quarters was treated medically. Recurrence (the reappearance of symptoms after a symptom-free interval of at least 6 months) occurred in one third of the patients during a follow up of almost 5 years.

In general there is agreement that nonsurgical treatment may alleviate symptoms of cervical spondylitic radiculopathy in the short term, but over a long period of time symptoms frequently recur. Progression from radiculopathy to myelopathy is unusual. The symptoms and findings associated with cervical radiculopathy are summarized in the following table:

<table>
<thead>
<tr>
<th>Disk Level</th>
<th>Root</th>
<th>Pain Distribution</th>
<th>Weakness</th>
<th>Sensory Loss</th>
<th>Reflex Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4–C5</td>
<td>C5</td>
<td>Medial scapular border, lateral upper arm to elbow</td>
<td>Deltoid, supraspinatus, infraspinatus</td>
<td>Lateral upper arm</td>
<td>Supinator reflex</td>
</tr>
<tr>
<td>C5–C6</td>
<td>C6</td>
<td>Lateral forearm, thumb and index finger</td>
<td>Biceps, brachioradialis, wrist extensors</td>
<td>Thumb and index finger</td>
<td>Biceps reflex</td>
</tr>
<tr>
<td>C6–C7</td>
<td>C7</td>
<td>Medial scapula, posterior arm, dorsum of forearm, third finger</td>
<td>Triceps, wrist flexors, finger extensors</td>
<td>Posterior forearm, third finger</td>
<td>Triceps reflex</td>
</tr>
<tr>
<td>C7–T1</td>
<td>C8</td>
<td>Shoulder, ulnar side of forearm, fifth finger</td>
<td>Thumb flexors, abductors, intrinsic hand muscles</td>
<td>Fifth finger</td>
<td>—</td>
</tr>
</tbody>
</table>

The clinical diagnosis of cervical DDD involves performance of imaging studies (plain films, MRI or CT, myelography, discography) and evaluation of symptoms. Neck pain is the main symptom of cervical radiculopathy.
myelopathy may include gait difficulties, spasticity, decreased manual dexterity, paresthesias in the extremities, urinary urgency or frequency, and specific extremity or generalized weakness. Cervical spondylitic myelopathy is associated with an insidious onset of symptoms and, in general, neurologic function undergoes episodes of worsening with intervening stable periods. Progression to total disability is unusual, although slight incremental neurologic deterioration may occur over time, resulting in extremity functional deficits. In contrast to cervical radiculopathy, pain is not a common presenting finding for cervical myelopathy.27

Physical findings associated with cervical myelopathy (adapted from Carette et al28, with permission)

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Clinical grading (performed on the basis of the extent of symptoms, signs, and functional impairment)</th>
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<tbody>
<tr>
<td>Hyperreflexia; hypertonia; clonus of the ankle, knee, or wrist; pathological reflexes or signs, such as the Babinski sign, Hoffmann’s sign (flexion and adduction of the thumb when the examiner flexes the terminal phalanx of the long finger), and Lhermitte’s sign (a sensation of electrical shock radiating down the spine, precipitated by neck flexion)</td>
<td>Mild = Sensory symptoms; subjective weakness; hyperreflexia (with or without Hoffmann’s sign or the Babinski sign); no functional impairment</td>
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<td></td>
<td>Moderate = Objective motor or sensory signs (a score of &gt;4 out of 5 on the Medical Research Council scale); either no or mild functional impairment (e.g., mild slowing of gait)</td>
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<tr>
<td></td>
<td>Severe = Objective motor or sensory signs with functional impairment (e.g., hand weakness, unsteady gait, sphincter disturbance)</td>
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Neck pain is one of the main symptoms of cervical DDD and a source of disability in the working population. Unfortunately, there is no data in the literature pertaining to the socio-economic effects of cervical DDD. In this report, we summarized the data available on the socio-economic effects of neck pain, assuming that it is caused mainly by cervical DDD.

Survey of workers suggest that the annual prevalence of activity limitations related to neck pain varies from 11% in the UK to 14.1% in Quebec, Canada.31 Nevertheless, very few studies reported on the socio-economic effects of neck pain.
In Ontario, the annual prevalence of work absenteeism involving neck pain in 1998 was 30 per 10,000 FTE (one FTE corresponds to 2000 hours of work in 1 year). The authors noted that male workers between the ages of 20 and 39 years were the most likely to experience an episode of work absenteeism involving neck pain.

There is no data in the literature pertaining to the socio-economic effects of cervical DDD and/or neck pain in Alberta.

4.1.2 Population Dynamics

Neck pain is one of the main symptoms of cervical DDD. In Canada, the Saskatchewan Health and Back Pain Survey conducted in 1995/1996 reported an annual incidence of neck pain (age and gender standardized annual cumulative incidence) of 14.6% (95% CI: 11.3, 17.9). The incidence of a new episode of neck pain was lower in older subjects than in younger ones and in men than in women. Based on claim data from the Ontario Workplace Safety & Insurance Board (WSIB) and using a weighted estimate of codes capturing neck pain cases, the annual prevalence of neck pain in Ontario was 11.3% (95% CI: 9.5, 13.1), with a higher prevalence for women (14%) than men (10.1%).

We were able to calculate the Alberta prevalence rates of the following diagnostic codes: 723.1(cervicalgia), 721.1 (cervical spondylosis with myelopathy) and 722.4 (degeneration of the cervical intervertebral disc), in four fiscal years. According to our calculations, the prevalence rate of cervicalgia in Alberta was 75.3/10,000 in 2004/2005, 74.6/10,000 in 2005/2006, 75.6/10,000 in 2006/2007 and 76.7/10,000 in 2007/2008. The prevalence rate of cervical spondylosis with myelopathy was 2.5/10,000 in 2004/2005, 2.8/10,000 in 2005/2006,

The peak incidence of cervical myelopathy/radiculopathy was noted in people between 50 and 54 years of age. The prevalence of DDD increases with age. The annual prevalence of neck pain varies from 30% to 50%. There are no longitudinal studies that would indicate an important correlation between disk degeneration changes on MRI and neck pain. In Alberta, the prevalence rates of cervicalgia, cervical spondylosis with myelopathy and degeneration of cervical intervertebral disc remained constant over four fiscal years.

There are few studies reporting the incidence and prevalence of cervical radiculopathy and/or myelopathy. A population-based study conducted in Minnesota over a period of 14 years reported an annual incidence of cervical radiculopathy of 107.3 per 100,000 men and 63.5 per 100,000 women. The peak incidence was noted for people between 50 and 54 years of age. A survey conducted in Sicily reported a prevalence of cervical radiculopathy of 3.5 per 1000 population.

The prevalence of DDD increases with age. An estimated 60% of individuals older than 40 years have radiographic evidence of cervical DDD. By age 65, some 95% of men and 70% of women have at least one degenerative change evident at radiographic examination. It is estimated that some 5 million adults in the U.S. are disabled to an extent by spine-related disorders, although only a small fraction of those are clear candidates for spinal surgery. The Nationwide Inpatient Sample (NIS) is a database maintained by the Agency for Healthcare Research and Quality that represents a 20% random sample of all discharges from nonfederal hospitals within the U.S., based on ICD-9-CM procedure codes. A study of NIS data for the years 1993 through 2003 showed that overall utilization of cervical spinal fusion in the U.S. increased from 26 per 100,000 to 50 per 100,000, with symptomatic DDD the primary diagnosis, representing about 83% of cervical DDD cases in 2003.
The Task Force on Neck Pain review\textsuperscript{35} found that the incidence of neck pain reported in the literature ranged from 0.055 per 1000 person years (disc herniation with radiculopathy) to 213 per 1000 persons (self-reported neck pain). The 12-month prevalence of neck pain ranged between 30\% and 50\%; the 12-month prevalence of activity-limiting pain was 1.7\% to 11.5\%. Neck pain was more prevalent among women and prevalence peaked in middle age. A recent study\textsuperscript{36} reported a 2 week prevalence of neck pain in Denmark of 31\%. The authors noted that the intensity of neck pain was moderately correlated with the degree of disability reported by patients on the Neck Pain and Disability Scale (NPDS).

### 4.2 Patterns of Care

#### 4.2.1 History

The majority of the vertebral implants designed during the last 50 years focused on disc replacement in the lumbar spine, whereas a few focused on the cervical spine. Several factors have influenced the slow progress with spinal arthroplasty. In contrast to knee and hip joints, in which ligamentous structures are of paramount importance in the maintenance of joint stability, the disc itself contributes a significant portion to spinal stability. The development of biomaterials for total disc replacement must take into consideration the high demands of strain imparted to the implant by the approximately 100 million flexion cycles during a lifetime (the optimal life time of a spinal implant is 30 to 50 years). Furthermore, prosthetic wear and the resulting debris, with its associated inflammatory reaction as seen in hip and knee arthroplasty may be a potential source of long-term failure for spinal arthroplasty.\textsuperscript{37}

The results of the first human trial in which this cervical prosthesis was used were reported in 1998. Since then, several artificial cervical discs have been developed (Prestige cervical disc, Bryan disc, PCM disc, ProDisc-C, Maverick and Flexcore).
The pursuit of cervical disc replacement has not been as vigorous as for their lumbar counterparts. Although the lumbar disc replacement is difficult and there is a risk of potential complications, the risks are even greater in the cervical spine.\textsuperscript{38}

Early attempts at cervical arthroplasty were met with failure. The first implantation of a cervical arthroplasty device in a human was described by Fernström in 1966. He used an intracorporal endoprosthesis shaped like a metal ball bearing, which he inserted into the disc space of both lumbar and cervical areas. Despite these pioneering attempts, Fernström himself admitted poor results. The placement of these devices has subsequently been abandoned in favor of cervical arthrodesis. In the 1980s there was a resurgence of interest in spinal arthroplasty, specifically lumbar arthroplasty.\textsuperscript{37}

With the reported success of lumbar arthroplasty devices, renewed enthusiasm has emerged for the prospects of a cervical arthroplasty device. In 1989, the Department of Medical Engineering at Frenchay Hospital, Bristol, United Kingdom, began the initial design process for an artificial cervical joint. The results of the first human trial in which this cervical prosthesis (called the Cummins–Bristol artificial cervical joint) was used were reported in 1998. Based on the initial experience with the Cummins artificial cervical joint, a second-generation design was implemented to allow more physiological cervical motion that would be restrained by that of the facet joints and the surrounding tissues. The new Frenchay cervical disc replaced the lower component of the Cummins joint, which initially was a hemispherical cup, with a shallow ellipsoid saucer. Later, the Frenchay cervical disc was renamed Prestige cervical disc.\textsuperscript{37,38} With the reported success of the modified Bristol discs, several other artificial cervical discs have reached the clinical testing stage. In contrast to the metal-on-metal design of the Bristol disc, a metal-on-plastic design called the Bryan disc emerged in the late 1990s. Named after its American inventor, Vincent Bryan, the disc consists of a polyurethane
core that articulates between two titanium alloy shells that include convex porous surfaces for bone ingrowth. Along the same lines as the metal-on-plastic concept, the PCM artificial disc was developed recently with two different designs to address the integrity of the posterior longitudinal ligament after cervical decompression. Rather than using a polyurethane core as in the Bryan disc, the PCM disc consists of the traditional UHMWPE compound found in hip and knee arthroplasties. It is structured for load bearing rather than being a ball-in-socket design.\textsuperscript{37,38}

A disc replacement that has been used in Europe since 1990 is the ProDisc (Spine Solutions, New York). It consisted of three pieces: two metal endplates and a polyethylene core. With the success of the lumbar ProDisc device, a similar construct for cervical arthroplasty was designed, called ProDisc-C.\textsuperscript{37,38}

Other arthroplasty devices are actively being developed and tested and will likely emerge in the coming years. The Maverick disc is a metal-on-metal design with anchoring keels similar to ProDisc and is being tested in Europe. Other new disc replacements not tested yet in humans are the Flexcore and a unique design disc made of polyethylene woven fibers and a bioactive material that allows bony ingrowths to anchor the device.\textsuperscript{38}

4.2.2 Procedures Overview and Trends

Conservative intervention consists of modified rest, a cervical collar, oral corticosteroid “dose-packs”, and NSAIDs.\textsuperscript{39} NSAIDs are first-line pharmacologic intervention for most cervical conditions; they reduce pain at low doses and decrease inflammation at high doses. All NSAIDs have a dose-related ceiling point for analgesia above which higher doses fail to provide additional pain relief. Oral corticosteroids treat inflammatory cervical radiculopathy. Other medication that may be used to treat cervical pain are antidepressants and opioids.\textsuperscript{29}
Cervical and cervicothoracic stabilization exercises form the cornerstone of the therapeutic exercise program. Cervicothoracic stabilization programs include cervical spine flexibility exercises, postural training and strengthening exercises. All these therapeutic programs need to be individualized and patient education plays a key role.

Surgical intervention is reserved for patients with persistent radicular pain who do not respond to conservative measures. In general, the decision to proceed with surgical intervention is made when a patient has significant extremity or myotomal weakness, severe pain, or pain that persists beyond an arbitrary “conservative” intervention period of 2 to 8 weeks.

Anterior cervical discectomy with fusion is a well-established treatment for symptomatic degenerative cervical disease. The anterior cervical discectomy is followed by the anterior interbody fusion. Several surgical techniques for fusion were described: Robinson technique (which involves the placement of a tricortical iliac crest wedge graft into the disc space), Cloward technique (which utilizes a bicortical dowel-shaped graft), Simmons technique (which utilizes a keystone-shaped graft), and the Bailey and Badgley technique (which involves developing and anterior trough in the vertebral bodies).

### 4.2.3 Access to Technology in Alberta

According to the expert we consulted (Dr. Hurlbert) the number of ACDA procedures performed in Alberta depends on the availability of staff, operation rooms and funds necessary to purchase the artificial discs.
There are two health regions in Alberta that provide ACDA: the Calgary Health Region and the Capital Health Region. Cervical fusion is provided in the two health regions mentioned before, and the Peace Country Health region.

The Alberta Waitlist Registry 2008 report for Spinal Vertebrae, discs and muscles of back surgical procedures (available at [http://www.ahw.gov.ab.ca/waitlist/AccessGoalCharts.jsp](http://www.ahw.gov.ab.ca/waitlist/AccessGoalCharts.jsp)) indicates an increase in the waiting time for these procedures from 11 weeks in September 2007 to 14 weeks in September 2008. We found no data on waiting times specific to cervical surgery.

We were unable to find a clinical pathway specific to cervical DDD. In an editorial published in 1999, Agrillo et al. discussed guidelines for the diagnosis and management of cervical spondylogenic myelopathy and cervical disc herniation, noting that the indications for surgical treatment and the type of surgery are based on clinical, radiological, and neuropsychological parameters.

In Alberta, patients with neck pain seen by their primary physicians are referred to orthopedic surgeons or neurosurgeons for evaluation of the need for surgery. Dr. Hurlbert noted that the final decision regarding the necessity of the surgery (either cervical fusion or ACDA) is made by the surgeon.

### 4.3 Health System Capacity

#### 4.3.1 Workforce Capacity

Using the hospital claims data provided by AHW, we estimate that the number of physicians performing cervical fusion or ACDA (more than 7 procedures) in Alberta is 24. There are 124 physicians who claim anesthesiology services and 19 surgical assistants. ACDA may be performed by neurosurgeons or by orthopedic surgeons. There are 34 neurosurgeons
and 19 orthopedic surgeons specialized in back and spine issues in Alberta.

Training sessions are offered by the companies producing the artificial cervical discs. Synthes Spine offers an 8 hour course, covering the design philosophy, indications and patient selection, a case review, and surgical technique for the implantation of the ProDisc-C. During this course, the surgeons participate in classroom lectures, case study reviews, and hands-on bioskills labs. They also review a real-time surgery moderated by experienced surgeon faculty. Cervitech Inc offers a similar Physician Training program for implanting the PCM. This program includes a presentation of surgical technique (including hands on with surgical instruments); a didactic overview, often conducted by a surgeon with PCM experience; hands on experience with the instruments in a cadaveric setting, or minimally in a “sawbones” workshop; and observation of an actual surgical case via a visit to live surgery or presentation of a video of live surgery.

According to Dr. John Hurlbert, our expert advisor, these courses are optional. Nevertheless, the companies producing the artificial cervical discs will not provide the disc if the surgeon performing the ACDA has not acquired the necessary experience with another surgeon considered to be an expert in implanting the disc.
5 Technology Effects and Effectiveness

5.1 Current Context

5.1.1 Technology

Table 1 presents the characteristics of the main artificial cervical devices used for cervical arthroplasty in North America.

The Bryan Cervical Disc is a non fusion artificial disc prosthesis. It is implanted between two vertebrae in the neck matching the depth of the endplate in a pocket milled into the bone. Two wings extend up and down on the anterior edge. The Bryan Cervical Disc is not fastened to the vertebrae with screws. The disc is made up of: two titanium shells, two titanium retaining wires, polyurethane nucleus, polyurethane sheath, and two titanium seal plugs. It is available in 5 diameters – 14mm, 15mm, 16mm, 17mm, and 18mm. The polyurethane nucleus component fits between and moves with respect to the two shells. The titanium alloy (ASTM F136) shells have inward facing shell posts that fit into flared holes in the nucleus for a controlled range of motion and for soft stops at the extremes of the full flexion/extension, full lateral bending and maximum translation.
During normal motion (approximately $\pm 4.9^\circ$ flexion/extension, $\pm 4.0^\circ$ lateral bending) the shell posts do not contact the nucleus.

The **Porous Coated Motion (PCM) implant** is comprised of upper and lower endplates made with a special material called cobalt chrome alloy. The metal endplates are bonded to the vertebrae, and the area between the two endplates acts like a ball and socket, allowing the upper half to slide and rotate forward and backward.

The **Prestige Cervical Disc system** is a two-piece articulating metal device that is inserted into the intervertebral disc space at a single cervical level using an open anterior approach. The device is manufactured from wrought type 316 stainless steel (ASIM F-138) and consists of two metal plates which interact via a ball and trough mechanism. The superior component of the implant contains the ball portion of the mechanism, and the inferior component incorporates the trough portion. The flat portion of each component, which contacts the vertebral endplate, is aluminum oxide grit blasted. Each component is affixed to the vertebral body by two bone screws through an anterior flange. The bone screws are held in place by a lock screw mechanism. In the implanted disc, the bone screws are divergent in the cephalic/caudal direction and convergent in the medial/lateral direction. The device assembly was designed to allow the following motions *ex vivo*: a minimum of 100 motion off the neutral
position in flexion/extension and lateral bending, unconstrained axial rotation, and 2mm of anterior/posterior translation.

The **ProDiscTM-C Total Disc Replacement** is made up of three components:

- an inferior CoCrMo (cobalt chromium molybdenum) alloy plate with a midline keel orientated anterior-posterior that is anchored into the endplate of the inferior vertebral body
- an Ultra High Molecular Weight Polyethylene (UHMWPE) insert that is pre-assembled snap-locked into a tray detail in the inferior CoCrMo alloy plate and provides the inferior convex bearing surface
- a CoCrMo alloy plate with a midline keel that anchors to the superior vertebral body and has a highly polished concave bearing surface that articulates with the convex UHMWPE spherical dome.
The endplate footprints range from 15-19 mm wide (medial-lateral) x 12-18 mm deep (anterior/posterior). Each endplate size is available in three disc heights (5, 6, and 7 mm) to accommodate a range of vertebral sizes. The bone contacting surfaces of the inferior and superior plates as well as both keels are titanium plasma spray coated. The maximum range of motion allowed by the ProDiscTM-C Total Disc Replacement device design is 200 in flexion/extension (17.50 for the 5mm Large, Large Deep, Extra Large, and Extra Large Deep implants), 200 in lateral bending (17.50 for the 5mm Large, Large Deep, Extra Large, and Extra Large Deep implants), and the device is unconstrained in axial rotation as measured through in vitro testing.

5.1.2 Procedural Comparison

Anterior cervical discectomy and fusion (ACDF) is currently considered definitive surgical treatment for symptomatic single-level DDD of the cervical spine. Following this procedure, the pressure on the spinal nerves is relieved (decompression) by blocking the movement in the cervical spine. The procedure involves an anterolateral surgical approach, decompression of the affected spinal level, discectomy, and emplacement of either autograft or allograft bone in the intervertebral space to stimulate the fusion between the vertebral endplates. A metal anterior cervical plate is attached to the adjoining vertebral bodies to stabilize the fusion site, maintain neck lordosis, and reduce the need for prolonged postoperative brace application that is needed following ACDF without an anterior plate.

Mummaneni et al described the ACDA technique used by their surgical team. The patient is positioned in supine and the neck is extended and supported dorsally with a roll to position the neck in a neutral or mildly lordotic position. The shoulders are caudally retracted to help with intraoperative fluoroscopic visualization. Before starting the surgery, the patient is
administered a prophylactic antibiotic and a steroid (like Dexamethasone) to help ameliorate intraoperative nerve root irritation. The anterior cervical approach is performed through a transverse right-sided incision made through a preexisting skin crease.

After the standard anterior cervical exposure is performed, a localizing fluoroscopic x-ray is obtained to identify and confirm the levels of intended arthroplasty. After localization of the appropriate levels, a self-retaining anterior cervical retractor is placed under the elevated edges of the longus colli muscles. Vertebral body distraction pins may be placed to enlarge the disc space, and all visible discs are removed from the endplates to expose the posterior longitudinal ligament. The posterior longitudinal ligament is also removed. If the disc space has significant spondylotic changes, a power drill may be used to remove the disc and osteophytes. Generous bilateral foraminotomies are created and care is taken to ensure removal of the uncovertebral joints bilaterally. Failure to adequately remove the uncovertebral joints may lead to new postoperative radiculopathy exacerbated during flexion of the implant. The distraction pins are removed, and the appropriate implant trial is then placed snugly into the disc space to confirm the size of the disc that will be placed later.

The surgeon should avoid oversizing the implant trial because an oversized artificial disc may limit the normal range of motion. Anteroposterior and lateral fluoroscopic images are usually obtained to ensure that the trial fits and is centered in the disc space. The disc is then inserted, taking care to align its rails with the channels cut into the endplates. The inserter is removed and the final impactor is used to seat the disc into position. Lateral and anteroposterior fluoroscopy is generally used again to confirm appropriate positioning and size of the implant.
Before leaving the operating room, the patient's neck is flexed and extended manually on the operating table while imaging the implant with lateral fluoroscopy to ensure appropriate motion of the device.

The ACDA procedure is performed at all cervical levels, excluding the C1-C2 and C2-C3 levels. Dr. Hurlbert explained that C1-C2 vertebrae do not have a true disc space; instead they articulate through the odontoid process and the lateral masses. Also, C2-C3 level almost never becomes involved in degenerative change, at least in a way that causes recognizable symptoms. Dr. Hurlbert noted that as the technology behind artificial discs improves and they eventually become used in trauma settings over the next decade or two, we might see ACDA procedures performed at the C2-C3 level, but the application will be extremely rare.

5.1.3 Health Canada Approval


5.2 Condition(s) and Limitations

5.2.1 Best Practice

Guidelines

There are no guidelines for ACDA specific to Alberta or Canada.

Selection of patients

The experts involved in the selection of cervical surgery patients in Alberta enumerated several indications for ACDA: non spondylotic neck with good or some range of motion at the level in question; radiculopathy, myelopathy from disc herniation predominantly; cervical
disc herniation or stenosis with radicular symptoms of greater than 2 months duration and unresponsive to nonsurgical treatment; cervical disc herniation with significant neurologic deficits (spinal cord injury, significant motor weakness or sensory loss); cervical stenosis with myelopathy (of any duration); previous fusion at adjacent level. High intensity of pain at the cervical level, spondylolisthesis (instability), facet arthritis, posterior spinal canal compression (may not get adequate decompression from anterior procedure), active infection, spinal tumor/metastasis, osteoporosis, significant spinal deformity, stenosis requiring corpectomy/vertebrectomy, acute vertebral fracture were cited as contraindications for ACDA. A possible indication for ACDA is axial neck pain confirmed to be from DDD. According to the experts consulted by our team, this is a rare if not nonexistent indication in Canada.

We reviewed the indications for ACDA reported in the literature. The indications for anterior ACDA are the same for cervical decompression: radiculopathy or myelopathy caused by either one or two levels of anterior cervical compression (central or paracentral disc herniation, spondylolisthesis). The goals are to restore the intervertebral disc height and neuroforaminal height to prevent recurrence of neurologic compression. Before considering total disc replacement, the patient should have failed to improve after an appropriate course of non-operative care, including active rehabilitation, activity modification and medication.

After a review of the literature, McAffe et al compiled a list of indications and contraindications for ACDA candidates. In 2005, Chi et al listed clinical indications and contraindications for ACDA derived from the inclusion and exclusion criteria used in FDA investigational studies of artificial cervical discs. In 2006, Goffin defined several categories of complications, the first one being wrong indications for artificial disc surgery. In this category,
Dr. Goffin included seven contraindications for ACDA. Recently, Auerbach et al \(^{46}\) retrospectively reviewed the charts of 167 patients who underwent cervical spine surgery and summarized the indications and contraindications to cervical total disc replacement. The indications and contraindications reported by these authors are presented in Table 2.

Mummaneni et al \(^{43}\) mention osteoporosis, cervical spondylosis with incompetent facets, cervical trauma with ligamentous or facet injury, cervical kyphosis and three or more levels of cervical spondylosis as contraindications for cervical arthroplasty. These authors note that patients with severe multilevel spondylosis or ankylosis are unlikely to experience the benefits of arthroplasty because their baseline cervical range of motion is very limited.

In a recent paper, Brown and Heller \(^{47}\) discuss patient selection for ACDA. In their opinion, the ideal cervical disc replacement candidate “should have a one- or two-level disc herniation with minimal spondylosis. The symptoms and signs should correlate well with the preoperative imaging studies. They should have failed to respond to at least 6 weeks of nonoperative management. The spinal cord or nerve root compression should be documented by magnetic resonance imaging and/or computer tomography (CT)/myelography. The patient’s chief complaint should be radicular or myelopathic symptoms, not axial neck pain.”

### 5.2.2 Other Jurisdictional Guidelines

The American Academy of Orthopedic Surgeons provided FDA with a draft guidance document for pre-clinical and clinical trial design for cervical and lumbar disc replacement systems (available at [http://www.fda.gov/ohrms/dockets/dockets/05d0113/05d-0113-gdl0001-01-vol1.pdf](http://www.fda.gov/ohrms/dockets/dockets/05d0113/05d-0113-gdl0001-01-vol1.pdf)) that lists the following indications and contraindication for disc replacement:

**Indications for Disc Replacement**

The primary indication for disc replacement is discogenic pain in a patient who displays
Contraindications for Disc Replacement

In addition to the general medical contraindications for any surgical procedure, a number of specific contraindications have been identified in the literature. These include:

1. Central Spinal Stenosis
2. Lateral Recess Stenosis
3. Facet arthrosis
4. Spondyloysis
5. Spondylolisthesis (Some grade I spondylolisthesis may be appropriate for some designs.)
6. Herniated nucleus pulposus with radiculopathy
7. Scoliosis (curve magnitude greater than ten degrees)
8. Osteoporosis
9. Post-operative pseudarthrosis
10. Post-operative deficiency of posterior elements resulting in incompetence of the facet joints

The FDA and the Center for Devices and Radiological Health provided indication/contraindications for the use of the ProDisc-C total disc replacement device in their report (obtained from Synthes Spine, Appendix 4).
5.3 Effects/Effectiveness

5.3.1 Safety

The anterior surgical approach to cervical DDD involves dissection and retraction of numerous vital vascular, respiratory, neural, and intestinal structures. The following complications following cervical surgery have been cited\textsuperscript{27} in the literature:

- Vocal cord paralysis from recurrent laryngeal nerve injury manifests as a hoarse, weak voice with a risk of aspiration due to inability to completely close the larynx. When symptoms persist for longer than 6 weeks, referral to an otolaryngologist is recommended for evaluation and possible vocal cord injection.

- Sympathetic chain injury manifests as ipsilateral miosis, ptosis, and anhidrosis.

- Dysphagia is estimated to occur transiently in about 8\% of the patients.

- Esophageal lacerations occur in 0.25 – 0.7\% of the patients.

- Vascular injuries (carotid sheath contents, superior and inferior thyroid arteries, and vertebral artery) are rare but can have important sequelae.

- Spinal cord injury, with an incidence of 0.1\% to 0.64\%, is the most devastating complication.

- Psuedoarthrosis occurs with a frequency of 88-90\% (single-level fusion), 73-80\% (two-level fusion) and 70\% (three-level fusion).

- Bone graft site complications (injury to superficial nerves, superior gluteal artery injury, iliac crest fracture) occur with an incidence of 20\%.
One of the safety issues reported with other devices is that the wearing of metal-on-metal implants result in the release of metal ions in the body. There have been no studies to show a higher risk of cancer, hypersensitivity, or other adverse effects of these metal ions. Among the cervical disc replacement devises, only the Prestige cervical disc has a metal on metal design, all others (Bryan, PoDisc-C and PCM artificial cervical discs) having a metal on polymer design. There is no literature on the release of metal ions by specific cervical devices.

Metallic debris has been documented in the paraspinal soft tissues of patients with posterior lumbar instrumentation, with particularly high amounts found in patients undergoing revision procedures for pseudarthrosis. Systemic metal ion distribution has been reported as elevated serum levels of nickel and chromium in patients with stainless steel spinal instrumentation. One recent study reports a significantly higher titanium concentrations in subjects with titanium spinal implants and titanium interbody devices when compared to controls.

### 5.3.2 Effectiveness in case series

We included in our review 14 case series. These studies provide low GRADE of evidence (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).

We categorized the case series according to the number of cervical levels ACDA was performed. Only one study did not specify the number of cervical levels included. The authors of this study reported a significant improvement in NDI, pain and SF-36 scores after 4 years of follow-up in patients implanted with the Prestige cervical disc.
Single-level ACDA

Three case series included patients with one level ACDA. The ACDA was performed using the Bryan cervical disc. The authors reported significant improvement in clinical outcomes at 12 months and 24 months follow-up.

One and two-level ACDA

Seven case series included patients with one or two-level ACDA. In five studies, the authors used the Bryan cervical disc, while two studies reported observational data on Pro-Disc C. All seven studies reported significant improvement in clinical outcomes at 12 and 24 months. One study involving the ProDisc-C reported a high rate of spontaneous fusion at 12 months postsurgery.

Up to four-level ACDA

Two case-series report data on patients with up to four-level ACDA, using the PCM cervical disc. One study reports significant improvement in clinical outcomes at 12 months follow-up. A subsequent publication by the same authors reports that the improvement in clinical outcomes at 3 years of follow-up was more significant in multiple-level than single-level ACDA patients. One study reports data on up to three-level ACDA patients, using the Bryan cervical disc. The authors noted a significant improvement in pain scores at 12 months of follow-up in patients that have already undergone cervical fusion or posterior foraminotomy.

5.3.3 Comparative Benefits and Risks

5.3.3.1 Comparative Benefits

The summary of the methodological quality assessment of these RCTs using the Cochrane Musculoskeletal Group Methodological Assessment Tool is presented in Table 6.
These RCTs provide high GRADE level of evidence (further research is very unlikely to change our confidence in the estimate of effect) on the single level ACDA compared to single level cervical fusion.

**Qualitative analysis**

**Coric et al. 2006**

This is a report from a single site of the Bryan FDA multi-center RCT that is still ongoing. Based on the analysis of the data from 33 patients (17 patients randomized to the Bryan disc treatment arm and 16 patients to the fusion treatment arm), the authors concluded that while the results are encouraging (similar improvements in the clinical parameters were observed in both groups, while in the ACDA group the motion was preserved at the treated level), long-term follow-up is needed to validate the theoretical advantage of arthroplasty – a reduction in adjacent-level degeneration.

The authors did not report details of allocation concealment, the outcomes of the patients who withdrew, analysis performed, blinding of outcome assessors, study participants and treatment providers. A table of demographic data by treatment group was included, but no statistical tests were performed to evaluate the comparability of the two groups at baseline. The inclusion/exclusion criteria were not reported. The clinical outcomes are presented as plots at different point in time during follow-up, but the tables of data used to construct the plots are not reported (including sample size used in the analysis, means and standard deviations of outcomes). There is no indication that statistical tests to compare the changes in clinical outcomes between the two treatment groups were performed.

We did not include this report in our meta-analysis because the data reported by the authors were insufficient.
Mummaneni et al. 2007

This is a report of an FDA-regulated IDE study that evaluates the safety and effectiveness of the PRESTIGE ST Cervical Disc System. The study is ongoing and this article reports an interim analysis of 250 patients at 2 years of follow-up. The authors concluded that the Prestige ST disc replacement maintains physiological segmental motion, and is as safe and effective as fusion for the treatment of cervical DDD.

The inclusion/exclusion criteria are clearly stated. The comparability of the two treatment groups at baseline was assessed, and results of the Fisher’s exact test reported. The loss to follow-up at 2 years was higher than 20% in the fusion group (follow-up rate of 75%), which affects the generalizability of the results. The authors did not report details of the outcomes of the patients who withdrew, blinding of the outcome assessors, study participants and treatment providers. Plots and tables present the mean values of the clinical outcomes of the two treatment groups, but not the standard deviations and sample size. It is not clear whether the same patients are included in all comparisons.

In conclusion, although the results are encouraging, the collection of information is not complete. In addition, the presentation of the results precludes the estimation of effects that can be used in a meta-analysis with any degree of confidence.

Murrey et al. in press

This article reports the results of an FDA-regulated IDE study evaluating the safety and effectiveness of the ProDisc-C compared to fusion. The clinical outcomes and adverse events of 209 patients up to 2 years of follow-up were reported. The authors concluded that the ProDisc-C total disc replacement is viable surgical option for patients with symptomatic cervical disease and may have both short and long-term benefits compared to the current standard of care.
The inclusion/exclusion criteria are clearly stated. The comparability of the two treatment groups at baseline was assessed, and results of the Fisher’s exact test reported. The authors did not report details of the outcomes of the patients who withdrew and the blinding of the outcome assessors, study participants and treatment providers.

Results are reported as percentage of patients experiencing overall success (defined as NDI success, neurological success, device success and absence of adverse events related to the implant or its implantation) at 24 months. The trial was initially conceived and powered as a non-inferiority trial using a dichotomized composite endpoint. The non-inferiority margin was 10%. Nevertheless, the manuscript generally reports tests of superiority. At some points in time and on some measures, the outcomes for the ProDisc-C patients are superior to the outcomes for the fusion patients, but there is little evidence of superiority for the ProDisc-C patients. Plots with distributions of scores are presented in this manuscript, but the standard deviations of these scores are not presented (although they presumably are presented as error bars in the plots - no description is given for what the error bars represent). More importantly, change scores and variability of change scores are not presented.

Nabhan et al. 2007

This is an RCT of effectiveness of the ProDisc-C prosthesis compared to fusion in 49 patients with radiculopathy after 1 year of follow-up. The authors concluded that the cervical spine prosthesis can maintain segmental micromotion within 1 year after surgery and the clinical results of ACDA and fusion are similar.

The inclusion/exclusion criteria are clearly stated. The comparability of the treatment groups at baseline was not assessed and no demographic data was reported. The authors did not report details of the outcomes of the patients who withdrew, blinding of the outcome assessors, study participants and treatment providers.
The authors reported the means and standard deviations of the clinical outcomes assessed at each point in time for each group and calculated the statistical significance of change in clinical outcomes between baseline and the follow-up point in each treatment group. The data allowed us to calculate the statistical significance (the t-tests) of the mean differences between the control and the intervention groups ($\mu_C - \mu_I$):

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>$\mu_C - \mu_I$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck Pain</td>
<td>2.00</td>
<td>0.042</td>
</tr>
<tr>
<td>Arm Pain</td>
<td>2.00</td>
<td>0.02</td>
</tr>
</tbody>
</table>

These results provide statistical evidence that the change in neck pain and arm pain scores were larger in the ACDA group than in the fusion group (p-values < 0.05), suggesting ACDA has better clinical outcomes than fusion at 1 year of follow-up. Nevertheless, the baseline Neck Pain and Arm Pain scores were not taken into account (because of lack of adequate information reported), which might affect the significance of the difference in change from baseline between the two groups.

Sasso et al. 2008

This is a report from 3 sites of a multicenter FDA IDE trial for the Bryan Cervical Disc. One hundred and fifteen patients were enrolled in the trial (56 patients in the ACDA arm and 59 in the fusion arm) and followed prospectively for 2 years. The authors concluded that cervical arthroplasty with Bryan cervical disc compares favorably with fusion.

The inclusion/exclusion criteria are clearly stated. The authors reported demographic data for both treatment groups and performed statistical tests to compare them. The two treatment groups were similar at baseline. The authors did not report details of the outcomes.
of the patients who withdrew, blinding of the outcome assessors, study participants and treatment providers.

At 1 year, only 6 patients were lost to follow-up (5%). The loss to follow-up increased dramatically at 24 months (71 patients in total at 24 months, 61%). This has the potential to introduce “selection bias”, and there is evidence of selection bias in the tables reported. In the absence of selection bias, the effects observed at a given point in time would be expected to be the same as a comparison of changes at 24 months. In the presence of selection bias, the “difference of differences” approach to the analysis would be preferable, as it would address differences in baseline characteristics. In their manuscript, Sasso et al. test differences at different points in time without adjusting or accounting for differences in scores at baseline. However, they provide enough information to calculate the means differences between the control and the intervention groups (\( \mu_C - \mu_I \)) at 24 months. We calculated the mean differences for all the clinical outcomes reported by the authors. The tables below provide the appropriate estimates of effect for this study.

<table>
<thead>
<tr>
<th></th>
<th>12 months difference</th>
<th>24 months difference</th>
<th>24 month difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \mu_C - \mu_I )</td>
<td>p-value</td>
<td>( \mu_C - \mu_I )</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>-4.10</td>
<td>0.0349</td>
<td>-5.90</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>-1.80</td>
<td>0.282</td>
<td>-5.90</td>
</tr>
<tr>
<td>NDI</td>
<td>7.90</td>
<td>0.012</td>
<td>11.5</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>9.80</td>
<td>0.057</td>
<td>17.10</td>
</tr>
<tr>
<td>Arm pain</td>
<td>10.30</td>
<td>0.036</td>
<td>10.10</td>
</tr>
</tbody>
</table>
From this table, it is evident that although there is statistical evidence for differences between groups at 24 months that favors the Bryan disc, there is no longer statistical evidence for these effects when tests account for the baseline scores.

Meta-analysis of outcomes

We included in our meta-analysis data from one published report on the Bryan cervical disc and unpublished data on Prestige and ProDisc-C provided by the companies (Medtronic Sofamor Danek USA, Inc. and Synthes Spine) manufacturing these devices. Because different devices were used for each trial, we chose to use a random effects model for each outcome, even if there was no statistical evidence of heterogeneity. Where possible, we used a comparison of changes from baseline as a measure of treatment effects. The only exceptions were for the ProDisc-C trial. For this trial, the SF-36 Physical Component Score, the SF-36 Mental Component Score, and the Neck Disability Index were not reported with changes from baseline. Consequently, for these measures in this trial, we used the mean comparison at 24 months as the measure of effect. A DerSimonian-Laird approach for continuous outcomes was used for calculating weights for the random effects models.

SF-36

The SF-36 Physical Component Score (PCS) and Mental Component Score (MCS) each have a population mean value of 50 and standard deviation of 10. For each of these scales, higher scores represent better function. Analysis of the SF-36 Physical Component Score (PCS) provided statistical evidence that the disc devices were superior to fusion (Weighted mean difference = 1.785; 95% CI = [0.0636; 3.5064]; z = 2.0324; P = 0.0421). Analysis of the SF-36 MCS did not provide evidence of a difference in treatment effects between cervical discs and

Analysis of the SF-36, neck and arm pain, and NDI scores did not provide evidence of a difference in treatment effects between cervical discs and
provide evidence of a difference in treatment effects between cervical discs and spinal fusion.

Analysis of the SF-36 PCS and NCS are presented in tables 7 and 8, and figures 1 and 2.

**Neck pain and arm pain**

The intensity of the neck pain and arm pain were measured using the visual analogue scale (VAS). The VAS used was a 100 mm horizontal line with polar anchors of no pain (0) and worst possible pain (100). Therefore, statistical evidence of a negative difference in the weighed mean scores would provide evidence of superiority of the cervical disc devices. At the 5% level of significance, the random-effects meta-analysis of neck and arm pain did not provide evidence that patients receiving cervical discs devices differed in the degree of improvement in pain when compared to patients who received spinal fusion. Results for neck and arm pain are presented in tables 9 and 10, and figures 3 and 5.

**Neck Disability Index**

The neck disability index (NDI) is a 10 item questionnaire with a maximum score of 50. Scores between 0 and 4 represent no disability, and scores of 35 or over represent complete disability. Statistical evidence of a negative difference in weighted mean scores would provide evidence of superiority of the cervical disc devices. Results are presented in table 11 and figure 5. At the 5% level of significance, the random-effects meta-analysis of neck and arm pain did not provide evidence that patients receiving cervical discs devices differed in the degree of improvement in the NDI when compared to patients who received spinal fusion.

We included in our review a non-randomized comparative study. This study provides moderate GRADE level of evidence (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate).
Wigfield et al. 2002

The authors conducted a prospective, nonrandomized study of 25 patients (12 in the ACDA group, 13 in the fusion group) with single level degenerative cervical disease. Comparison of the NDI scores showed a statistically significant improvement in the ACDA group. The improvement in the fusion group was not statistically significant. This study showed that the adjacent-level movement has increased in the fusion patients compared to ACDA patients at 12 months of follow-up. Nevertheless, the results of this study do not clarify whether ACDA has a protective influence on adjacent intervertebral discs.

The results of this study should be considered with caution. The authors did not adjust for the baseline NDI scores, which were higher in the ACDA group. Moreover, the selection of patients in a nonrandomized fashion may introduce selection bias and affect the generalizability of the results.

We also included in our review four HTA reports. The evidence presented and the conclusions that emerged from these HTA assessments are summarized in Table 12.

National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance

The NICE guidelines regarding the prosthetic intervertebral disc replacement in the cervical spine were developed based on a rapid literature review performed in 2005. The authors included in their review 2 RCTs (6 months of follow-up) and 3 case series that reported clinical data on the Prestige I, Prestige II and Bryan cervical disc arthroplasty performed in 165 patients.

The resulting NICE guidance stated that the evidence available suggested that there were no major safety concerns about the use of prosthetic intervertebral disc replacement in the cervical spine, and there was evidence of short-term efficacy.
Ontario Health Technology Advisory Committee (OHTAC) update on the artificial disc for lumbar and cervical degenerative disc disease ²

This HTA report is an update of a previous report produced in 2004. The authors performed a literature search of articles published between 2003 and September 2005.

The report included an overview of 6 case series that reported observational data on 192 Bryan cervical discs implanted. The authors noted the low quality of the sparse evidence available on effectiveness and safety of ACDA and concluded that the effectiveness and safety of ACDA could not be determined.

Blue Cross and Blue Shield Association report on artificial disc arthroplasty for treatment of degenerative disc disease of the cervical spine ⁷¹

This report published in February 2008 focused on the Prestige ST cervical disc arthroplasty compared to fusion. The authors reviewed the IDE study reported by FDA, which involved 265 patients receiving the Prestige ST cervical disc.

The reviewers noted that although the study results consistently demonstrated statistical noninferiority for ACDA versus fusion in all three primary outcome variables, and for the overall success composite outcome, the neurological status was the only primary outcome variable for which statistical superiority was shown. However, quantitative data on the neurological status were not available, which precluded the analysis of its clinical meaning and relevance. Further, the study failed to demonstrate statistical superiority for ACDA in terms of the NDI. Finally, failure to blind patients and physician outcomes assessors to the study treatment allocation could have biased the study results, favoring disc arthroplasty over fusion.

The authors of the report noted that the evidence from the IDE trial did not permit conclusions on the long-term performance of ACDA and adverse events. The available...
evidence also was insufficient to permit conclusions as to whether or not ACDA affected the postsurgical development of adjacent-level DDD. By contrast, conclusions on the relative safety of cervical disc arthroplasty appeared sufficiently supported in the short term. Nevertheless, the evidence presented in the IDE trial did not permit conclusions as to whether artificial intervertebral disc arthroplasty for the cervical spine improved the net health outcome or was beneficial as an established alternative.

**Artificial intervertebral disc replacement (AIDR). Report released February/March 2006 by the Medical Services Advisory Committee (MSAC), Australia**

This report reviewed the clinical effectiveness, safety and cost effectiveness of lumbar and cervical arthroplasty.

Evidence for the effectiveness of cervical AIDR versus cervical spinal fusion was derived from one RCT. The conclusion from the RCT was that the Prestige II disc is a viable alternative to cervical spinal fusion. The authors of the report identified the following limitations of the RCT:

• A limited number of participants were enrolled.

• The trial did not report full data and measures of variance at all time points.

• The trial included relatively short-term follow-up.

• The participants, investigators and outcome assessors were not blinded to treatment, which, combined with the relatively subjective nature of many of the outcomes assessed, may have led to bias in the results obtained.

The safety of cervical AIDR was assessed from one randomised controlled trial (RCT) comparing ACDA and cervical spinal fusion, 11 case series and one health technology assessment (HTA) report. No statistically significant differences in the total number of adverse events experienced by participants allocated to cervical ACDA and those randomised to
cervical spinal fusion were observed. The adverse events reported in the case series reviewed included new or worsening pain, haematomas, temporary dysphonia or other transient vocal cord problems, revision decompression surgery, migration or suspected migration of the prosthesis, adjacent level surgery and removal of the prosthesis with or without subsequent cervical spinal fusion. Each of these adverse events occurred at a rate of less than 14 per cent in each of the individual case series, with the exception of one study in which all participants were reported to experience transient dysphagia. Similar adverse events and rates of adverse events were reported in the identified HTA report.

Cervical AIDR was found to be more costly than cervical spinal fusion, irrespective of the fusion method used.

In the absence of adequate evidence of effectiveness, MSAC recommended that public funding for AIDR in the cervical spine should not be supported.

5.3.3.2 Comparative risks

Anderson et al 73 report the adverse events and reinterventions in the FDA approved IDE RCT comparing one level ACDA with Bryan cervical disc to one level cervical fusion. Four hundred sixty-three patients with cervical radiculopathy and/or myelopathy were randomized to receive either ACAD or fusion. The authors compared the rates of adverse events in the two investigational groups using chi-square analysis. There were no statistically significant differences in the rates of anesthesia, medical, technical, and neurological adverse events between the two groups. Overall, more events (anesthesia, medical, technical, surgical and acute neurologic change) occurred in the ACDA group primarily from higher incidence of dysphagia, cardiac related events and more superficial wound infections. None of these were rated as severe, life threatening/disabling or fatal. Significantly more life threatening/disabling
and fatal events (medical, surgical and outcome related) occurred in the fusion group. With regard to reinterventions, there were significantly more reinterventions in the fusion groups compared to the ACDA group. The authors concluded that the overall safety was clinically similar between the two treatment groups.

Mummaneni et al.\textsuperscript{43} reported the number of reinterventions and the adverse events occurring in each treatment group of an FDA approved IDE RCT comparing ACDA with the Prestige cervical disc to fusion. Though no statistical tests were performed, the authors concluded that ACDA seems to be as safe as fusion for the treatment of one level cervical DDD.

The cervical fusion procedure involves emplacement of either autograft or allograft bone in the intervertebral space to stimulate the fusion between the vertebral endplates. Allograft bone has several drawbacks, including risk of infectious disease transmission; possible immunological reaction to the allograft; and, possible limited commercial availability of appropriate graft material.\textsuperscript{74} The use of autograft bone in ACDF has potentially substantial morbidities at the harvest site, generally the iliac crest. These include moderate-to severe, sometimes prolonged pain; deep infection; adjacent nerve and artery damage; and, increased risk of stress fracture.\textsuperscript{75} These additional risks associated to the cervical fusion procedures need to be taken into account when comparing the risk profiles of ACDA and cervical fusion.

### 5.4 Delivery Context

#### 5.4.1 Delivery Considerations

The surgical techniques used for both ACDA and cervical fusion are similar up to the point of interbody fusion/arthroplasty.\textsuperscript{43,68} None of the authors of the articles reviewed noted
the need for new equipment for performing ACDA, except for the cervical disc itself. The expert consulted by our team (Dr. Hurlbert) confirmed that performing ACDA does not require additional equipment beyond cervical fusion. Currently, the ACDA procedures are performed only in hospital settings, because they require overnight staying.

5.4.2 Related procedures

We did not identify any related procedures or follow-up requirements specific to ACDA.

5.4.3 Implementation Considerations

Mummaneni et al\textsuperscript{43} compared surgical and hospitalization data of ACDA patients to cervical fusion patients. Statistical significant differences were noted in the operative time (1.6 hours for ACDA versus 1.4 hours for fusion), the average number of days in the hospital (1.1 days for ACDA versus 1 day for fusion) and the need to wear an external orthosis after surgery (31.2\% of ACDA patients versus 59.1\% of fusion patients). Similar findings were reported by Sasso et al\textsuperscript{68}, with statistically significant longer mean operative time (1.7 hours versus 1.1 hours), longer mean hospital stay (0.9 days versus 0.6 days) and higher percentage of patients wearing orthosis after surgery (40\% versus 92\%) in the ACDA group compared to the fusion group.

These statistical significant differences may not be clinically significant. According to Dr. Bouchard, a member of the Expert Advisory Group, “saving 0.1 day of length of stay is not significant unless we are dealing with a high volume procedure, which ACDA is not. Same goes for surgical times that are within 30 minutes of each other.” Moreover, Dr. Bouchard noted that the use of orthosis after surgery is highly variable from surgeon to surgeon.
The expert consulted by our team (Dr. Hurlbert) pointed out that to achieve spinal fusion, a bone graft is used to promote two bones growing together into one. The patient’s own bone will grow into and around the bone graft and incorporate the graft bone as its own. The bone graft is usually harvested from the patient’s iliac crest (autograft), technique that is associated with several complications (such as graft site chronic pain, infection, bleeding, damage to the lateral femoral cutaneous nerve and pelvis bone fracture).

6 Economic Evaluation

6.1 Literature Review Findings

The economic literature on ACDA is minimal. We found only one economic analysis of the impact of greater utilization of ACDA. Singh et al\textsuperscript{76} noted that initial pricing of $7,500 to $10,000 per implant has been projected for lumbar disc arthroplasty. They anticipated that spinal arthroplasty will capture 47.9\% of the U.S. market by 2010, or roughly $2.18 billion dollars – up from 2.8\% of the market in 2005.

Chi et al.\textsuperscript{44} noted that in the United States, as of 2005, the average cost of single or double level ACDA was between $10,000 and $15,000, with a device cost between $5,000 and $7,000. This was before any FDA approval of artificial disc devices, so the cost has potentially decreased since Chi’s analysis. Chi notes the U.S. market is roughly 150,000 fusions per year. Even if a small percentage of these switch to ACDA procedures, it would still be much greater than the Alberta market. Hence, Alberta, especially if the United States continues with further approvals of ACDA devices, is unlikely to adjust either world-wide demand or prices for these procedures.
Economic Analysis

6.1.1 Unit Costs

Data reported in this section were provided by Alberta Health and Wellness. The dataset ranges from fiscal years (April through March) 2004/05 to 2006/07, with physician claim data also available from April through February of fiscal year 2007/08. We analyzed cost data for patients were are living in Alberta and had either artificial disc replacement (Health Service Code 92.31R on the Alberta Health Care Insurance Plan), cervical disc fusion/discectomy at one level (procedures 92.31E and 93.01B), cervical disc fusion/discectomy at two levels (procedures 92.31M and 93.02A) or cervical disc fusion/discectomy at 3+ levels (procedures 92.3N, 92.31P and 93.02B) done in Alberta. Where applicable, the cost of fusions also includes anterior cervical plating for two, three, four or five vertebrae (procedures 89.78S, 89.78T, 89.78U, 89.78V, respectively) and harvesting of an autogenous bone graft (procedure 90.09B). We did not have data on clinical evaluations and examinations (procedures in the 03.* class) or decompression of the cervical spine.

Costs are broken down into two parts. One is hospital costs that are directly billed to Alberta Health and Wellness. The second part is physician and support costs, which are billed according to the Alberta Health Care Insurance Plan. All costs are adjusted to 2007 dollars, using the Statistics Canada CPI index for services in the province of Alberta.

Hospital costs are broken into five parts. Direct costs include salaries, drugs, medical and surgical supplies for services provided directly to patients, along with direct administration costs. Indirect costs are associated with general administration and support services. Drug
allocation costs are drugs not directly assigned to specific patients, while drug costs are patient specific. Supply costs include costs such as operating room supplies and drugs dispensed, which can be assigned directly to patients.

From Alberta Health and Wellness hospital cost data, 439 procedures have cost data available – 240 for one-level cervical disectomy fusions, 107 for two-level fusions, 82 for three-or-more-level fusions, and 10 for cervical artificial disc replacements. Of these, 137 procedures (with two being disc replacements) took place in 2004/05, while the rest took place in 2005/06. The breakdown of costs between the different cohorts is presented in Table 13. ACDA procedures are more expensive, in part due to the cost of the device. The cost of fusions increases as the number of levels increases. Direct and indirect costs are also slightly higher for ACDA than for fusions at the one-level. Median length of stay in the hospital ranges from 2 days for ACDA and one-level fusions, to 3 days for two-level fusions, to 4 days for three-level fusions. Caution must be exercised with these numbers, due to the low number of ACDA procedures with costing data recorded.

We obtained the personnel pay data from the Schedule of Medical Benefits, Part B, of the Alberta Health Care Insurance Plan (July 2008). Physician pay is set at a base rate, with additions for such items as working nontraditional hours. Adjustments are also made for other types of personnel (anesthesiologist, surgical assistant, etc) that file a claim for the type of procedures listed above.*

The costing breakdown is given in Tables 13 and 14. Fees for physicians completing ACDA procedures are relatively less expensive than one-level fusions. Fees go down as higher levels are done. This is due to the composition of the groups: 93.01B, occipital cervical fusion

* Most of the claims (988) in the four fiscal years (2004-2008) are for surgeons. The second most frequent claims are for anesthesiologists (802), followed by second qualified surgical assistants (119) and regular surgical assistants (58).
with instrumentation, has a higher base rate than an anterior cervical discectomy, and these procedures make up 5% of the one-level fusions. For two and three-level fusions, there are significant numbers of other cervical spinal fusions completed (codes 93.02A and 93.02B), which have lower base amounts than an anterior cervical discectomy at the same level.

In sum, the median amount spent on hospital and physician fees for ACDA procedures is $16,131. The median cost for a one-level fusion is $9,338, while the median cost for a two-level fusion is $11,720 and the median cost for a three-or-greater level fusion is $13,213.

The total estimated cost of fusion and ACDA procedures in fiscal year 2006/2007 was $4,382,472. This represents an increase of $689,396, or 18.6%, from the 2005/2006 total of $3,693,076.

The ACDA procedures and the fusion procedures, if they serve as substitutes, will result in expected costs seen in Table 15. There, two different cost assumptions are used – one, where all ACDA procedures will average $16,131 in 2007 dollars; and two, where differences in the costs between ACDA levels are similar to the cost differences between fusion levels. As this is a short-run analysis, the population is held constant. With the costs averaging out, having all fusions replaced by ACDA procedures will cost approximately $6.4 million, while having all cervical disc operations performed by fusions will cost $4.3 million. If the ACDA costs increase as the number of levels increase, then ACDA procedures will cost approximately $7.4 million.

Breaking down the number of procedures by the age of the patients, 15% of the procedures were performed on patients in their 30s, while 29% were performed on patients in their 40s, 27% in their 50s, and 24% on patients above 60 years old. The aging of the population in Alberta will probably lead to increase costs due to higher
demand. Medical cost inflation is also likely to occur, further increasing the total estimated costs.

The long run effects of having an ACDA procedure done are still unknown at this time. Most studies up to this point, such as Sasso et al., have reported up to two-year follow-up. Goffin et al. found, at one year, clinical success was 90% for ACDA with the Bryan disc. Nabhan et al. note that, as of 2007, it is still too early to judge whether ACDA is effective over the long-term. Hence, no economic impact can be determined from certain long range costs, such as fewer physician follow-up visits. From an individual’s perspective, a median of 101 days is needed off work to recover from ACDA, while cervical discectomy and fusion procedures need a median of 222 days to recover, producing economic savings from increased productivity and less disability benefits. The failure rate of these devices in the short-term appears to be relatively small, as Anderson et al. note that more cervical spine revisions occurred in a fusion group over a 24 month period following surgery. Post-24 months, the failure rate has currently not been analyzed, so potential costs from further procedures to replace the artificial discs in the long-term cannot be determined.

6.1.2 Costs of Services Avoided

We were unable to determine the long term cost of services that could be avoided by replacing cervical fusion with ACDA in Alberta, due to lack of provincial data on follow-up visits for the procedure.

ACDA procedures and fusions are likely to be offsetting. Anderson et al. note that ACDA has been developed as a substitute for fusion, with the main benefit of added motion. The demand for surgical treatment of neck pain varies depending upon age. Hence, the opportunity cost of ACDA will be the resources used in a fusion procedure.
Sasso et al.\textsuperscript{22} noted that ACDA patients report less pain than fusion patients, based off the neck disability index and SF-36 physical component at 24 months, to a 5\% significance level. This implies, for the short-run, that fewer resources will be needed in follow-up pain management when compared to cervical fusion. Again, due to the relatively short time frame, the critical question of whether this will continue for five or ten years, or for the life of the device, has not been answered in the literature.

Long-term costs and procedures (e.g. beyond two years) have not been determined yet in the literature. These potential costs include revisions of fusions due to arthritis or degeneration of neighboring discs, in which case further fusion or other medical follow-ups would occur. Chi et al.\textsuperscript{79} note that there is no long term data on the failure rate of artificial discs over a long time period, though cervical implants have smaller loads to bear than other artificial implants, such as the lumbar spine, hip or knee. Hence the amount of future health resources to be consumed on ACDA follow-ups cannot be determined.

\textbf{6.1.3 Demand Estimates}

The demand for surgical treatment of neck pain varies depending upon age. The prevalence of neck pain will be many times the demand, but nonsurgical visits will occur for both subpopulations – those that have surgery and those that don’t. The proportion of those with neck pain who go on to have either cervical fusion or disc replacement varies depending on the age. Table 16 shows the prevalence of surgery among Albertans, using 2006/2007 intervention figures and 2007 population estimates. Those in the 40 to 59 age brackets are most likely to have fusions, while younger individuals (30 to 39) have a higher likelihood of having an ACDA procedure completed.
The number of surgical procedures in Alberta increased from 161 (90 one level, 51 2-level and 20 3+ level) in 2004/2005 to 258 (162 one level, 51 2-level, and 45 3+ level) in 2007/2008 for fusion, and from 2 in 2004/2005 to 21 in 2007/2008 for ACDA. In Alberta, more than half (55%) of all procedures are done in Calgary region, and 44% are done in Capital Health region.

A main implication for future demand is whether artificial disc replacements are approved for patients with more potential complications such as older individuals, and for more spinal levels. As one gets older, while there is a slightly smaller rate of cervical fusions, fusions tend to be of 3 or more levels. These procedures are currently not done with artificial disc replacements, and hence would not adjust future demand for ACDA procedures.

Using Alberta Health and Wellness hospital claim data, the number of procedures can be calculated by type of procedure. The numbers are presented in Figure 6 by fiscal year, from April to March, with fiscal year 2007/08 ending in February.

The number of unique patients was 1008. Of those, 867 had one intervention recorded, 114 had two interventions recorded (i.e. two hospital or physician claims recorded separately), and 27 had three or more interventions recorded. The breakdown by gender was 596 men and 412 women. The region of residence is presented in Table 17, showing that residents of the Calgary Health Region had higher utilization rates for higher level fusions and ACDA than residents in the Capital Health Region, with rural residents more likely than urban residents to get a one-level fusion.

The number of procedures delivered in each region is presented in Table 18.† The numbers of all procedures increase markedly over time in all regions. Due to 2007/08 data still being processed, numbers for that fiscal year may appear artificially low.

Using the 2007 population estimate of 2,825,848 for those aged 15 and up in Alberta, the rate for these procedures is 14 per 100,000 individuals. Figure 7 shows the rates of fusion procedures and ACDA procedures over the three complete fiscal years. The rate of

† In all cases, the region of the provider (the physician) was the same as the region of delivery (the hospital).
interventions increases despite accounting for the increased population over the three years, suggesting that surgeries are a higher utilized option for individuals with neck pain.

6.1.4 Results of Economic Evaluation

ACDA procedures initially cost more, as noted above, at current demand levels. The difference is nearly $7,000 -- $16,131 for a one-level ACDA versus $9,388 for a one-level fusion. Two and three-level fusions increase in cost by 26% and 41%, respectively, over the cost of a one-level fusion. Follow-up costs cannot be accurately determined at this time due to the short follow-up period of studies analyzing the efficacy of the artificial discs. Relative health measures are not included in cost evaluations. The analysis will depend on the weight one places on how much or little pain a patient feels, as well as expectations of future medical cost inflation and increases in the patient population in Alberta.

7 Discussion

7.1 Assessment Limitations

The follow-up period of most of the studies included in this report is limited to 2 years (24 months), which precludes any conclusions on the long term effectiveness and safety of the ACDA procedure.

The economic impact from certain long range costs of ACDA, such as fewer physician follow-up visits, could not be determined because the lack of published data. The failure rate of these cervical devices is unknown, so potential costs from further procedures to replace the artificial discs cannot be determined.
In the absence of adequate data (economic and long-term clinical data), performing a cost-effectiveness analysis of ACDA compared to fusion was not possible.

### 7.2 Evolving Developments

The case series reviewed reported that clinical outcomes of single- or multiple-level ACDA are improving after two or more years of follow-up, suggesting that ACDA is a viable treatment option for cervical DDD. Several randomized controlled trials proved the statistical equivalence of single-level ACDA compared to single-level fusion in terms of effectiveness and safety. At this time, there is no data regarding the outcomes of multiple-level ACDA, compared to multiple-level fusion.

The main difference in the outcome of ACDA compared to fusion is the preservation of spine mobility. At this time, there is no evidence to support the hypothesis that preserving the mobility of the spine by using an artificial cervical disc provides a better long-term outcome than fusion by limiting the adjacent level DDD. The follow-up period of most of the studies included in this report is limited to 2 years (24 months), which precludes any conclusions on the long-term effectiveness and safety of the ACDA procedure. Several randomized controlled trials are ongoing, and more data will be available in the near future.

The Alberta Foundation for Medical Research released a paper in 2001, “Decisions on the status of health technologies, by David Hailey and Christa Harstall,” which dealt with the definition of experimental. They pointed out that according to Section 21 of the Alberta Health Care Insurance Act (Alberta Health Care Insurance regulations), it is the Minister who reviews the evidence and determines if a particular service is required or it is experimental or applied research. Also, the authors examined the role that dissemination may play. A new technology may be widely disseminated but with little scientific proof. They acknowledge that
devices and technologies, as compared to pharmaceuticals, may rapidly evolve through several versions and operator expertise.

In their review of coverage decisions, Hailey and Harstall comment favorably on the scheme outlined by Blue Cross Blue Shield Technology Evaluation program. Technologies are assessed against a framework of 5 criteria:

1. The technology must have final approval form the appropriate regulatory bodies
2. The scientific evidence must permit conclusions to be drawn concerning the efficacy of the technology based on health outcomes (emphasis on well designed and conducted investigations published in peer-reviewed journals)
3. The technology must improve the net health outcome (benefits must outweigh risks)
4. The technology must be as beneficial as any of the established alternatives.
5. The improvement must be attainable outside investigational setting.

Applying these criteria to the technology under review in this report, we noted that there are three cervical artificial discs approved by Health Canada (criterion 1), several completed trials which concluded that ACDA is at least as effective and safe as cervical fusion in short term (criteria 2, 3 and 4) and evidence from case series showing benefit of ACDA in typical surgical settings (criterion 5).

### 7.3 Impacts on Alberta Health System

ACDA can be considered as acceptable clinical practice for cervical degenerative disc disease (DDD). It is comparable to the alternative surgical approach, cervical fusion with respect to rates of complications, re-intervention rates and short-term safety. This is true for a
single level of fusion or arthroplasty. However, this Review does not permit such a conclusion, as yet, for multiple-level arthroplasty, for which experience and long-term outcomes are limited.

Sound neurosurgical expertise to perform this procedure exists in Alberta. Moreover, there are already established and utilized fee codes, which permit care selection by neurosurgeons and orthopedists (92.31R – artificial disc replacement, cervical disc; this is in addition to the anterior cervical discectomy and fusions for 1-4 levels).

While anterior cervical discectomy with fusion remains a well-established treatment for symptomatic cervical DDD, ACDA provides a similar degree of clinical improvement, does not differ in safety, does not require autologous bone graft with any morbidity this might entail, and does not require new equipment, other than the artificial disc itself. Regrettably, but not surprisingly, these outcomes cannot be confirmed in long-term follow-up studies, nor is it known whether ACDA affects future development of adjacent-level cervical DDD. Without this information, ACDA does not replace cervical fusion, notwithstanding comparative safety and effectiveness. Accordingly, and for these reasons, the clinical implications for Alberta would be to ensure appropriate training and competence in those who perform arthroplasty procedures; and, encourage the development of a comprehensive clinical practice guideline, which defines the indications or comparative features important to selecting arthroplasty over fusion; and, maintain a watching brief on long-term studies of arthroplasty to determine if the favorable features of short-term studies are retained, hence suggesting there will be increasing use of this technology.

The implications for Alberta from a cost perspective are not insignificant but need to be carefully integrated. Our attempt to account for the implications of ACDA shows that the one-level ACDA procedure costs the Province of Alberta more than the one-level fusion
procedure ($13,335 compared to $6,356). The number of surgical procedures in Alberta increased from 161 (90 one level, 51 2-level and 20 3+ level) in 2004/2005 to 258 (162 one level, 51 2-level, and 45 3+ level) in 2007/2008 for fusion, and from 2 in 2004/2005 to 21 in 2007/2008 for ACDA. These date show an increasing demand for these procedures, a trend that is expected to continue in coming years. The total cost to Alberta would be $6,371,745 if 100% of the cervical procedures performed in the Province were ACDA (assuming that one-level, 2-level and 3+ level ACDA have the same cost) and $4,280,577 if 100% of the cervical procedures were cervical fusion.

These data and assumptions must not be confused for an economic evaluation, which comprehensively considers all costs and all benefits for those receiving arthroplasty versus fusion. Accordingly, it would appear prudent to undertake a cost-effectiveness analysis of ACDA versus fusion, at least for single-level procedures, taken from a societal perspective, and inclusive of long-term outcomes, with particular emphasis on adjacent joint cervical disc degenerative disease.

8. Conclusions

Degenerative disc disease (DDD) of the spine includes a wide spectrum of degenerative abnormalities, either age-related or pathologic. The prevalence of DDD increases with age. An estimated 60% of individuals older than 40 years have radiographic evidence of cervical DDD. By age 65, some 95% of men and 70% of women have at least one degenerative change evident at radiographic examination. In Alberta, the prevalence of cervicalgia, cervical spondylosis with myelopathy and degeneration of cervical intervertebral discs remained constant from 2004 to 2007.
Artificial cervical disc arthroplasty (ACDA) is a surgical procedure that may replace cervical fusion in selected patients suffering from cervical DDD. The main outcome of ACDA that sets it apart from fusion is the preservation of the spine mobility. Fusion alters the normal biomechanics of the spine, which may result in the acceleration of the adjacent-level disease and subsequent reoperation. Preserving the range of spinal motion rather than fusing the degenerating spine may limit the progression of the disease to the adjacent level.

The literature reviewed showed that both ACDA and cervical fusion have similar complication and reintervention rates. Moreover, our meta-analysis of clinical outcomes using data from one published RCT and two sources of unpublished data confirmed the conclusions of the studies reviewed, demonstrating no significant difference in clinical outcomes between ACDA and cervical fusion at 2-year follow-up. The effectiveness and safety profiles of ACDA appear similar to that of cervical fusion in the short term. The data available show sufficient equivalence of clinical outcomes to conclude that ACDA is a viable alternative to cervical fusion.

The surgical techniques used for both ACDA and cervical fusion are similar up to the point of interbody fusion/arthroplasty. None of the authors of the articles reviewed noted the need for new equipment for performing ACDA, except for the cervical disc itself.

The number of cervical fusion and ACDA procedures performed in Alberta during the last four years shows an increase in the utilization of these procedures, even if the prevalence rates of cervicalgia and degeneration of the cervical intervertebral disc remained constant. Given the advances in the technology, the rapid spreading of the new technology, and the expected benefits of ACDA, we expect the increasing trend to continue in the following years.
In the absence of adequate data (economic and long-term clinical data), performing a cost-effectiveness analysis of ACDA compared to fusion was not possible. Therefore, we cannot determine at this time if ACDA is more cost-effective than cervical fusion.

There are several completed and ongoing trials that have proved that ACDA is at least as effective and safe as cervical fusion in short term. Hence, ACDA may not be considered an experimental procedure, but more data regarding the long term effectiveness and cost-effectiveness are needed to decide if it will replace the cervical fusion for the treatment of cervical DDD in the near future.
REFERENCE LIST


(40) Lied B, Sundseth J, Helseth E. Immediate (0-6 h), early (6-72 h) and late (>72 h) complications after anterior cervical discectomy with fusion for cervical disc degeneration. Discharge after 6 h is feasible. *Acta Neurochir* 150, 111-118. 2008.


TABLES
### Table 1. Artificial cervical disc devices

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Licensed in Canada</th>
<th>Material</th>
<th>Bearing Surface</th>
<th>Articulating Surfaces</th>
<th>Constraint</th>
<th>Center of Rotation</th>
<th>Fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan Cervical Disc System</td>
<td>MEDTRONIC SOFAMOR DANEK USA, INC.</td>
<td>YES 2003-05-06</td>
<td>Titanium alloy Polyurethane</td>
<td>Metal on polymer</td>
<td>2</td>
<td>Unconstrained</td>
<td>Mobile</td>
<td>Milled cavities Bone ingrowth</td>
</tr>
<tr>
<td>PCM* Artificial Cervical Disc Implant System</td>
<td>WALDEMAR LINK GMBH AND CO. KG</td>
<td>YES 2007-05-29</td>
<td>CoCrMo UHWPE</td>
<td>Metal on polymer</td>
<td>2</td>
<td>Semiconstrained</td>
<td>Fixed</td>
<td>Bone ingrowth</td>
</tr>
<tr>
<td>Prestige Cervical Disc System</td>
<td>MEDTRONIC SOFAMOR DANEK USA, INC.</td>
<td>NO</td>
<td>Stainless steel</td>
<td>Metal on metal</td>
<td>1</td>
<td>Semiconstrained</td>
<td>Mobile</td>
<td>Screw</td>
</tr>
<tr>
<td>PRODISC-C Total Disc Replacement</td>
<td>SYNTHES SPINE</td>
<td>YES 2007-10-02</td>
<td>CoCrMo</td>
<td>Metal on polymer</td>
<td>1</td>
<td>Semiconstrained</td>
<td>Fixed</td>
<td>Keel</td>
</tr>
</tbody>
</table>

PCM - Porous Coated Motion  
CoCrMo - Cobalt Chromium Molybdenum  
UHWPE - Ultra High Molecular Weight Polyethylene
# Table 2. Indications and contraindications for ACDA

<table>
<thead>
<tr>
<th>Author</th>
<th>Indications for ACDA</th>
<th>Contraindications for ACDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAfee et al</td>
<td>1. Cervical DDD requiring surgical treatment at one to three levels for symptoms or signs of cervical radiculopathy and/or myelopathy, with or without axial neck pain.</td>
<td>1. Ankylosing spondylitis, rheumatoid arthritis, ossification of the posterior longitudinal ligament or diffuse idiopathic skeletal hyperostosis.</td>
</tr>
<tr>
<td></td>
<td>2. Requires surgical treatment at one to three levels from C3 to T1 that has failed conservative treatment lasting at least 6 weeks for any or more of the following: (1) disc herniation with radiculopathy, (2) spondylotic radiculopathy, (3) disc herniation with myelopathy or (4) spondylotic myelopathy.</td>
<td>2. Insulin-requiring diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>3. The focal compressive lesion must be documented by computer tomography (CT), myelography or magnetic resonance imaging (MRI).</td>
<td>3. Prior cervical spinal infection</td>
</tr>
<tr>
<td></td>
<td>4. The patient must have an abnormal neurologic sign indicative of radiculopathy or myelopathy: abnormal reflex, sensation or motor strength in a corroborative dermatome or myotome.</td>
<td>4. Chronic steroid use or a medical condition requiring chronic steroid administration</td>
</tr>
<tr>
<td></td>
<td>5. 18 to 65 years of age</td>
<td>5. Morbid obesity</td>
</tr>
<tr>
<td>Chi et al</td>
<td>1. Presence of radiculopathy and/or myelopathy attributable to cervical disc degeneration at one to two levels</td>
<td>6. Pregnancy</td>
</tr>
<tr>
<td></td>
<td>2. Symptoms and findings referable between the C3 and C7 levels</td>
<td>7. Axial neck pain as the solitary symptom (Note: In contrast, a patient undergoing lumbar disc replacement who is an ideal candidate has isolated mechanical back pain and no extremity symptoms or signs).</td>
</tr>
<tr>
<td></td>
<td>3. Presence or absence of neck pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Failure of conservative treatment (minimum of 6 weeks)</td>
<td>8. Prior cervical laminectomy or laminoplasty and or prior cervical fusion surgery</td>
</tr>
<tr>
<td></td>
<td>5. Radiographic confirmation of spinal cord and/or nerve root compression corresponding to symptoms</td>
<td>9. Acute traumatic fracture and/or disc herniation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Structural instability and/or kyphosis of cervical spine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. Predominant posterior stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Osteoporosis and related metabolic bone disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13. Chronic steroid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14. Insulin-dependent diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Chronic steroid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16. Axial neck pain only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17. Diagnosis of ankylosing spondylitis, ossified posterior longitudinal ligament, or diffuse idiopathic skeletal hyperostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18. Systemic illnesses (such as osteoporosis, rheumatoid arthritis etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19. Spondylotic myelopathy</td>
</tr>
<tr>
<td>Goffin 2006</td>
<td>1. Pure axial neck pain</td>
<td>2. Preoperative dynamic lateral flexion and extension radiographs of the cervical spine demonstrate inadequate motion at the operative level</td>
</tr>
<tr>
<td></td>
<td>2. Preoperative dynamic lateral flexion and extension radiographs of the cervical spine demonstrate inadequate motion at the operative level</td>
<td>3. Significant facet arthrosis</td>
</tr>
<tr>
<td></td>
<td>3. Significant facet arthrosis</td>
<td>4. Advanced spondylosis and ossification of the posterior longitudinal ligament (OPLL) – relative contraindications</td>
</tr>
<tr>
<td></td>
<td>4. Advanced spondylosis and ossification of the posterior longitudinal ligament (OPLL) – relative contraindications</td>
<td>5. Preoperative instability on dynamic flexion-extension images.</td>
</tr>
<tr>
<td></td>
<td>5. Preoperative instability on dynamic flexion-extension images.</td>
<td>6. Systemic illnesses (such as osteoporosis, rheumatoid arthritis etc.)</td>
</tr>
<tr>
<td></td>
<td>6. Systemic illnesses (such as osteoporosis, rheumatoid arthritis etc.)</td>
<td>7. Spondylotic myelopathy</td>
</tr>
<tr>
<td></td>
<td>7. Spondylotic myelopathy</td>
<td>8. Summary of other relative contraindications and absolute contraindications for ACDA.</td>
</tr>
</tbody>
</table>

ARTIFICIAL DISC ARTHROPLASTY (ACDA) © 2009, University of Calgary
Table 2 (contd)

<table>
<thead>
<tr>
<th>Author</th>
<th>Indications for ACDA</th>
<th>Contraindications for ACDA</th>
</tr>
</thead>
</table>
| Auerbach 2008     | 1. Symptomatic cervical disc disease at one or two vertebral levels between C3–T1 confirmed by imaging (magnetic resonance imaging [MRI], computed tomography [CT], or myelography) showing herniated nucleus pulposus (HNP), spondylosis, or loss of disc height  
2. Failed 6 weeks of conservative therapy  
3. Between 20 and 70 years of age  
4. No contraindications | 1. ≥3 vertebral levels requiring treatment  
2. Cervical instability (translation>3 mm and/or >11° rotational difference to that or either adjacent level)  
3. Known allergy to implant materials (titanium, polyethylene, cobalt, chromium, and molybdenum)  
4. Cervical fusion adjacent to the level to be treated  
5. Posttraumatic vertebral body deficiency/deformity  
6. Facet joint degeneration  
7. Neck or arm pain of unknown etiology  
8. Axial neck pain as the solitary presenting symptom  
9. Severe spondylosis (bridging osteophytes, disc height loss>50%, and absence of motion)  
10. Osteoporosis/osteopenia  
11. Prior surgery at the level to be treated  
12. Active malignancy; any patient with history of invasive malignancy, unless treated and asymptomatic for at least 5 years  
13. Systemic disease (AIDS, HIV, Hepatitis B or C, and Insulin-dependent diabetes)  
14. Other metabolic bone disease (ie, Paget’s and osteomalacia)  
15. Morbid obesity (BMI>40 or weight>100 lb over ideal body weight)  
16. Pregnant or trying to become pregnant in next 3 years  
17. Active local/systemic infection  
18. Presently on medications that can interfere with bone/soft tissue healing (ie, steroids)  
19. Autoimmune spondyloarthropathies (rheumatoid arthritis) |
<table>
<thead>
<tr>
<th>Author, date of publication</th>
<th>Sample</th>
<th>Artificial cervical disc and # of levels</th>
<th>Follow-up</th>
<th>Complications</th>
<th>Clinical outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACDA</td>
<td>Fusion</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>#</td>
<td>Age (years)</td>
<td>Gender</td>
<td>#</td>
<td>Age (years)</td>
<td>Gender</td>
</tr>
<tr>
<td>Coric 2006&lt;sup&gt;46&lt;/sup&gt;</td>
<td>7</td>
<td>47.1% male</td>
<td>16</td>
<td>Mean age: 43</td>
<td>Bryan</td>
<td>1 level</td>
</tr>
<tr>
<td>Mummaneni 2006&lt;sup&gt;43&lt;/sup&gt;</td>
<td>76</td>
<td>46% male</td>
<td>265</td>
<td>Mean age: 44</td>
<td>Prestige ST</td>
<td>1 level</td>
</tr>
</tbody>
</table>
Table 3 (contd)

<table>
<thead>
<tr>
<th>Author, date of publication</th>
<th>Sample</th>
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<th>Clinical outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACDA</td>
<td>Fusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>#</td>
<td>Age (years)</td>
<td>Gender</td>
<td>#</td>
<td>Age (years)</td>
<td>Gender</td>
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<tr>
<td>Murrey (in press)</td>
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<tr>
<td></td>
<td>103</td>
<td>Mean age:42.1%male</td>
<td></td>
<td>106</td>
<td>Mean age:43.5%male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ProDisc-C 1 level</td>
<td>24 months</td>
<td></td>
<td>Three ACDA patients did not achieve AE success (the absence of adverse events) due to 2 implant related and 1 implantation events. Seven fusion patients did not achieve AE success due to: neck pain/pseudoarthrosis requiring revision; allograft and plate subsidence requiring revision; dysphagia; chronic pain, cervical myofascial dysfunction, and dysphagia associated with plate migration requiring revision; postoperative wound infection at the anterior cervical wound characterized as a SLTAE; and revision of fusion due to SLTAE neck pain. Nine patients in the fusion group and 2 patients in the ACDA group required a secondary surgical procedure (revision, removal or reoperation of the implant or supplemental fixation).</td>
<td>At 24 months, the neurological success rate was higher in the ACDA group compared to the fusion group, but the difference was not statistically significant. The NDI success (≥15 point improvement) was higher in the ACDA group compared to the fusion group, but the difference was not statistically significant. There was statistically significant improvement of the overall SF-36 scores from baseline in both groups. Rx: in ACDA patients, ROM was 8.4° preop and 9.4° at 24 months; in fusion patients ROM was 7.7° preop and 0.9° at 24 months.</td>
</tr>
<tr>
<td>Nabhan 2007</td>
<td>19</td>
<td>NS</td>
<td>21</td>
<td>NS</td>
<td>ProDisc-C 1 level</td>
<td>1 year Subarachnoid hemorrhage in the ACDA group (1)</td>
</tr>
</tbody>
</table>

Nabhan 2007

21
Table 3 (contd)

<table>
<thead>
<tr>
<th>Author, date of publication</th>
<th>Sample</th>
<th>Artificial cervical disc and # of levels</th>
<th>Follow-up</th>
<th>Complications</th>
<th>Clinical outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ACDA</td>
<td>Fusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td># Age (years) Gend</td>
<td># Age (years) Gend</td>
<td>Bryan 1 level</td>
<td>24 months</td>
<td>Reinterventions ACDA: fusion for adjacent level disease (3) Fusion: posterior cervical fusion for symptomatic nonunion (1), revision of fusion for nonunion (1), fusion for adjacent level disease (2)</td>
</tr>
<tr>
<td>Sasso 2007&lt;sup&gt;**&lt;/sup&gt;</td>
<td>56</td>
<td>Mean age: 42</td>
<td>53.6 %</td>
<td>male</td>
<td>59</td>
<td>Mean age: 46.1</td>
</tr>
</tbody>
</table>

*WHO adverse events grades: grade 1 = mild; grade 2 = moderate, grade 3 = severe, grade 4 = life threatening or disabling, grade 5 = fatal

£ This is a report of data from a single investigational site of a multicenter RCT reported by Mummaneni et al.

NDI = Neck Disability Index
ROM = range of motion
SF-36 = Short Form Health Survey
SLTAE = Sever or Life Threatening Adverse Event
VAS = Visual Analogue Scale (pain intensity)
<table>
<thead>
<tr>
<th>Author, date of publication</th>
<th>Sample</th>
<th>Artificial cervical disc and # of levels</th>
<th>Follow-up</th>
<th>Complications</th>
<th>Clinical outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wigfield 2002&lt;sup&gt;29&lt;/sup&gt;</td>
<td>12</td>
<td>Mean age: 49, 75% male</td>
<td>13</td>
<td>Mean age: 57.8, 77% male</td>
<td>NS 1 level</td>
<td>12 months</td>
</tr>
</tbody>
</table>

The ACDA may be reserved for use in patients with advanced disease and previous fusions, with the primary goal of preserving motion at the operative site.
### Table 5. Observational studies and case series

<table>
<thead>
<tr>
<th>Author, date of publication</th>
<th>Sample</th>
<th>Artificial cervical disc and # of levels</th>
<th>Follow-up</th>
<th>Complications</th>
<th>Clinical outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amit 2007</td>
<td>22 (22 devices)</td>
<td>Age range: 39-79 Mean age: 51</td>
<td>Bryan 1 level</td>
<td>12 months</td>
<td>No complications reported.</td>
<td>Significant improvement in VAS, SF-36 mental and physical and NDI scores at 12 months follow-up. Bryan disc arthroplasty achieves neurological decompression, symptom relief and functional restoration. In addition, movement at the operated level is maintained.</td>
</tr>
<tr>
<td>Bertagnoli 2005</td>
<td>16 (20 devices)</td>
<td>Age range: 32-60 Mean age: 48.3</td>
<td>ProDisc-C 1 and 2 levels</td>
<td>12 months</td>
<td>No complications reported.</td>
<td>Significant improvement of preoperative VAS and ODI scores at 12 months follow-up. Significant change in ROM from 3 weeks to 12 months follow-up. ProDisc-C arthroplasty provides significant improvement in pain and functional outcome scores, and did not result in any spontaneous fusions at the level of the surgery or at adjacent levels.</td>
</tr>
<tr>
<td>Duggal 2004</td>
<td>26 (30 devices)</td>
<td>Age range: 30-67 Mean age: 43.3±7.33</td>
<td>Bryan 1 and 2 levels</td>
<td>24 months</td>
<td>Increased post-operative radicular pain (1 case) Transient unilateral vocal cord paralysis (1 case) Dysphagia (1 case) Device migration (1 case)</td>
<td>A statistically significant improvement in the mean NDI scores was seen between preoperative and late postoperative scores. A trend toward improvement in the SF-36 physical and mental components was found. Insertion of the Bryan Cervical Disc prosthesis following anterior cervical disectomy appears to be safe and provides good preliminary clinical results.</td>
</tr>
<tr>
<td>Goffin 2003</td>
<td>103 single-level 43 bi-level</td>
<td>Age range: 26-79 (single-level) 28-62 bi-level</td>
<td>Bryan 1 and 2 levels</td>
<td>24 months</td>
<td>Prevertebral hematoma (2) Residual myelopathy (1) Unresolved pain (2) Disc herniation (1) Temporary dysphonia (1) CSF leak (1)</td>
<td>86% of single-level patients and 96% of bi-level patients were assessed as excellent, good or fair on Odom’s classification at 12 months follow-up. Discectomy and implantation of the Bryan cervical disc prosthesis alleviates symptoms, supports maintenance of motion, and is safe with a quick recovery.</td>
</tr>
<tr>
<td>Heidecke 2008</td>
<td>54 (59 devices)</td>
<td>Age range: 26-58 Mean age: 47</td>
<td>Bryan 1 and 2 levels</td>
<td>2 years</td>
<td>One patient developed radicular symptoms due to newly occurred osteophytes one year after surgery. Retropharyngeal haematoma (1).</td>
<td>80% of the patients had excellent outcome on Odom’s scale at 2 years after surgery. Loss of function (ROM &lt;3º) was found in 12% out of 59 discs at 2 years after surgery. Implantation of the Bryan disc resulted in excellent or good neurological outcome in all patients. The surgical technique was safe and without complications.</td>
</tr>
<tr>
<td>Author, date of publication</td>
<td>Sample</td>
<td>Artificial cervical disc and # of levels</td>
<td>Follow-up</td>
<td>Complications</td>
<td>Clinical outcomes</td>
<td>Conclusions</td>
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</tr>
<tr>
<td>Lafuente 2005⁵⁴</td>
<td>46 (46 devices)</td>
<td>Age range: 33-70 Mean age: 47.6</td>
<td>60.9% male</td>
<td>Bryan 1 level</td>
<td>12 months</td>
<td>Worsening of muscle spasm (1) Dysphonia (3) Prosthesis removed and replaced with interbody cage (1).</td>
</tr>
<tr>
<td>Mehren 2006⁵²</td>
<td>54 (77 devices)</td>
<td>NS</td>
<td>NS</td>
<td>ProDisc-C 1 and 2 levels</td>
<td>12 months</td>
<td>HO that led to restrictions of the ROM (8). Spontaneous fusion (7). There was a statistically significant higher rate of HO in multi-level versus single-level cases.</td>
</tr>
<tr>
<td>Pimenta 2004⁴³</td>
<td>53 (82 devices)</td>
<td>Age range: 26-68</td>
<td>39.6% male</td>
<td>PCM 1, 2, 3 and 4 levels</td>
<td>1 year</td>
<td>Anterior displacement of prosthesis (1) McAfee Grade 1 HO (1)</td>
</tr>
<tr>
<td>Pimenta 2007⁴⁴</td>
<td>140 (229 devices)</td>
<td>Age range: 28-77 single-level 28-80 multi-level</td>
<td>39.4% male (single-level) 40.6% male (multi-level)</td>
<td>PCM 1, 2, 3 and 4 levels</td>
<td>3 years</td>
<td>HO (1) Reintervention (5)</td>
</tr>
<tr>
<td>Robertson 2004⁴³</td>
<td>17</td>
<td>Age range: 32 - 75 Mean age: 50</td>
<td>58.8% male</td>
<td>Prestige I Disc NS</td>
<td>4 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Sahoo 2006⁵⁵</td>
<td>20</td>
<td>Age range: 31 - 50</td>
<td>70% male</td>
<td>Bryan 1 level</td>
<td>24 months</td>
<td>Temporary hoarseness of voice (1)</td>
</tr>
<tr>
<td>Author, date of publication</td>
<td>Sample</td>
<td>Artificial cervical disc and # of levels</td>
<td>Follow-up</td>
<td>Complications</td>
<td>Clinical outcomes</td>
<td>Conclusions</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>----------------------------------------</td>
<td>------------</td>
<td>---------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Sekhon 2005&lt;sup&gt;55&lt;/sup&gt;</td>
<td>15 (24 devices)</td>
<td>Age range: 27 - 60 Mean age: 44</td>
<td>40% male</td>
<td>Bryan 1, 2 and 3 levels</td>
<td>&gt;12 months</td>
<td>Blood transfusion (2) Reintervention (1) Persistent dysphagia (1) Subluxation (1) Clicking of the disc (1) Residual neurological symptoms (2)</td>
</tr>
<tr>
<td>Wang 2006&lt;sup&gt;56&lt;/sup&gt;</td>
<td>83 (102 devices)</td>
<td>Age range: 34 - 58 Mean age: 49</td>
<td>52% male</td>
<td>Bryan 1 and 2 levels</td>
<td>24 months</td>
<td>Esophageal injury(1) Spontaneous fusion (1) Worsening of pre-operative cervical kyphosis (2)</td>
</tr>
<tr>
<td>Yang 2008&lt;sup&gt;57&lt;/sup&gt;</td>
<td>19 (23 devices)</td>
<td>Age range: 35-52 Mean age: 42.5</td>
<td>63% male</td>
<td>Bryan 1 and 2 levels</td>
<td>24 months (average)</td>
<td>Position deflexion of the prosthesis metal endplates (4 levels)</td>
</tr>
</tbody>
</table>

HO = Heterotopic Ossifications  
JOA = Japanese Orthopedic Association  
NDI = Neck Disability Index  
ODI = The Oswestry Disability Index  
ROM = Range of Motion  
SF-36 = Short Form Health Survey  
TIGT = Treatment Intensity Gradient Test  
VAS = Visual Analogue Scale (pain intensity)
Table 6. Summary of the methodological quality assessment (Cochrane Musculoskeletal Injuries Group)

<table>
<thead>
<tr>
<th></th>
<th>Concealment</th>
<th>ITT Analysis</th>
<th>Blinding of assessors</th>
<th>Baseline</th>
<th>Blinding of patients</th>
<th>Blinding of treatment provider</th>
<th>Care programs</th>
<th>Inclusion/Exclusion criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Diagnostic test</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coric 2006</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mummaneni 2007</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Murrey (in press)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nabhan 2007</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sasso 2007</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 7a. SF-36 Physical Component Score. (mean differences)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>%Weight (fixed)</th>
<th>%Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan</td>
<td>3.4</td>
<td>[-1.3865; 8.1865]</td>
<td>12.93</td>
<td>12.93</td>
</tr>
<tr>
<td>ProDisc-C</td>
<td>2.0</td>
<td>[-1.1178; 5.1178]</td>
<td>30.48</td>
<td>30.48</td>
</tr>
<tr>
<td>Prestige ST</td>
<td>1.3</td>
<td>[-0.9885; 3.5885]</td>
<td>56.58</td>
<td>56.58</td>
</tr>
</tbody>
</table>

MD = mean difference
95%-CI = 95% confidence interval

Table 7b. SF-36 Physical Component Score (summary estimate)

<table>
<thead>
<tr>
<th></th>
<th>WMD</th>
<th>95%-CI</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects model</td>
<td>1.785</td>
<td>[0.0636; 3.5064]</td>
<td>0.0421</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.785</td>
<td>[0.0636; 3.5064]</td>
<td>0.0421</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference
95%-CI = 95% confidence interval

Table 8a. SF-36 Mental Component Score (mean differences)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>%Weight (fixed)</th>
<th>%Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan</td>
<td>4.70</td>
<td>[-0.7682; 10.1682]</td>
<td>13.01</td>
<td>20.37</td>
</tr>
<tr>
<td>ProDisc-C</td>
<td>-1.76</td>
<td>[-5.1651; 1.6451]</td>
<td>33.55</td>
<td>35.89</td>
</tr>
<tr>
<td>Prestige ST</td>
<td>-0.10</td>
<td>[-2.7981; 2.5981]</td>
<td>53.44</td>
<td>43.75</td>
</tr>
</tbody>
</table>

MD = mean difference
95%-CI = 95% confidence interval

Table 8b. SF-36 Mental Component Score. (summary estimate)

<table>
<thead>
<tr>
<th></th>
<th>WMD</th>
<th>95%-CI</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects model</td>
<td>-0.0325</td>
<td>[-2.0048; 1.9399]</td>
<td>0.9743</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.2818</td>
<td>[-2.6542; 3.2179]</td>
<td>0.8508</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference
95%-CI = 95% confidence interval

Table 9a. Arm Pain (mean differences)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>%Weight (fixed)</th>
<th>%Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan</td>
<td>-6.00</td>
<td>[-21.1394; 9.1394]</td>
<td>11.29</td>
<td>11.29</td>
</tr>
<tr>
<td>ProDisc-C</td>
<td>1.11</td>
<td>[-8.5558; 10.7758]</td>
<td>27.70</td>
<td>27.70</td>
</tr>
<tr>
<td>Prestige ST</td>
<td>2.20</td>
<td>[-4.3129; 8.7129]</td>
<td>61.01</td>
<td>61.01</td>
</tr>
</tbody>
</table>

MD = mean difference
95%-CI = 95% confidence interval
Table 9b. Arm Pain (summary estimate)

<table>
<thead>
<tr>
<th></th>
<th>WMD</th>
<th>95%-CI</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects model</td>
<td>0.9722</td>
<td>[-4.1149; 6.0594]</td>
<td>0.708</td>
</tr>
<tr>
<td>Random effects model</td>
<td>0.9722</td>
<td>[-4.1149; 6.0594]</td>
<td>0.708</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference  
95%-CI = 95% confidence interval

Table 10a. Neck Pain (mean differences)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>%Weight (fixed)</th>
<th>%Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProDisc-C</td>
<td>-3.65</td>
<td>[-12.9049; 5.6049]</td>
<td>23.68</td>
<td>28.33</td>
</tr>
<tr>
<td>Prestige ST</td>
<td>0.20</td>
<td>[-5.3257; 5.7257]</td>
<td>66.44</td>
<td>58.28</td>
</tr>
</tbody>
</table>

MD = mean difference  
95%-CI = 95% confidence interval

Table 10b. Neck Pain (summary estimate)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects model</td>
<td>-1.8969</td>
<td>[-6.4010; 2.6071]</td>
<td>0.4091</td>
</tr>
<tr>
<td>Random effects model</td>
<td>-2.4972</td>
<td>[-8.0101; 3.0157]</td>
<td>0.3746</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference  
95%-CI = 95% confidence interval

Table 11a. Neck Disability Index (mean differences)

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95%-CI</th>
<th>%Weight (fixed)</th>
<th>%Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan</td>
<td>-5.20</td>
<td>[-13.4142; 3.0142]</td>
<td>14.18</td>
<td>14.18</td>
</tr>
<tr>
<td>ProDisc-C</td>
<td>0.83</td>
<td>[-4.6558; 6.3158]</td>
<td>31.80</td>
<td>31.80</td>
</tr>
<tr>
<td>Prestige ST</td>
<td>-2.40</td>
<td>[-6.6093; 1.8093]</td>
<td>54.01</td>
<td>54.01</td>
</tr>
</tbody>
</table>

MD = mean difference  
95%-CI = 95% confidence interval

Table 11b. Neck Disability Index (summary estimate)

<table>
<thead>
<tr>
<th></th>
<th>WMD</th>
<th>95%-CI</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects model</td>
<td>-1.77</td>
<td>[-4.8636; 1.3237]</td>
<td>0.2621</td>
</tr>
<tr>
<td>Random effects model</td>
<td>-1.77</td>
<td>[-4.8636; 1.3237]</td>
<td>0.2621</td>
</tr>
</tbody>
</table>

WMD = weighted mean difference  
95%-CI = 95% confidence interval
Table 12. HTA reports

<table>
<thead>
<tr>
<th>HTA report (organization,year)</th>
<th>Type of disc</th>
<th>Evidence included</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic intervertebral disc replacement in the cervical spine - update (NICE,2005)</td>
<td>Bryan, Frenchay (Prestige I) and Prestige II</td>
<td>2 RCTs and 3 case series</td>
<td>The resulting NICE guidance stated that the evidence available suggested that there were no major safety concerns about the use of prosthetic intervertebral disc replacement in the cervical spine, and there was evidence of short-term efficacy.</td>
</tr>
<tr>
<td>Artificial discs for lumbar and cervical degenerative disc disease (OHTAC,2006)</td>
<td>Bryan</td>
<td>6 case series</td>
<td>Because of the lack of data available, the effectiveness and safety of ACDA could not be determined.</td>
</tr>
<tr>
<td>Artificial intervertebral disc arthroplasty for treatment of degenerative disc disease of the cervical spine (Blue Cross Blue Shield, 2008)</td>
<td>Prestige ST Disc</td>
<td>The Prestige Disc IDE RCT</td>
<td>The evidence from the IDE trial did not permit conclusions on the long-term performance of ACDA and adverse events. The available evidence also was insufficient to permit conclusions as to whether or not ACDA affected the postsurgical development of adjacent-level DDD. By contrast, conclusions on the relative safety of cervical disc arthroplasty appeared sufficiently supported in the short term. The evidence did not permit conclusions as to whether artificial intervertebral disc arthroplasty for the cervical spine improved the net health outcome or was beneficial as established alternatives.</td>
</tr>
<tr>
<td>Artificial intervertebral disc replacement (Total disc arthroplasty). (Medical Services Advisory Committee, 2006)</td>
<td>Prestige II (effectiveness)</td>
<td>One RCT (effectiveness)</td>
<td>In the absence of adequate evidence of effectiveness, MSAC recommended that public funding for AIDR in the cervical spine should not be supported.</td>
</tr>
</tbody>
</table>

IDE = Investigational Device Exemption
### Table 13. Hospital costs

<table>
<thead>
<tr>
<th>Type of cost</th>
<th>ACDA</th>
<th>Fusion - 1 level</th>
<th>Fusion - 2 level</th>
<th>Fusion - 3 level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>$5,085</td>
<td>$4,348</td>
<td>$5,801</td>
<td>$6,809</td>
</tr>
<tr>
<td></td>
<td>$4,088 - $5,555</td>
<td>$3,149 - $6,882</td>
<td>$4,139 - $7,810</td>
<td>$5,097 - $12,196</td>
</tr>
<tr>
<td>Indirect</td>
<td>$1,594</td>
<td>$1,382</td>
<td>$1,679</td>
<td>$2,157</td>
</tr>
<tr>
<td></td>
<td>$1,553 - $2,121</td>
<td>$1,079 - $1,943</td>
<td>$1,280 - $2,312</td>
<td>$1,537 - $3,606</td>
</tr>
<tr>
<td>Drug Allocation</td>
<td>$159</td>
<td>$130</td>
<td>$166</td>
<td>$189</td>
</tr>
<tr>
<td></td>
<td>$137 - $226</td>
<td>$93 - $178</td>
<td>$116 - $208</td>
<td>$144 - $281</td>
</tr>
<tr>
<td>Drug</td>
<td>$14</td>
<td>$15</td>
<td>$21</td>
<td>$41</td>
</tr>
<tr>
<td></td>
<td>$9 - $26</td>
<td>$4 - $42</td>
<td>$9 - $41</td>
<td>$19 - $85</td>
</tr>
<tr>
<td>Supply</td>
<td>$6,483</td>
<td>$481</td>
<td>$1,116</td>
<td>$1,949</td>
</tr>
<tr>
<td></td>
<td>$221 - $7,207</td>
<td>$152 - $1,453</td>
<td>$293 - $1,786</td>
<td>$965 - $2,775</td>
</tr>
<tr>
<td>Total</td>
<td>$13,335</td>
<td>$6,356</td>
<td>$8,783</td>
<td>$11,145</td>
</tr>
<tr>
<td></td>
<td>$6,008 - $15,135</td>
<td>$4,477 - $10,498</td>
<td>$5,837 - $12,157</td>
<td>$7,762 - $18,943</td>
</tr>
</tbody>
</table>

Totals given are median values in 2007 dollars; ranges are 25\textsuperscript{th} - 75\textsuperscript{th} percentiles.

### Table 14. Physician costs

<table>
<thead>
<tr>
<th></th>
<th>ACDA</th>
<th>Fusion - 1 level</th>
<th>Fusion - 2 level</th>
<th>Fusion - 3 level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Physician</td>
<td>$1,562.93</td>
<td>$1,715.83</td>
<td>$1,662.27</td>
<td>$1,285.05</td>
</tr>
<tr>
<td>Other Clinicians</td>
<td>$1,232.76</td>
<td>$1,265.72</td>
<td>$1,274.61</td>
<td>$783.29</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$2,795.68</td>
<td>$2,981.54</td>
<td>$2,936.88</td>
<td>$2,068.34</td>
</tr>
</tbody>
</table>

- total number 39 533 224 198
- billing codes 92.31R 92.31E 92.31M 92.31N 93.01B 93.02A 93.01P 93.02B

### Table 15. Costs to Alberta based on percentage of ACDA/cervical fusion

<table>
<thead>
<tr>
<th>ACDA</th>
<th>Fusion</th>
<th>Total Cost (1)</th>
<th>Total Cost (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100%</td>
<td>$4,280,577</td>
<td>$4,280,577</td>
</tr>
<tr>
<td>25%</td>
<td>75%</td>
<td>$4,803,369</td>
<td>$5,056,378</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
<td>$5,326,161</td>
<td>$5,832,179</td>
</tr>
<tr>
<td>75%</td>
<td>25%</td>
<td>$5,848,953</td>
<td>$6,607,979</td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
<td>$6,371,745</td>
<td>$7,383,780</td>
</tr>
</tbody>
</table>

Cost assumptions

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACDA-1</td>
<td>$16,131</td>
<td>$16,131</td>
</tr>
<tr>
<td>ACDA-2</td>
<td>$16,131</td>
<td>$20,164</td>
</tr>
<tr>
<td>ACDA-3</td>
<td>$16,131</td>
<td>$22,785</td>
</tr>
</tbody>
</table>
Table 16. Proportions, in 2006/2007, of interventions, by age and procedure, per 100,000 individuals

<table>
<thead>
<tr>
<th>Age</th>
<th>ACDA</th>
<th>1 level</th>
<th>2 level</th>
<th>3 level</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 29</td>
<td>1.869</td>
<td>0.623</td>
<td>0.249</td>
<td></td>
</tr>
<tr>
<td>30 to 39</td>
<td>1.344</td>
<td>6.910</td>
<td>1.536</td>
<td>1.344</td>
</tr>
<tr>
<td>40 to 49</td>
<td>0.362</td>
<td>11.040</td>
<td>4.886</td>
<td>4.705</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.680</td>
<td>12.011</td>
<td>4.986</td>
<td>6.346</td>
</tr>
<tr>
<td>60 to 69</td>
<td>1.185</td>
<td>6.717</td>
<td>3.556</td>
<td>9.878</td>
</tr>
<tr>
<td>70 and up</td>
<td>0.000</td>
<td>5.483</td>
<td>3.917</td>
<td>6.267</td>
</tr>
</tbody>
</table>

Table 17. Number of cervical fusions and ACDA procedures in 4-year study period by region

<table>
<thead>
<tr>
<th>Region of Residence</th>
<th>ACDA</th>
<th>Fusion - 1 level</th>
<th>Fusion - 2 level</th>
<th>Fusion - 3 level</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calgary</td>
<td>30</td>
<td>202</td>
<td>110</td>
<td>108</td>
<td>450</td>
</tr>
<tr>
<td>Capital</td>
<td>6</td>
<td>196</td>
<td>48</td>
<td>53</td>
<td>303</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>241</td>
<td>99</td>
<td>78</td>
<td>428</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>639</td>
<td>257</td>
<td>239</td>
<td>1181</td>
</tr>
</tbody>
</table>

Table 18. Number of interventions (cervical fusion and ACDA) by delivery region and fiscal year

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>ACDA</th>
<th>Fusion - 1 level</th>
<th>Fusion - 2 level</th>
<th>Fusion - 3 level</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004/05</td>
<td></td>
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Note: The * represents a cell that has a value too small for public release.
FIGURES
Figure 1. SF-36 Physical Component Score (PCS) random-effects meta-analysis

Horizontal lines represent the 95% CI for the estimate for each trial. The size of the squares for each trial is proportional to the weight given to each trial in the meta-analysis. The horizontal tips of the diamond provide the 95% CI for the random-effects estimate.
Figure 2. SF-36 Mental Component Score (MCS) random-effects meta-analysis

Horizontal lines represent the 95% CI for the estimate for each trial. The size of the squares for each trial is proportional to the weight given to each trial in the meta-analysis. The horizontal tips of the diamond provide the 95% CI for the random-effects estimate.
Figure 3. Arm Pain random-effects meta-analysis

Horizontal lines represent the 95% CI for the estimate for each trial. The size of the squares for each trial is proportional to the weight given to each trial in the meta-analysis. The horizontal tips of the diamond provide the 95% CI for the random-effects estimate.
Figure 4. Neck Pain random-effects meta-analysis

Neck Pain

Horizontal lines represent the 95% CI for the estimate for each trial. The size of the squares for each trial is proportional to the weight given to each trial in the meta-analysis. The horizontal tips of the diamond provide the 95% CI for the random-effects estimate.
Figure 5. Neck Disability Index random-effects meta-analysis

Horizontal lines represent the 95% CI for the estimate for each trial. The size of the squares for each trial is proportional to the weight given to each trial in the meta-analysis. The horizontal tips of the diamond provide the 95% CI for the random-effects estimate.
Figure 6. Number of procedures (ACDA and cervical fusion) in Alberta

![Bar chart showing the number of procedures (ACDA and cervical fusion) in Alberta from 2004/05 to 2007/08. The chart displays the number of procedures for ACDA, 1 level, 2 level, and 3+ level procedures.]

Figure 7. Rates of ACDA and cervical fusion in Alberta

![Bar chart showing the rates of ACDA and cervical fusion in Alberta from 2004/05 to 2006/07. The chart displays the rates per 100,000 people for ACDA and cervical fusion at 1 level, 2 level, and 3+ level.]
Appendix 1

Artificial Cervical Disc
Search

MEDLINE (OVID)
Cochrane CENTRAL Register of Controlled Trials (OVID 1st Quarter 2008)
Health Technology Assessment Database (OVID 1st Quarter 2008)
1. exp back pain/ or exp disckectomy/ or exp spinal diseases/
2. intervertebral disk/ or spinal fusion/
3. degenerative disc disease.tw.
4. 1 or 2 or 3
5. cervical.tw.
6. 4 and 5
7. exp cervical vertebrae/
8. 6 or 7
9. dis$ adj3 (artificial or prosth$ or arthrodesis or arthroplasty or replacement)).tw.
10. arthroplasty/ or arthroplasty, replacement/ or joint prosthesis/ or prosthesis design/ or "prostheses and implants"/ or prosthesis failure/ or prosthesis implantation/
11. 9 or 10
12. 8 and 11
13. (cervical adj3 dis$ adj3 (artificial or prosth$ or arthrodesis or arthroplasty or replacement)).tw.
14. ((bryan adj2 (disc$ or disk$)) or (prestige adj2 (disc$ or disk$)) or "cervitech PCM" or "prodisc C" or (Cervicore adj2 (disc$ or disk$)) or (Mobi-C adj2 (disc$ or disk$)) or (SECURE-C adj2 (disc$ or disk$)) or "kineflex-c" or ("Spinal Kinetics M6" adj2 (disc$ or disk$)) or (PCM adj2 (disc$ or disk$)) or ("porous coated motion" adj2 (disc$ or disk$)) or (Flexicore adj2 (disc$ or disk$)) or ("Medtronic Sofamor Danek Prestige" adj2 (disc$ or disk$))).tw.
15. 12 or 13 or 14
16. limit 15 to yr="1998 - 2008")
17. limit 16 to animals
18. limit 16 to (humans and animals)
19. 17 not 18
20. 16 not 19
21. limit 20 to case reports
22. 20 not 21

EMBASE (OVID)
1. exp spine disease/ or exp spine fusion/
2. backache/ or intervertebral disk/ or intervertebral disckectomy/ or spine surgery/ or vertebrae/
3. degenerative disc disease$.tw.
4. 1 or 2 or 3
5. cervical.tw.
6. 4 and 5
7. cervical spine/
8. 6 or 7
9. exp joint prosthesis/ or exp prosthesis failure/
10. arthroplasty/ or bone prosthesis/ or implantation/ or prosthesis/ or “prostheses
    and orthoses” or prosthesis infection/ or prosthesis fixation/ or prosthesis loosening/
11. dis$ adj3 (artificial or prosthе$ or arthrodesis or arthroplasty or
    replacement)).tw.
12. 9 or 10 or 11
13. 8 and 12
14. (cervical adj3 dis$ adj3 (artificial or prosthе$ or arthrodesis or arthroplasty or
    replacement)).tw.
15. ((bryan adj2 (disc$ or disk$)) or (prestige adj2 (disc$ or disk$)) or "cervitech
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    (disc$ or disk$))).tw.
16. 13 or 14 or 15
17. limit 16 to yr="1998 – 2008"
18. limit 17 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks
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    horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile
    or sheep or swine)
19. limit 17 to human
20. 18 and 19
21. 18 not 20
22. 17 not 21
23. case report/
24. 22 and 23
25. 22 not 24

Cochrane Database of Systematic Reviews (OVID 1st Quarter 2008)
1. (cervical adj3 dis$ adj3 (artificial or prosthе$ or arthrodesis or arthroplasty or
    replacement)).tw,kw.
2. ((bryan adj2 (disc$ or disk$)) or (prestige adj2 (disc$ or disk$)) or "cervitech
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    disk$)) or (Flexicore adj2 (disc$ or disk$)) or ("Medtronic Sofamor Danek Prestige" adj2
    (disc$ or disk$))).tw,kw.
3. 1 or 2
DARE Database of Reviews of Effects (OVID 1st Quarter 2008)
NHS Economic Evaluation Database (OVID 1st Quarter 2008)

1. (cervical adj3 dis$ adj3 (artificial or prosth$ or arthrodesis or arthroplasty or replacement)).tw.
2. ((bryan adj2 (disc$ or disk$)) or (prestige adj2 (disc$ or disk$)) or "cervitech PCM" or "prodisc C" or (Cervicore adj2 (disc$ or disk$)) or (Mobi-C adj2 (disc$ or disk$)) or (SECURE-C adj2 (disc$ or disk$)) or "kineflex-c" or ("Spinal Kinetics M6" adj2 (disc$ or disk$)) or (PCM adj2 (disc$ or disk$)) or ("porous coated motion" adj2 (disc$ or disk$)) or (Flexicore adj2 (disc$ or disk$)) or ("Medtronic Sofamor Danek Prestige" adj2 (disc$ or disk$))).tw.
3. 1 or 2
4. limit 3 yr="1998 - 2008")

EconLit (EBSCO)

1. (cervical and dis* and (artificial or prosth$ or arthrodesis or arthroplasty or replacement))[All Fields]
2. ((bryan and (disc* or disk*)) or (prestige and (disc* or disk*)) or "cervitech PCM" or "prodisc C" or (Cervicore and (disc* or disk*)) or (Mobi-C and (disc* or disk*)) or (SECURE-C and (disc* or disk*)) or "kineflex-c" or ("Spinal Kinetics M6" and (disc* or disk*)) or (PCM and (disc* or disk*)) or ("porous coated motion" and (disc* or disk*)) or (Flexicore and (disc* or disk*)) or ("Medtronic Sofamor Danek Prestige" and (disc* or disk*))[All Fields]
3. 1 or 2
4. limit 3 yr="1998 - 2008")
Appendix 2

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 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.
SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Total Cervical Disc Replacement
Device Trade Name: ProDisc™-C Total Disc Replacement
Applicant's Name and Address: Synthes Spine
1302 Wrights Lane E.
West Chester, PA 19380

Date of Panel Recommendation: None
Premarket Approval Application (PMA) Number: P070001
Date of Notice of Approval of Application: December 17, 2007

II. INDICATIONS FOR USE

The ProDisc™-C Total Disc Replacement is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable symptomatic cervical disc disease (SCDD). Symptomatic cervical disc disease is defined as neck or arm (radicular) pain and/or a functional/ neuroradiological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, or X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or loss of disc height. The ProDisc™-C Total Disc Replacement is implanted via an open anterior approach. Patients receiving the ProDisc™-C Total Disc Replacement should have failed at least six weeks of non-operative treatment prior to implantation of the ProDisc™-C Total Disc Replacement.

III. CONTRAINDICATIONS

The ProDisc™-C Total Disc Replacement should not be implanted in patients with the following conditions:

- Active systemic infection or infection localized to the site of implantation
- Osteoporosis defined as DEXA bone density measured T-score ≤ -2.5
- Marked cervical instability on neutral resting lateral or flexion/extension radiographs; translation > 5mm and/or > 11° of rotational difference to either adjacent level
- Allergy or sensitivity to the implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Severe spondylosis characterized by bridging osteophytes or a loss of disc height > 50% or an absence of motion (<2°), as this may lead to limited range of motion and may encourage bone formation (e.g., heterotopic ossification, fusion)
• Clinically compromised vertebral bodies at the affected level due to current or past trauma (e.g., by radiographic appearance of fracture callus, malunion, or nonunion)
• Patients with SCDD at more than one level

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ProDisc™-C Total Disc Replacement labeling.

V. DEVICE DESCRIPTION

The ProDisc™-C Total Disc Replacement is made up of three components:

• an inferior CoCrMo (cobalt chromium molybdenum) alloy plate with a midline keel orientated anterior-posterior that is anchored into the endplate of the inferior vertebral body
• an Ultra High Molecular Weight Polyethylene (UHMWPE) insert that is pre-assembled snap-locked into a tray detail in the inferior CoCrMo alloy plate and provides the inferior convex bearing surface
• a CoCrMo alloy plate with a midline keel that anchors to the superior vertebral body and has a highly polished concave bearing surface that articulates with the convex UHMWPE spherical dome.

The endplate footprints range from 15-19 mm wide (medial-lateral) x 12-18 mm deep (anterior-posterior). Each endplate size is available in three disc heights (5, 6, and 7 mm) to accommodate a range of vertebral sizes.

The bone contacting surfaces of the inferior and superior plates as well as both keels are titanium plasma spray coated.

The maximum range of motion allowed by the ProDisc™-C Total Disc Replacement device design is 20° in flexion/extension (17.5° for the 5mm Large, Large Deep, Extra Large, and Extra Large Deep implants), 20° in lateral bending (17.5° for the 5mm Large, Large Deep, Extra Large, and Extra Deep implants), and the device is unconstrained in axial rotation as measured through in vitro testing.

The plates are manufactured from CoCrMo alloy conforming to ISO 5832-12 “Implants for surgery -- Metallic Materials -- Part 12: Wrought cobalt-chromium-molybdenum alloy”. The insert is manufactured from ultra-high molecular weight Polyethylene (UHMWPE) conforming to ISO 5834-2 “Implants for surgery -- Ultra-high molecular weight polyethylene -- Part 2: Molded forms”. The surfaces of both inferior and superior plates that abut the bone are plasma sprayed with Titanium CP conforming to ISO/DIS 5832-2 "Implants for surgery -- Metallic materials -- Part 2: Unalloyed titanium".
**Table 1: Implant Components**

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VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-operative alternative treatments for SCDD include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.

When conservative attempts fail to alleviate the pain and/or neurological deficits caused by SCDD, the most common treatment is decompression of the affected nerves and spinal cord. Surgical decompression of the affected nerves and spinal cord is most often accomplished by removal of the diseased cervical disc, known as cervical disectomy, and associated osteophytes.

Most cervical decompressions are followed by the insertion of a bone graft into the space after the disc is removed to maintain intervertebral height and facilitate fusion of the adjacent vertebrae. This is most commonly accompanied by the placement of an anatomical plate anterior to the bone graft to immobilize the vertebral segment and provide stability. This procedure is known as an anterior cervical disectomy and fusion (ACDF).

SCDD may also be treated surgically using another approved artificial cervical disc.

VII. MARKETING HISTORY

The ProDisc™-C Total Disc Replacement has been commercially available in markets outside of the United States since December, 2002. The device has not been withdrawn from the market for any reason relating to the safety and effectiveness of the device. The countries in which ProDisc™-C Total Disc Replacement is available are provided in the table below.
Table 2: Global Distribution

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</tbody>
</table>

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events were reported during a multi-center, prospective, randomized, non-inferiority clinical study comparing 103 patients implanted with the ProDisc™-C Total Disc Replacement to 106 control patients who received an anterior cervical disectomy and fusion (ACDF).