Artificial cervical and lumbar disc implants:
A review of the literature.

By

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Background:

Degenerative disc disease (DDD) is one of the most frequently encountered spinal disorders[1]. Lumbar and cervical disc degeneration is commonly seen. Cross-sectional studies have shown that over half of the middle age population demonstrated radiological or pathological evidence of cervical spondylosis[2,3,4]. Cervical spondylosis is often asymptomatic, however, 10%-15% of individuals have associated root or cord compression[5]. In the cervical spine, DDD can result in significant pain, instability and radiculopathy and/or myelopathy. Several causes have been cited as the possible source of these symptoms, including the loss of disc space height, loss of foraminal volume, disc bulging or protruding osteophytes causing neural compression. With regard to the lumbar spine, symptomatic disc degeneration is believed to be a common cause of chronic low back pain[1].

The exact pathogenesis of degenerative disc disease (DDD) remains unknown. However, it is believed that degenerative disc disease is genetically determined, mechanically induced and biologically mediated. It has been shown that natural aging may be the only significant contributor to degenerative changes in the cervical disc[4,5,6]. Hartwig et al[6] investigated the pattern of degeneration of the cervical spine among two groups - one with and one without occupations that impose stress on the lumbar spine. They found that in both groups, degenerative changes were correlated with age instead of occupation. In a multiple logistic regression analysis, Zejda et al[4] found that age was the only significant contributor to the x-ray degenerative changes within the cervical spine among coal miners. Studies of lumbar disc degeneration suggest that lumbar disc degeneration is more common in the highly loaded lower lumbar spine. These studies also show that back pain is not necessarily correlated or associated with morphologic or biomechanical changes in the discs[10].

The widespread belief that patients with cervical radicular symptoms will eventually develop overt myelopathy is not supported by good evidence[7]. It has been shown that untreated patients with cervical degenerative disc will not necessarily develop into progressive disability[7]. Further, it has also been shown that the DDD does not remain static over lengthy periods of time [7].

At present, a wide array of treatment options, operative or non-operative, for DDD are available[7-15]. These treatments include anti-inflammatories, exercise, weight loss, physical therapy, discectomy with or without fusion, intradiscal electrothermal therapy, prosthetic disc nucleus device, disc arthroplasty or bioengineered nucleus pulposus replacement.

When symptoms are refractory to conservative therapy, surgical treatment is usually considered. The goals of surgical treatments are to decompress neural compression, restoration of vertebral alignment and stabilization. Decompression involves removal of the soft disc or osteolytic structures that compress the neural elements. Alignment restoration involves restoration of the disc space height and neural foraminal height. Stabilization involves elimination of motion in order to induce resorption of posterior osteophytes[21].

Common surgical techniques to treat cervical DDD include discectomy with or without fusing the two adjacent vertebral bodies[13,21]. However, over the past 50 years, spinal fusion has generally become the standard surgical care for numerous pathologic conditions of the spine including DDD[16,17]. The hypothesis behind spinal fusion is that the spinal pain experienced by patients is mainly associated with continued motion at the affected disc level. As such, stabilization of the affected disc or motion segment will provide pain relief[8,18,19].

It has been shown that discectomy without fusion results in spontaneous fusion in up to 80% of the cases[18,21]. Autogenous tricortical graft is the traditional graft for discectomy and fusion. The graft is usually obtained from the patient's iliac crest[21]. This type of graft is both osteoconductive and osteoinductive (as opposed to osteoconductive only with the allograft) which usually results in reliable fusion and its ability to maintain structural integrity. The most common approach to discectomy is through the anterior approach, even though it can be done posteriorly. The most cited anterior discectomy procedure in the literature is the one according to Smith, Robinson and Clowart[21].

A number of studies have demonstrated that single level fusion without instrumentation (plate, cage) with Smith and Robinson autograft have non-union rates between 0% - 20%[13,18,21,24]. However, when multiple levels are fused, the non-union rates have been shown to increase up to 68%, especially if allograft is used[13,18,21].

The harvesting of iliac crest bone can be associated with short and long term morbidity in up to 22% of the cases[21,30,31]. Most frequently reported problems include post operative pain, wound hematoma, infection, pelvic fracture, nerve palsy and chronic donor site pain[30,31]. In a Cochrane Systematic Review, Jacobs et al (2004) note that 2.4% of patients reported these complications.[21]. It has also been documented that anterior cervical discectomy and fusion as treatment for adjacent segment disease is a difficult procedure. There is an increased rate of recurrent laryngeal nerve injury, vertebral and or carotid artery injury, perforation of the oesophagus or trachea, post operative dysphagia, hematoma, pseudo arthrosis, collapse of interbody graft and potential hardware problems[18,20,36]. This procedure requires more dissection than the traditional single level operation.[20].

In summary, cervical spinal fusion is designed to eliminate the normal motion of one or more vertebral segments. Fusion is successful in many cases because the motion itself is the root cause of pain due to the inability of the degenerative vertebral segment to support the weight of the body comfortably. Thus, when the problematic segment is fused, it no longer moves and therefore cannot cause pain[19,22]. However, it should be noted that documenting and confirming that the cause of pain in each patient comes from the intervertebral disc is problematic[37,55]. Experts argue that solid fusion of the vertebrae associated with DDD merely masks the true disease process by eliminating the intervertebral motion and its normal physiological function. Further, many authors argue that when the vertebral segment is fused it causes stress and increased motion in the segment adjacent to the fused levels. This phenomenon, in turn,

may initiate or accelerate the degenerative disease process adjacent to the fused level[9,10,l19,22,23]. Thus the emergence of artificial vertebral disc implants.

The premise behind artificial vertebral disc implantation is that abnormal motion will be corrected, that the intervertebral space height will be restored, physiological curvature and the instantaneous axis of rotation will be normalized, that the corrected normal intervertebral motion will be maintained over time, and patients will experience pain relief and return to function[9,10,19,22,25,26,27]. It should be noted that the implantation of artificial intervertebral discs represents an opposite philosophy in treating DDD as compared to spinal fusion. The purpose of implantation of artificial disc is motion preservation, while spinal fusion is motion elimination.

One of the major arguments against spinal fusion is that spinal fusion accelerates the development of the adjacent segment degeneration[9,10,l19,22,23]. Based on case series reports, various authors[16,32-35] have shown that there appeared to be an increased incidence of adjacent segment degeneration after arthrodesis. The most widely quoted data came from a study by Hilibrand et al[32]. In his case series of 374 patients who had a total of 409 anterior cervical fusions for the treatment of cervical spondylosis with radiculopathy or myelopathy or both, Hilibrand et al[32] observed the occurrence of symptomatic adjacent segment disease at a relatively constant incidence rate of 2.9% per year during the 10 year post operation follow-up. Using survival analysis methods, the authors predicted that 25.6% of the patients who had an anterior cervical arthrodesis would have new disease at an adjacent level within 10 years after the operation. However, contrary to the hypothesis that fusions accelerate degeneration of the adjacent segment, Hilibrand et al[32] observed that the risk of new disease at an adjacent level was significantly lower following a multi-level arthrodesis than it was following single level arthrodesis. In this article[32] and its recent follow-up[16], Hilibrand et al concluded that the results of their studies suggested that adjacent segment disease was indeed a common problem, however, it may reflect the natural history of the underlying cervical spondylosis instead of the effect of the cervical fusion.

Objectives:

In September 3, 2004 the WCB of BC, through the Evidence Based Practice Group, received a proposal to provide funding for a trial on the evaluation of the role and potential benefits of artificial cervical discs (Bryan's disc) in WCB patients.

As such, the primary objectives of this systematic review are:

a) to investigate the safety and effectiveness of intervertebral cervical disc implants, in particular, Bryan's disc, in treating DDD;
b) to investigate its relative advantage compared to cervical fusion in treating DDD.

The secondary objective of this review is to summarize available systematic reviews on artificial disc implantation in general.

Materials and Methods:

Literature searches, up to October 25, 2004, were undertaken on commercial medical literature databases including Cochrane Database of Systematic Review (CDSR), American College of Physicians (ACP) Journal Club, Cochrane Central Register of Controlled Trials (CCTR), BIOSIS Previews®, CINAHL®, EMBASE®, Ovid MEDLINE® In-Process, Ovid Other Non-Indexed Citations®, Ovid MEDLINE®. Other non commercial databases including Bandolier, the US Agency for Healthcare Research and Quality, the US Institute for Clinical System Improvement and the NHS Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (DARE) at the University of York Database; websites of members of the International Network of Agencies for Health Technologies Assessment (including Alberta, Ontario and the Quebec Office of Health Technology Assessment in Canada, the US, Great Britain, France, New Zealand, Australia, Sweden and Denmark), the US Food and Drug Administration and Health Canada. Websites of other WCBs in Canada (including Alberta and Ontario) and in the US (Washington State, Colorado and Minnesota); private health insurance companies (including Aetna, Blue Cross Blue Shields, Regence, Humana, Permanente Medical group, Tuft, Western Health Advantage and Cigna); websites of orthopaedics and/or spine surgeon associations including the US, the UK, Canada, Australia and other agencies including the US NIH and the US Department of Veterans Affairs were also searched.

The primary literature searches were conducted in order to identify primary research on artificial cervical disc. These searches were undertaken by employing keywords: bryan cervical disc prosthesis OR cervical disc prosthesis OR intervertebral cervical disc prosthesis OR artificial cervical disc OR artificial cervical implants OR artificial cervical disc implants OR prestige cervical disc OR cummins disc (or discs) OR bristol disc (or discs) OR cummins cervical disc OR bristol cervical disc OR prestige cervical OR prestige artificial cervical OR prestige cervical disc OR cummins artificial cervical disc OR cummins cervical disc OR prodisc-c implant OR prodisc-c artificial cervical disc OR prodisc-c cervical disc OR prodisc c implant OR prodisc c artificial cervical disc OR prodisc c cervical disc OR prodisc c OR prodisc-c OR cervicore device OR cervicore artificial cervical disc OR cervicore cervical disc OR cervicore artificial disc OR cervicore disc (or discs) OR pmc prosthesis OR pmc cervical disc OR pmc implant OR pmc disc OR pmc artificial cervical disc OR prestige implant. The search was limited to human application of artificial cervical disc. There were 22 published primary research papers identified from the initial searches. Of these 22 articles, 15 were relevant to this systematic review.

Secondary, non systematic, searches were undertaken in order to identify reviews or systematic reviews on artificial vertebral discs in general (lumbar, thoracal or cervical). This search was conducted by employing keywords (artificial discs OR artificial disc implant OR artificial disc prosthesis) AND (review OR systematic review). The secondary searches were undertaken on Cochrane Database of Systematic Review (CDSR), American College of Physicians (ACP)

Journal Club, Ovid MEDLINE®, Bandolier, the US Agency for Healthcare Research and Quality, the US Institute for Clinical System Improvement, websites of members of the International Network of Agencies for Health Technologies Assessment (including Alberta, Ontario and the Quebec Office of Health Technology Assessment in Canada, the US, Great Britain, French, New Zealand, Australia, Sweden and Denmark and the US Department of Veterans Affairs).

Results:

Artificial Intervertebral Disc.

The structure, function and pathology of peripheral joints, such as hip and knee, are fundamentally different than the functional spinal unit[10]. The function of peripheral joints is to allow a wide range of mainly rotatory movements by means of cartilaginous interfaces. On the other hand, the intervertebral disc is not a simple cartilaginous interface joint. It is a mixed structure consisting of a peripheral collagenous bands (annulus fibrosus) uniting the adjacent vertebral endplates[14]. This band is composed of 15-20 concentric layers of alternating oblique fibres. In the center lies a core of mucopolysacharide gel and proteoglycans (nucleus pulposus). The nucleus pulposus is extremely hydrophylic, thus generating tension in the peripheral annulus, like air in a tire, even in the absence of external loading[70]. The highly complex structure of the disc allows small movements along and around the 3 main axes of vertebra. As a result, the center of rotation is constantly modified along two axes simultaneously. In peripheral joints, stability is achieved by ligamentous structures. In the axial spine, the disc, on its own, provides a major stability factor, for example, alternating arrangements of collagen fibers in the annulus which creates an efficient system to control and restrict rotation. Peripheral joint degeneration consists essentially of the destruction of cartilaginous surfaces followed by subchondral bone destruction and deformation of surfaces. The movement on the destroyed joint surface creates pain. As such, a 'simple' replacement of these surfaces would alleviate the pain and increase joint functions. On the other hand, spinal disc degeneration consists of a decrease in the hydrophilic properties of the nucleus as well as the appearance of annulus tears. In the functional spine unit, the disc is not the only mobile structure and secondary osteoarthritic modifications of the facet joints influence disc degeneration and vice versa. Further, the origin of pain in the functional spine unit, at present, is not well understood and appears to be more complex than in the peripheral joints. It should also be noted that it is estimated that the spine undergoes approximately 100 million flexion cycles during a lifetime and approximately 6 million per year of slight motion during breathing[23]. On the other hand, it is estimated that 30 million cycles appear to be the optimal life length of a disc implant and 10 million cycles should be the minimum number that any implant should withstand. As such, it can be concluded that to develop an artificial disc is a more complex undertaking than developing artificial peripheral

joints. It should also be noted that testing procedures and models to evaluate the long term results of spinal artificial discs have not been established or validated[69].

Intervertebral disc replacement has been under investigation since the 1950s[10]. In the late 1950s, Nachemson injected self-hardening liquid silicone rubber into cadaver disc and undertook some basic biomechanical testing to demonstrate a relative restoration of some disc properties. The first disc prosthesis was implanted by Fernström in the late 1950s. This consisted of a metal ball (in fact it was an SKF ball bearing) that was implanted into the disc space after lumbar disc excision[70]. To date, various designs have been proposed, patented and some have been implanted in human beings. An article by Szpalski, Gunzburg and Mayer[10] provides a comprehensive historical overview on spine arthroplasty designs. However, among these different designs, two key principles appear to be important [10]:

a. To reproduce the viscoelastic properties of the disc. These are usually made from various silicone or other polymers. However, some of the designs rely on springs and or piston systems. Some are injected in monomer and polymerized in-situ. One such design that is currently under investigation includes the PDN® disc nucleus[71].
b. To reproduce the motion characteristics of the disc. These are mechanical devices made from metal with some implants also incorporating polyethylene couples. These designs are inspired by peripheral joint prosthesis.

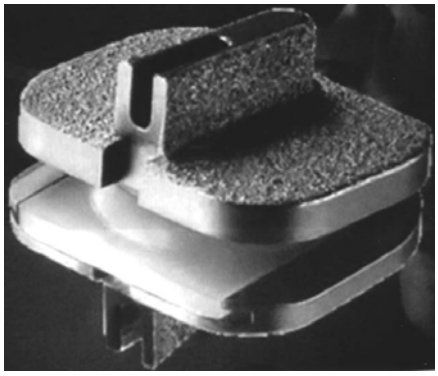
Some devices attempt to combine both principles. Devices that attempt to reproduce the viscoelastic properties of the disc are currently at early stage. It should also be noted that stem cell[72] and gene therapy[73] have been tested in treating DDD. As such, in this review, the EBPG concentrates on those devices that have attempted to reproduce the motion characteristics of the disc. Devices that have been approved by either the US FDA and or the Health Canada's Therapeutic Products Directorate Medical Device section, with emphasize on the cervical artificial disc are the main focus of this review. Brief descriptions on some of these artificial discs, cervical, lumbar and PDN® disc nucleus, are given below.

The Bryan Total Cervical Disc® is designed as a low friction, wear resistant elastic nucleus. This nucleus is set between and articulates with two Ti plates covered with porous coating and screwed to the vertebral bodies. A flexible membrane surrounds the construct. Theoretically, it allows range of motion in all planes[23]. This device has been approved for use in Canada since October 2003[63] and currently is under the US FDA investigational device exemption trial.

Figure 1. Bryan's Cervical disc.

Bristol - Cummins - Frenchay cervical disc is the early predecessor of this series of Prestige discs I, II, ST and the most recent one STLP[74]. The Prestige disc is basically a ball and socket type metal on metal disc made from stainless steel. At present, the Prestige ST is under the US FDA Investigational Device Exemption study.

Figure 2. Prestige ST cervical disc.



The Prodisc-C cervical implant is a metal on polymer implant. It consists of two forged CoCrMo alloy endplates and an ultra high molecular weight polyethylene inlay element[75]. The polyethylene insert is fixed to the inferior end plate. At present, the Prodisc-C is under the US FDA Investigational Device Exemption study.

Figure 3. Prodisc - C cervical disc.

This device features opposing Co-Cr bearing surfaces that are nested to provide a center of rotation below the bottom base plate for flexion and extension, and a center of rotation above the top base plate for lateral bending. The vertebral body contact surfaces of the base plate feature a Ti plasma spray and 2 spikes[76].

Figure 4. CerviCore (FlexCore) cervical disc.

This device features two porous-surfaced Co-Cr end plates with a polyethylene bearing surface attached to the caudal end plate. The surfaces of end plates are coated with TiCaP. The articulating surface of this device extends across the entire bearing surface. As such, it creates a larger radius of articulation and increased translation through rotational arc[77].

Figure 5. Porous Coated Motion (PCM) cervical disc.

This is a mobile bearing implant made from CoCrMo with ultra high molecular weight polyethylene articulating bearing surface[78]. This device has just recently been granted approval by the US FDA. In Canada, Charité III lumbar disc has been granted permission by Health Canada since 2003.

Figure 6. Charité III lumbar disc.

The ProDisc is an articulating disc with polyethylene core. The metal end plates are plasma sprayed with Ti and have two vertical fins for fixation in the end plates. At present, the ProDisc II is under the US FDA Investigational Device Exemption study[79].

Figure 7. ProDisc II lumbar disc.

Figure 8. PDN prosthetic disc nucleus device.

This device is intended for patients with discogenic back pain whose vertebral segment(s) are not so degenerated that immobilization of the affected vertebrae is the only reasonable alternative[14]. The goal of this device is to relieve LBP while maintaining disc height and allowing normal flexibility[80]. The PDN device is composed of hydrogel pellet that is encased in a polyethylene jacket. The pellet is a co-polymer of polyacrylonitrile and polyacrylamide. The ratio of these two polymers determines the water absorbing and binding behaviour of the finished hydrogel. The ability to absorb water allows the device to restore or maintain disc height[14]. This device increases disc height by increasing circular tension. Early results showed a high rate of device migration[80].

Experts have expressed concern regarding the possibility of device failure and bodily reaction towards wear-related particles from artificial disc implants, particularly for the cervical implants due to the proximity with vital organs[10,60,69]. Even though, in-vitro simulator process has been conducted[47], Anderson et al[81] published small 'in-vivo' case series on this issue based on data from Bryan and Prestige discs.

Of the approximately 5500 patients, world wide, treated with the Bryan disc, 11 were known to have been explanted (none was due to device failures, no further information was given with regard to the cause of explantation). Six of these 11 explanted devices were returned to the manufacturer for further analysis, two of which had periimplant tissues sampled at the time of revision. These two samples were retrieved at 13 and 13.6 months post implantation. Of more than 300 Prestige discs that have been implanted, 3 were known to have been explanted (none was due to device failure). In two of these 3 samples, periimplant tissue samples were taken. These two samples were explanted at 18 and 39 months post implantation[81]. Based on these 4 samples of the two prostheses types, Anderson et al[81] concluded that simulator generated reports predicted adequate wear-related characteristics for both Bryan and Prestige cervical disc for a minimum of 40 years. Comparison of simulated data with those of the retrieved specimens indicated that the wear was less than predicted in simulators by 5 to 10 fold. The inflammatory response seen in the periprosthetic tissues was minimal and not characteristic of inflammatory responses in failed diarthrodial joint arthroplasties.

Published early reviews on artificial cervical and/or lumbar disc.

1. Disc prostheses and arthrodesis in degenerative disease of the lumbar spine[56].

   This is a literature review produced by the Health Technology Assessment Unit of the French National Agency for Accreditation and Evaluation in Health (ANAES). ANAES is a member of the International Network of Agencies for Health Technologies Assessment. The full version of this review is available in French and had to be mail ordered. Given the date of the publication (May 2000), the Evidence Based Practice Group decided to evaluate the English version (summary) that is available online.

   In this summary, there was no information on the type of prosthetic discs, type of review (systematic or non systematic) as well as the methodology employed in conducting this review. However, the report states that the 'document has been independently produced using rigorous scientific methods and comes from a review of the international literature and from consultation with experts'. As such, the EBPG did not assign any level of evidence. However, it is most likely that this is a systematic review document.

   In its conclusion, ANAES stated that:

   - Even though some surgeons had more than 10 years experience, the use of disc prosthesis could not be regarded as routine practice. It suggests that the use of these devices be restricted to a small number of centres which were equipped to carry out a properly designed clinical studies.
   - A follow up period of ≥ 10 years was important because of the potential complications which might occur in the long term, such as degradation of fixation material and or degradation of the components subject to friction.
   - The Agency suggested the development of a central registry for prostheses for evaluation purposes.

2. Prosthetic intervertebral disc replacement[57-59] (Level 1 evidence).

   In November 2004, the UK National Health Services' (NHS) National Institute for Clinical Excellence (NICE) issued a guideline regarding prosthetic intervertebral disc replacement[58] following thorough consultations[59]. The guide was based on a systematic review published by the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) in November 2002[57]. ASERNIP-S is a non commercial service provided by the Royal Australasian College of Surgeons (RACS).

   In its systematic review, the ASERNIP-S conducted a systematic literature search on Medline, PreMedline, EMBASE, Current Contents, PubMed, Cochrane Library and Science Citation Index from the inception of the databases until October 2002. The authors also searched other databases including The York Centre for Reviews and Dissemination (DARE), the US Clinicaltrials.gov, the UK National Research Register, SIGLE (System for Information on Grey Literature in Europe, a commercial database) and Grey Literature Reports 2002. (The EBPG could not find the publisher of this

report). The authors also searched relevant online journals (did not specify which journal) and the Internet (did not specify which websites). Boolean search term was employed for these searches (the authors did not specify the words being used). Articles were retrieved when the abstract contained safety and efficacy data on prosthetic intervertebral disc replacement that came from a randomized controlled trial (RCT), other controlled or comparative studies (CT), case series and case reports. The English abstracts of non English papers were included if it contained safety and efficacy data. The review was limited to lumbar prosthetic devices that were at the time available on the market (thus, earlier models of lumbar prosthetic device, e.g. SB Charité model I and II, which were not in production anymore were not retrieved and appraised). There was no information on the process of the review included in this document. However, a separate document provides information on the standard review procedure adopted by ASERNIP-S[64]. These review procedures comply with most standard high quality procedures on systematic reviews.

The authors found 1 non randomized comparative study (one level vs. bi level replacement) and 9 case series. All of these studies were on SB Charité III lumbar disc models. Two RCTs in progress were also identified, including the RESORD (Randomized European Study on Replacement of the Disc: Hope Hospital, Salford, UK) and SB Charité III Intervertebral Dynamic Disc Spacer FDA Study (The EBPG appraised the outcome of this RCT separately, below, based on data available on the US FDA websites).

With regard to safety, the authors found that the surgical complication rates varied between 13% - 45%. However, definition of complications was different across studies. Re-operation rate varied from 3% - 24%. Rates of implant related problems ranged from 1% - 4%. With regard to its efficacy, overall clinical results were judged to be satisfactory, good or excellent in at least 60% of cases in 3 studies which used these criteria. Two of 4 studies reporting pain relief found a statistically significant reduction in either low back or leg pain in the majority of patients. Of 4 studies reporting RTW, 67% - 87% patients RTW while 1 study did not find any difference in work status pre- and post-implant.

The authors concluded that the benefit of prosthetic lumbar disc in patients 45 years and older remain unresolved in the literature. Concerns were also expressed with regard to:

- Potential side effects including persisting low back pain, spinal infection, damage to nerve roots, cauda equinae, great vessels, and the pre-sacral plexus.
- Life expectancy of the device.
- Lack of RCTs as well as the fact that, at the time, 'spinal fusion' procedures were, just then, embarking on RCT studies in an attempt to document is safety and efficacy.
- Training and or facility.

As such, in its Consultation and Guidance[58, 59], NICE stated that the current evidence on the safety and efficacy of prosthetic intervertebral disc

replacement is not adequate to support the use of this procedure without special arrangements for consent and for audit or research.

3. Procedure brief: Artificial cervical disc replacement[60].

This is another systematic review conducted by the ASERNIP-S. However, in this procedure brief, the EBPG failed to obtain any information leading to the selection of primary studies presented in this review. Three primary studies on cervical disc prosthesis were presented - one study on Bryan's cervical disc and two on Bristol-Cummins (subsequently referred to as Prestige) disc

One study on the Bryan cervical disc is most likely a subset of Reference 42 that is appraised below. As such this study is not appraised here.

One small, case control type study on the Cummins (aka. Bristol or later known as Prestige) cervical disc stated its objectives as comparing the Cummins disc (n = 12) with interbody fusion (n = 13) with respect to radiographic changes in angulation occurring at adjacent levels. The authors stated that the fusion group showed a significant ($p < 0.001$, Fisher's exact test) increase in adjacent level movement at 1 year follow-up when compared to the Cummins disc. This result suggested that the fusion resulted in a greater degree of motion at adjacent spinal levels while the Cummins disc was more protective against undesirable motion in adjacent levels, while maintaining motion at the prosthetic site. The EBPG was not able to appraise or verify these important comments due to the fact that the reference stated by ASERNIP-S regarding this study is incorrect. The reference on this case-control study as stated by ASERNIP did not contain data or even discuss this study.

The third study, was on the Cummins disc, reported a series of 20 patients for an average follow-up of 2.4 years with regard to complications. This study is most likely a subset of Reference 49, as such it is not appraised further.

Due to the discrepancy in references cited by ASERNIP-S in this systematic review, the EBPG is exercising high caution with regard to this appraisal and its conclusions. As such, the EBPG does not assign any level of evidence to this systematic review.

Important information presented in this systematic review is on the ongoing two pilot studies currently being conducted in Australia (one on the Bryan disc and one on the Cummins type). The EBPG will follow up on this study when it has been published.

4. Rapid review: Artificial intervertebral (lumbar) disc replacement[61] (Level 1 evidence).

This is another systematic review on artificial lumbar disc conducted by the ASERNIP-S. The objective of this rapid review was to investigate the safety and efficacy of lumbar prosthetic discs that were commercially available at the time. As such, the review was limited the SB Charité III lumbar disc. The authors conducted systematic searches on various commercial databases including Medline, PreMedline, Embase, Current

Contents, PubMed, Cochrane Library, Science Citation Index, SIGLE and Grey Literature Reports databases using Boolean search term from the inception of each respected database until October 2002. The authors also searched non commercial databases including the York's DARE, The US Clinicaltrials.gov and the UK National Research Register. There was no limitation imposed with regard to the language of publications.

Articles were obtained if the abstract contained safety and efficacy data on prosthetic intervertebral disc replacement in the form of RCTs, other controlled studies, case series and case reports. There were 11 studies identified - one was a non randomized comparative study, 9 were case series and one study that was identified but was not recovered. There were 2 RCTs in progress that were identified, i.e. the RESORD study and the SB Charité III FDA approval study (this study is appraised and presented below).

The authors found that significant reductions in leg and or back pain were noted in several studies with one study reporting that 65% of their patients still experienced a reduction in pain at an average of 2 years post surgery. Good or excellent outcomes ranged from 24% to 79% of the patient samples. Poor outcomes were reported in two studies at a rate of 7% and 14%. One study reported that 2/5 patients had recovered motor symptoms following disc replacement. However, the authors found that the quality of these studies were low.

The literature also suggested that complications were frequent. Total complication rates reported in these studies ranged from 17% to 45%. Two studies reported complication rates of 13% and 17%, which the authors claimed to be attributable to the anterior surgical approach utilized. Implant migration was noted in 3 of 4 studies which measured this outcome and were reported at the rates of 4.3%, 7% and 43.6%. Implant failures were reported in 2 studies at a rate of 1% and 17%. Re-operation ranged from 3% to 24%. One of these studies showed that only 25% of revised surgical patients benefited from this second procedure.

In its conclusion, ASERNIP-S cautiously stated that artificial lumbar discs might be effective in reducing pain but high levels of complications could occur. ASERNIP-S suggested that further research was needed to refine the design and placement of the discs as well as to compare prosthetic discs with alternative techniques such as spinal fusion.

5. Total disc replacement for chronic low back pain: background and a systematic review of the literature[62] (Level 1 evidence).

The purpose of this systematic review on the comparison of intervertebral disc arthroplasty to arthrodesis was to collate information on clinical results, radiologic results in terms of loosening, subsidence of the implant and polyethylene wear, the mobility of the motion segment, the incidence of adjacent segment degeneration and the incidence of facet joint degeneration at the operated level, perioperative complication rates, the availability and possibility of salvage procedure in case of artificial disc implant failure,

removal procedure without major complications in cases of device failure, and the indication for arthroplasty of a vertebral motion segment.

The authors searched four commercial databases, including Cochrane Library, Current Contents, Medline and Cinahl (from inception to January 2002 or December 2001), by employing various search strings which were adequate in identifying published studies in order to answer the purpose of the review. One of the authors did manual searches on references from selected articles (no further information). On these searches, the authors did not impose any limitation on the date and language of publication. Articles were excluded on the basis of title and abstract when it was evident that one of the interventions used was not an intervertebral disc prosthesis, the indication on which patients received was not for DDD at the lumbar level, the outcome parameter was not a clinical measure, the articles had not been published in a peer-reviewed journals, or the articles were on older models of implants which were not in use anymore. The manuscript selection processes, categorization of study designs and the methodological quality evaluation were considered adequate.

There were 430 articles identified through these electronic searches. Of these, 418 were discarded due to irrelevancy, based on the title and abstracts. Of the remaining, 12 articles were retrieved and five of these were excluded further. Manual searching yielded 13 additional references. Eleven of these 13 were excluded for various reasons, including 5 due to their unavailability in any library in the Netherlands. As such, nine articles, including six retrospective cohort studies, one cross-sectional study and two prospective cohort studies were reported. The authors concluded that all of these studies contained many methodological flaws.

The authors concluded that short-term results (1 - 68 months) appeared to be comparable to results of arthrodesis. However, it should be noted that these studies were of low quality. None of the published articles addressed the issues of potential long-term problems of an artificial joint as experienced in total hip or knee replacement, despite the fact that SB Charité III lumbar disc had been on the market for > 10 years. The majority of lumbar disc arthroplasties were performed in patients aged 30-50 years old. Drawing from the results of total hip arthroplasty, the authors cautioned that in this age group there was a 30% revision rate within a 10 year follow-up period. Further, the authors concluded that none of the studies addressed the issue of radiologic loosening (as precursor of clinical loosening such as in hip arthroplasty), issues on subsidence of the artificial disc and issues on foreign body reactions to polyethylene wear. These studies did not show consistent results with regard to the mobility of the operative and adjacent segment degeneration. The complication rate was highly variable and was described in different ways and related to multiple different variables.

The authors concluded that, at present, there was no consistent evidence that disc replacement could reliably, reproducibly, and over time demonstrate clinical efficacy with continued segment with less adjacent segment disease.

The authors acknowledged the limitations of their systematic review including database coverage and possibility of publication bias.

6. Artificial discs: Applications to cervical and lumbar spinal surgery for degenerative disc disease[63] (Level 1 evidence).

This document was produced by a health technology assessment organization in Ontario. This report, also, provided information that artificial lumbar disc SB Charité III and Bryan cervical disc have been licensed for use in Canada since October 7, 2003 and May 6, 2003, respectively. Meanwhile, Raymedica's PDN (prosthetic disc nucleus)-SOLO product is under investigation by Health Canada since January 2004. However, this document did not comprehensively state the methodology employed in this review. To mitigate this problem the EBPG has been in contact, through e-mail on December 7, 2004, with Ms. K. Kaulback of the Medical Advisory Secretariat in Toronto, requesting complete information on the methodology of this review. The EBPG received the literature search strategy through e-mail on January 5th, 2005.

The purpose of this review was to summarize the safety and efficacy, including comparative efficacy, of artificial disc products and prosthetic disc nucleus. Specifically, the authors seek to answer questions on safety, including device failure, of the artificial devices and its outcomes compared to alternative approaches - particularly spinal fusion.

The authors searched INAHTA, Cochrane, Medline, Embase (both, from 1996 - November 2003), Medline In-Process and Other non-indexed citations, as well as conducting a manual search. The authors employed various combinations of keywords and subject headings, including intervertebral disk degeneration, spine fusion, spine disease lumbar spine, cervical spine, backache, intervertebral diskectomy, artificial disc, joint prosthesis, disk replacement and arthroplasty. The search was limited to English and French language literatures and to human subjects. There was no information on the criteria of inclusion and exclusion or the review methods. The search on these 2 databases yielded 438 citations, of which 130 were selected for further review. Nine studies were selected for final review.

The authors summarized that:

- Intervertebral prostheses (artificial disc and disc nucleus) have been widely used in Europe and Asia.
- At present, two intervertebral prosthesis, i.e. artificial lumbar disc SB Charité III and Bryan cervical disc are approved for use in Canada.
- Safety data suggested that adverse events were primarily associated with any surgery to the spine, not just intervertebral prostheses placements.
- Based on limited reports in the literature, neither intervertebral prosthesis device failure or debris production was likely to occur.
- Prosthetic disc nucleus was newer, targeted less severe disease and had not been sufficiently evaluated to draw any conclusions regarding its safety or efficacy.

- Comparative efficacy data for intervertebral disc prosthesis and spinal fusion is currently sparse.

Published primary studies on artificial cervical disc.

Published literature on artificial cervical disc, including Pointillart, Bryan's cervical disc, Cummins (a.k.a Frenchay or later as Prestige) cervical disc is summarized in Table 1. To date, there are 9[38-46], 1[48] and 5[49-53] published primary clinical research papers on Bryan's, Pointillart and Cummins (or Frenchay or Prestige I and II) cervical disc products. With the exception of 2 (most likely the data came from the same study) multicenter randomized controlled trials (RCT) on Prestige II disc versus anterior cervical discectomy with fusion[51,53], all of these primary research studies took the form of case reports or case series (Level 4-5 evidence). In some of these studies, the possibility of data overlap or multiple publications cannot be excluded. The only published RCT on artificial cervical disc[51,53] (Prestige II vs. discectomy and fusion) was of poor quality. As such, the results and conclusions of these studies are inconclusive.

With regard to Bryan's cervical disc, all of the patients in these case series showed improvement, including pain and quality of life as measured by SF-36, Neck Disability Index, preservation of joint movement at the surgical level and return to work rates compared to pre operation. However, it should be noted that the majority of these studies have methodological shortcomings (please see 'Note' column in Table 1). The longest follow-up period of these studies was only 24 months, with some of these studies presenting overlapping data. Data on complications was also addressed in some of these papers.

The US FDA Investigational Device Exemption RCT on Charité III® artificial lumbar disc.

In the FDA Talk Paper dated October 26, 2004[65] and subsequent letter of approval to the manufacturer[66], the US FDA approved the application of Charité III® lumbar artificial disc for use in the US. The approval was awarded after the completion of a 16-center randomized controlled trial study on the safety and effectiveness of Charité III® lumbar artificial disc compared to spinal fusion cage among patients with DDD[67]. DePuy Spine Inc., the manufacturer of the Charité III® lumbar artificial disc, conducted this non-inferiority randomized, prospective clinical trial comparing the clinical results of treatment between Charité III® and anterior interbody fusion using the BAK/L® fusion cage. The objective of this study was '…to determine whether the Charité artificial disc was any less safe and effective than a commercially available spinal fusion cage using bone graft'[65]. With regard to the outcome of this study, the FDA Talk Paper[65] stated that '…the study showed that two years after surgery, patients treated with the artificial disc did no worse than patients treated with intervertebral body fusion. The rates of adverse events from use of the artificial disc were similar to those from treatment with fusion. In addition, the study showed that there was no statistically significant relationship between motion at the level where the disc was implanted and the patient's relief from pain..'.

Important points from the FDA approval letter[66] and the US Department of Health and Human Services Clinical Review[67] paper include:

- The implant is indicated for spinal arthroplasty in skeletally mature patients with DDD at one level from L4-S1. Patients should not have > 3 mm of spondylolisthesis at the disease level and the patient should have failed at least 6 months of conservative treatment. Conservative treatments may include discectomy, laminotomy or laminectomy or nucleolysis at the same level to be treated. DDD is defined as discogenic back pain with degeneration of the disc confirmed by the patient history and radiographic studies.
- Complete exclusion criteria include those patients that had had previous or other spinal surgery at any level except prior discectomy, laminotomy, laminectomy or nucleolysis at the same level, multiple level degeneration, previous trauma to the L4, L5 or S1 levels in compression or burst, non-contained or extruded herniated nucleus pulposus, mid sagittal stenosis of < 8 mm (by CT or MR), spondylolisthesis > 3 mm, lumbar scoliosis (>11^0 sagittal plane deformity), spinal tumor, active systemic or surgical site infection, facet joint arthrosis, arachnoiditis, isthmic spondylolisthesis, chronic steroid use, metal allergy, pregnancy, autoimmune disorders, psychosocial disorders, morbid obesity (BMI > 40), bone growth stimulator use in the spine, investigational drug or devise use within 30 days, osteoprosis or osteopenia or metabolic disease, positive single or bilateral straight leg raising test.
- The requirement for surgeons to finish company provided training before employing the implant.

- For the manufacturer to conduct post market surveillance using 366 patients in the original study (201 randomized subjects, 67 training investigational subjects and 98 control subjects) for 5 years post implantation. The primary end point of the study is to evaluate the 'Overall Success' which is defined as improvement of at least 15 points in the Oswestry Disability Index (ODI) score compared to the baseline score; no device failures requiring revision, re-operation or removal; absence of major complication which is defined as major vessel injury or major neurological deterioration; and maintenance or improvement in neurological status vs. baseline, with no permanent neurological deficits compared to baseline status.
- Manufacturer should submit annual report of these post market surveillance patients. The report should include data on overall success, surgical interventions at the index or adjacent levels, pain measured at rest using visual analog scales (VAS), quality of life measurement using the SF-36, disc height, displacement of the device, incidence of radiolucency, correlation of range of motion with VAS score, ODI score and overall success, evaluation of adjacent segment degeneration and neurological status.
- In case of failure (as well as implant removal), whenever possible, implant should be removed and failure analysis should be done.

Aside from the issue on the accuracy of DDD diagnosis, its relation to chronic low back pain and the choice of BAK cage as comparative (thus 'gold standard') treatment for DDD, the EBPG found discrepancies in the conduct of this study. This critical appraisal is based on the information available on the US Department of Health and Human Services Clinical Review[67] and the Statistical Review for expedited PMA (P040006) Charité® artificial disc, DePuy Spine[68]. Major design problems within this study include:

- The unavailability of statistical analysis planning in the protocols. Statistical analysis planning was then submitted by the manufacturer, however, this plan was submitted after most of trial data were available. Further, there was no information regarding the blinding of the data services company hired by the manufacturer.
- Twenty three (11%) of Charité patients and 14 (14%) of the BAK patients were not included in the intention to treat analysis. At the time of analysis, these patients were either overdue for the 24 months follow-up or have not reached the 24 months follow-up. This violation may be considered as breaking the randomization procedure.
- There was violation on the inclusion and exclusion criteria among patients, even though the proportion was similar among both groups. Further, no patients who violated the protocol were excluded from the primary effectiveness analysis.
- There were differences in the demographic characteristics among BAK and Charité patients. These differences, included weight, BMI and pre-operation activity levels, on which BAK patients were heavier and less active than Charité patients. These differences were not taken into account in further analysis.

- There was no interim analysis planned (thus the p-value was not adjusted) by the manufacturer. However, data analysis was done prior to the completion of the study.
- Higher incidence of non device-related pain, wound infection and device-related additional surgery at operative level was observed among Charité group compared to the BAK group.
- Even though the mean flexion/extension ROM was reported, the lateral bending and axial rotation were not reported in this study.
- Among Charité patients, 14% had no pain relief or had their pain worsen and an additional 13% had only partial pain relief.

Even though the primary short term outcome of the study supported the hypothesis of non inferiority, given these discrepancies, the results of the study should be interpreted with caution.

Reimbursement status of artificial cervical disc in other workers' compensation boards and private insurances.

- **Workers' compensation board in Canada and the US.**

  The EBPG searched the websites of various workers' compensation boards in Canada, including Yukon[82], Nunavut[83], Alberta[84], Saskatchewan[85], Manitoba[86], Ontario[87], Nova Scotia[88], New Brunswick[89], Newfoundland[90] and Prince Edward Island[91], and several workers' compensation boards in the US, including Washington State Department of Labor and Industry[92],Colorado State Department of Labor and Employment[93], Ohio Bureau of Workers' Compensation[95] and Minnesota Department of Labor and Industry[94]. The purpose of this exercise was to find information on the reimbursement policy of these boards regarding artificial intervertebral disc for treating degenerative disc disease. The search failed to identify any information in that regard.

- **Private health insurance reimbursement policy:**

  Based on the available published literatures, Cigna[100], Blue Cross of California[98] and the Regence Group[97] concluded that implantation of prosthetic intervertebral discs experimental and investigational for DDD or post-laminectomy syndrome and would therefore not provide coverage.

  As of March 2005, Aetna[96] considers Charite artificial disc medically necessary for spinal arthroplasty in skeletally mature persons with DDD at one level from L4 to S1 who have failed at least six months of conservative management. However, the artificial cervical disc is still considered experimental and investigational, thus is not reimbursed under current scheme.

  Searches on the Tufts Health Plan Clinical Coverage Criteria and Non-covered Technologies websites[99] did not provide any information on the reimbursement status of artificial intervertebral discs.

Summary and Conclusions:

- The concept of establishing spinal pain as being caused by Degenerative Disc Disease is still problematic and unclear.
- Artificial intervertebral disc has been in use for almost two decades in mainly European and some Asian countries
- As of December 29, 2003, there are two artificial disc implants that have been licensed for use in Canada. These products include SB Charité III for lumbar disc and Bryan Cervical Disc Prosthesis.
- Recently, SB Charité III has been approved by the US FDA for use in treating pain associated with lumbar spinal disc degeneration. The approval was given, based on the US FDA investigational device exemption multicenter RCT study conducted by the manufacturer. It should be noted that our appraisal of this study suggests some areas of concern.
- At present, Prosthetic Disc Nucleus is under investigation in Canada and the US.
- Despite the claims that Bryan's cervical disc has been implanted in over 5000 patients worldwide, to date, there are only 9 published papers on the application of Bryan's cervical disc. These publications are all case series types (level 4-5 evidence).
- The insertion of artificial cervical disc has many technical issues and is not without risk. Complications, including the need for re-surgery, device migration and physiological bodily response to the wear debris of the implant have been reported.
- Due to the lack of direct comparison published data on cervical disc prosthesis against, for example, discectomy with or without fusion, as well as long term follow-up (> 10 years) safety and efficacy of artificial cervical disc still cannot be established. It is expected that, in the near future, short-term randomized controlled trial data will be available from the US FDA Device Exemption Study results.
- As such, at present, artificial intervertebral disc, in particular artificial cervical discs, should be considered still at an experimental stage.

Table 1. Cervical disc arthroplasty: summary of published primary research.

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

38	Bryan, multi center European countries.	Large case series (level 4-5).	Inclusion: patients with disc herniation or spondylosis with radiculopathy & or myelopathy that hadn't responded to conservative treatment (*no duration of treatment mentioned*).
			
			Exclusion: previous cervical spine surgery involving any other device, axial neck pain as the solitary symptom, significant cervical anatomical deformity or clinical instability, active infection.
				- 2 tools (relief of preoperative symptoms as measured by CSRS**, relief of objective neurological signs) combined, scored and categorized according to modified Odom's criteria*** .
				- QoL: SF-36.
				- 'Clinical Success' was defined as those with Odom's category of *Excellent, Good & Fair*.
					41 men & 56 women, aged 26-79 years.
					90 segments with radiculopathy, 13 with myelopathy.
					75 due to herniation, 33 due to spondylosis.
					Implanted at: 11 at C4-C5, 42 at C5-C6, 44 at C6-C7.
					Only partial data available & reported i.e. 46 for 1 year follow-up and 9 for 2 years follow-up.
						• At 1 year follow-up 87% clinical success. Odom's criteria: 70% excellent, 4% good, 13% fair, 13% poor. 86% demonstrated flexion/extension ROM at the implant level of ≥ 2^{O}.
						• At 2 years follow-up 89% clinical success. Odom's criteria: 78% excellent, 0% good, 11% fair and 11% poor. 100% demonstrated flexion/extension ROM at the implant level of ≥ 2^{O}.
						• Complications:
						  • 1 temporary dysphonia
						  • 1 re-operation at 3 months due to pain
						  • 1 re-operation 26 hrs post surgery due to hematoma
						  • 2 unresolved pain
						  • No device failure or explants
						• No subsidence.
						• 1 evidence of anterior/posterior device migration over 2 mm.
							- 'Clinical Success' criteria is somewhat misleading due to the inclusion of fair category.
							- The category used in Odom's criteria is somewhat misleading due to the numbers of individual parameters measured in the primary tools.
							- Single level only.
							- Possible overlap of patients with Ref 41 & 42.
							- Incomplete data reported.

39	Bryan, Canada.	Small case series (level 5).	Inclusion: C-6 radiculopathy without myelopathy that hadn't responded to conservative treatment (*no duration of treatment mentioned*). No evidence of spontaneous fusion nor instability nor malalignment at that or other levels.	Subjective radicular pain relief.	- 2 men, aged 33 and 46 years. - C6 radiculopathy. - ongoing symptoms for 2-3 years, worsening in the past 4 months.	• Immediate post-operative relief of radicular pain (*no level of pain measured/specified*). • Discharged home 1 day post-operation. • 3 weeks follow-up showed that disc height and spinal alignment have been restored. Device stayed in place. • 9 months follow-up excellent resolution of symptoms (*no level of pain measured/specified*).	- Very small case series. - Single level only. - Possible overlap of patients with Ref 40.

* see appendix 1 for level of evidence.
** CSRS is The Cervical Spine Research Society questionnaire to measure subjective symptoms.
*** modified Odom's criteria have 4 categories including *Excellent* i.e. improvement in most (≥ 80%) of the preoperative signs and symptoms, with little deterioration (≤ 10%), G*ood* i.e. improvement in some (≥ 70%) of the preoperative signs and symptoms, with some deterioration (≤ 15%), *Fair* i.e. improvement in half (≥ 50%) of the preoperative signs and symptoms, with some deterioration (≤ 20%), *Poor* i.e. i.e. improvement in few (< 50%) of the preoperative signs and symptoms, or significant deterioration (> 20%).

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
40	Bryan, Canada.	Case series (level 5).	Inclusion: cervical radiculopathy refractory to non-operative medical therapy, main symptom was arm pain, had pre-operative motion at the symptomatic level. Exclusion: main symptom was neck pain, history of trauma, infection, radiologic evidence of instability, comorbidity including rheumatoid arthritis, renal failure, osteoporosis, cancer preoperative corticosteroid medications.	- neurological outcomes (*no specification nor reported*) - QoL: SF-36 and Neck Disability Index (NDI) outcomes measured at pre-op, 1.5, 3, 6, 12 & 24 months.	- 26 patients, 30 implantation. - 18 with radiculopathy, 6 myelopathy & 2 with both. - 18 due to herniations, 7 due to osteophytes, 1 due to both. - 70% with arm pain, 74% with neck pain. - implanted: 1 at C4-C5, 13 at C5-C6, 16 at C6-C7.	• Statistically significant different ($p < 0.05$) in the mean NDI pre-op and 24 months follow up (18.7 and 4.75, respectively). • Trend toward improvement in the physical and mental components of SF-36 (*based on the graph for physical component, the trend may not be linear and improvement peaked at 12 months*). No data shown for the mental component. • 17/18 radiculopathy patients return to work within 0.2 – 12 months post op (median 2.8 months). • 7/8 myelopathy patients return to work within 0.33 – 3 months post-op (median 2.3 months). • Mean post-op sagittal ROM at the treated disc space was 10.1^0 pre-op and 7.8^0 post-op, statistically not significant different (*data from 16/26 patients only*). • Complications: - 1 experienced increase radicular pain post-op & improved within several weeks. - 1 had transient unilateral vocal cord paralysis & resolved within 6 weeks. - 1 persistent dysphagia for 6 weeks 1 possible device migration at 2 years post-op. -3/4 patients with prior fusion with plate had symptomatic disc herniation adjacent to the earlier fusion. - No LCS leaked nor wound infection. - No prosthesis subsidence. - No revision surgery.	- Canadian data. - Given the nature of multiple outcome measurements & the fact that the authors did not report the number of statistical test, multiple comparison can't be excluded. - Single and 2 levels. - Possible overlap of patients with Ref 39.

* see appendix 1 for level of evidence.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
41	Bryan, multi center European countries.	Large case series (level 4-5).	Inclusion: patients with disc herniation or spondylosis with radiculopathy and or myelopathy, hadn't responded to conservative treatment. Exclusion: previous cervical surgery involving any other device, axial neck pain as solitary symptom, significant cervical anatomic deformity, clinical instability, active infection.	- 2 tools (relief of preoperative symptoms as measured by CSRS**, relief of objective neurological signs) combined, scored and categorized according to modified Odom's criteria*** . - QoL: SF-36. - 'Clinical Success' was defined as those with Odom's category of *Excellent, Good & Fair*. - Anticipated success rate was calculated based on literature review on anterior cervical discectomy & fusion outcomes.	- 97 patients, 41 males 56 females. - Age 26 - 79 years. - 90 with radiculopathy & 13 with myelopathy. - 75 due to herniation, 33 due to spondylosis - implanted: 11 at C4-5, 42 at C5-6, 44 at C6-7. - 60/97 patients have been followed for 6 months. - 30/60 have been followed for 12 months.	• Clinical success rate: - at 6 months: 86% clinical success, radiculopathy has better rate than myelopathy; - at 12 months: 90% clinical success, myelopathy has better rate than radiculopathy. • Odom's criteria: - at 6 months: 68% excellent, 8% good, 10% fair & 8% poor; - at 12 months: 80% excellent, 3% good, 7% fair & 10% poor. • Complications: - 1 re-surgery due to unresolved pain due to operation on the wrong level. The right level was then implanted; - 1 temporary dysphonia after re-surgery of the above case; - 1 re-surgery due to persistent pain at 3 months; - 1 re-surgery 26 hours post-op due to hematoma; - 1 persistent right shoulder, arm & sternum at 6 months; - 1 persistent non specific shoulder pain at 6 months. • ROM: - at 6 months, 53/57 had flexion-extension ≥ 2^0; - at 12 months, 21/24 had flexion-extension ≥ 2^0. • No device failure or explantations reported. • At 6 & 12 months patients had slightly higher and slightly lower mental & physical components, respectively, of the SF-36 scores compared to the US population norms. It is not statistically significant.	- From multiple center in Europe. - Single level treatment only. - Possible overlap of patients with Ref 38 & 42. - The use of 85% threshold to claim success for the procedure is misleading due to the origin of the threshold data. - 'Clinical Success' criteria is somewhat misleading due to the inclusion of fair category. - The category used in Odom's criteria is somewhat misleading due to the numbers of individual parameters measured in the primary tools. - Incomplete data reported.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

42	Bryan, multi center European countries.	Large case series (level 4-5).
		The study was expanded to evaluating single & bi level.
			Inclusion: patients with disc herniation or spondylosis with radiculopathy and or myelopathy, hadn't responded to conservative treatment for at least 6 weeks.
			
			Exclusion: previous cervical surgery involving any other device, axial neck pain as solitary symptom, significant cervical anatomic deformity, radiographic instability, active infection.
			Radiographic instability was defined as translational instability > 2 mm, angular motion > 11^0 > than adjacent level.
				- 2 tools (relief of preoperative symptoms as measured by CSRS**, relief of objective neurological signs) combined, scored and categorized according to modified Odom's criteria*** .
				- QoL: SF-36.
				- 'Clinical Success' was defined as those with Odom's category of *Excellent, Good & Fair*.
				- Anticipated success rate threshold was calculated based on literature review on anterior cervical discectomy & fusion outcomes.
					- 146 patients: 103 single level & 43 bilevel.
					- 67 males, 79 females.
					- Age 26 - 79 years.
					- 134 with radiculopathy & 24 with myelopathy.
					- 94 due to herniation, 72 due to spondylosis.
					- 126/146 patients have been followed for 6 months.
					- 115/126 have been followed for 12 months.
					- 49/89 have been followed for 24 months (single level cases only).
						• Single level clinical success rate:
						- at 6 months: 83/92 clinical success;
						- at 12 months: 76/89 clinical success;
						- at 24 months: 44/49 clinical success.
						• Bi level clinical success rate:
						- at 6 months: 28/34 clinical success;
						- at 12 months: 25/26 clinical success.
						• Complications in single level:
						- 1 re-surgery due to unresolved pain due to operation on the wrong level. The right level was then implanted.
						- 1 temporary dysphonia after re-surgery of the above case.
						- 1 re-surgery due to persistent pain at 3 months.
						- 1 re-surgery 26 hours post-op due to hematoma.
						- 1 persistent right shoulder, arm & sternum at 6 months.
						- 1 persistent non specific shoulder pain at 6 months.
						- 1 adjacent level implantation due to disc herniation.
						- 1 severe disphonia after 2nd surgery.
						• Complications in bi-level:
						- 4 re-surgery due to hematoma, ongoing nerve root compression, pharyngeal tear, oesophageal wound.
						- 1 device repositioned.
						- 1 LCS leak.
						• No device failure or explantations reported.
						• Device position (radiological analysis):
						  • No subsidence.
						  • 2 device migrations (in single & bi-level each) & 1 suspected migration.
						  • The authors did not indicate the timing of the device migrations.
							- From multiple center in Europe.
							- Single & bi-level treatment.
							- The single level patients possibly same with Ref 38 & 41.
							- Slightly different inclusion & exclusion criteria than Ref 38 & 41.
							- The use of 85% threshold to claim success for the procedure is misleading.
							- 'Clinical Success' criteria is somewhat misleading due to the inclusion of fair category.
							- The category used in Odom's criteria is somewhat misleading due to the numbers of individual parameters measured in the primary tools.
							- Only partial data reported.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

42	Continued					• QoL:
						  • QoL was measured by employing the SF-36.
						  • At 6,12 and 24 months, single level patients had higher physical and mental component scores compared to pre-operative. However, the physical component scores at 6,12 and 24 months were lower than the US norms while the mental component score were slightly higher than the norm.
						  • At 6 & 12 months, bi-level patients had physical and mental component scores higher than their pre-operative. However, these scores were lower than the US norm scores.
						• ROM (flexion/extension):
						  • At 1 year follow up, 88% (only 90/103 levels reported) and 86% (49/86 levels reported) of the patients in the single & bi-level studies, respectively, showed flexion/extension ≥ 2^0.
						  • At 2 years 93% (only 46/103 levels reported) of the single level patients exhibited flexion/ extension ≥ 2^0.
							- With regard to ROM results, the authors did not provide any information on the ROM status prior to surgery.
							- Given the large SD on the mean ROM presented in Table 4, it is more appropriate to present the median of ROM instead of mean.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
43	Bryan, country unclear, most likely Canada (Australia & Canada authors).	Small case series (level 5).	Inclusion: had radiculopathy (12 patients) & or myelopathy (2 patients). Majority had pain in upper extremity (< 30% had neck pain). Exclusion: none given.	- Outcome assessed at pre-op, 1.5, 3, 6, 12, 24 months. - QoL: self administered Neck Disability Index & SF-36. - Radiological Cobb angle. - Late x-ray follow-up was defined as follow-up period of ≥ 6 months based on unpublished data that there was no different in Cobb angles between 6 and 24 months.	- Patients had at least 6 months of clinical & radiological follow-up post operative. - 14 cases: 9 males & 5 females. - Mean age 42 years (range 30 – 56 years). - 9 implanted at C5-6 and 6 at C6-7 (1 patient bi-level). - mean follow-up duration 12 months (range 6-24 months).	• All discharged day after surgery. • 13/14 return to previous occupation (5/6 on disability or WCB RTW). No time period specified. • Complication: o 1 had temporary 6 weeks vocal cord paralysis; o 1 persistent axial neck pain. • There was no significant different in ROM pre-op with early and late follow-up (probably due to small sample size). However, mean pre-operative ROM (8.96^0) was wider than the early (7.14^0) and late (8.25^0) mean follow-up ROM. • Post operatively, all patients demonstrated varying degree of kyphosis at the treated level. • The functional spinal unit angle became more kyphotic pos-operatively. • There was no significant different with regard to pre-operative Cobb angles with early and late post-operative (again probably due to small sample size). However, mean Cobb angle was wider (12.20^0 ± SD 13.41^0) than early (11.76^0 ± SD 12.41^0) or late (10.36^0 ± SD 15.48^0) radiological follow-up. • The NDI scores were significantly lower at the early and late follow-up compared to pre-operative. • Even though there was slight improvement, there was no significant different with regard to physical and mental component of SF-36 at pre-op, early and late follow-up.	- Patient selection was not clear in this small case series. - Possible overlap with Ref. 39 & 40. - Student's t-test being employed was inappropriate in this case due to the small sample size & heterogeneity of the data. - The number of statistical test being performed did not adjust for multiple comparison.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
44	Bryan, Canada.	Abstract only, Small case series (level 5).	Inclusion: had radiculopathy & or myelopathy . Exclusion: none given.	- QoL: self administered McGill Pain Index, Neck Disability Index & SF-36. - X-ray up to 24 months (no other info).	- 20 implants (no info on number of patients, levels etc).	• X-ray showed preserved motion at the operated levels up to 24 month follow-up (no other info). • Marked improvement on McGill Pain Index, Neck Disability Index and SF-36 (no other info). • Varying degrees of post –operative kyphosis were observed compared to pre-operative studies (no other info).	- Possible overlap with Ref. 39, 40 & 43. - Authors hypothesized that post-op kyphosis (previously unreported pos-op finding) may be a risk factor for neck pain. - Authors emphasized the importance of long term assessment in order to assess the occurrence of adjacent segment disease post artificial neck disc implant.
45	Bryan, Australia.	Small case series (level 5)	Inclusion: had MRI demonstrated spinal cord compression and or clinical cervical myelopathy. Exclusion: kyphotic deformity, severe multilevel spondylotic disc degeneration, spinal cord injury with possible instability, pure radiculopathy due to posterolateral disc protrusion or foraminal stenosis, when affected disc space could not be visualized on lateral supine cervical x-ray.	- Oswestry Neck Disability Index. - Subjective arm & neck symptom levels. - Post operative evaluation done at 24 hrs post-op, 6 weeks, 3 & 6 months and the yearly. - Odom's criteria were employed to determine surgical success.	- 7 patients: 4 males and 3 females. - Mean age 43 years (range 31-55 years). - Mean duration of symptoms was 16 months (range 3 weeks to 72 months) 2/7 were current smokers. - 7/7 had pre-op neck symptoms, 6/7 had pre-op arm symptoms.	• 9 prosthetics inserted. • Mean follow-up period 6 months, range 1-17 months. • 7/7 RTW 2- 4 weeks post-operative. • The authors combined all patients with largely different follow-up period in presenting and making conclusion for the outcomes. The authors claimed that there was significant different between pre-op and post-op on the Oswestry Neck Disability Index, subjective neck and arm symptoms and the Nurick grade. However, given the nature of the data presented it is difficult to make such conclusions.	- 2 sample t-test employed was inappropriate due to small sample size & heterogeneity of data.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
45	Continued			- Nurick grading for neurological assessment.	- 2/7 had acute disc herniations. - 6/7 had pre-operative loss of cervical lordosis. However, 0 had pre-operative kyphotic deformity. - 3/7 had pre-op myelopathic dysfunction of at least Nurick grade II. - 5/7 had both myelopathic & radiculopathic signs & symptoms pre-operatively. - 4/7 patients had possible spinal cord edema or myelomalacia (from MRI). - 6/7 had osteopathic compression. - 2/7 had significant disc herniation.		
46	Bryan, Australia.	Case report (level 5).	Inclusion: myeloradiculopathy with 2 level spinal cord compression. Exclusion: N/A.	-	- 49 years old female with C5-6 and C6-7 spinal cord compression. - 3 months history of weakness and pain in left arm.	▪ No surgical complication. ▪ Pain and numbness improved (no other info). ▪ 1 day post-op x-ray showed normal flexion-extension level at the treated level ▪ Discharge 48 hours post-operative. ▪ 6 weeks follow-up showed patient neurologically intact with no pain or paraesthesia and had normal neck motion. ▪ RTW 2 weeks post-operative. ▪ 11 months x-ray and CT scan showed no evidence of complications.	- This probably is the first reported bi-level artificial neck implant.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes
48	Pointillart, France.	Complications small case reports (level 5).	Inclusion: had cervicobrachial pains for > 3 months. MRI showed soft disc herniation Exclusion: no intervertebral instability.	- Description of complications.	- 10 patients, 5 males and 5 females. - Aged 25-49 years. - Levels: C5-C6 in 6 patients and C6-C7 in 4 patients.	• No complications during the intraoperative or early postoperative periods. • 2/10 had persistent pain: 1 need revision surgery that required prosthetic removal and arthrodesis, 1 need re-operation that had not been done. • X-ray from 8/10 did not show any mobility at the operated levels. Among these 8 patients, 2 showed evidence of osteophyte fusion and 5 showed circumferential fusion between the 2 vertebral bodies at 1 year follow ups.	- The author/ inventor of this implant concluded that the design of this particular disc failed the intended purpose of the implant i.e. the absent of mobility in the implanted levels.
49	Cummins (Frenchay or Bristol) cervical disc, UK.	Small case series (level 5).	Inclusion: spondylosis with myelopathy, radiculopathy or myelopathy, DDD. All with or without previous history of fusion or laminectomy or congenital fusion on different segments. Exclusion: N/A.	-No specific tools.	- 20 patients, 11 males and 9 females, on 22 joints (2 patients had two-level implants). - Aged 25-67 years. - Follow-up duration 3 - 65 months.	• 18/20 were re-examined. • 16/18 showed joint movement up to 5 years follow up. 2/18 whom did not show joint movement probably due to relatively large disc space distraction at time of implantation. • Mean flexion-extension movement was 5^0. • No radiological evidence of spontaneous fusion or osseus incorporation of the implant. • No patient required additional motion segment surgery. • Interspace height was preserved in all patients • No subsidence into vertebral bodies. • No wear debris were seen *(by x-ray)*. • 16/20 patients had pain improvement (*no quantification*). 3/20 was considered treatment failure due to persistent or worsened pain. • Patients with radiculopathy improved markedly. Patients with myelopathy were stable or improved (*no quantification*).	- This is a report on the first generation of Cummins disc - This disc has evolved & now known as Prestige disc. - Complications occurred were thought to be caused by poor screw placement, the use of uniform size joint regardless of the patient's anatomy and manufacturing error.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

49	Continued					• Complications:
						  • At time of surgery: 1 transient hemiparesis due to drill injury at spinal cord; 1 deltoid muscle paresis.
						  • 5/5 patients with 1st generation disc: 3/5 partial screw pullouts, 1 broken screw, 1 joint subluxation with persistent dysphagia.
						  • 15/15 patients with AO screw: 2/15 had partial screw pullout, 1/15 broken screw, 1/15 transient hemiparesis, 3/15 persistent mild dysphagia, 1/15 need joint removal due to manufacturing error and persistent pain.	

50	Cummins (Frenchay or Bristol) cervical disc (predecessor of Prestige I), UK.	Small case series (level 5).	Inclusion: spondylosis with myelopathy, radiculopathy or myelopathy, DDD. All with or without previous history of fusion or laminectomy or congenital fusion on different segments. Exclusion: N/A.	- QoL: SF-36, Neck Disability Index (NDI), VAS pain, European Myelopathy Scale (EMS). - X-ray .	- The characteristics of patients presented were on 17 patients (whole cohort that still alive). - Mean (± SD) age 50±11 years, range 52-75 years. - 10/17 males, 7/17 females. - 9/15 had previous neck operation.	• 15/20 original cohort were reported. • Flexion-extension range at 36 and 48 months were smaller compared to pre-op. The mean (range) (degree) flexion-extension at pre-op, 36 and 48 months was 7.5 (1-15), 4.9 (0-10) and 5.7 (0-12), respectively. • Improved SF-36 (mental and physical), VAS arm and neck pain, NDI and EMS at 48 months. At 48 months, physical SF-36, mental SF-36, VAS arm pain, VAS neck pain, NDI and EMS improved by 11.5%, 13.4%, 56%, 43%, 30.5% and 2.8%, respectively, compared to pre-op. • At 4 years follow-up, 8/11 still working. • No complication observed during this follow-up.	- Subset of Ref 49's patient. Reported longer follow-up period. - Incomplete follow-up. - Unclear methodology, eg. VAS pain scoring system.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

51	Prestige II, Switzerland.	**Multicentre randomized controlled trials**, UK, Belgium, Australia & Switzerland (level 2).	Objectives: to compare the Prestige II (intervention group/IG) with anterior cervical fusion with iliac crest bone graft (control group/CG) for treatment of single level DDD.
			
			Inclusion: cervical DDD defined as an intractable radiculopathy or myelopathy caused by neuroradiologically documented disc herniation or osteophyte formation. Had only single level DDD at C4-5 to C6-7 only. Unresponsive to conservative treatment for ≥ 6 weeks or the presence of progressive symptoms or signs of nerve root compression while conservative management continued. Had to be > 18 years. Pre-operative Neck Disability Index score > 30.
			
			Exclusion: had previous surgery at cervical spine or presenting with cervical spine condition other than symptomatic cervical disc disease that required surgical treatment and did not have osteopenia or osteoporosis or osteomalacia or cancer.
				- QoL: neck disability index (NDI) and SF-36.
				- VAS arm and neck pain.
				- Follow-up x-ray were collected and submitted to site independent for review.
				- 1 clinician directly involved with the surgery conducted the follow-up evaluation.
				- Complication level of severity was based on the WHO criteria i.e. grade 1 noticeable to patient but doesn't interfere with routine activity, Grade 2 interferes with routine activity but responds to symptomatic therapy or rest, Grade 3 significantly limit the patient's ability to perform routine activities despite symptomatic therapy.
					- 27 and 28 patients enrolled in the IG and CG, respectively.
					- Mean age of IG and CG were 44 and 43 years, respectively.
					- IG: 17 males & 10 females. CG: 12 males & 16 females.
					- No different between IG and CG with regard to smoking status, alcohol use, WCB status, race & educational level at recruitment.
						• 37/55 available for 12 months follow-up and 9/37 available for 24 months.
						• Follow-up at 6 weeks and 3,6,12, 24 months.
						• X-ray: at 12 months only partial results available. Motion analysis showed maintenance of motion in the IG and no 'significant' motion in the CG.
						• NDI: up to 24 months follow-up, both group showed improvement in the NDI score (n varies on each time). The improvement was statistically equivalent between two groups.
						• Neck pain and arm pain improved significantly during the first 6 weeks post-op in both groups and after that remain relatively stable in both groups.
						• SF-36: both groups showed improvement in the physical and mental part. The difference between both groups was not statistically significant.
						• Complications:
						  • IG: 17 complications. 1 Grade 2 due to malposition of the disc (5 weeks post op had neck pain), 14 temporary events including 1 transient recurrent palsy, 1 dysphagia, 6 residual neck pain and 2 with permanent neck and arm pain.
						  • CG: 19 complications including 3 re-vision surgery due to incorrect graft size, contaminated graft & hematoma at graft site; 11 intermittent arm and neck pain; 4 other temporary events. 16/19 was Grade 2 and 2/19 was Grade 3. 3 had continuous persistent neck pain.
							- No description of the study population.
							- No sample size calculation.
							- No statistical method incl. analytical principle.
							- Randomization method unclear.
							- No blinding.
							- No hypothesis.
							- Interim analysis most likely didn't take into account division of p-value.
							- The authors concluded because the result of anterior fusion was very satisfying as such it would be difficult to prove short term superiority of artificial disc.

Table 1 (cont'd)

Ref no.	Type of implant, Country	Study design (Level of evidence*)	Objectives, Inclusion and exclusion Criteria	Outcome tools	Characteristics of patients	Results	Notes

52	Cummins (Frenchay or Cummins generation 2), UK.	Case series (level 5).	Objectives: to assess the safety of the surgical technique, the stability of the device once implanted and the motion permitted by the joint.
			
			Inclusion:
			- Radiculopathy or myelopathy with CT or MRI evidence of compression by osteophytes or herniated disc *in the presence* of adjacent surgical or congenital cervical fusion.
			- Or patients with radiologic evidence of asymptomatic DDD adjacent to the symptomatic disc even if there was no history of fusion.
			
			Exclusion: non explained.
				- QoL: Neck Disability Index (NDI), SF-36, the European Myelopathy Score (EMS).
				- VAS neck and arm pain.
				- Follow-up at 6 weeks, 3, 6, 12, 24 months.
					- 15 patients: 10 males and 5 females.
					- mean (± SD) age 48 ± 18 years.
					- Device inserted between C3-C4 and C6-C7 (no further data).
						• At 24 months follow-up 14/15 showed angular motion preservation at the surgical level.
						• At 24 months, improvement was seen in VAS arm and neck pain, NDI, SF-36 physical and mental scores, and EMS. The different was not statistically significant compared to pre-op (small sample size ?).
						• 8/11 patients RTW at 24 months compared to 3/11 working pre-op.
						• Complications:
						  • 2 transient hoarseness.
						  • No evidence of wound or periprosthetic infection.
						  • 2/60 screws broke after 6 months.
						  • No joint dislocation.
						  • No subsidence of the device into vertebral body.
						  • 6 persistent or progressive neck/arm pain at 12 months.
						  • 3 re-surgery were done, one for foraminotomy, one laminectomy and one fusion.
							- This is considered as pilot study of the 2nd generation Cummins disc. There may be overlap of patients with Ref. 50.

53	Probably Prestige II, multicentre (abstract only).	**Multicentre randomized controlled trials**, UK, Belgium, Australia & Switzerland (level 2).	Inclusion: primary single level cervical disc disorder with radiculopathy and/or myelopathy. Exclusion: non explained.	- QoL: Neck Disability Index (NDI), SF-36, the European Myelopathy Score (EMS). - VAS neck and arm pain. - Follow-up at 6 weeks, 3, 6, 12, 24 months. - Primary end point was NDI.	- 4 multi nation centers recruiting 60 patients, randomized into receiving artificial disc or anterior discectomy with fusion (no info on population, randomization, blinding etc). - 36 patients were reported at 12 months follow up.	• At 12 months, no device related complications. • At 12 months, both groups showed clinical improvement. However, patients in the artificial disc group showed greater clinical improvement compared to fusion group. • No further data.	- Information available in abstract format. - Type of disc was not stated (most likely Prestige II). - High possibility of patient overlap with Ref. 51.

Appendix 1. Workers' Compensation Board of BC - Evidence-based Practice group. Grades of quality of evidence [adapted from 1,2,3,4].

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic reviews of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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