17 Erin Street,
Richmond VIC 3144
Australia

APPENDICES TO MSAC APPLICATION

USE OF ARTIFICIAL DISC REPLACEMENT IN PATIENTS WITH CERVICAL DEGENERATIVE DISC DISEASE

January 2010

To be read in conjunction with MSAC application form

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LIST OF ABBREVIATIONS

ABS	Australian Bureau of Statistics
ACDF	Anterior cervical discectomy and fusion
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australia Refined Diagnosis Related Groups
CDA	Cervical disc arthroplasty
CI	Confidence interval
CT	Computerised tomography
DDD	Degenerative disc disease
DRG	Diagnosis related group
EMBASE	Experta Medica Database
FDA	Food and Drug Administration
HTA	Health technology assessment
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICER	Incremental cost-effectiveness ratio
IDE	Investigational device exemption
IDP	Intradisc pressure
MBS	Medicare Benefits Schedule
MCID	Minimum clinically important difference
MCS	Mental component summary
MEDLINE	Medical Literature Analysis and Retrieval System Online
M-H	Mantel-Haenszel
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NDI	Neck disability index
NHMRC	National Health and Medical Research Council
NHS	National Health Survey
NSAID	Non-steroidal anti-inflammatory drug
PCS	Physical component summary
QALY	Quality-adjusted life year

RCT	Randomised controlled trial
ROM	Range of motion
RSA	Roentgen stereometric analysis
SD	Standard deviation
SF-36	Short form-36
SF-6D	Short form 6-dimension
TEC	Technology evaluation center
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organisation

APPENDIX 1: DESCRIPTION OF SERVICE

Appendix 1 relates to question 2.1- Description of service, in Section 2 of the MSAC application form.

SUMMARY OF MEDICAL DEVICE

In order to avoid the adverse effects/drawbacks associated with anterior cervical discectomy and fusion (ACDF), artificial cervical discs were developed in the 1990s and gradually launched onto the spinal disease market since early 2000. The benefits of artificial cervical discs include the mimicking of natural disc motion while still acting as a spacer to maintain lordosis, balance, joint mechanics, alignment, and foraminal height to reduce pain and improve function.

Artificial discs can be categorised based on several criteria, such as articulation, material, design, fixation, and kinematics (Chang *et al*, 2007). For an artificial disc to be successful, it should have natural spinal kinematics and be able to maintain biomechanical parameters and intradiscal pressures at the treated level and the entire spine. The procedure is safe and uncomplicated (Riina *et al*, 2008).

Disc replacement could possibly become the next gold standard in the treatment of degenerative cervical spine disease, hence rigorous study to ensure *in vivo* efficacy and safety is mandatory (Pickett *et al*, 2005). As a consequence, there have been numerous attempts to test the use of artificial cervical discs. In fact, the randomised head-to-head studies outlined in this application (Heller *et al* (2009), Mummaneni *et al* (2007) and Murrey *et al* (2009)) clearly demonstrate the benefits of CDA as a treatment option.

Current artificial discs available for the treatment of cervical degenerative disc disease in Australia include: Medtronic's Prestige® and Bryan®, Synthes' Prodisc-C® and DePuy Spine's Discover™ artificial disc. These are outlined in turn below. Though this is not an exhaustive list of the CDA options available, it is considered representative of the Australian market.

Bryan® Cervical Artificial Disc

The Bryan® cervical artificial disc comprises a closed unit with proprietary polyethylenecore, articulating with a polished titanium surface that is part of the titanium shell. The shell is enclosed in a polyurethane membrane (**Figure 1**). This device permits semi-constrained multiplanar motion over a variable axis of rotation to similar limits as a normal disc. The implant is secured by milling of the vertebral endplates of the adjacent vertebrae to accept the shell contour of the implant and facilitate subsequent bony in-growth to the implant surface cavities (Amit and Dorward, 2007).

Figure 1 Bryan® cervical artificial disc – Medtronic

Source: Coric *et al* (2006)

Prestige® Cervical Artificial Disc

The Prestige® artificial cervical disc comprises a ball-and-trough design to provide approximate physiologic motion, by a combination of rotational and translational movement of the ball within the trough. The artificial disc is inserted in the intervertebral disc and the anterior surfaces of the device are attached to the vertebral bodies by four bone screws held in place by two locking screws (see **Figure 2**). This device has been the subject to substantial testing in a USA FDA IDE trial. A modified device with an identical articulation, though without the fixation screws is available in Australia (Prestige LP).

To accommodate individual patient anatomy, the device comes in a range of heights (6 and 8 mm) and depths (12 and 14 mm).

Figure 2 Prestige® cervical disc prosthesis – Medtronic

Source: Riina *et al* (2008)

Prodisc-C® Artificial Disc

The Prodisc-C implant is a ball-and-socket/semi-constrained design consisting of two metal plates, and a polyethylene isnert, (which is secured to the lower end plate creating a snap mechanism). The metal end plates have a keel design for enhanced primary stability and fixed axis of rotation. The end plate coverage of titanium plasma spray coating allows bony in-growth and long-term fixation. The polyethylene inlay, which comes in 5 mm, 6 mm or 7 mm sizes, determines the height of the prosthesis (see **Figure 3**).

As with the other discs available, this design mechanism allows restoration of segmental motion, foraminal height, dynamic function, spinal balance, and stability of the cervical spine.

Figure 3 Prodisc-C® artificial disc prosthesis- Synthes

Source: Bertagnoli *et al* (2005)

Discover™ Artificial Disc

Similar to the Prodisc-C® implant, the Discover™ Artificial Cervical Disc is also characterised by the fixed-core-ball-and-socket configuration which enables preservation of range of motion (ROM) of the treated spinal segment. It is comprised of a titanium alloy superior endplate that articulates with a polyethylene core that is mechanically fixed to the inferior titanium alloy endplate. The Discover™disc, as is the case with the other discs, is intended to restore disc height and sagittal alignment, provide biomechanical stability, and maintain mobility at the treated segment (see **Figure 4**).

Figure 4 Discover™ Artificial Cervical Disc (Johnson & Johnson)

Source: Discover™ Product Information (2007)

SUMMARY OF IMPLANTATION PROCEDURE

The procedure involves surgical insertion of an artificial disc. Under general anaesthesia, the patient is placed in the supine position. The anterior cervical spine is exposed and, after standard decompression of the neural elements, an artificial disc prosthesis is placed between the vertebrae instead of fusion (National Institute for Health and Clinical Excellence, 2005).

Many surgeons are familiar with ACDF procedures; however there are some specific surgical considerations which must be given for cervical disc arthroplasty (CDA). For example, a complete discectomy is needed with complete removal of all osteophytes. As there will continue to be motion, surgeons must be certain to avoid the potential of dynamic compression in the foramen. This is not a consideration with ACDF (Jaramillo-de la Torre *et al* 2008). In addition, it is thought that residual osteophytes may resorb after a fusion; this will not be the case after CDA.

It is generally thought that the posterior longitudinal ligament should be removed with CDA even though this is not always done with ACDF. This ensures that a complete decompression has been achieved and that the disc space has been mobilised to facilitate parallel distraction, restoration of the intervertebral height, and mobility of the segment (Jaramillo-de la Torre *et al* 2008). Although the cartilaginous endplate is removed for CDA, the bony endplate is preserved to minimise the risk of implant subsidence. The vertebral endplates should be burred until there are two parallel surfaces to facilitate even insertion of the device, and allow appropriate surface contact between the endplates and device.

With implantation of an artificial cervical disc, proper midline identification and intra-operative guidance via fluoroscopy is critical. This is in contrast to a graft for ACDF which can be placed eccentrically, without compromise of the outcome. After implantation of the disc, over-distraction of the interbody space should be avoided since it may lead to nerve root stretch, facet joint overload, and/or loss of motion (Jaramillo-de la Torre *et al* 2008).

This is the generic surgical technique for the implantation of an artificial cervical disc. It should be noted that there will be slight variations in surgical technique depending on the type of artificial disc that is being implanted and patient characteristics. Slight differences in technique will be required due to variations in disc design (e.g. pins versus screws) and there may be alternate approaches to achieving initial disc stabilisation.

APPENDIX 2: CLINICAL NEED, PUBLIC HEALTH SIGNIFICANCE AND PATIENT SELECTION

Appendix 2 relates to questions asked in Section 5 of the MSAC application form. For reference, questions 5.1 to 5.3 have been re-iterated below.

5.1 Provide a summary of information about the condition for which the proposed procedure is to be used.

5.2 Please provide a copy of any data available to support the information described in 5.1 above

5.3 In which patients with the condition will the proposed service be used?

SUMMARY OF INFORMATION REGARDING THE CONDITION

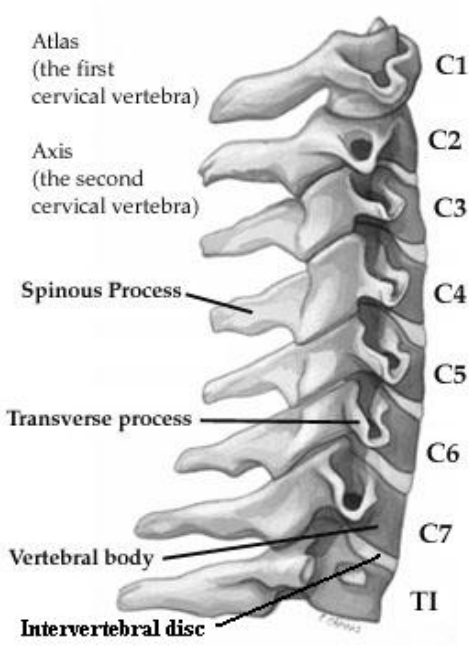
Background

The human cervical spine, shown in **Figure 5,** consists of seven cervical vertebrae with intervertebral discs that lie between the vertebral bodies (except between C1 and C2). Intervertebral discs are made up of annulus fibrosis (ie, a fibrocartilaginous capsule) that surrounds the nucleus pulposus (ie, the semigelatinous centre of the disc) to serve as a flexible but stable coupling between the vertebral bodies. Spine stability is provided by the structure of the annulus while the nucleus enables equal force distribution along the spine due to its elastic nature. Approximately 25 per cent of the height of the cervical vertebral column is attributed to intervertebral discs (Cherry, 2002).

Cervical degenerative disc disease (DDD) is a manifestation of spinal spondylosis that causes deterioration of the intervertebral discs of the cervical spine. While the exact causes of DDD are unclear, it is associated with aging, during which discs begin to lose proteoglycans, leading to moisture loss. The degenerated disc becomes inelastic, with development of microfissures and herniation of the nucleus pulposus. This is usually followed by collapse of the index level segment, which affects the structure of the spinal column (Blue Cross Blue Shield, 2008).

The bone spurs that result from disc degeneration cause narrowing of the foramen or central spinal canal. In the foramen, there may be nerve root impingements which may result in pain and impaired nerve function. Symptoms of cervical DDD include arm pain, weakness, and paresthesias associated with cervical radiculopathy. Disc herniation, osteophytes, kyphosis or instability that compress the spinal cord in the central spinal canal result in myelopathy, which is manifested by changes in gait and balance, weakness in the arms and legs and numbness of the arms or hands. Fine motor coordination of the hands may be impaired (Blue Cross Blue Shield, 2008).

Figure 5 Cervical spine anatomy



Source: http://www.hughston.com/hha/a.cspine.htm

Clinical need/ burden of disease

The current prevalence and incidence of cervical degenerative disc and radiculopathy and/or myelopathy in the Australian setting is unclear. Therefore, the number of individuals who may be eligible for artificial cervical disc replacement is uncertain. In order to approximate these figures, prevalence data of back problems and disorders of the intervertebral disc were derived from the Australian Institute of Health and Welfare (AIHW) and The National Health Survey of Australia conducted in 2004 – 2005. The AIHW defines back problems as episodes of back pain resulting in at least moderate pain, and moderate or greater limitations in walking and/or undertaking usual activities (Mathers *et al*, 1999). The focus on 'back pain' (dorsalgia) as distinct from 'neck pain', which one would expect to be characteristic of cervical DDD, is due to neck pain's inclusion in the ICD-10 code for dorsalgia (M54). As such, the estimates provided here are represent an upper limit, as they include other manifestations of dorsalgia.

The AIHW (2008) reported that between 2004 and 2005, back problems affected 16.0 per cent and 14.7 per cent of the total male and female population of Australia, respectively.. Back problems and disorders of the intervertebral disc were the third most commonly reported long-term condition in 2004 – 2005 after long- and short- sightedness.

The most recent National Health Survey (NHS), conducted by the Australian Bureau of Statistics (ABS) in 2007 – 2008, reported the prevalence of back and disc disorders to be 14.0 per cent (ABS

2009). Moreover, back pain is one of the common causes of prevalent disability in those aged 65 years and over (ABS, 2004).

In the 2004 – 2005 NHS, greater than one in five respondents reported the cause of their long-term condition was work-related. Back pain/problems and disc disorders were the most commonly reported work-related condition (39%) (ABS, 2004).

Spinal diseases

Epidemiological data suggest cervical disc disease affects men slightly more than women. The correlation between the aging process and cervical DDD has been demonstrated in radiological studies on disc degeneration and osteophyte formation. The mean age range for symptomatic herniated cervical discs is mid 40–50s.

Patients with cervical DDD lose water content in the nucleus pulposus, which causes disc space narrowing and loss of disc height, in turn perturbing normal motion at affected disc spaces. In addition, the gelatinous interior of the disc is gradually replaced with fibrous cartilage, which leads to loss of the natural elasticity of motion. Abnormal motion promotes the degenerative process. The most common cervical disc degenerated levels are C5/C6 and C6/C7 (Cherry, 2002).

Protrusion of the nucleus may occur through annulus fissures causing disc herniation. Disc herniation may compress or irritate the spinal nerve roots causing sensations of pain or numbness one arm, known as radiculopathy. Occasionally, disc herniation may compress the spinal cord causing tetraparesis (weakness and numbness of the arms and legs).

Osteophytes form along the spine at the margins of the intervertebral discs and facet joints and may compress or irritate the cervical nerve root and/or spinal cord at the affected levels. This process of encroachment on neural spaces is called stenosis.

As a result of the degenerative process, many patients develop co-morbidities. These include, though are not limited to, cervical spondylosis, myelopathy and radiculopathy. Cervical spondylosis is defined as the effects of the degenerative process on the neck. These include degeneration of the synovial facet and neurocentral joint, manifested by arthritic changes with loss of articular cartilage and osteophyte formation, loss of disc height with osteophyte formations and changes in the mechanical behaviour with changes in the stiffness and range of motion in the joints. In some cases, motion segments can have reduced movement, whereas others may have increased motion and may be unstable such as in the condition of spondylolisthesis.

Cervical myelopathy has a number of causes. The most common is cervical spondylotic myelopathy where the condition is caused by spinal stenosis—the narrowing of the spinal canal and compression of the spinal cord caused by the effects of cervical spondylosis particularly from

osteophyte formation. Other compressive causes include large chronic disc herniations. Symptoms of cervical myelopathy include numbness, weakness, and clumsiness of the upper extremities and weakness of the lower extremities with a progressive disturbance of gait (Cherry, 2002). These symptoms worsen progressively over time.

Radiculopathy is caused by compression of a spinal nerve root – as distinct from compression of the spinal cord. The symptoms are upper limb pain and numbness with possible weakness in the affected muscles. Radicular pain relief and aggravation is directly linked to neck and head position. Neck flexion and head tilts/rotations away from the affected arm aid in pain relief (Cherry, 2002). Radiculopathy can be caused by disc herniation or by the effects of cervical spondylosis. In the former case, a piece of intervertebral disc becomes displaced and directly compresses a nerve root. In the latter case, osteophyte formation of the disc margins, the facet joints and the neurocentral joints cause compression of the exiting nerve root in the nerve root canal.

Current treatment regimes

Patients with cervical DDD can be treated non-operatively including rest, pain medication, non-steroidal anti-inflammatory drugs (NSAIDs), and medical therapies such as axial traction, anti-inflammatory and analgesic medications, and physical therapy (physiotherapy and massages). Furthermore, epidural and selective nerve root injections can also be helpful in certain patients, particularly in those with radiculopathy. Patients who continue to experience pain, numbness, or weakness, despite non-operative therapy, however, are potential candidates for surgical treatment. The most common indications for surgery involving degenerative cervical conditions are progressive neurological dysfunction such as intractable radiculopatic pain that is refractory to an adequate course of non-operative treatment and progressive cervical myelopathy.

A surgical procedure, ACDF, is currently the "gold standard" for treatment of cervical degenerative disc disease, with 1,085 procedures performed in Australia in the 2008 calendar year. While ACDF may be deemed to be the "gold standard" in terms of efficacy, it is not without problems. Cervical fusion has been proven to increase motion at the adjacent levels of the cervical spine. This, in turn, can cause stress and an increase in intradiscal pressure to the adjacent levels of the fused site (Hermann *et al* (2004), Robertson *et al* (2005). There is evidence that these added stresses lead to adjacent segment degeneration including disc herniations, instability, spinal stenosis, and facet joint arthritis (Riina *et al* 2008). The incidence of adjacent segment disc degeneration is relatively high after ACDF and seems to increase with time after surgery. However, it is unclear if this is caused by the mechanical effects of the fusion or simply represents the natural history of the disease of disc degeneration. It is reasonable to assume that both factors have an effect although the relative contribution of each is unknown.

With these issues in mind, the need for a superior treatment option is clear.

EVIDENCE IN SUPPORT OF THE INFORMATION DESCRIBED IN 5.1

See the reference list for a copy of all relevant articles.

ESTIMATES OF THE TOTAL NUMBER OF PATIENTS WITH THE CONDITION

As outlined previously in **Appendix 2**, the number of patients in Australia with cervical DDD is uncertain. In order to approximate these figures, prevalence data of back problems and disorders of the intervertebral disc may be derived from the AIHW and The National Health Survey (NHS) of Australia conducted in 2004 – 2005. The focus on 'back pain' (dorsalgia) as distinct from 'neck pain', which one would expect to be characteristic of cervical DDD, is due to neck pain's inclusion in the ICD-10 code for dorsalgia (M54). As such, the estimates provided here are represent an upper limit, as they include other manifestations of dorsalgia.

The AIHW (2008) data reported that between 2004 and 2005, back problems affected 16.0 per cent and 14.7 per cent of the total male and female population of Australia, respectivel,. The most recent NHS in 2004 reported the prevalence of back problems to be 15.1 per cent.

A more accurate approach to estimating patients with the condition is by using data on ACDF in Australia as a proxy. Although this does not reflect the total population with cervical DDD *per se*, it reflects the patient population who would qualify for inclusion for treatment by CDA. Further detail is provided below.

ESTIMATES OF THE NUMBER OF PATIENTS WITH THE CONDITION WHO WOULD USE CDA

Cervical disc replacement will replace anterior cervical fusion (Medicare Benefits Schedule (MBS) item No. 48660) in a proportion of cases. As the MBS Item 48660 is used for anterior fusion in either the lumbar, thoracic or cervical spine, assumptions are required to determine the proportion of these patients who would be eligible for CDA.

According to MBS statistics , the number of patients treated with an anterior fusion in the lumbar, thoracic or cervical spine fusion in 2006, 2007 and 2008 calendar years was 868, 965 and 1085,

respectively (**Table 1**). The Spine Society estimates that 80% of these cases would be in the cervical spine and of those cases, 30% would be replaced by CDA.

Table 1 Total number of Australian patients with cervical DDD eligible for CDA.

Calendar year	2006	2007	2008	2009 [a]	2010 [b]	2011 [b]	2012 [b]	2013 [b]
Total number of patients treated with anterior fusion in lumbar, thoracic or cervical spine.	868	965	1,085	1,244	1,353	1,477	1,602	1,727
Estimated number of patients treated with anterior fusion in cervical spine	694	772	868	995	1,082	1,182	1,282	1,382
Estimated number of patients treated with CDA	N/A	N/A	N/A	N/A	N/A	355	385	415

Abbreviations: CDA = cervical disc arthroplasty; DDA = degenerative disc disease
Note: Analysis assumes that CDA is listed for reimbursement on the MBS from 2011 onwards
[a] 2009 figures were estimated based on MBS statistics for the first quarter.
[b] 2010-2012 figures are projected assuming linear growth on the basis of the historical data presented

Sensitivity analyses with the percentage of substitution varied are presented in **Table 2**. Based on the assumption that 50% of patients who qualified for ACDF would to opt to undergo CDA, there would be approximately 641 cases in 2011 and up to 691 cases in 2013. If the level of preference for CDA increased and substitution was 70%, there would be approximately 827people treated with CDA in 2011 and up to 967 people in 2013. These levels of substitution are extremely unlikely given that many patients presenting with cervical DDD have either significant facet osteoarthritis at the target level; very narrowed disc space (> 50%), an active infection or have had a previous laminectomy (not lamminotomy or lamminoforaminotomy) and are therefore contraindicated to undergo CDA.

It is not considered likely that cervical disc arthroplasty would be performed in any circumstances other than when an ACDF would be performed. It is not expected that there are individuals who have rejected ACDF as a treatment option but would accept CDA. That is, there is no expectation of growth in the population due to under-utilisation of ACDF.

Table 2 Sensitivity analyses for total number of Australian patients with cervical DDD eligible for CDA

Calendar year	**2006**	**2007**	**2008**	**2009[a]**	**2010[b]**	**2011[b]**	**2012[b]**	**2013[b]**
Total number of patients treated with anterior fusion in lumbar, thoracic or cervical spine.	868	965	1,085	1,244	1,353	1,477	1,602	1,727
Estimated number of patients treated with anterior fusion in cervical spine	694	772	868	995	1,082	1,182	1,282	1,382
Estimated number of patients treated with CDA (30% of above)						355	385	414
Estimated number of patients treated with CDA (50% of above)						591	641	691
Estimated number of patients treated with CDA (70% of above)						827	897	967

Abbreviations: CDA = cervical disc arthroplasty; DDD = degenerative disc disease
Note: Analysis assumes that CDA is listed for reimbursement on the MBS from 2011 onwards
[a] 2009 figures were estimated based on MBS statistics for the first quarter.
[b] 2010-2012 figures are projected estimates

APPENDIX 3: LITERATURE SEARCHES

Appendix 3 relates to questions asked in Section 9 of the MSAC application form. For reference, the pertinent questions from Section 9, addressed here, have been re-iterated below.

9.1 Provide a copy of the literature search which has been undertaken to identify evidence in support of the safety and effectiveness of the proposed service.

A literature search was conducted to identify studies which described the efficacy and safety of CDA for the treatment of cervical DDD. The literature searches were not limited by date.

The search strategy is described below.

Primary databases

Searches were conducted in the primary databases indicated in **Table 3**.

Table 3 Electronic databases searched during the review of artificial disc replacement in degenerative disc disease patients

Database	Date searched
Medline and EMBASE [a]	22 June 2009
Cochrane Library	24 June 2009

[a] Using the EMBASE.com interface

Comprehensive details of the literature searches performed using the primary databases are presented in **Table 4** and **Table 5**.

Table 4 EMBASE.com search results for artificial cervical disc replacement in degenerative disc disease patients (searched on 22 June 2009)

	Keywords/search history	Results
1	Bryan	6,437
2	Prestige	1,331
3	Prodisc	171
4	Discover	11,767
5	'porous coated motion'	11
6	'artificial disc'	209
7	'metal on metal'	661
8	'metal on plastic'	38
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	20,462
10	'degenerative disc disease'	708
11	'herniated disc'/exp	14,069
12	'anterior cervical discectomy and fusion'	299
13	'radiculopathy'/exp	18,831
14	'discogenic pain'/exp	287
15	'spinal disease'/exp	103,014
16	'post discectomy syndrome'	10
17	'intervertebral disc displacement'	10
18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	118,535
19	'disc replacement'	433
20	'arthroplasty'/exp	53,650
21	'replacement'	162,605
22	'prosthesis implantation'/exp	34, 387
23	'prostheses and implants'/exp	288,740
24	'spinal fusion'/exp	13,594
25	'cervical vertebrae'/exp	21,655
26	'intervertebral disc'/exp	9,358
27	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	494,085
28	'surgery'/exp	3,041,113
29	#27 AND #28	304,985
30	'cervical vertebrae'/exp	21,655
31	'spine'/exp OR 'spinal' OR 'cervical'	417,834
32	disc OR discs OR disk OR disks	83,344
33	(#30 OR #31) AND #32	24,543
34	#9 AND #18 AND #29 AND #33	314
35	#34 AND [humans]/lim	299

Table 5 Cochrane search results for artificial cervical disc replacement in degenerative disc disease patients (searched on 24 June 2009)

	Keywords/search history	Results
1	(bryan):ti,ab,kw	16
2	(prestige):ti,ab,kw	42
3	(prodisc):ti,ab,kw	14
4	(discover): ti,ab,kw	625
5	'porous coated motion':ti,ab,kw	3
6	'artificial disc':ti,ab,kw	72
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	756
8	degenerative disc disease:ti,ab,kw	85
9	herniated disc:ti,ab,kw	126
10	anterior cervical discectomy and fusion:ti,ab,kw	66
11	spinal disease:ti,ab,kw	1120
12	post discectomy syndrome:ti,ab,kw	3
13	intervertebral disc displacement:ti,ab,kw	474
14	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	1647
15	disc replacement:ti,ab,kw	101
16	arthroplasty:ti,ab,kw	2,795
17	prosthesis implantation:ti,ab,kw	1300
18	'prostheses and implants':ti,ab,kw	490
19	cervical vertebrae:ti,ab,kw	504
20	intervertebral disc:ti,ab,kw	775
21	(#15 OR #16 OR #17 OR #18 OR #19 OR #20)	5,636
22	surgery	79,060
23	(#21 AND #22)	3,882
24	spine OR spinal OR cervical	16,721
25	disc OR discs OR disk OR disks	2,373
26	(#24 OR #25)	18,400
27	(#7 AND #14 AND #23 AND #26)	49

Secondary databases

A review of databases maintained by health technology assessment (HTA) agencies was undertaken to identify additional evidence. The list of secondary databases searched is presented in **Table 6**.

Table 6 HTA websites searched

Country	Organisation(s); webpage(s)
Australia	Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S); http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm Centre for Clinical Effectiveness, Monash University; http://www.med.monash.edu.au/healthservices/cce/evidence/ Health Economics Unit, Monash University; http://chpe.buseco.monash.edu.au
Austria	Institute of Technology Assessment / HTA unit; http://www.oeaw.ac.at/ita/e1-3.htm
Canada	Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS); http://www.aetmis.gouv.qc.ca/site/index.php?home Institute of Health Economics (IHE); http://www.ihe.ca/index.html Canadian Agency for Drugs and Technologies in Health (CADTH); http://www.cadth.ca/ Canadian Health Economics Research Association (CHERA/ACRES)—Cabot database; http://www.mycabot.ca Centre for Health Economics and Policy Analysis (CHEPA), McMaster University; http://www.chepa.org Centre for Health Services and Policy Research (CHSPR), University of British Columbia; http://www.chspr.ubc.ca Health Utilities Index (HUI); http://www.fhs.mcmaster.ca/hug/index.htm Institute for Clinical and Evaluative Studies (ICES); http://www.ices.on.ca
Denmark	Danish Institute for Health Technology Assessment (DIHTA); http://www.dihta.dk/publikationer/index_uk.asp Danish Institute for Health Services Research (DSI); http://www.dsi.dk/engelsk.html
European Union	The European Network for Health Technology Assessment (EUnetHTA); http://www.eunethta.net/Communication/
Finland	FINOHTA; http://finohta.stakes.fi/EN/index.htm
France	L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES); http://www.anaes.fr/
Germany	German Institute for Medical Documentation and Information (DIMDI) / HTA; http://www.dimdi.de/dynamic/en/index.html
The Netherlands	Health Council of the Netherlands Gezondheidsraad; http://www.gr.nl/adviezen.php
New Zealand	New Zealand Health Technology Assessment (NZHTA); http://nzhta.chmeds.ac.nz/
Norway	Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38
Spain	Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology; Assessment Agency (AETS) http://www.isciii.es/htdocs/en/index.jsp Catalan Agency for Health Technology Assessment (CAHTA); http://www.aatrm.net/html/en/Du8/index.html
Sweden	Swedish Council on Technology Assessment in Health Care (SBU); http://www.sbu.se/www/index.asp INAHTA – International Network of Agencies for Health Technology Assessment; http://www.inahta.org/ Centre for Medical Health Technology Assessment (CMT); http://www.cmt.liu.se/english?l=en
Switzerland	Swiss Network on Health Technology Assessment (SNHTA); http://www.snhta.ch/home/portal.php
United Kingdom	National Health Service Quality Improvement: Scotland (NHS QIS); http://www.nhshealthquality.org/nhsqis/43.0.140.html National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/ University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/ National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/
United States	Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm Centers for Medicare & Medicaid Services' (CMS) http://www.cms.hhs.gov/EOG/ Harvard School of Public Health—Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/ US Blue Cross/ Blue Shield Association Technology Evaluation Center http://www.bcbs.com/consumertec/index.html

Selection criteria

Inclusion and exclusion criteria were developed *a priori* to determine eligibility of relevant studies assessing patient outcomes following artificial cervical disc replacement (**Table 7**).

Table 7 Inclusion and exclusion criteria for health outcomes following artificial cervical disc replacement

Characteristics	Inclusion	Exclusion
Participants	In patients with cervical DDD and cervical radiculopathy and/ or myelopathy, who have failed non-operative treatment	Lumbar spinal diseases patients
Intervention	Artificial cervical disc replacement including • Medtronic – Prestige • Medtronic – Bryan • Synthes – Prodisc • J & J – Discover	• Other artificial cervical disc replacement procedures • Disc nucleus replacement • Non-operative procedures
Comparator	ACDF	• Other artificial cervical disc replacement procedures • Disc nucleus replacement • Non-operative procedures
Outcomes	Efficacy: • Reduction in pain (rating scores, etc) • Adjacent segment degeneration • Reduced secondary disorders and co-morbidities • Quality of life • Emotional wellbeing • Device failure (revision, re-operation or removal)	None defined
	Safety: • Complication (neurological damage, pain, spinal infection, etc) • Adjacent segment degeneration • Polyethylene wear	None defined

Abbreviations: ACDF = anterior cervical discectomy and fusion; DDD = degenerative disc disease

Results from literature search

All articles at the end of **Table 4** and **Table 5**, identified through the literature searches, were reviewed. Initially, this was performed using the publication title and, where available, the abstract. **Table 8** summarises the reasons publications were excluded from consideration (including EMBASE, Medline, Cochrane and HTA websites).

A total of 299 publications were identified from the EMBASE/Medline search, 49 studies from the Cochrane library and five additional studies from HTA databases. Following a review of the title and abstract (where available), 277 articles were excluded and the remaining 21 sourced for full

review. After reviewing the full text, four articles were excluded. Two papers were only available in Chinese and one was the wrong intervention. One study by Peng-Fei and Yu-Hua (2008) compared cervical disc prosthesis replacement and interbody fusion in 24 patients. The publication did not report on a specific brand of artificial disc, nor did it report the clinical or safety outcomes of interest and was subsequently excluded.

In addition, a manual search of the reference lists of included studies was undertaken. One further study of relevance by Chang *et al* (2007b) was found, which compared the ROM between artificial disc and ACDF. Of the 17 included studies, eight examined the Bryan® disc, five the Prestige® disc, four the Prodisc-C® and no study was found that examined the Discover™ disc. While the additional study by Chang *et al* (2007b) examined both the Prestige® and Prodisc-C®, it has, for simplicity, been listed under the Prestige® heading in both **Table 9** and **Appendix 4**.

Table 8 Summary of exclusion of citations from literature search

	Embase & Medline	Cochrane library	HTA websites
Number of citations retrieved by search	299	49	5
Number of consolidated citations with duplicates removed [a]	298		
Number of citations excluded after title/abstract review			
Not an RCT, controlled comparative study or systematic review	199		
Wrong indication (ie, not cervical DDD)	41		
Wrong intervention (not an artificial disc replacement)	37		
Total number of citations excluded	**277**		
Number of citations reviewed as full text	**21**		
Not an RCT, controlled comparative study or systematic review	0		
Wrong indication (ie, not cervical DDD)	0		
Wrong intervention (not an artificial disc replacement)	2		
Not available in English	2		
Total number of citations excluded after full text review	**4**		
Total number of included studies from databases	**17**		
Total number of studies from manual search of reference lists	**1**		
Total number of included studies	**18**		

Abbreviations: DDD = degenerative disc disease; HTA = health technology assessment; RCT = randomised controlled trials
[a] Duplicates were removed manually using Reference Manager Version 10.0

The 18 studies identified in the literature search are summarised in **Table 9**. After thorough examination of the included studies, it was evident that multiple publications referred to data from the same randomised controlled trial (RCT). Publications reporting the whole study population, and with the longest follow-up periods, were given preference to studies that had included only a sub-set of patients from the larger trial, or conducted interim analysis over a shorter follow-up period. This information, including which study each publication refers to, and which publication will be discussed for each study in **Appendix 4**, is included in **Table 9**.

Table 9 Studies identified in literature search

Study	Reference	Included in previous MSAC submission (1090)	Included for discussion in Appendix 4	Notes
Bryan®				
United States Food and Drug Administration (FDA) investigational device exemption (IDE) study for Bryan® artificial disc.	Heller J.G, Sasso R.C, Papadopoulos S.M, Anderson P.A, Fessler R.G, Hacker R.J, *et al* (2009) Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion. Spine 34(2):101–107.	No	Yes	The pivotal publication reporting *efficacy* outcomes after follow up for 2 years.
	Anderson P.A., Sasso R.C., Riew K.D. (2008) Comparison of adverse events between the Bryan artificial cervical disc and anterior cervical arthrodesis. Spine 33(12): 1305 – 1312	No	Yes	The pivotal publication reporting *safety* outcomes after follow up for 3 years.
	Coric D., Finger F., Boltes P. (2006) Prospective randomized controlled study of the Bryan Cervical Disc: Early clinical results from a single investigational site. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2005. Journal of Neurosurgery: Spine 4(1): 31 – 35	No	No	One investigational site within the larger trial and, therefore, contains duplicate data.
	Sasso R.C, Best N.M, Metcalf N.M and Anderson P.A. (2008a) Motion analysis of Bryan Cervical Disc Arthroplasty versus anterior discectomy and fusion: Results from a prospective, randomised, multi-center, clinical trial. J Spinal Disord 21(6):393–399.	No	Yes	Provides new efficacy data on motion from the same trial.
	Sasso R.C., Best N.M. (2008b) Cervical kinematics after fusion and Bryan disc arthroplasty. J Spinal Disord Tech 21(1): 19 – 22	No	No	Reports radiographic data for the first 22 patients enrolled in the study and, therefore, contains duplicate data.
	Sasso R.C., Smucker J.D., Hacker R.J., Heller J.G. (2007a) Clinical outcomes of BRYAN Cervical Disc arthroplasty: A prospective, randomized, controlled, multicenter trial with 24-month follow-up. Journal of Spinal Disorders and Techniques 20(7): 481 – 491	No	No	Reports clinical outcomes from a sub-set of the FDA trial including 3 investigational sites and, therefore, contains duplicate data.
	Sasso R.C., Smucker J.D., Hacker R.J., Heller J.G. (2007b) Artificial disc versus fusion: A prospective, randomized study with 2-year follow-up on 99 patients. Spine 32(26): 2933 – 2940	No	No	Reports clinical outcomes from a sub-set of the FDA trial including 3 investigational sites and, therefore, contains duplicate data.
Comparative trial	Rabin D., Pickett G.E., Bisnaire L., Duggal N. (2007) The kinematics of anterior cervical diskectomy and fusion versus artificial cervical disc: A pilot study. Neurosurgery 61(3): Suppl. Ons-100-Ons-104.	No	Yes	A small comparative study.

Study	Reference	Included in previous MSAC submission (1090)	Included for discussion in Appendix 4	Notes
Prestige®				
FDA regulated IDE study for Prestige® artificial disc.	Mummaneni P.V., Burkus J.K., Haid R.W., Traynelis V.C., Zdeblick T.A. (2007) Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: A randomized controlled clinical trial. Journal of Neurosurgery: Spine 6(3): 198 – 209	No	Yes	The primary publication reporting efficacy and safety for Prestige after follow up for 2 years.
	Technology Evaluation Center (2008). Artificial intervertebral disc arthroplasty for treatment of degenerative disc disease in the cervical spine. Blue Cross Blue Shield Vl 22. No 12: 1-24.	No	No	Examines the results of the IDE study and, therefore, contains duplicate data.
Multicentre RCT	Porchet F and Metcalf N.H. (2004). Clinical outcomes with the Prestige II cervical disc: preliminary results from a prospective randomized clinical trial. Neurosurgical focus 17(3): E6	Yes	Yes	Provides supportive evidence from a smaller RCT.
Single centre RCT	Riina J., Patel A., Dietz J.W., Hoskins J.S., Trammell T.R., Schwartz D.D. (2008) Comparison of single-level cervical fusion and a metal-on-metal cervical disc replacement device. Am J. Orthop. 37(4): E71 – 77	No	Yes	Reports a small, single centre RCT.
Cadaveric spine study	Chang U.-K., Kim D.H., Lee M.C., Willenberg R., Kim S.-H., Lim J. (2007a) Range of motion change after cervical arthroplasty with ProDisc-C and Prestige artificial discs compared with anterior cervical discectomy and fusion. Journal of Neurosurgery: Spine 7(1): 40 – 46	No	Yes	Reports *range of motion* in 18 cadaveric spines.
	Chang U.-K, Kim D.H., Lee M.C., Willenberg R., Kim S.-H., Lim J. (2007b) Changes in adjacent-level disc pressure and facet joint force after cervical arthroplasty compared with cervical discectomy and fusion. J Neurosurg Spine 7:33–39.	No	Yes	Reports on *adjacent disc pressure* and *facet joint force* in 18 cadaveric spines.
Prodisc-C®				
FDA regulated IDE study for Prodisc-C®.	Murrey D, Janssen M, Delamarter R, Goldstein J, Zigler J, Tay B *et al* (2009) Results of the prospective, randomized, controlled multicenter Food and Drug Administraion investigational device exemption study of the ProDisc-C® total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. The Spine Journal 9:275–286.	No	Yes	The primary publication reporting safety and efficacy for the Prodisc-C®.
RCT conducted in Germany	Nabhan A, Steudel W.I, Nabhan Ah, Pape D and Ishak B. (2007a) Segmental kinematics and adjacent level degeneration following disc replacement versus fusion: RCT with three years of follow-up. Journal of long-term effects of medical implants, 17(3):229-236.	No	Yes	The primary publication reporting three years of follow-up for all 49 patients.

Study	Reference	Included in previous MSAC submission (1090)	Included for discussion in Appendix 4	Notes
	Nabhan A., Ahlhelm F., Pitzen T., Steudel W.I., Jung J., Shariat K., Steimer O., Bachelier F., Pape D. (2007b) Disc replacement using Pro-Disc C versus fusion: A prospective randomised and controlled radiographic and clinical study. European Spine Journal 16(3): 423 – 430	No	No	A sub-set of patients (N=33) from the Murrey *et al* (2009) study and, therefore, contains duplicate data.
	Nabhan A., Ahlhelm F., Shariat K., Pitzen T., Steimer O., Steudel W.I., Pape D. (2007c) The ProDisc-C prosthesis: clinical and radiological experience 1 year after surgery. Spine 32(18): 1935 – 1941	No	No	The preliminary results (one year after surgery) for all 49 patients enrolled in the Murrey *et al* (2009) study. Since these are preliminary results of data included in the Murrey *et al* (2009) study, this study was excluded.
Discover™				
No publications identified.				

Abbreviations: FDA = Food and Drug Administration; MSAC = Medical Services Advisory Committee; NA = not applicable

APPENDIX 4: SUMMARY OF THE EVIDENCE

Appendix 4 relates to questions asked in Section 10 of the MSAC application form. For reference, questions 10.1 to 10.4 have been re-iterated below.

10.1 From the literature search described in Section 9.1, provide a list of the studies which support the use of the service for the proposed indication(s).

10.2 Classify the studies in 10.1 according to the hierarchy of evidence

10.3 Provide a summary of the evidence for the effectiveness and safety of the service based on the studies in 10.1.

10.4 Based on the studies, assess the effectiveness and safety of the new service compared with that of the comparator identified in Section 8

CHARACTERISTICS OF THE INCLUDED STUDIES

A summary of the included studies is presented in **Table 10**.

Of the 17 included publications, only the study reported by Porchet and Metcalf (2004) was included in the previous MSAC submission, Application 1090. Since then, a significant body of evidence has been published describing the efficacy and safety of CDA for the treatment of cervical DDD. Quality was assessed using National Health and Medical Research Council (NHMRC) dimensions and designations of levels of evidence.

Table 10 Characteristics of the included studies evaluating CDA for the treatment of DDD

Study	Author (year) Country	Study design	Population characteristics	Comparator	Quality
Bryan®					
United States Food and Drug Administration (FDA) investigational device exemption (IDE) study for Bryan® artificial disc.	Heller *et al* (2009) USA	Prospective, multi-centre, randomised, controlled trial May 2002 to October 2004 24 months follow-up	Patients with single-level cervical DDD causing radiculopathy or myelopathy in skeletally mature patients (21 or older) from C3-C7, failed conservative care for 6 weeks, NDI score of ≥30%. Bryan (n = 242), ACDF (n = 221)	ACDF	Level II
	Anderson *et al* (2008) USA	Prospective, randomised, multicentre study (FDA approved) (IDE clinical study) Recruitment/ study period not reported 24 months follow-up	As above	ACDF	Level II
	Coric *et al* (2006) USA	Prospective, randomised controlled multicentre trial April 2002 – August 2004 24 months follow-up	Patients with primary, single-level cervical DDD producing radiculopathy and/ or myelopathy were randomised to undergo anterior cervical discectomy with either allograft fusion and anterior plate or artificial cervical disc placement Bryan (n = 17) ACDF (n=15)	ACDF	Level III-1
	Sasso *et al* (2008a) USA	Prospective, multi-centre, randomised, controlled trial May 2002 to October 2004 24 months follow-up	Patients with single-level cervical DDD causing radiculopathy or myelopathy in skeletally mature patients (21 or older) from C3-C7, failed conservative care for 6 weeks, NDI score of ≥30%. Bryan (n = 242), ACDF (n = 221)	ACDF	Level II

	Sasso *et al* (2008b) USA	Prospective, consecutive enrolment, randomised study May 2002 – April 2003 24 months follow-up	Patients with single-level cervical radiculopathy or myelopathy, resistant to non-operative treatment Bryan (n = 9), ACDF (n = 13)	ACDF	Level III-1
	Sasso *et al* (2007a) USA	Prospective, randomised, three centre, clinical trial Recruitment/ study period not reported 24 months follow-up	Patients with single-level, symptomatic, cervical radiculopathy or myelopathy refractory to non-operative interventions Bryan (n = 56), ACDF (n = 59)	ACDF	Level II
	Sasso *et al* (2007b) USA	Prospective, randomised, three centre, clinical trial Recruitment/ study period not reported 24 months follow-up	Patients with single-level, symptomatic, cervical radiculopathy or myelopathy refractory to non-operative interventions Bryan (n = 56), ACDF (n = 59)	ACDF	Level II
Retrospective pilot study	Rabin *et al* (2007) Canada	Retrospective pilot study Recruitment/ study period not reported 24 months follow-up	Ten patients with single-level artificial disc were matched to ten patients with single-level ACDF based on age and sex Bryan (n = 10) ACDF (n=10)	ACDF	Level III-2
Prestige®					
FDA regulated IDE study for Prestige® artificial disc.	Mummaneni *et al* (2007) USA	Prospective, randomised multicentre study (data reviewed and submitted to FDA) October 2002 – August 2004 24 months follow-up	Patients enrolled across 32 investigational US sites that underwent surgery for DDD. Prestige (n = 276), ACDF (n = 265)	ACDF	Level II
	Technology evaluation centre (2008) UK	Systematic review	As above	ACDF	Level I

Multicentre RCT	Prochet and Metcalf (2004) UK	Prospective, randomised controlled clinical trial Recruitment/ study period not reported 24 months follow-up	Patients with cervical DDD with single-level disease in C4-5 to C6-7. Prestige (n = 27), ACDF (n = 28)	ACDF with iliac chest autograft ACDF	Level II
Single centre RCT	Riina *et al* (2008) USA	Prospective, randomised single centre study (FDA) Recruitment/ study period not reported 24 months follow-up	Patients with cervical DDD (defined as intractable radiculopathy, myelopathy, or both) assigned to artificial disc or ACDF). Prestige (n = 10); ACDF (n = 9)	ACDF	Level III-1
Cadaveric spine study	Chang *et al* (2007a) USA	Retrospective, comparative cohort study Recruitment/ study period not reported	Human cadaveric cervical spines (C3–T2 specimens) obtained from Science Care Anatomical and International Biological, Inc. Prestige (n = 18)	ACDF with dense cortical allograft (Osteotech)	Level III-2
	Chang *et al* (2007b)	As above	As above	ACDF with dense cortical allograft (Osteotech)	Level III-2
ProDisc-C®					
FDA regulated IDE study for Prodisc-C®.	Murrey *et al* (2009) USA	Prospective, multicentre, randomised controlled trial August 2003 – October 2004 24 months follow-up	Patients with symptomatic cervical DDD causing radiculopathy, unresponsive to non-operative treatment ProDisc-C (n = 103) ACDF (n = 106)	ACDF	Level II
RCT conducted in Germany	Nabhan *et al* (2007a) Germany	Prospective, randomised controlled trial April 2004 – May 2005 36 months follow-up	Patients with clinical evidence of radiculopathy, not responding to a trial of conservative treatment and or progressive radicular deficits ProDisc-C (n = 25) ACDF (n = 24)	ACDF	Level II

	Nabhan *et al* (2007b) Germany	Prospective, randomised controlled trial April 2004 – December 2004 24 weeks follow-up	Patients suffering from symptomatic soft disc herniation, not responding to a trial of conservative treatment and or progressive radicular deficits. ProDisc-C (n = 16), ACDF (n = 17)	ACDF	Level II
	Nabhan *et al* (2007c) Germany	Prospective, randomised controlled trial April 2004 – May 2005 12 months follow-up	Patients with clinical evidence of radiculopathy, not responding to a trial of conservative treatment and or progressive radicular deficits ProDisc-C (n = 25) ACDF (n = 24)	ACDF	Level II
Discover™					
No publications identified.					

Abbreviations: ACDF = anterior cervical discectomy and fusion; DDD = degenerative disc disease; FDA = Food and Drug Administration; MRI = magnetic resonance imaging; NDI = neck disability index

[a] Both Prestige and ProDisc cervical discs were used in the study analysis
[b] A USA Technology Evaluation Center (TEC) Assessment also reviews the results of the Mummaneni *et al* (2007) study

EFFICACY AND SAFETY OF CERVICAL DISC ARTHROPLASTY

BRYAN® CERVICAL ARTIFICIAL DISC

Of the eight publications examining the Bryan® cervical artificial disc for the treatment of cervical DDD, seven contained data from the United States Food and Drug Administration (FDA) investigational device exemption (IDE) study for Bryan® artificial disc. Five of the studies presented Level II evidence, while the remaining three presented Level III evidence. There was considerable overlap between publications. Four reports were from single centres within the multi-centre trial, and three reported various safety and efficacy outcomes at two and three years follow-up. The primary efficacy and safety data are reported in Heller *et al* (2009) and Anderson *et al* (2008), with supportive evidence from Sasso *et al* (2008a). Additional data were obtained from a small comparative study conducted by Rabin *et al* (2007).

Heller *et al* (2009)

Eligible patients were skeletally mature (≥ 21 years) with single-level cervical DDD and radiculopathy or myelopathy from C3 – C7, who had failed conservative care for six weeks and had a neck disability index (NDI) score of ≥ 30 per cent. Patients were randomly assigned in a 1:1 ratio to either the Bryan® Artificial Cervical Disc or ACDF. Blinding for investigators and patients was maintained throughout confirmation of eligibility and informed consent. Patients were evaluated pre-operatively, at surgical discharge and then at 1.5, 3, 6, 12, and 24 months after surgery. There was minimal loss to follow-up (< 10% in each treatment arm).

Pain and function were assessed using the neck disability index, the SF-36 and numerical rating scales for neck and arm pain. The primary endpoint for the study, however, was a composite measure termed 'overall success', which comprised the primary effectiveness and a number of safety measures. To be considered an overall success, patients had to achieve all of the following:

- at least a 15 point improvement in their NDI scores;
- maintenance or improvement in their neurological status;
- no serious adverse events related to the implant or implant/surgical procedure; and
- no subsequent surgery or intervention that was classified as 'failure'.

The achievement of the primary outcome, overall success, is presented in **Table 11**. At 24 months, overall success was achieved in 82.6% (95%CI: 77.1%–87.3%) of the patients in the Bryan® artificial disc group and 72.7% (95% CI: 65.8%–78.8%) in the ACDF group. This difference of 9.9% (95% CI: 2.0%–17.9%) was statistically significant ($P = 0.010$). A similar difference was found at the 12-month follow-up interval ($P = 0.004$).

Table 11 Neck disability index, neurological, and overall success at 24 months

Period	Bryan® artificial disc group (n=242)[a]	ACDF group (n=221)[a]	Non-inferiority (δ=10%)[b]	Superiority (*P* value)[c]
Neck disability index success				
Success	197 (86.0%)	153 (78.9%)	< 0.001	0.035
Failure	32 (14.0%)	41 (21.1%)		
Neurological success				
Success	215 (93.9%)	175 (90.2%)	< 0.001	0.111
Failure	14 (6.1%)	19 (9.8%)		
Overall success				
Success	190 (82.6%)	141 (72.7%)	< 0.001	0.010
Failure	40 (17.4%)	53 (27.3%)		

Data source: Heller et al (2009): Table 2, page 105

[a] Results are based on no. of patients observed at follow-up
[b] Non-inferiority *P* value calculated by z-test
[c] One-sided superiority *P* were obtained by Fisher exact test

Statistically significant reductions ($P < 0.001$) in NDI scores were noted for both groups at every follow-up interval. The Bryan® artificial disc group, however, had significantly greater score improvements at all intervals when compared to the control group ($P = 0.025$ at 24 months). The proportion of patients who had a greater than 15-point reduction in NDI score was also statistically higher in the Bryan® artificial disc group compared to the ACDF group ($P < 0.001$). In addition, significant reductions in both neck and arm pain from baseline scores occurred in both groups at each follow-up interval.

The Bryan® artificial disc group demonstrated significantly greater improvements in neck pain at all postoperative intervals. At 24 months, the mean postoperative SF-36 physical component summary (PCS) and mental component summary (MCS) scores had significantly improved in both groups, though no statistical differences were present between groups remained once 24 months had lapsed. At earlier follow-up time points, however, (1.5–12 months) improvements were significantly greater in the Bryan® artificial disc group. Rates of neurological success were similar for both treatment groups at 24 months follow-up.

Though the data were not reported, it was observed that a greater percentage of patients in the Bryan® artificial disc group had returned to work at 1.5 and 3 months after surgery compared with patients in the ACDF group, however there was no statistical differences between the groups at 24 months. Overall, the median return-to-work interval for the Bryan® artificial disc patients was 48 days - significantly shorter ($P = 0.015$) than the ACDF patients (61 days).

There were a substantial number of withdrawals from the study following randomisation before surgery was carried out. Eighty patients withdrew from fusion surgery and 37 from arthroplasty surgery. There were no demographic differences between those that withdrew and those that did not. The most commonly given reason for withdrawal was dissatisfaction with the intended treatment. There is potential bias from this event.

This study was funded by the manufacturer of the prostheses used in the study. The paper does not discuss control of funding bias in the study.

Anderson *et al* (2008)

The study by Anderson *et al* (2008) reported adverse events associated with Bryan® cervical disc (n=292) and ACDF (n=221) after three years in the same FDA-approved IDE study. Adverse events were identified as episodes that may affect patient outcome, require intervention or, if required, further diagnostic tests or monitoring. The events identified were classified using a four point scale adapted from the World Health Organisation (WHO). Grade 1 events were the least severe, requiring no treatment and having no effect on the clinical outcome. Grade 4 events required interventions (ie, operations), were life threatening, caused permanent disability or even death. Grade 1 and 2 were classified as non-serious adverse events while Grade 3 and 4 adverse events were classified as serious adverse events.

Procedure-related adverse events occurring within six weeks of surgery are presented in **Table 12**. Overall, medical events occurred in 14.9% of Bryan® cervical disc and 15.4% of ACDF patients. This difference was not statistically significant (p=0.07), though it should be noted that there were more than double the amount of Grade 3-4 medical events within six weeks of surgery in the ACDF relative to the Bryan arm of the study.

Table 12 Medical events occurring within 6 weeks of surgery

Author (year) Country	Event	WHO Grade						*P*
		Bryan (n=242)			ACDF (n=221)			
		1–2	3–4	Total	1–2	3–4	Total	
Anderson *et al* (2008) USA	Cancer	0	0	0	0	0	0	
	Cardiovascular	5	0	5	0	0	0	
	Gastrointestinal	4	2	6	1	4	5	
	Infection	4	0	4	3	0	3	
	Dermatologic/allergy	6	0	6	4	0	4	
	Psychiatry	0	0	0	3	1	4	
	Pulmonary	5	1	6	3	4	7	
	Genitourinary	0	0	0	0	0	0	
	Musculoskeletal	1	0	1	4	0	4	
	Endocrine	1	0	1	3	0	3	
	Central nervous system	5	2	7	2	2	4	
	Death	0	0	0	0	0	0	
	Total (%)	31 (12.8)	5 (2.1)	36 (14.9)	23 (10.4)	11 (4.9)	34 (15.4)	0.07

Data source: Anderson *et al* (2008): Table 2, page 1307.
Abbreviations: USA = United States of America

Over the 24-month follow-up period, slightly more surgery-related and neurological adverse events occurred in the prosthesis group compared to the ACDF group (33.9% versus 29.0%, respectively); however this

difference was not significant. This difference was primarily due to more complaints of dysphagia and more superficial wound infections in the artificial disc group. More serious neurologic related adverse events of grade 3 and 4, however, were reported in the ACDF group compared with the Bryan® artificial disc group (36.2% versus 30.2%, respectively; $P = 0.012$). The additional adverse events experienced by the ACDF group were primarily due to additional operations for treatment of persistent symptoms (eg, neck and arm pain) and pseudarthrosis.

Significantly fewer ($P = 0.045$) re-operations on the cervical spine occurred in patients treated with Bryan® artificial disc (5.4%) when compared to patients treated with ACDF (7.7%) (**Table 13**). The total number of cervical spine re-operations was also statistically greater in the ACDF group compared with the artificial disc group (n=21 versus n=14, respectively). Overall re-operations were performed at the index level 12 times and at the adjacent level 11 times in the ACDF group, compared with 7 and 8 times in the Bryan® artificial cervical disc group. Four patients in the ACDF and one in the Bryan® artificial disc group had more than one re-operation. No deaths were reported in this investigation.

Table 13 Re-operations following cervical arthroplasty or arthrodesis

	Bryan (n=242)		**Arthrodesis (n=221)**		
	Patients n (%)	**Total operations n (%)**	**Patients n (%)**	**Total operations n (%)**	***P***
Cervical spine					
Index	6	6	8	10	0.056
Adjacent	6	7	7	9	0.08
Both levels	1	1	2	2	
Total	*13 (5.4)*	*14 (5.8)*	*17 (7.7)*	*21 (9.5)*	*0.045*
Thoracolumbar spine					
Upper extremity	10 (4.1)	10 (4.1)	8 (3.6)	9 (4.1)	0.13
Shoulder	2	4	6	7	
Carpal tunnel	4	4	2	2	
Ulnar nerve transposition	1	1	1	1	
Thoracic outlet release	0	0	1	1	
Total	*7 (2.9)*	*9 (3.7)*	*10 (4.8)*	*11 (5.0)*	*0.56*
Total	**17 (7.0)**	**19 (7.8)**	**18 (8.1)**	**20 (9.0)**	**0.15**

Data source: Anderson *et al* (2008): Table 6, page 1310

Sasso *et al* (2008a)

The study by Sasso *et al* (2008a) investigated the importance of motion maintenance in order to delay or avoid adjacent segmental degeneration. Kinematic analysis was conducted at the target level and adjacent motion segments in patients enrolled in the FDA-approved IDE study. Upright lateral flexion and extension radiographs were obtained preoperatively and at 3, 6, 12 and 24 months follow-up. Angular motion at each

time frame was measured by two independent radiologists. To measure the intervertebral motion, angular ROM was determined on the flexion and extension radiographs.

The mean preoperative angular motion of the Bryan® and fusion group was 6.43 (±3.42) degrees and 8.39 (±4.54) degrees, respectively ($P > 0.05$). At two years follow-up, the ROM in the Bryan® group increased to 7.95 (±4.70) degrees; this was statistically significant compared with preoperative ($P < 0.001$). In the ACDF group, the ROM at the treated level significantly decreased to 0.87 (±0.62) degrees. Postoperatively, at two years follow-up, no statistical differences were present in adjacent motions compared with preoperative motion in the two groups at both the cranial and caudal segment in the Byran® group. There was no settling or displacement of the Bryan® disc arthroplasty over the course of the study.

This study demonstrated that the Bryan® disc had no significant change in ROM at the operated level and at adjacent levels postoperatively. Furthermore, the Bryan® disc preserved motion at the operated level compared with ACDF. A detrimental increase in anterior/posterior translation at the adjacent level was also found to occur in patients treated with ACDF. It is suggested that the Bryan® disc reduces risk for degenerative translational motion.

Rabin *et al* (2007)

The retrospective study by Rabin *et al* (2007) compared postoperative *in vivo* kinematic properties of the operated and adjacent segments in patients with single-level artificial disc implants and matched patients treated with single-level ACDF. Kinematic parameters assessed included ROM, anteroposterior translation and disc height. These parameters were assessed preoperatively, and during early and late follow-up phase (ie, up to 24 months).

The results from this study showed the prosthesis implant significantly improved ROM and translation at the surgical level, compared to the ACDF group at early and late follow-up evaluations. As demonstrated through paired t-tests, prosthesis implant patients in both arms demonstrated increased translation at the surgical level in comparison to all patients preoperatively. In this 24-month study period, no significant difference in adjacent segmental disease development and kinematics was noted between the study arms. *In vivo* kinematic analysis proved difficult to interpret due to the comparison among different anatomic spine levels as the cervical spine kinematic baseline varies between anatomic levels. Also, out-of-plane motion, patient effort, and patient body habitus obscuring anatomic detail may all contribute to error. Overall, no significant kinematic differences were detected at adjacent segments in either the artificial disc or ACDF treated groups. This finding may be due to the short duration of the study. The authors have proposed longer follow-up periods to allow full evaluation of the two procedures.

PRESTIGE® CERVICAL ARTIFICIAL DISC

There were six publications examining the Prestige® cervical artificial disc for the treatment of cervical DDD. The primary efficacy and safety data from the US, FDA-approved IDE study of Prestige® are reported in Mummaneni *et al* (2007). Studies by Porchet and Metcalf (2004), Riina *et al* (2008) and Chang *et al* (2007a and 2007b) were also included in the review of the Prestige® cervical artificial disc. A health technology assessment conducted by the Technology Evaluation Center (TEC) (TEC (2008)) evaluating results of the clinical trial by Mummaneni *et al* (2007) was also identified but has not been included for discussion as it contains duplicate data. Chang *et al* (2007) examined ROM (C3-T2 specimens) using cadaveric specimens that includes both the Prestige® and Prodisc-C® artificial discs. The Prestige® results are presented here, while the Prodisc-C® artificial disc results are presented later.

Mummaneni *et al* (2007)

The multicentre RCT by Mummaneni *et al* (2007) compared clinical and radiographic outcomes of Prestige® cervical artificial disc surgery with ACDF in a group of symptomatic single-level cervical DDD patients. Patients (n=541) were enrolled at 32 sites within the US between October 2002 and August 2004 and randomly assigned to treatment with either the Prestige® artificial disc or ACDF. All patients were adults (ie, > 18 years) with single-level symptomatic DDD between C-3 and C-7 and intractable radiculopathy, myelopathy, or both. Patients were excluded if they had multiple level symptomatic DDD or evidence of cervical instability on dynamic flexion-extension radiographs, sagittal-plane translation of greater than 3.5 mm, or sagittal-plane angulation of greater than 3.5 mm, or sagittal-plane angulation of greater than 20 degrees at a single level.

The primary end point of the trial was 'overall success' which was based on a patient's successful outcomes with regard to NDI score (> 15 point increase from pre- to postoperative score) and maintenance or improvement in neurological status. Additionally, to be considered an overall success, a patient could not have suffered a serious implant-associated or implantation procedure-associated adverse event or have undergone a second surgery classified as a failure. These criteria are similar to those specified in other studies discussed above. Patients were examined in the clinic setting at 1.5, 3, 6, 12, and 24 months after surgery. Other clinical outcome measures including the SF-36, the NDI, and neck pain and arm pain numeric rating scales were used to evaluate the patient's condition before and after surgery. Neurological status and work status were also documented.

The outcomes of this study are presented in **Table 14**. Mean operative time, mean blood loss and mean hospitalisation duration were similar between the prosthesis and ACDF groups. The prosthesis group had a reduced implant removal rate (5 versus 9, respectively; $P = 0.2870$), a significantly lower revision rate (0

versus 5, respectively; $P = 0.0277$) and a significantly lower supplemental fixation rate (0 versus 9, respectively; $P = 0.0031$) compared to the ACDF group. The Prestige® artificial disc group also had a significantly lower re-operation rate at the adjacent segment level (3 versus 9 patients; $P = 0.0492$) and external orthosis rate (31.2% versus 59.1%; $P < 0.009$) compared to the ACDF group. The NDI success criterion is based on the improvement in relation to the preoperative NDI score. NDI scores of 15 points or greater were classified as a successful outcome. At 12 and 24 months follow up, both groups reported NDI scores of greater than 30 points; all patients, therefore, had a successful outcome. Higher neurological success rates were reported in the artificial disc group (92.8%) than the ACDF group (84.3%). This difference was statistically significant ($P = 0.005$). No additional surgical procedure, for example revision to ACDF or removal of the device, that would be classified as "failure" and no serious adverse event classified as prosthesis implant related were reported. Overall success rates for the artificial disc group were significantly higher than the ACDF group at 12 and 24 months following surgery (77.6% versus 66.4% and 79.3% versus 67.8%, respectively).

Table 14 Clinical and radiographic outcomes in single-level cervical DDD patients

Author (year) Country	Outcomes	Prestige (n = 276)	ACDF (n = 265)	P value
Mummaneni *et al* (2007) USA	Mean operative time (hrs)	1.6	1.4	
	Mean blood loss (mL)	60.1	57.5	
	Mean hospitalisation duration (days)	1.1	1.0	
	Implant removal (%)	5 (1.8)	9 (3.4)	
	Mandatory re-operation (patients)	3 *	9	
	External orthosis (%)	31.2 *	59.1	
	Neurological success [a] (%)	92.8	84.3	0.005
	Pre-operative outcomes scores [b]			
	NDI [mean (SD)]	56 (15)	56 (16)	0.2815
	Neck pain score [mean (SD)]	68 (23)	69 (22)	0.3781
	Arm pain score [mean (SD)]	59 (29)	62 (28)	0.4812
	SF-36 PCS [mean (SD)]	32 (7)	32 (8)	0.1744
	SF-36 MCS [mean (SD)]	42 (12)	43 (12)	0.0621
	Overall success at 12 months (%)	77.6 *	66.4	0.0040

Abbreviations: ACDF = anterior cervical discectomy and fusion; MCS = mental component summary; NDI = neck disability index; PCS = physical component summary; SD = standard deviation; USA = United States of America

[a] Maintenance or improvement in neurological status was based on 3 parameters (sensory, motor, reflex) however no detail was provided on how these were measured

[b] All outcomes scores were obtained from TEC Assessment: Artificial Intervertebral Disc Arthroplasty for Treatment of Degenerative Disc Disease of the Cervical Spine, 2008

* There was a statistically significant difference between the two groups; $P = 0.0492$ (log-rank test) and $P < 0.009$ (Fisher's exact test) for the re-operations and external orthosis, respectively.

Porchet and Metcalf (2004)

Porchet and Metcalf (2004) compare the Prestige® prosthesis to ACDF for the treatment of single-level degenerative disease. There were 27 patients randomised to receive anterior CDA with Prestige II disc and 28

patients randomised to receive ACDF with iliac crest autograft. To meet inclusion criteria, patients must have had cervical DDD, defined as an intractable radiculopathy or myelopathy caused by neuroradiologically documented disc herniation or osteophyte formation. Only patients with single-level disease in C4–5 to C6–7 were eligible for the study protocol. Patients were required to have been unresponsive to non-operative treatment for approximately six weeks, or had progressive symptoms or signs of nerve root compression while non-operative management continued. Although not explicitly stated, the clinical outcomes (see **Table 15**), appear to relate to mean values of treatment outcomes.

NDI improvement in the prosthesis group was significantly lower than ACDF at 24-months follow-up ($P < 0.05$, non-inferiority margin = 10). Throughout the study period, neck pain improvement was not statistically significant between the two treatment groups, however arm pain was significantly different ($P < 0.05$, non-inferiority margin = 10). Neurological status was assessed and scaled based on four measurements including motor, sensory, reflexes and the foraminal compression tests. Although the scoring of the scale was not detailed, higher scores indicate a better clinical outcome. Patients treated with the Prestige® artificial disc had higher neurological scores than patients treated with ACDF at all follow-up time points. There was no significant difference in the distribution or frequency of adverse events between the two groups, though it is noted that there was a statistically significant difference in arm pain between groups at all postoperative intervals up to 24 months.

Table 15 Clinical outcomes of single-level cervical degenerative disc disease patients

Author (year) Country	**Follow up (months)**	**Clinical outcomes [a]**							
		NDI [b, c]		**Neck pain (VAS) [c, d]**		**Arm pain (VAS) [c, d]**		**Neurological Status [e]**	
		Prestige	ACDF	Prestige	ACDF	Prestige	ACDF	Prestige	ACDF
Porchet and Metcalf (2004) UK	Baseline	53	60	13.3	14.9	13.9	14.2	92	84
	1.5	19	25	5.9	5.3	3.6	4.9	96	91
	3	16	22	5.7	5.4	4.1	5.3	96	95
	6	19	21	7.0	5.5	4.9	5.6	98	95
	12	17	19	5.5	5.5	4.9	6.1	98	97
	24	10 *	22	4.7	5.9	4.4*	7.7	99	94

Data source: Porchet and Metcalf (2004), results were read off figures 6 and 7, page 42

Abbreviations: ACDF = anterior cervical discectomy and fusion; NDI = neck disability index; UK = United Kingdom; VAS = visual analogue scale

[a] Mean NDI, VAS (neck and arm pain) and neurological scores of participants undergoing cervical disc replacement or spinal fusion. Measures assumed to be means. No SD reported.

[b] The NDI is a questionnaire containing 10 questions used to measure cervical pain and disability associated with activities of daily living. Lower scores represent less pain and disability

[c] Results read off Figure 6 of Porchet and Metcalf (2004) therefore results are approximate

[d] 20-point composite score. Lower scores represent a better outcome

[e] Results read off Figure 7 of Prochet and Metcalf (2004) therefore results are approximate

* Statistically significant difference observed between the two groups

Riina *et al* (2008)

Riina *et al* (2008) compared treatment with Prestige® artificial cervical disc with ACDF in 19 patients with cervical DDD. Patients were included if they had C3–C4 to C6–C7 disc involvement at only a single level and if their disease did not improve after six weeks of non-operative treatment. Those who had progressive signs of spine or nerve root compression were also considered eligible for the study.

The authors of this study reported similar outcomes to Porchet and Metcalf (2004) as shown in **Table 16**. Ninety per cent of prosthesis group patients were satisfied with the result of their surgery and, if they were diagnosed with cervical DDD again, 100 per cent indicated they would have the surgery again. There were no statistical differences in NDI, SF-36, neck and arm pain all showed improvement between the arthroplasty and the ACDF groups. Group differences were not statistically significant. Radiographic outcomes indicate the artificial disc maintained implant stability and seven patients (87.5%) in the investigational group had angular motion between 4° and 20°. ACDF groups achieved 100 per cent fusion rate, though, as reported in Schwab *et al* (2006), ACDF has been shown to increase adjacent segmental motion which can, in turn, accelerated disc degeneration.

Table 16 Clinical and radiographic outcomes in symptomatic cervical disc disease patients

Author (year) Country	Outcomes	Prestige (n=10)	ACDF (n=9)
Riina *et al* (2008) USA	Mean operative time (hrs)	2.0	1.6
	Mean hospitalisation duration (hrs)	23	23
	Mean neck pain score	17.9	17.4
	Mean arm pain score	17.2	8.9
	Mean NDI score	18.9	22.3
	Neurological status		
	Motor function (%)	100	100
	Sensory function (%)	77.8	85.7
	Radiographic success [a] (12 and 24 months) (%)	77.8, 87.5	100, 100
	Functional spinal unit success rate (%)	100	100
	PCS (%)	77.8	100
	MCS (%)	66.7	57.1
	Patient satisfaction (%)	88.9	85.7

Data source: Riina et al (2008): Page E75–E76

Abbreviations: ACDF = Anterior cervical discectomy and fusion; MCS = Mental Component Summary; NDI = Neck Disability Index; PCS = Physical Component Summary; USA = United States of America

[a] Determination of motion across artificial discs is objective (flexion-extension x-rays) and quantitative accuracy is limited as radiographic success is dependent on patient co-operation while being x-rayed.

Chang *et al* (2007a and 2007b)

Chang *et al* (2007a) and Chang *et al* (2007b) assessed biomechanical characteristics of 18 cadaveric spines after cervical arthroplasty with artificial discs (Prestige® and ProDisc-C®) and ACDF. All specimens were obtained from Science Care Anatomical and International Biological, Inc. Biochemical tests were performed on the treated level (C6 – C7), levels superior (C5 – C6) and inferior levels (C7 – T1) in the following six modes: flexion, extension, left and right lateral bending, and left and right axial rotation. The results indicated that Prestige® artificial discs increased ROM in all modes: extension (47%), flexion (10%), bending (55%), and rotation (50%). ROM decreased at all adjacent levels in all modes of motion by at least 10% when compared to pre-operative measures. In particular, extension at the inferior level decreased ROM by 12 per cent. Comparatively, according to Chang *et al* (2007a), ACDF resulted in decreased ROM for all motion modes by 18 – 44 per cent, though increased at adjacent levels by 3 – 20 per cent.

In arthroplasty-treated specimens, the adjacent-level intradisc pressure (IDP) showed little difference from that of the intact spine at both proximal and distal levels. In fusion-treated specimens, the IDP increased at the posterior annulus fibrosus on extension and at the anterior annulus fibrosus on flexion at the proximal level. At the distal level, the IDP change was not significant. The facet force changes were minimal in flexion, bending, and rotation modes in both arthroplasty and fusion-treated spines. Significant changes were noted in the extension mode only. In extension, arthroplasty models exhibited significant increases of facet force at the

treated level. Chang *et al* (2007b) observed that, in the fusion model, the facet forces decreased at the treated segment and increased at the adjacent segment.

Overall, results suggest use of the Prestige® artificial cervical disc maintains, if not increases, physiological ROM at the surgically treated segment compared to ACDF treated segments. The two artificial discs also maintained adjacent-level IDPs near the preoperative values in all modes of motion.

PRODISC-C® ARTIFICIAL DISC

There were five publications reporting the clinical and safety outcomes for the Prodisc-C® artificial disc for cervical DDD patients. The primary data were from a large prospective, controlled, multicentre FDA-IDE study of the Prodisc-C® versus ACDF (Murrey *et al* 2009). Three publications published in 2007 by Nabhan *et al* that evaluated the Prodisc-C® artificial cervical disc were found to have considerable overlap in recruitment and study participants. Consequently the most up to date results are discussed. Chang *et al* (2007a) and Chang et al (2007b) report the efficacy of Prestige® and Prodisc-C® artificial disc prosthesis. The ProDisc-C® artificial disc findings are presented below.

Murrey *et al* (2009)

In this study, 209 patients were randomised on a 1:1 ratio to receive treatment with the Prodisc-C® artificial disc or ACDF. The surgeon and surgical staff were not blinded to group assignment as preparation requirements were needed for both procedures. The patients remained blinded to randomisation until immediately post-surgery. The main inclusion criteria were that the patient had symptomatic cervical disc disease causing intractable, debilitating radiculopathy from one vertebral segment between C3 and C7, was unresponsive to non-operative treatment for at least six weeks, and had a NDI score of 15/50 or more. Patients were followed up for 24 months.

The primary outcome was 'overall success' which was a composite measure incorporating NDI success, neurological success, device success and absence of adverse events. Results are presented in Table 17. The overall success rate was 72.3% for the Prodisc-C® group and 68.3% for the ACDF group at 24-months follow-up (P = 0.0105).

Table 17 Overall success criteria at 24 months

Outcome measure	FDA success criteria			MCID success criteria		
	ACDF (%)	Prodisc-C (%)	*P* value [a]	ACDF (%)	Prodisc-C (%)	*P* value [a]
Neurological exam	88.0	90.9	0.638			
NDI	78.3	79.8	0.467	85.9	84.8	0.500
Adverse events	93.4	97.1	0.330			
Device success	91.5	98.1	0.033	91.5	98.1	0.033
Surgery again (yes or maybe)				96.6	95.9	0.550
Absence of pseudoarthrosis/absence of bridging bone				91.1	97.0	0.067
VAS arm or neck pain				87.8	87.8	1.000
No strong narcotics and/or muscle relaxants				81.5	89.9	0.073
Total	68.3	72.3	0.0105 [b]	60.4	72.7	0.047

Data source: Murrey *et al* (2009): Table 4, page 285
Abbreviations: ACDF = anterior cervical discectomy and fusion; FDA = Food and Drug Administration; MCID = minimum clinically important difference; NDI = Neck disability index; VAS = visual analog scale
[a] Fisher one sided exact test
[b] Blackwelder's test for noninferiority

Neurological success was defined as maintenance or improvement in each of the neurologic evaluations including sensory, motor and reflex functions. Failure to meet any one of these criteria led to the patient being deemed a failure for neurological success at that time-point. At six months, there was a statistically significant difference favouring the Prodisc-C® group with 94.6% of patients achieving success compared with 85.1% in the ACDF group ($P = 0.046$). At 24 months, neurological success rate was higher in the Prodisc-C® group but the difference was not significant.

All patients showed significant improvement in NDI scores at all follow-up periods compared with baseline ($P < 0.0001$). At the three-month follow-up there was a statistically significant difference favouring the Prodisc-C® group compared with the fusion group ($P = 0.05$). At 24 months, the mean score of the Prodisc-C® group was 21.4±20.2, whereas the mean score for the fusion group was 20.5±18.4 ($P = 1.00$). The success rate (ie, more than a 15 point improvement from baseline) was higher in the Prodisc-C® group at all follow-up time points compared to the ACDF group; however this difference was only significant at three months. There were also significant improvements from baseline in neck and arm pain according to VAS scores in both treatment groups; however, there was no significant difference between groups. SF-36 success was defined as improvement from baseline in the composite of the MCS and PCS components. At 24-months follow-up, 80.8% of Prodisc-C® patients and 74.4% of fusion patients were successful in the PCS. The MCS showed that 71.8% of Prodisc-C® and 68.9% of fusion patients were successful.

Secondary surgical procedures were defined as any revision, removal, or re-operation of the implant or supplemental fixation. Overall, nine (8.5%) patients in the ACDF group and two (1.9%) in the Prodisc-C® group required a secondary surgical procedure. In the ACDF group, five patients required a revision, one a re-operation and three a supplemental fixation. In the Prodisc-C® group, two removals were required. Device success was defined as no revision, removal or re-operation of the implant or supplemental fixation. Using these criteria, there was a statistically significant difference favouring Prodisc-C® compared with ACDF as success was achieved in 98.1% of Prodisc-C® patients compared with 91.5% of ACDF patients($P = 0.033$). There was no statistically significant difference in the overall number of adverse events between the two groups.

Nabhan *et al* (2007a)

This was a prospective, RCT of 49 enrolled patients with clinical evidence of radiculopathy, who were not responding to conservative treatment, to receive either ProDisc-C® (n=25) or ACDF (n=24). Eight patients were not eligible for inclusion and one was not available for follow-up leaving 40 included patients. Clinical symptoms such as neck and arm pain were investigated preoperatively and postoperatively one, two, and three years after surgery. Roentgen stereometric analysis (RSA) is a radiographic technique used to measure micromotion in the spine. Nabhan *et al* (2007a) used RSA to present intervertebral mobility results of prosthesis and ACDF treated patients.

Table 18 presents the clinical outcomes from Nabhan *et al* (2007a) detailing VAS mean (SD) values for neck and arm pain. In the Prodisc-C® group, the VAS neck pain mean score decreased significantly from 6.0 (±1.2) preoperatively to 1.7 (±0.4) three years post-surgery. Likewise, VAS arm pain mean values decreased significantly from 7.3 (±1.4) preoperatively to 1.2 (±0.3) three years post surgery. Mean (±SD) values for neck and arm pain measured using VAS in the ACDF group produced similar results to the prosthesis group. Overall, three years after surgery, the relief of both neck and arm pain was better in the prosthesis group without significant difference ($P = 0.06$ and $P = 0.1$ for neck and arm pain, respectively).

Table 18 Visual Analogue Scale (VAS) for Neck and Arm Pain in mono-segmental cervical DDD patients

Author (year) country	Follow up (weeks)	Clinical outcome [a]			
		Neck Pain (VAS)		Arm Pain (VAS)	
		ProDisc-C	ACDF	ProDisc-C	ACDF
Nabhan *et al* (2007a) Germany	Preoperatively	6.0 (1.2)	6.2 (0.9)	7.3 (1.4)	7.2 (1.5)
	Postoperatively	3.5 (0.6)	2.9 (0.7)	1.8 (0.4)	1.6 (0.4)
	One year	1.8 (0.5)	2.0 (0.5)	1.4 (0.2)	1.5 (0.3)
	Two year	1.8 (0.5)	2.7 (0.4)	1.2 (0.3)	1.9 (0.2)
	Three years	1.7 (0.4)	2.5 (0.4)	1.2 (0.3)	1.7 (0.2)

Data source: Nabhan *et al* (2007a): Table 2, page 233.

Abbreviations: VAS = visual analogue scale

[a] Mean (SD) are given for each time for ProDisc-C prosthesis group (n = 19) and ACDF group (n = 21)

The results from Nabhan *et al* (2007a) also showed a significant improvement in cervical spine segmental motion in the Proddisc-C® group for extension at the postoperative, one year, two year and three year follow-up ($P = 0.001$, $P = 0.03$, $P = 0.01$ and $P = 0.023$, respectively). Segmental motion was also significantly different for right-sided axial rotation and right-sided bending, at all follow-up time points. These data support the conclusion that cervical motion at the operated level can be maintained in patients treated with Prodisc-C®.

Chang *et al* (2007a and 2007b)

The studies by Chang and colleagues have been described previously. When compared to baseline measures, Prodisc-C® artificial discs increase ROM in all modes: extension (54%), flexion (27%), bending (10%), and rotation (17%). ROM decreased at all adjacent levels in all modes of motion by 10 per cent, in particular extension at the inferior level decreased ROM by 29 per cent. Comparatively, ACDF resulted in decreased ROM at the index level for all motion modes by 18–44 per cent, but increased ROM at adjacent levels by 3–20 per cent.

Results from Chang *et al* (2007b), indicated that there were no statistically significant differences in IDP at the adjacent level in the Prodisc-C® group relative to the intact spine (< 10% difference). In the ACDF group, however, at the superior level, the IDP was increased (46.5 ± 18.8%, $P = 0.686$) at the posterior annulus fibrosus during extension and was also increased during flexion (33.9 ± 8.9%, $P = 0.686$).

Overall, Nabhan *et al* (2007a) and Chang *et al* (2007) suggest use of ProDisc-C® artificial discs maintains intervertebral mobility and segmental stability.

DISCOVER™ ARTIFICIAL DISC

At present there are no published clinical papers reporting on the Discover™ artificial disc. Clinical studies are currently underway; however the interim analyses for these results are not yet available.

POOLED EFFICACY RESULTS

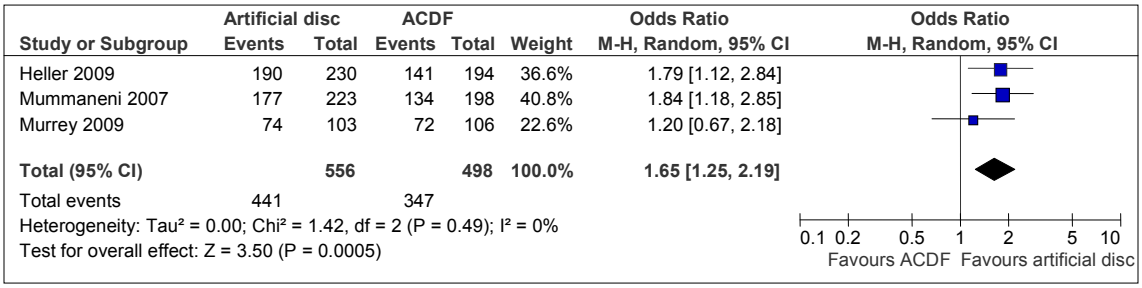
In order to compare the efficacy of the artificial cervical disc replacement when compared to ACDF, results of the primary endpoint outcome in the three FDA-approved IDE studies were pooled using Review Manager Version 5.0. Pooling of 'overall success' in the cervical artificial disc group versus 'overall success' in the ACDF group for the Heller *et al* (2009), Mummaneni *et al* (2007) and Murrey *et al* (2009) was possible due to comparable definitions of the primary outcome and similar follow-up time points. The parameter 'overall success' encompasses important safety and effectiveness aspects of the treatments and is the basis for FDA approval.

For statistical robustness, three meta-analyses were performed to calculate a pooled odds ratio, pooled relative risk and pooled risk difference. Results of the meta-analyses are shown in **Figure 6**, **Figure 7** and **Figure 8**.

The findings, regardless of the analysis performed, confirmed what was observed in each individual study. That is, significantly more patients treated with cervical artificial disc achieved 'overall success' at two years post-surgery compared with patients treated with ACDF.

Results in **Figure 6** demonstrate that the pooled odds (95% confidence interval) of achieving 'overall success' two years after surgery is significantly greater for patients treated with the cervical artificial disc compared with patients treated with ACDF (1.65 [1.25 – 2.19]).

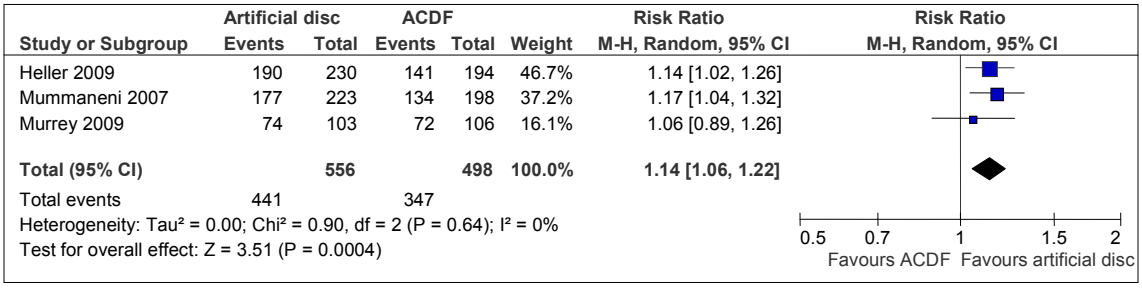
Figure 6 Achievement of 'overall success' at 24 months follow up in cervical artificial disc versus ACDF: pooled odds ratio, 95% Confidence Interval (CI)



Abbreviations: ACDF = anterior cervical discectomy and fusion; CI = confidence interval; M-H = mantel-haenszel

Similarly, results in **Figure 7** show that the pooled relative risk (95% confidence interval) of achieving an 'overall success' outcome two years after surgery is significantly greater in the cervical artificial disc group compared with the ACDF group (1.14 [1.06–1.22]).

Figure 7 Achievement of 'overall success' at 24 months follow up in cervical artificial disc versus ACDF: pooled risk ratio, 95% Confidence Interval (CI)

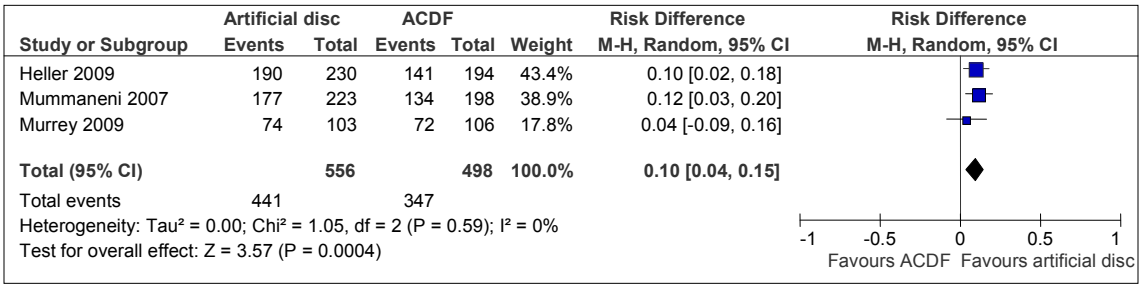


Abbreviations: ACDF = anterior cervical discectomy and fusion; CI = confidence interval; M-H = mantel-haenszel

The pooled risk difference (95% confidence interval) results shown in

Figure 8 also support the same conclusion. Patients treated with the cervical disc were found to be significantly more likely to achieve 'overall success' at two years follow-up compared with ACDF patients (0.10 [0.04–0.15]).

Figure 8 Achievement of 'overall success' at 24 months follow up in cervical artificial disc versus ACDF: pooled risk difference, 95% Confidence Interval (CI)



Abbreviations: ACDF = anterior cervical discectomy and fusion; CI = confidence interval; M-H = mantel-haenszel

These results confirm the conclusions from the large, prospective RCTs comparing artificial cervical disc and ACDF. Evidence shows that patients treated with CDA for DDD achieved superior clinical outcomes and required fewer re-operations, thus resulting in better overall success, compared to patients treated with ACDF. This result is important as it clearly demonstrates the benefits of CDA in terms of clinical outcomes with an obvious impact on patient morbidity and quality of life (which is explored in greater detail in Appendix 5).

SUMMARY OF EFFICACY AND SAFETY DATA

Since the initial MSAC application for artificial disc replacement (Application 1090), there has been a significant increase in the body of evidence published on the efficacy and safety of artificial cervical disc.

Three large, prospective, RCT's have been conducted as part of FDA-approved IDE studies for the Bryan®, Prestige® and Prodisc-C® artificial cervical disc. The primary outcome in each trial, 'overall success', included both efficacy and safety results. This outcome was consistently achieved by significantly more patients treated with cervical artificial disc compared to ACDF.

Specifically, overall success was achieved in 82.6% (95% CI: 77.1%–87.3%) of the patients in the Bryan® artificial disc group and 72.7% (95% CI: 65.8%–78.8%) of patients in the ACDF group at 24 months follow up in Heller *et al* (2009). This difference of 9.9% (95% CI: 2.0%–17.9%) was statistically significant (P = 0.010). In Mummanemi *et al* (2007), overall success rates for the Prestige artificial disc group were significantly higher (P = 0.053) than the ACDF group at 24 months following surgery (79.3% versus 67.8%, respectively). In Murrey *et al* (2009), the overall success rate was 72.3% for the Prodisc-C® group and 68.3% for the ACDF group at 24-months follow-up (P = 0.0105).

A further difference of note between artificial cervical disc and ACDF observed in these studies was the number of re-operations required. In Anderson *et al* (2008), re-operations on the cervical spine occurred in 5.4% of patients treated with Bryan® artificial disc and 7.7% of patients treated with ACDF (P = 0.045). The total number of cervical spine re-operations was also statistically greater in the ACDF group compared with the artificial disc group (21 versus 14, respectively; P value not reported). Overall re-operations were performed at the index level 12 times and at the adjacent level 11 times in the ACDF group, compared with 7 and 8 times in the Bryan® artificial cervical disc group, respectively. Four patients in the ACDF and one in the Bryan® artificial disc group had more than one re-operation. In the study by Mummaneni *et al* (2007), the Prestige® artificial disc group had a significantly lower re-operation rate at the adjacent segment level compared with ACDF (3 versus 9 patients, respectively; P = 0.0492). In the study by Murrey *et al* (2009), one patient in the ACDF group required a re-operation and three a supplemental fixation. In the Prodisc-C® group, no re-operations or supplemental fixations were required.

In addition, the median return-to-work intervals were significantly different (P = 0.015) with Bryan® artificial disc patients returning to work after 48 days compared to ACDF patients who returned after 61 days.

Together, these clearly demonstrate the benefits associated with CDA. The advantages associated with improved success, reduced need for re-operation and more rapid return to work are compelling. Benefits are accrued to the patient through improved health and reduced morbidity. Further, the reduced need for re-operation has advantages to the individual as well as to the government health care budget. Finally, the ability to achieve more rapid return to work benefits the individual's quality of life and society as a whole by reducing the productivity loss to society.

For this reason, an economic evaluation is presented in Appendix 5 to demonstrate that these benefits are achieved at an acceptable incremental cost.

APPENDIX 5: ECONOMIC EVALUATION AND BUDGET IMPACT

Appendix 5 relates to questions asked in Section 11 of the MSAC application form. For reference, questions 11.3 and 11.6 have been re-iterated below.

11.3 List the components of the service and their respective costs as well as the source(s) of information used to derive the costs

11.6 Provide a formal economic evaluation if required

ECONOMIC EVALUATION

BACKGROUND

With the new body of evidence recently published on the efficacy and safety of the cervical artificial disc, cervical disc arthroplasty (CDA) has been demonstrated to be clinically superior to anterior cervical discectomy and fusion (ACDF) in treating patients with cervical degenerative disc disease (DDD). Based on three extensive randomised control trials (RCTs), overall success (as defined in **Appendix 4**) was consistently achieved by more patients treated with CDA compared to ACDF. Further, a statistically significant reduction in the number of re-operations for CDA was reported. Additionally, patients receiving CDA were able to return to workforce 13 days sooner than those receiving ACDF, thereby minimising productivity losses (Heller *et al* 2009).

Given these benefits, a formal economic evaluation of CDA versus ACDF is justified. On this basis, a cost-utility study of CDA versus ADCF for patients with cervical DDD was conducted. A summary of the results is presented in **Table 19** below.

Table 19 Incremental cost per QALY gained

Cost/QALY (Societal perspective)	Base-case estimate
Incremental cost	$1,607
Incremental QALY gained	0.1173
ICER	$13,702

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

As shown in **Table 19**, the base-case analysis estimated the total incremental cost of CDA to be approximately $1,607 with an incremental quality-adjusted life year (QALY) of 0.1173 gained. The incremental cost-effectiveness ratio (ICER) is, therefore, estimated to be $13,702 per QALY.

A series of sensitivity analyses presented in **Table 35** further show that the ICER remains well within the range of what is typically considered cost-effective in the Australian setting. The ICER is most sensitive to the price of the cervical disc. Altering the perspective of the model to take a healthcare budget perspective only (by excluding societal costs) also impacts upon the results.

Based on the overall estimate of cost-effectiveness, it can be concluded that CDA represents good value for money for the treatment of individuals with cervical DDD. Furthermore, as discussed below, the budget impact on the health care system as a whole is marginal at $1.4m in the first year of listing, increasing to $1.7m in the third year. CDA is, however, marginally cost saving to the Medicare Australia budget.

The methodology and the results themselves are discussed in further detail below.

A REVIEW OF LITERATURE ON THE COST-EFFECTIVENESS OF CDA

A literature search was conducted with the aim of identifying any published economic evaluations of CDA in individuals with cervical DDD. Specifically, the search focused on revealing any relevant economic models or cost-effectiveness or cost-utility studies. The EMBASE.com database, which includes MEDLINE and EMBASE, was searched using the search strategies outlined in **Table 20**. A total of 128 citations were identified.

Table 20 Economics literature search strategy

Database (dates covered)	Search terms	Number of articles
EMBASE.COM (Includes MEDLINE and EMBASE 1966 to present) [Searched on 21 August 2009]	#1 'degenerative disc disease' OR 'herniated disc'/exp OR 'herniated disc' OR 'anterior cervical discectomy and fusion' OR 'radiculopathy'/exp OR 'radiculopathy' OR 'discogenic pain'/exp OR 'discogenic pain' OR 'spinal disease'/exp OR 'spinal disease' OR 'post discectomy syndrome' OR 'intervertebral disc displacement' AND ('disc replacement' OR 'arthroplasty'/exp OR 'arthroplasty' OR replacement OR 'prosthesis implantation'/exp OR 'prosthesis implantation' OR 'prostheses and implants'/exp OR 'prostheses and implants' OR 'spinal fusion'/exp OR 'spinal fusion' OR 'cervical vertebrae'/exp OR 'cervical vertebrae' OR 'intervertebral disc'/exp OR 'intervertebral disc') AND ('surgery'/exp OR 'surgery') AND ('cervical vertebrae'/exp OR 'cervical vertebrae' OR 'spine'/exp OR 'spine' OR 'spinal' OR 'cervical') AND (disc OR discs OR disk OR disks)	6, 344
	#2 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'health economics'/exp OR 'health economics' OR 'cost minimization analysis'/exp OR 'cost minimization analysis' OR 'cost minimisation analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'qaly'/exp OR 'qaly' OR 'life year saved'	449, 369
	#3 1 AND 2	***128***

An initial review was performed on these 128 citations using title and, when available, abstract. The exclusion criteria used against the title and abstract of these papers identified are presented in **Table 21**.

Table 21 Economics literature search exclusion criteria

Exclusion criteria	Number of papers excluded	Papers remaining
Not an economic evaluation	115	13
Not for cervical degenerative disc disease	11	2
Not cervical disc arthroplasty	1	1

One paper was included for the full text review (Bhadra *et al* 2009). After reviewing the full paper, it was excluded from further discussion as it is not a full economic evaluation. The study did not address the incremental cost of CDA relative to its incremental benefits. The study simply reported the cost and benefits of the interventions (in terms of Short Form 12 questionnaire), but failed to evaluate the incremental cost-effectiveness. There are no relevant economic evaluations of CDA compared to ACDF in the treatment of patients with cervical DDD.

APPROACH USED IN THE ECONOMIC EVALUATION

An economic evaluation was conducted to determine the value for money of single-level CDA, relative to single-level ACDF in adult patients with cervical DDD. A cost-utility approach was taken by measuring the health outcome of interest in terms of QALYs. The final results, as reported in **Table 19**, are presented in terms of the incremental cost per QALY gained. This approach appropriately adjusts health outcomes for patient morbidity and accounts for patient preferences for particular health states.

ACDF was selected as the comparator on the basis that it is the most commonly used method to treat individuals with cervical DDD. This approach is supported by the previous MSAC assessment report (MSAC application 1090 Assessment Report), which has acknowledged that ACDF is an appropriate comparator in the Australian setting. Although ACDF is the accepted current practice, various ACDF techniques are commonly performed. The four techniques include non-instrumented ACDF, ACDF with screws and plate, ACDF with interbody cage and ACDF with screws, plate and interbody cage. The economic analysis adopted the same approach as the earlier MSAC assessment report by accounting for the relative use of all four techniques.

Throughout the economic evaluation, a conservative approach was taken with all assumptions such that any potential inaccuracies would disadvantage CDA treatment. Such conservative assumptions include, for example, the exclusion of costs associated with Osteo Conductive bone substitutes that are frequently placed

into interbody fusion cages. This could add considerably to the cost of ACDF. As such, any divergence in any of the stated assumptions will serve to improve the overall outcome for CDA.

PATIENT POPULATION

The population of interest is adults who have failed non-operative treatment and have radiculopathy and/or myelopathy with changes secondary to degeneration of the disc or disc prolapse. On the basis of the available clinical evidence, the base-case economic evaluation considers those individuals requiring single-level surgery. It is, however, acknowledged that some individuals may require multiple-level intervention. Rather than introduce uncertainty into the economic modelling by making assumptions about the efficacy in these patients, the economic evaluation does not consider the cost-effectiveness in these individuals. This is notwithstanding the obvious clinical need in such patients.

STRUCTURE OF THE ECONOMIC MODEL

The economic evaluation was conducted using a Markov process, with a cohort expected value analysis performed to generate the results. The expected values are calculated by multiplying the percentage of cohort in each health state by the incremental cost or utility assigned to that health state. These are then summed across all health states and cycles to obtain the overall expected value associated with each surgical option.

This economic evaluation adopts a societal perspective. As such, it includes costs to the healthcare system and the cost of productivity losses. Out-of-pocket expenses to the individuals undergoing surgery and their families, however, are excluded from the analysis. The evaluation applies the full schedule fees of Medicare Benefits Schedule (MBS) items with, when applicable, adjustment for multiple operation rules. All costs are expressed in 2009 prices.

The economic model was developed using TreeAge Pro 2009. The model has a time horizon of five years with monthly cycles. Although a longer time horizon could be justified on the basis of an incremental difference in downstream re-operations, extrapolation of these data beyond a five-year period may introduce unreasonable uncertainty into the analysis. On this basis, the duration is limited to five years. This could potentially bias the results against CDA.

Half-cycle correction was not applied. As the model is structured such that very few patients will transfer between health states in the final stage of the model, it was deemed inappropriate in this instance.

A discount rate of 5% was applied to both costs and outcomes.

No subgroup analyses were conducted. A number of sensitivity analyses were undertaken, however, aiming to explore whether changes in key assumptions would alter the conclusions drawn. As shown in the discussion of these below, the results were shown to be robust.

HEALTH STATES IN THE ECONOMIC MODEL

The economic model has two distinct surgical arms – one capturing costs and benefits associated with CDA and another similarly for ACDF. There are a total of six health states in each of the two surgical arms, aggregating to twelve health states in total. All twelve distinct health states are tabulated below (**Table 22**), along with the corresponding brief descriptions.

Table 22 Health states included in the economic model

CDA arm	ACDF arm
Surgery: One-month period applied to individuals undergoing CDA	Surgery: One-month period applied to individuals undergoing ACDF
Success: Ongoing post-surgery period for individuals who meet the overall success criteria	Success: Ongoing post-surgery period for individuals who meet the overall success criteria
Failure: Ongoing post-surgery period for individuals who do not meet the overall success criteria	Failure: Ongoing post-surgery period for individuals who do not meet the overall success criteria
Index re-operation: One-month period applied to individuals undergoing re-operation at the index level	Index re-operation: One-month period applied to individuals undergoing re-operation at the index level
Adjacent re-operation: One-month period applied to individuals undergoing re-operation at the adjacent level	Adjacent re-operation: One-month period applied to individuals who undergoing re-operation at the adjacent level
Multiple level re-operation: One-month period applied to individuals undergoing re-operation at the both the index and adjacent level	Multiple level re-operation: One-month period applied to individuals who undergoing re-operation at the both the index and adjacent level

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

A simplified schematic of the economic model tree is depicted in **Figure 9**.

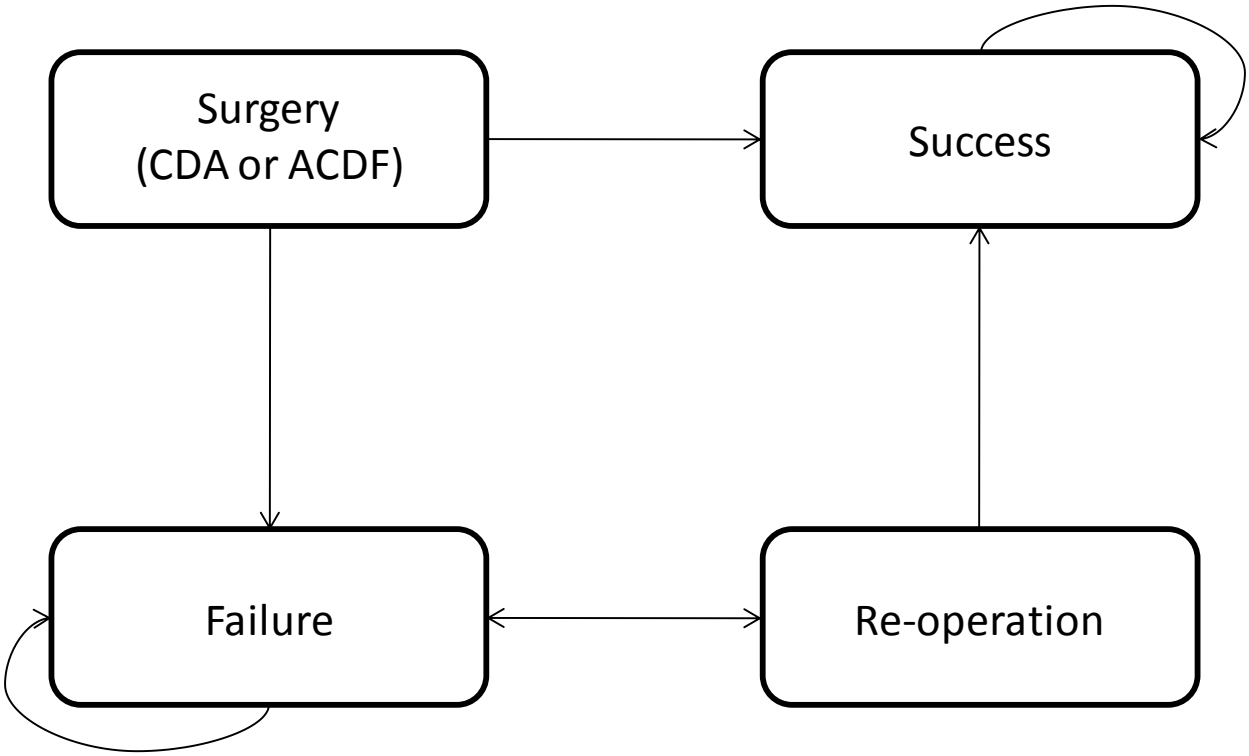
As shown, the model commences immediately before surgery takes place. As such, all individuals enter the model in the 'surgery' health state, where they undergo work-up and surgery procedures. At the end of the first cycle, individuals transition to one of the post-surgery health states on the basis of whether they have met the overall success criteria or not.

If an individual meets the overall success criteria, they then enter the 'success' health state and remain in this state for the duration of the model. This assumption means that individuals cannot transition from success to either failure or re-operation. The latter is justified by the definition of overall success used in the studies, which stipulates that the need for re-operation means a failure to meet the overall success criteria. The former

is a conservative assumption, as 24-month outcomes data were used in the economic model. This means that any individual who initially meets the overall success criteria but subsequently transitions to failure will be treated as a failure from the first post-operative cycle of the model. This simplifying assumption is potentially biased against CDA.

If, however, an individual fails to meet the overall success criteria, they would transit to the 'failure' state. Once entering the 'failure' state the patients may, according to the specified transition probabilities, go on to undergo a re-operation (see **Table 24**). Re-operations at the index level, the adjacent level, or both index and adjacent levels are accounted for in the model. Following a re-operation, overall success is re-assessed with individuals then transiting again to either the 'success' or 'failure' health state and continue as described above.

Figure 9 Summarised schematic of the economic model (ACDF and CDA)



KEY ASSUMPTIONS IN THE ECONOMIC ANALYSIS

There are a number of key assumptions inherent in the economic evaluation. Though many of these are discussed more comprehensively at other points in this report, they are listed in brief below for transparency:

- Those individuals achieving overall success are assumed to remain so for the duration of the model. As discussed above, this assumption is appropriate and conservative.

- Those individuals achieving the overall success do not require re-operation. This is consistent with the definition of overall success applied in the key studies (Heller *et al* 2009; Mummaneni *et al* 2007; Murrey *et al* 2009), which stipulates that any individual requiring re-operation would fail to meet the overall success criteria.

- Autogenous bone grafting (autografting) is the sole method used to fuse the intervertebral space for fusion stabilisation. This is consistent with the methodology outlined in the MSAC assessment report. It is conservatively estimated that this procedure does not impact on patient outcomes or influence hospital length of stay.

- One cage is required for a single-level cervical interbody fusion. This is, again, consistent with the methodology outlined in the MSAC assessment report.

- The duration of the hospital stay following surgery is equal for the CDA and ACDF procedures. This is a conservative estimate.

- The proportion of individuals achieving overall success following re-operation is assumed equal to the success rate following the initial surgical procedure.

- Should individuals originally treated with CDA require re-operation at the index level, the ACDF procedure would be utilised.

- Should individuals originally treated with CDA require a re-operation at the adjacent level, the CDA procedure would be utilised.

- Should individuals originally treated with CDA require a re-operation at both the index and adjacent level, the ACDF procedure would be utilised.

- In the case of multiple level re-operation, the surgery is assumed to cost an additional 50% of a single-level ACDF procedure. This assumption has a negligible impact on the result as a small proportion of individuals required such surgery.

VARIABLES USED IN THE ECONOMIC MODEL

The resource utilisation pertaining to CDA and ACDF was drawn primarily from the previous MSAC assessment report discussed above (MSAC application 1090 Assessment Report) and are summarised in **Table 27** and **Table 28**, respectively.

Note that there are currently no national clinical guidelines applicable to either CDA or ACDF for Australia. As a consequence, additional advice from local clinical experts from the Spine Society of Australia was sought and incorporated into the model. This input related primarily to the patterns of healthcare resource use.

Other clinical inputs such overall success, re-operation rates and quality of life were drawn from the RCTs discussed in **Appendix 4**.

Cost data relating to hospitalisations was sourced from the most recent version of the Australia Refined Diagnosis Related Groups (AR-DRG) publication (Round 12 AR-DRG 5.1). The estimated cost of hospitalisation accounts for the number of procedures performed at private and public hospitals. The unit costs of the artificial discs were provided by the sponsors, whilst the costs of the instruments used in the ACDF procedures were taken the MSAC assessment report.

With regards to the cost of the surgical procedure, the total cost of the CDA procedure *per se* that is applied in this economic analysis comprises one proposed MBS item that would be appropriate for intervertebral disc replacement procedures specifically in the cervical region. The proposed cost is equivalent to the existing MBS item 48691, which describes *lumbar* artificial intervertebral total disc replacement.

CLINICAL VARIABLES

The economic model drew the effectiveness data for both CDA and ACDF from three RCT studies (Heller *et al* 2009; Mummaneni *et al* 2007; Murrey *et al* 2009). All three RCTs consistently reported a statistically significant higher proportion of CDA patients achieving overall success at the 24-month follow-up, compared to patients receiving ACDF. The primary outcome, expressed as the overall success rate, from these RCT studies have comparable definitions and similar follow-up time points, allowing for appropriate pooling (see **Figure 6** through **Figure 8**). Overall success is a composite outcome encompassing important safety and effectiveness aspects of the treatments.

The average overall success rates used in the economic model are shown in **Table 23**. The averages were calculated by weighting the results from the three RCTs by the number of patients. On average, overall

success was achieved in 79.3% of patients treated with CDA versus 69.7% in individuals treated with ACDF ($P < 0.01$). This result is consistent with the pooled efficacy analysed in **Appendix 4**.

Though these RCTs were limited to a 24-month follow-up period in all instances, the differences in the proportions of overall success presented the trials appear to stabilise at the end of the trial period. On this basis, the economic analysis assumes the overall success rates are maintained for the duration of the economic model. As discussed above, this is appropriate. Note that by assuming the 24-month overall success data are used from the first post-operative cycle in the model, a conservative approach is taken.

Table 23 Probability of overall success for CDA and ACDF at 24 month of follow-up

	CDA			ACDF		
	Achieving overall success	**Total no. of participants**	**Success rate**	**Achieving overall success**	**Total no. of participants**	**Success rate**
Heller *et al* 2009	190	230	82.61%	141	194	72.68%
Mummaneni *et al* 2007	177	223	79.37%	134	198	67.68%
Murrey *et al* 2009	74	103	71.84%	72	106	67.92%
Weighted average			**79.32%**			**69.68%**

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

With respect to re-operations, the data were sourced from a study by Anderson *et al* (2008). Anderson and colleagues based their analysis on the same RCT reported by Heller *et al* (2009), focussing instead on safety outcomes over a follow-up period of up to three years. It was observed that re-operations following spinal surgery occurred more frequently in the ACDF group, compared to the CDA group. Over the three-year follow-up, the total number of re-operations performed was 21 in the ACDF group, statistically greater than 14 in the CDA group (*P*-value not reported). The number of re-operations in ACDF was higher for all the spinal levels (index level, adjacent level, and both index and adjacent levels), as shown in **Table 24**. This result emphasises the safer profile associated with the use of artificial cervical disc, compared to fusion.

Note that the relative improvement in re-operations associated with CDA at the three-year follow-up compared to the two-year follow-up is intuitive. Re-operations are typically required after a sufficient period of time has elapsed since the initial surgical procedure. While there is a clinical argument that re-operation rate may continue to diverge beyond the three-year follow-up, there are no data available to support this claim and Anderson *et al* (2008) data are relied upon for the analysis.

The re-operation data reported by Anderson *et al* (2008) required manipulation prior to being applied to the economic model. Specifically, the rate of re-operations over the three-year follow-up was reported, while the economic model requires monthly probabilities. The conversion calculation is presented in **Table 24**. The per

cycle probabilities of re-operations following surgery are 0.91% and 1.04% in the CDA and ACDF group, respectively.

Table 24 Probability of re-operations for CDA and ACDF

Row		CDA	ACDF	Source
	Number of re-operations			
A	At index level	6	10	Anderson et al (2008)
B	At adjacent level	7	9	Anderson et al (2008)
C	At both index and adjacent levels	1	2	Anderson et al (2008)
D	Total	14	21	Anderson et al (2008)
E	Number of patients	242	221	Anderson et al (2008)
F	Proportion of patients failing to meeting the overall success criteria	20.68%	30.32%	Table 23
	Rate of re-operation in the failure group			
G	At index level	11.99%	14.92%	A/(E x F)
H	At adjacent level	13.98%	13.43%	B/(E x F)
I	At both index and adjacent levels	2.00%	2.98%	C/(E x F)
J	Total	27.97%	31.34%	D/(E x F)
	Probability of re-operation used in the economic model			
	Probability of re-operations in the failure group per cycle (one month)			
N	**Probability of re-operations**	**0.91%**	**1.04%**	**=1-(1-J)^(1/36)**

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

Note that personal communication with Anderson revealed that the data reported in **Table 24** relate to a follow-up period of *up to* 36 months. As re-operations are more likely to occur after some time following surgery has elapsed, the inclusion of individuals who had not been followed for 36 months may lead to an underestimate in the number of re-operations. On the basis of the results observed, therefore, it is important to note that this may be another source of a bias against CDA. This potential bias is not considered, however, due to data limitations.

UTILITY WEIGHTS

The utility weights applied in the economic model were based on the transformation of 36-item short form (SF-36) data collected during the RCT reported in Heller *et al* (2009). The SF-36 data were transformed into the preference-based health-related quality of life index (SF-6D) using the revised algorithms originally developed by Brazier *et al* (2002). See Brazier *et al* (2008) for further detail.

Table 25 presents the relevant SF-6D utility weights derived from data reported by Heller *et al* (2009). The health-related quality of life data were collected prior to surgery and again six weeks, three months, six months, 12 months and 24 months post-surgery. These currently unpublished data were split according to overall success or failure for each study arm. As expected, the SF-6D data of the CDA group show improvement in quality of life at all post-operative time points, compared to the ACDF group. The difference was most pronounced shortly following surgery, gradually diminishing over the 24-month follow-up period. These findings give support to the hypothesised advantages associated with the use of the artificial replacement disc. In particular, they demonstrate that individuals receiving CDA recover more rapidly and are capable of resuming normal daily activities at an earlier stage.

Table 25 SF-6D transformed from SF-36 reported in the study by Heller *et al* 2009

Row number	Follow-up time point in Heller *et al* (2009)	CDA		ACDF		Source
		Success	Failure	Success	Failure	
A	Pre-surgery					Unpublished data [a]
B	6-week follow-up					Unpublished data [a]
C	3-month follow-up					Unpublished data [a]
D	6-month follow-up					Unpublished data [a]
E	12-month follow-up					Unpublished data [a]
F	24-month follow-up					Unpublished data [a]

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty; SF-6D = 6-dimension short form
[a] Data derived from Heller *et al* (2009) study using techniques of Brazier *et al* (2002)

The SF-6D data were, however, not available at the one and two months follow-up. The utility data at these time points were required for modelling. They were, therefore, calculated and are presented below. For clarity, the method of deriving the utility weights at each time point is described below. The final utility weights as used in the economic model are presented in **Table 26**.

Firstly, the utility weights at the one-month follow-up were used in the economic model as a proxy for the utility weights assigned to the 'surgery' and 're-operation' health states. During these health states, individuals experience different quality of life according the type of treatment received. In the first month of the model, there is no distinction between individuals meeting the overall success criteria or otherwise. The utility weights for this cycle must, therefore, appropriately reflect this structure. The formula for deriving utility weights, for each arm, for the one-month follow-up is the following.

$$(\text{Six-week utility} - \text{Pre-surgery utility}) * (2/3) + \text{Six-week utility}$$

Note that, in each study arm, the six-week utility weight appropriately accounts for the proportion of individuals meeting the overall success criteria to derive a weighted average. That is

- Six-week utility in the CDA arm = (Probability of overall success * [redacted] + [(1 – probability of overall success) * [redacted]

- Six-week utility in the ACDF arm = (Probability of overall success * [redacted] + ((1 – probability of overall success) * [redacted]

Utility weights for the second post-operative month were interpolated in the similar manner, with the exception being that all utility weights used in the calculations were treatment- and success criteria-specific.

Table 26 SF-6D as used in the economic model

Health state/cycle in economic model	CDA		ACDF		Source
	Success	Failure	Success	Failure	
Surgery and re-operation	[redacted]		[redacted]		Derived
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	Derived
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	Table 25, Row C
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	Table 25, Row D
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	Table 25, Row E
Cycle 23	[redacted]	[redacted]	[redacted]	[redacted]	Table 25, Row F

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

It is important to note that the ACDF group in the RCT reported by Heller *et al* (2009) received allografting rather than autografting. Autografting has been associated with donor site complications such as chronic pain, reducing quality of life and extending the post-surgical recovery period. Pollock *et al* (2008) studied the occurrence of donor site complications in 76 patients undergoing iliac crest bone harvesting for ACDF. It was found that the donor site pain was present but often minor. There is, however, lack of reliable quantifiable information regarding the donor site pain from autografting and the impact this has on health-related quality of life. The economic analysis, therefore, conservatively assumed no adjustment for this disutility in the base-case analysis. This could potentially bias the results against CDA but the impact of a change in this assumption was explored in the sensitivity analyses.

The SF-36 data were also reported in Mummaneni *et al* (2008) study, but was not incorporated in this analysis as data were not collected at appropriate time points, thereby failing to appropriately capture difference in health-related quality of life between CDA and ACDF.

COST INPUTS

The four general categories of cost components comprise the following:

- medical costs associated with CDA and ACDF
- costs of hospitalisation
- cost of prostheses/instruments
- societal cost of productivity loss

These cost components are discussed below and presented in **Table 27** to **Table 32**.

Medical services associated with CDA and ACDF

The costs of medical services include medical consultations, radiographic examinations, surgical services, surgical assistance, and anaesthesia management. The multiple operation rules stipulated in the MBS were also applied when appropriate to ensure costs weren't overestimated.

Clinical work-up

To ensure individuals' eligibility and suitability, a number of procedures are administered prior to surgery. These work-up procedures are common to both CDA and ACDF procedures. The services comprise three consultations, one computerised tomography (CT) scan and one magnetic resonance imaging (MRI) scan. See **Table 32** for more detail.

Surgical procedures

As discussed earlier, the healthcare resource utilisation associated with CDA and ACDF was drawn primarily from the MSAC assessment report of Application 1090, with costs and obsolete items updated to the current MBS schedule (August 2009). The medical cost associated with CDA comprised the cost of performing the procedure, providing surgical assistance, and the cost of managing anaesthesia. Note that MBS items for anaesthesia-related services have changed substantially since the time the MSAC assessment report was published. Appropriate new MBS items for anaesthesia were identified by matching the item descriptions. A list of medical services relevant to CDA and ACDF are tabulated in **Table 27** and **Table 28**. Each table provides a brief description of medical services, the source of the services, the full MBS schedule fee, proportion of MBS fees claimable and total costs. The proportion of MBS fees claimable (Column C) was adjusted according to the multiple operation rules as set in MBS. Note that the multiple operation rules were

not applicable for CDA. The rules, however, were applied for ACDF as these patients undergo more than one operation, thereby rendering these rules applicable.

Note that the proposed MBS item relating to cervical artificial disc replacement was included in the costing of CDA (see **Table 27**). The average total cost of medical services associated CDA was estimated to be $2,536 per person per procedure.

Table 27 Cost of medical services associated with CDA, per patient per procedure

Service	Source	Full MBS schedule fee	% of fee claimable	Total cost
Column	**A**	**B**	**C**	**E=B x C**
Discectomy of 1-level intervertebral disc, cervical decompression, and placing of artificial cervical disc (with fluoroscopy)	Proposed item, based on MBS 48691[a]	$1695.20	100%	$1695.20
Examination in preparation for the administration of an anaesthesia	MBS 17615	$80.85	100%	$80.85
Initiation of management of anaesthesia	MBS 20600	$187.00	100%	$183.00
Anaesthesia perfusion time units (2.41–2.50 hours)	MBS 23113	$243.10	100%	$237.90
Assistance provided to discectomy	MBS 51303	$339.04	100%	$339.04
Total cost of CDA per patient per procedure				***$2,535.99***

Abbreviations: ACDF= anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty; MBS = Medicare benefits schedule

[a] Note that, based on Medicare Australia statistics, medical service (MBS item 48691) is the most commonly claimed item for lumbar artificial intervertebral total disc replacement, compared to the other total disc replacement item (MBS items 48692 and 48693). From December 2006 to April 2009, approximately 94% of all total disc replacement was claimed under MBS item 48691. For simplicity, the economic analysis assumed 100% usage of this service.

The medical services relating to CDA and ACDF are generally comparable. However, ACDF patients require the following two additional services:

(1) Harvesting of bone grafts, and

(2) Longer initiation and administration of anaesthesia.

All patients undergoing ACDF require bone grafts to knit together the two vertebrae where the degenerated disc was removed. Autografting and allografting are the two available techniques of bone grafting. There is little published information as to which method of bone grafting is commonly adopted in Australia. Furthermore, examining MBS data is unhelpful as these procedures are not restricted to ACDF. This economic analysis assumes autografting for all ACDF patients. This assumption is consistent with the previous MSAC assessment report for application 1090. Autogenous bone grafts are taken from the patients' own lilac crest, which may lead to donor site complications. These complications are completely averted with the use of the artificial disc, as bone grafting is not required with CDA. This advantage of CDA, however, is not explicitly accounted for in the economic analysis.

Patients treated with ACDF require longer initiation and administration of anaesthesia, as ACDF procedures are generally longer and often more complicated than CDA. Ten minutes of anaesthesia time was assumed for the non-instrumented and ACDF with interbody cage treatment options. In more complicated cases involving screws and plates, 20 minute of anaesthesia time were allowed. Again, these assumptions are consistent with previous MSAC assessment report for application 1090.

As shown in **Table 28**, the average medical cost of medical services associated ACDF is estimated to be $2,658 per person per procedure. Similar to CDA, the medical cost associated with ACDF consisted of the cost of performing the procedure, providing surgical assistance, and the cost of managing anaesthesia. Note that there are four different techniques of ACDF, which are (1) non-instrumented, (2) ACDF with screws and plate, (3) ACDF with interbody cage, and (4) ACDF with screws, plate and interbody cage. The proportionate use (weighting) of each was based on sales data from DePuy Spine and Medtronic Australia. These proportions are presented in **Table 28**. This is at odds with the previous MSAC assessment report, which took the simplifying approach of weighting each of the procedures equally. On the basis of these estimates, it could be said that this simplification was not entirely appropriate.

Furthermore, the MBS item codes were modified slightly in from the MSAC assessment report, with MBS item number 40332 not being applied. In the overwhelming majority of cases (at least 95%), CDA would be performed where the indication is for radiculopathy (ie, nerve root compression, not spinal decompression). MBS item number 40332 would, therefore, be technically incorrect as the spinal cord is not to be decompressed. Admittedly, however, the distinction may be viewed by some as minor and it is possible that that a number of cases of anterior fusion for radiculopathy alone are charged as MBS item number 40332 in practice. This, however, does not have a marked influence on the final results. In the interests of being technically correct, however, MBS item 48660 is used in all instances in this application, with the relevant addition of MBS item number 40330 for the associated spinal compression procedure. Additionally, there would be very few cases that are performed in Australia without some form of internal fixation. This has been appropriately added to the costs outlined in **Table 28**. This is consistent with medical practice.

Follow-up

Over the follow-up period, individuals require consultations and x-rays. Individuals are ordinarily scheduled for medical consultations at six weeks, 12 weeks and 12 months post-surgery. The number of follow-up consultations is assumed equal between the arms of the economic model.

Follow-up x-rays are performed at these consultations, with the total number of x-rays differing between arms. Those undergoing ACDF require two follow-up x-rays, usually occurring at six weeks and 12 months after surgery. Those receiving CDA require only one x-ray, at the six-week follow-up. Those treated with ACDF usually require additional x-rays in comparison to those undergoing CDA to ensure that satisfactory healing of the bone graft.

Table 32 provides details on resources used over the follow-up period.

Table 28 Cost of medical services associated with ACDF, per patient per procedure

Service	Source	MBS Schedule fee	% of fee claimable	Total cost
Column	**A**	**B**	**C**	**E = B x C**
Non-Instrumented ACDF (0% weighting)				
Spinal fusion (anterior interbody) to cervical, thoracic or lumbar regions - 1 level	MBS 48660	$1,023.25	100.00%	$1,023.25
Spinal rhizolysis involving exposure of spinal nerve roots – 1 level [a]	MBS 40330	$902.55	50.00%	$451.28
Harvesting of (autogenous) bone graft – small quantity [a]	MBS 47726	$133.50	25.00%	$33.38
Examination in preparing for the administration of anaesthesia	MBS 17615	$80.85	100.00%	$80.85
Initiation of management of anaesthesia on cervical spine and/or cord	MBS 20600	$187.00	100.00%	$187.00
Anaesthesia perfusion time units (2.51–3.00 hours)	MBS 23114	$261.80	100.00%	$261.80
Assistance provided to cervical decompression and harvesting of bone graft	MBS 51303	$301.58	100.00%	$301.58
Subtotal cost				*$2,339.13*
ACDF with screws and plate (25.5% weighting)				
Spinal fusion (anterior interbody) to cervical, thoracic or lumbar regions - 1 level	MBS 48660	$1,023.25	100.00%	$1,023.25
Spinal rhizolysis involving exposure of spinal nerve roots – 1 level [a]	MBS 40330	$902.55	50.00%	$451.28
Segmental internal fixation of spine [a]	MBS 48684	$889.80	25.00%	$222.45
Harvesting of (autogenous) bone graft – small quantity [a]	MBS 47726	$133.50	25.00%	$33.38
Examination in preparing for the administration of anaesthetic	MBS 17615	$80.85	100.00%	$80.85
Initiation of management of anaesthesia for extensive spine and/or spinal cord procedures	MBS 20670	$243.10	100.00%	$243.10
Anaesthesia perfusion time units (3.01–3.10 hours)	MBS 23115	$280.50	100.00%	$280.50
Assistance provided to cervical decompression and harvesting of bone graft	MBS 51303	$346.07	100.00%	$346.07
Subtotal cost				*$2,680.87*
***ACDF with interbody cage* (30.5% weighting)**				
Spinal fusion (anterior interbody) to cervical, thoracic or lumbar regions - 1 level	MBS 48660	$1,023.25	100.00%	$1,023.25
Spinal rhizolysis involving exposure of spinal nerve roots – 1 level [a]	MBS 40330	$902.55	50.00%	$451.28
Segmental internal fixation of spine [a]	MBS 48684	$889.80	25.00%	$222.45
Harvesting of (autogenous) bone graft – small quantity [a]	MBS 47726	$133.50	25.00%	$33.38
Examination in preparing for the administration of anaesthesia	MBS 17615	$80.85	100.00%	$80.85
Initiation of management of anaesthesia on cervical spine and/or cord	MBS 20600	$187.00	100.00%	$187.00
Anaesthesia perfusion time units (2.51–3.00 hours)	MBS 23114	261.8	100.00%	$261.80
Assistance provided to spinal fusion, segmental internal fixation and harvesting of bone graft	MBS 51303	$346.07	100.00%	$346.07

Service	Source	MBS Schedule fee	% of fee claimable	Total cost
Column	**A**	**B**	**C**	**E = B x C**
Subtotal cost				*$2,606.07*
***ACDF with screws, plate and interbody cage* (52% weighting)**				
Spinal fusion (anterior interbody) to cervical, thoracic or lumbar regions - 1 level	MBS 48660	$1,023.25	100.00%	$1,023.25
Spinal rhizolysis involving exposure of spinal nerve roots – 1 level [a]	MBS 40330	$902.55	50.00%	$451.28
Segmental internal fixation of spine [a]	MBS 48684	$889.80	25.00%	$222.45
Harvesting of (autogenous) bone graft – small quantity [a]	MBS 47726	$133.50	25.00%	$33.38
Examination in preparing for the administration of anaesthesia	MBS 17615	$80.85	100.00%	$80.85
Initiation of management of anaesthesia for extensive spine and/or spinal cord procedures	MBS 20670	$243.10	100.00%	$243.10
Anaesthesia perfusion time units (3.01–3.10 hours)	MBS 23115	$280.50	100.00%	$280.50
Assistance provided to cervical decompression and harvesting of bone graft	MBS 51303	$346.07	100.00%	$346.07
Subtotal cost				*$2,680.87*
Average cost of ACDF procedures				***$2,658.06***

Abbreviations: ACDF = anterior cervical discectomy and fusion; MBS = medicare benefits schedule

[a] Note that multiple operation rule is applied - 100% for the item with the greatest Schedule fee, plus 50% for the item with the next greatest Schedule fee, plus 25% for each other items (for more information, refer to Note T8.3 in the MBS book or http://www9.health.gov.au//mbs/fullDisplay.cfm?type=note&q=T8.3&qt=noteID&criteria=multiple%20operation)

Cost of hospitalisation

The cost of hospitalisation presented in **Table 29**, was sourced from the most recent AR-DRG publication (Round 12 AR-DRG 5.1). The calculation of hospitalisation cost was based on DRG items I09A and I09B. The prosthesis component of the total cost was subtracted from the average of these DRGs in order to avoid double-counting, as the cost of prostheses was captured separately in this economic analysis.

The average cost of hospitalisation was estimated to be approximately $11,300 per separation, see **Table 29**. The hospitalisation cost was calculated by averaging the costs between DRG I09A and I09B across the private and public hospitals, and weighting these by the respective number of separations.

Analysis of effectiveness reveals no evidence on the difference in the duration of hospitalisation between CDA and ACDF. The hospitalisation cost of $11,300 per separation is, therefore, assumed equal for both surgical techniques. This assumption, however, is conservative since input from experts indicates that a difference is expected. Specifically, it is anticipated that an individual treated with ACDF with autografting requires a longer duration of hospital stay (up to two days longer) and hence incurs more costs, compared to those treated with CDA.

Table 29 Cost of hospitalisation

AR-DRG	Average cost	No. of separations	Total cost	Source
Public hospital				
I09A	$26,007.00	833		(Round 12 Public AR-DRG 5.1: Average total cost – cost of prosthesis)
I09B	$12,918.00	1,561		(Round 12 Public AR-DRG 5.1: Average total cost – cost of prosthesis)
Private hospital				
I09A	$14,459.00	1,215		(Round 12 Private AR-DRG 5.1: Average total cost – cost of prosthesis)
I09B	$7,996.00	5,643		(Round 12 Private AR-DRG 5.1: Average total cost – cost of prosthesis)
Weighted average cost of hospitalisation per separation [a]			***$11,296.79***	

Abbreviations: AR-DRG= Australian-Refined Diagnosis Related Group
[a] Weighted by number of separations

Cost of prostheses/instruments

The costs of prostheses/instruments associated with CDA and ACDF are shown in **Table 30**.

The costs of the replacement discs used in the CDA procedure were provided by the sponsors. These were estimated as averaging $[redacted] per disc. As the average cost is used in the base-case analysis, the actual acquisition cost of each of the discs may vary from the estimate provided in **Table 30**. A range of prices were, therefore, tested in the sensitivity analyses to investigate the impact on the cost-effectiveness.

The cost of instruments used for ACDF was calculated on the basis of information from the MSAC 1090 assessment report in conjunction with the August 2009 Prostheses List (Department of Health and Ageing) (http://www.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheseslist.htm) . The minimum benefit from the Prostheses List was used in all cases. The costs of instruments for ADCF were averaged across the four ACDF techniques using the weightings derived from the Spine Society (as presented originally in **Table 28**). Note that non-instrumented ACDF incurs no cost in this category. As such, it was omitted from the table below. The average cost of instruments used in ACDF was estimated to be approximately $3,887 per patient per procedure.

Table 30 Costs of prostheses/instruments used in CDA and ACDF

Procedure	Unit cost	Number of unit required	Total cost	Source
CDA				
Average cost of replacement disc	[redacted]	1	[redacted]	Calculated from manufacturer prices [a]
Average cost per disc per CDA			[redacted]	
ACDF				
Fusion with screws and plate (15% weighting)				
Screws	$200.00	4	$800.00	Prostheses List, August 2009
Plate [b]	$1,800.00	1	$1,800.00	Prostheses List, August 2009
Subtotal			*$2,600.00*	
Fusion with interbody cage plate (33% weighting)				
Interbody cage	$2,503.00	1	$2,503.00	Prostheses List, August 2009
Subtotal			*$2,503.00*	
Fusion with screws, plate and interbody cage plate (52% weighting)				
Screws	$200.00	4	$800.00	Prostheses List, August 2009
Plate	$1,800.00	1	$1,800.00	Prostheses List, August 2009
Interbody cage	$2,503.00	1	$2,503.00	Prostheses List, August 2009
Subtotal			*$5,103.00*	
Total average cost of instruments per ACDF			***$3,887.01***	

Abbreviations: ACDF = anterior cervical discectomy and fusion; CDA= cervical disc arthroplasty; MSAC = Medical Services Advisory Committee

[a] The calculated acquisition cost is based on the following prices: Bryan disc = [redacted] per disc, Discover disc = [redacted] per disc, Prestige = [redacted] per disc and Prodisc = [redacted] per disc

[b] Assumes cervical plate size of >55mm

Societal costs of productivity loss

To capture the important societal cost of surgical treatment of cervical DDD, the economic analysis included an estimate of the costs associated with an individual's reduced capacity to work and undertake usual daily activities in the period following surgery. Such costs are an important consideration in the current analysis, as they represent an important difference between CDA and ACDF. Moreover, such productivity losses are important when adopting a societal perspective in decision making. Reduced productive capacity has important societal implications. In addition to the potential for productivity losses to impact upon the economy as a whole, the impact on the individual should not be underestimated. A reduced capacity to undertake usual daily activities will ordinarily impact on leisure time of either the individual or those close to individual. When adopting a societal perspective, as MSAC's 'Economics Section of the MSAC Guidelines' recommends, inclusion of these productivity or 'indirect' costs is crucial.

This application adopts the friction cost method of calculating the cost of productivity losses (Koopmanschap *et al* 1995; Koopmanschap and Rutten 1996). This method for measuring the indirect cost of disease yields estimates that are considerably lower than those from the traditional method of human capital (Koopmanschap *et al* 1999). The results from the friction cost method are, therefore, considered conservative. The friction cost method assumes that a proportion of productivity losses due to work absence are absorbed by the remaining workforce or upon the individuals' return to work after an absence. It should be noted, however, that adopting a societal perspective requires non-wage productivity to also be captured. The average wage rate is therefore used as a proxy for all productivity losses, thereby appropriately valuing non-wage productivity.

While there is no clear consensus as to what rate of friction should be applied in an economic evaluation, a rate of 80% has previously been applied in work done by those that originally developed the methodology (Koopmanschap *et al*, 1995). The economic model, therefore, assumed the friction rate of 80%. To assess the impact of this on the results, productivity costs were excluded in a sensitivity analysis. The productivity loss was estimated at approximately $3,182 per month per patient (**Table 31**).

Table 31 Productivity loss calculation

Parameter	Value	Source
Average monthly income	$3,977.11	ABS series 6302.0
Friction rate	80%	Assumption
Monthly productivity loss (model input)	***$3,181.68***	$3,977.11 * 80%

Abbreviations: ABS = Australian Bureau of Statistics

The review of the RCTs presented in **Appendix 3** demonstrates that individuals receiving CDA are typically able to resume normal movement and return to work earlier than those receiving ACDF. This represents a significantly reduced productivity loss for those patients receiving CDA, compared to ACDF. Specifically, the Heller *et al* (2009) study reported that, on average, CDA patients were able to return to work sooner than those undergoing ACDF (medium of 1.58 months v 2.01 months, $P = 0.015$). A consistent observation, but of a much larger magnitude, was reported in other studies. Steinmetz *et al* (2008) reported that patients receiving CDA returned to work 3.33 months post-surgery, compared to 7.32 months for ACDF. Conservatively, the findings of Heller *et al* (2009) were used in the base-case analysis, while sensitivity analyses were conducted using the results observed in the study by Steinmetz *et al* (2008).

Summary of costs applied in the economic evaluation

Table 32 presents the list of all the cost units used into the economic analysis. For compatibility with the economic model, the cost data are tabulated by health state by surgical procedure.

Table 32 Unit costs applied per health state for CDA and ACDF

Resource	Cost input	Source	No. of units consumed for CDA	No. of units consumed for ACDF	Cost input for CDA	Cost input for ACDF
Row	**A**	**B**	**C**	**D**	**E = A x C**	**F = A x D**
'Surgery' health State						
Work-up:						
Initial consultation	$142.65	MBS 110	1	1	$142.65	$142.65
Subsequent consultation	$71.35	MBS 119	2	2	$142.70	$142.70
CT scan	$240.00	MBS 56220	1	1	$240.00	$240.00
MRI Scan	$358.40	MBS 63173	1	1	$358.40	$358.40
Surgery:						
Medical service fee associated with CDA	$2,545.19	Table 27	1	-	$2,545.19	-
Medical service fee associated with ACDF	$2,658.06	Table 28	-	1	-	$2,658.06
Cost of hospitalisation	$11,296.79	Table 29	1	1	$11,296.79	$11,296.79
Cost of prostheses used for CDA	[redacted]	Table 30	1	-	[redacted]	-
Cost of instruments used for ACDF	$3,887.01	Table 30	-	1	-	$3,887.01
Productivity loss per month	$3,181.68	Table 31	1.58	2.01	$5,027.05	$6,395.18
'Success' health state						
Doctor consultation (follow-up)	$71.35	MBS 110	3	3	$214.05	$214.05
x-ray (follow-up)	$71.35	MBS 58100	1	2	$67.15	$142.70
'Failure' health state						
Doctor consultation (follow-up)	$71.35	MBS 110	3	3	$214.05	$214.05
X-ray (follow-up)	$71.35	MBS 58100	1	2	$71.35	$142.70
'Index re-operation' health state						
Work-up:						
Initial consultation	$142.65	MBS 110	1	1	$142.65	$142.65
Subsequent consultation	$71.35	MBS 119	2	2	$142.70	$142.70
CT scan	$240.00	MBS 56220	1	1	$240.00	$240.00
MRI Scan	$358.40	MBS 63173	1	1	$358.40	$358.40
Surgery:						
Medical service fee associated with ACDF	$2,658.06	Table 28	1	1	$2,658.06	$2,658.06
Cost of hospitalisation	$11,296.79	Table 29	1	1	$11,296.79	$11,296.79
Cost of instruments used for ACDF	$3,887.01	Table 30	1	1	$3,887.01	$3,887.01

Resource	Cost input	Source	No. of units consumed for CDA	No. of units consumed for ACDF	Cost input for CDA	Cost input for ACDF
Row	**A**	**B**	**C**	**D**	**E = A x C**	**F = A x D**
Productivity loss per month	$3,181.68	Table 31	2.01	2.01	$6,395.18	$6,395.18
'Adjacent re-operation' health state						
Work-up:						
Initial consultation	$142.65	MBS 110	1	1	$142.65	$142.65
Subsequent consultation	$71.35	MBS 119	2	2	$142.70	$142.70
CT scan	$240.00	MBS 56220	1	1	$240.00	$240.00
MRI Scan	$358.40	MBS 63173	1	1	$358.40	$358.40
Surgery:						
Medical fee associated with CDA	$2,545.19	Table 27	1	-	$2,545.19	-
Medical fee associated with ACDF	$2,658.06	Table 28	-	1	-	$2,658.06
Cost of hospitalisation	$11,296.79	Table 29	1	1	$11,296.79	$11,296.79
Cost of prostheses used for CDA	[redacted]	Table 30	1	-	[redacted]	-
Cost of instruments used for ACDF	$3,887.01	Table 30	-	1	-	$3,887.01
Productivity loss per month	$3,181.68	Table 31	1.58	2.01	$5,027.05	$6,395.18
'Multiple level re-operation' health state						
Work-up:						
Initial consultation	$142.65	MBS 110	1	1	$142.65	$142.65
Subsequent consultation	$71.35	MBS 119	2	2	$142.70	$142.70
CT scan	$240.00	MBS 56220	1	1	$240.00	$240.00
MRI Scan	$358.40	MBS 63173	1	1	$358.40	$358.40
Surgery:						
Medical fee associated with ACDF	$2,658.06	Table 28	1.5	1.5	$3,987.08	$3,987.08
Cost of hospitalisation	$11,296.79	Table 29	1.5	1.5	$16,945.19	$16,945.19
Cost of instruments used for ACDF	$3,887.01	Table 30	1.5	1.5	$5,830.52	$5,830.52
Productivity loss per month	$3,181.68	Table 31	2.01	2.01	$6,395.18	$6,395.18

Abbreviations: ACDF = anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty; CT = computerised tomography; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging

RESULTS OF THE ECONOMIC EVALUATION

Base-case analysis

Table 33 presents the base-case incremental cost and QALY gained. The incremental cost per QALY gained was estimated at $13,702, which falls well within the bounds of what is typically considered to be cost-effective. This result suggests CDA offers good value for money.

Table 33 Results of the base-case economic analysis

Parameter	CDA	ACDF	Incremental Change	ICER
Cost	$30,540	$28,933	$1,607	
QALY	3.4254	3.3081	0.1173	
Incremental cost per QALY				*$13,702*

Abbreviations: ACDF =anterior cervical discectomy and fusion; CDA= cervical disc arthroplasty; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Note that the results presented in **Table 33** were generated on the basis of a number of conservative assumptions that could bias the results in favour of ACDF.

In terms of outcomes, applying the 24-month overall success data from the first post-operative cycle of the model could underestimate the quality of life benefit of CDA over the period up to 24 months. Additionally, the model does not include a disutility associated with patient pain and discomfort due to bone grafting, which is characteristic of ACDF only.

In terms of costs, the possibility of reducing the length of stay in hospital by avoiding the need for a bone graft when treated with CDA may overestimate the incremental cost associated with CDA.

Though it is true that a number of key differences are included in the economic model, the approach has erred on the conservative side in cases in which there is substantial uncertainty regarding the difference between the two techniques. This conservatism may disadvantage CDA by overestimating the incremental cost per QALY gained.

Supplementary analyses

Supplementary analyses were conducted with an aim to present the cost-effectiveness ratio of each of the four discs considered in the base-case analysis. These additional analyses were based the actual acquisition cost of each artificial disc, rather than the average price. **Table 34** shows the total incremental cost, QALY gained and the ICER by disc.

Table 34 Results of supplementary economic analyses

	CDA	ACDF	Incremental Change	ICER
Supplementary analysis 1: Bryan disc				
Cost	[redacted]	[redacted]	[redacted]	
QALY	3.4254	3.3081	0.1173	
Incremental cost per QALY				[redacted]
Supplementary analysis 2: Discover disc				
Cost	[redacted]	[redacted]	[redacted]	
QALY	3.4254	3.3081	0.1173	
Incremental cost per QALY				[redacted]
Supplementary analysis 3: Prestige disc				
Cost	[redacted]	[redacted]	[redacted]	
QALY	3.4254	3.3081	0.1173	
Incremental cost per QALY				[redacted]
Supplementary analysis 4: ProDisc disc				
Cost	[redacted]	[redacted]	[redacted]	
QALY	3.4254	3.3081	0.1173	
Incremental cost per QALY				[redacted]

Abbreviations: ACDF=Anterior Cervical Discectomy and Fusion; CDA= Cervical Disc Arthroplasty; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year

SENSITIVITY ANALYSES

A number of one-way sensitivity analyses were conducted to explore in the impact of changes in key assumptions and parameters. **Table 35** presents the increment cost, incremental benefits and ICER.

Table 35 Sensitivity analyses

Scenarios	Incremental cost	Incremental QALY gained	ICER
Base-case analysis	$1,607	0.1173	$13,702
Cost input			
Increasing the average cost of the artificial disc by 20%	$3,341	0.1173	$28,489
Decreasing the average cost of the artificial disc by 20%	- $127	0.1173	CDA offers additional benefits at a lower total average cost per treated individual
Increasing the friction rate from 80% to 100%	$1,166	0.1173	$9,937
Decreasing the friction rate from 80% to 50%	$2,269	0.1173	$19,349
Excluding productivity costs (ie, adopting a healthcare budget perspective only)	$3,373	0.1173	$28,760
Clinical input			
Increasing the rate of overall success for CDA by one standard deviation, that is from 79.32% to 84.84%	$1,008	0.1426	$7,065
Decreasing the rate of overall success for CDA by one standard deviation, that is from 79.32 to 73.79%	$2,223	0.0913	$24,346
Applying return-to-work data as reported in Steinmetz *et al* (2008), that is 3.33 months for CDA and 7.32 month for ACDF	- $10,882	0.1173	CDA offers additional benefits at a lower total average cost per treated individual
Assuming no difference in the rate of re-operation, that is setting rate of re-operation for CDA equal to that for ACDF	$1,857	0.1196	$15,528
Assuming all re-operations are at the index level in the CDA arm	$1,438	0.1173	$12,262
Assuming all re-operations are at the adjacent level in the CDA arm	$1,675	0.1173	$14,277
Assuming all re-operations are at both the multiple level in the CDA arm	$2,148	0.1173	$18,311
Increasing the incremental utility of overall success between CDA and ACDF in the first two post-operative months by 50% [a]	$1,607	0.1196	$13,436
Decreasing the incremental utility of overall success between CDA and ACDF in the first two post-operative months by 50% [a]	$1,607	0.1157	$13,893
Model structure			
Including a disutility of 0.1 associated with autografting during ACDF	$1,607	0.1082	$14,856
Increasing the discount rate from 5% to 7%	$1,663	0.1125	$14,775
Decreasing the discount rate from 5% to 3%	$1,547	0.1224	$12,635

Abbreviations: ICER= Incremental Cost-effectiveness Ratio; QALY = Quality-Adjusted Life Year

[a] This sensitivity analysis was performed by adjusting the observed six-week utility such that the difference between the utility associated with overall success in the CDA and ACDF arms was either increased or decreased by 50%. According to the methodology outlined around Table 25 and Table 26, this leads to adjustments in the utility weights applied to the first two cycles of the economic model.

CONCLUSIONS

The analyses have demonstrated that the use of cervical artificial disc provides value for money for treating patients with cervical DDD, when compared to ACDF. While the analysis adopted a number of potentially conservative assumptions, the base case ICER is well within the boundary of being cost-effective in the Australian setting at an ICER of $13,702 per QALY. While the sensitivity analyses did reveal some sensitivity to certain parameters and assumptions, the results proved to be robust nonetheless. In all cases, they remained within the bounds of reasonable cost-effectiveness.

BUDGET IMPACT

This section presents the estimates of net financial impact resulting from the introduction of CDA as an alternative to the treatment of cervical DDD with ACDF. The financial impact was estimated from the perspectives of both Medicare Australia and the whole of healthcare system. The incremental financial cost per patient was derived based on the difference in costs of CDA and ACDF presented in the economic evaluation. The reimbursement rate of all MBS items was set at 85%. The analyses were conducted with an assumption of one surgery per patient per year. This, however, may not be likely due to the need for re-operations in some individuals, as reported in Anderson *et al* (2008). Since re-operations are expected to occur more frequently in the ACDF group, the financial impact for CDA presented below is likely to be over-estimated.

Number of eligible patients

The projected number of eligible patients treated with CDA was presented earlier in **Appendix 3**. For ease of reference, the projections are replicated in **Table 36**. In summary, the number of patients with cervical DDD eligible for ACDF was projected to be 1,182 in 2011 with an increase to 1,282 and 1,382 in 2012 and 2013 respectively. It was anticipated that approximately 30% of these eligible patients would switch to CDA. Based on this proportion, the total number of patients receiving CDA was estimated to be 355 in 2010 increasing to 385 and 415 in 2011 and 2012.

Table 36 Projected number of patients with cervical DDD eligible for CDA

Row		2011	2012	2013	Reference
A	Estimated number of patients treated with ACDF in cervical spine	1182	1282	1382	Appendix 3, Table 1
B	Proportion of eligible patients switched to CDA	30%	30%	30%	Appendix 3, Table 1
C	Estimated number of ACDF patients switched to CDA	355	385	415	Row C = row A x row B

Abbreviations: ACDF = anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

Cost implications to healthcare sector

The cost to the whole of healthcare system included the cost of medical services, cost of hospitalisation and cost of prostheses/instruments.

Note that any costs, incurred by the healthcare system or not, due to re-operations are not included. These costs are incurred by only a proportion of individuals and are, for the purposes of simplicity, excluded from consideration. Further, the indirect cost such of productivity loss was excluded. Such costs fall outside the

perspective of the healthcare system. All other costs presented in **Table 32** are included, as they are all incurred by the healthcare system.

The incremental cost of CDA was estimated to be $4,300 per patient per year (based on $22,790 of costs incurred by patients treated with CDA and $18,490 incurred by patients treated with ACDF). On the basis of the number of patients expected to switch from ACDF to CDA presented in **Table 36**, the total financial impact to the whole healthcare system was estimated to be between $1.5 million in the first year of listing. This increases to $1.8 million in the third year.

Table 37 Net financial impact to the whole of healthcare system

Row		Year 1	Year 2	Year 3	Reference
A	Incremental cost of CDA	$4,300	$4,300	$4,300	Calculated from unit costs presented in Table 32
B	Estimated number of ACDF patients switched to CDA	355	385	415	Table 36, row C
C	Total financial impact	$1,524,683	$1,653,675	$1,782,667	Row C = row A x row B

Abbreviations: ACDF = anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty
Note: The analysis assumes that CDA is listed on the MBS from 2010 onwards

Cost implications to Medicare Australia

The costs incurred to Medicare Australia included specifically the medical services covered by the MBS item. The costs of hospitalization and prostheses/instruments are outside the boundary of the MBS budget.

Note that, as shown in **Table 38**, while CDA is associated with a net cost overall, the procedure is associated with a cost saving to the Medicare Australian budget. This cost saving is driven by a lower cost of medical procedures associated with CDA relative to ACDF ($2,454 versus $2,658). Most notably, CDA avoids the need for nerve decompression, segmental fixation and bone graft. Overall there is an expected cost saving to Medicare Australia of approximately $153 per patient. Across the entire Medicare Australia budget, this amounts to a cost saving of between $54,259 and $63,439 per annum during the first three years of listing.

It is acknowledged that, the patient numbers used throughout this application are calculated from the number of procedures currently performed under the Medicare Australia umbrella. This, in turn, means that the calculated Medicare costs used in these calculations may be underestimated due to the outpatient services to public sector patients (eg outpatient follow-up consultations) not being included. Nonetheless, it should be acknowledged that the exclusion of these costs has no impact on the incremental cost between CDA and ACDF as resource utilisation of these items is the same regardless of the technology used. The impact of this simplification, therefore, should not be overstated.

Table 38 Net financial impact to Medicare Australia

Row		Year 1	Year 2	Year 3	Reference
A	Incremental cost of CDA	-$153.01	-$153.01	-$153.01	Calculated from unit costs presented in Table 32
B	Estimated number of ACDF patients switched to CDA	355	385	415	Table 36, row C
C	Total financial impact	-$54,259	-$58,849	-$63,439	Row C = row A x row B

Abbreviations: ACDF = anterior cervical discectomy and fusion; CDA = cervical disc arthroplasty

SUMMARY OF THE ECONOMIC EVALUATION AND BUDGET IMPACT

The economic evaluation was informed by a comprehensive review of the literature, which produced a total of 17 publications of RCT data that were not included in the previous MSAC assessment of CDA in 2006. The strength of the newly published evidence was demonstrated thought grading of the 17 newly identified studies according to NHMRC criteria. This resulted in one Level I, ten Level II, three Level III-1 and three Level III-2 publications. These data were then appropriately used to inform the economic evaluation.

A conservative approach was taken throughout the economic evaluation, with any substantial areas of uncertainty excluded from consideration. For example, although professional opinion indicates that when compared to ACDF, patients undergoing CDA experience shorter operating time, reduced length of hospital stay, no detrimental outcomes associated with autogenous bone grafting, there is a lack of solid observational data to support these claims. These benefits were, therefore, excluded. This has the potential to underestimate the value for money offered by CDA relative to ACDF. As such, any divergence in any of the stated assumptions will serve to improve the overall outcome for CDA. Furthermore, the way in which the overall success data were used in the model adds to this by potentially underestimating the quality of life gains to be had from CDA.

In addition to these considerations, CDA may also be associated with other clinical or economic effects, such as reduced utilisation of community services and fewer days of restricted activity. Again, these were not included in the present study.

Nonetheless, when compared to ACDF in the base-case analysis, CDA was associated with QALY gains of 0.1173 and the cost per QALY gained was estimated to be AU$15,372. This is well within the bounds of what is ordinarily considered to be cost-effective and, therefore, represents good value for money. Furthermore, the sensitivity analyses undertaken (see **Table 35**) demonstrate that the results, and the

conclusions to be drawn from them, are robust. This serves to add to weight to the conclusion of cost-effectiveness.

Finally, it should be noted that, in addition to the cost-effectiveness of CDA, the intervention has only a marginal impact on the healthcare budget as a whole. This is driven by the low patient numbers (due to CDA being used only to replace ACDF rather than treat individuals who are currently untreated) and the moderate incremental cost of the procedure itself. Moreover, CDA is expected to offer cost savings to the MBS budget through the avoidance of a number of associated medical procedures.

APPENDIX 6: REFERENCES

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