CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

ARTIFICIAL DISC REPLACEMENT FOR DEGENERATIVE DISC DISEASE OF THE CERVICAL SPINE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) has been asked to review the scientific literature on the safety and efficacy of artificial spinal disc replacement for the treatment of neck pain caused by cervical degenerative disc disease because of the publication of recent new clinical trials comparing artificial disc replacement with spinal fusion.

CTAF has previously reviewed the literature on the safety and efficacy of artificial spinal disc replacement for the treatment of low back pain caused by lumbar degenerative disc disease, but has not previously reviewed the literature for the treatment of neck pain caused by cervical degenerative disc disease.

BACKGROUND

Neck Pain and Cervical Degenerative Disc Disease

Cervical degenerative disc disease results from spinal spondylosis and causes deterioration of the intervertebral discs of the cervical spine. Desiccation of the discs leads to collapse of the index level segment and leads to abnormal motion of the spinal column.

Symptoms of degenerative disc disease (DDD) include neck pain, arm pain, weakness and paresthesias associated with nerve root compression. Disc herniation, osteophytes, and kyphosis can lead to spinal cord compression and myelopathy. Symptoms of the myelopathy can include arm and leg weakness, numbness of the arms or hands or changes in gait or balance.

The prevalence of DDD increases with aging. It has been estimated that 80% of individuals older than 55 have evidence of degenerative disc disease on X ray[1]. In one natural history study, up to 45% of patients have one episode of cervical radicular pain and up to 33% have intermittent attacks[2].

Treatment of Cervical Degenerative Disc Disease

The ideal treatment of compressive cervical radiculopathy has been debated. Some patients will improve without any specific treatment[2, 3].

Usually the first step is conservative treatment. Patients who have radicular symptoms but who do not have weakness or myelopathy can be treated conservatively. Conservative treatment can include analgesics, a short course of steroids, avoidance of provocative activities, cervical traction, neck immobilization, or use of a cervical pillow and physical therapy.

Surgery is typically indicated when six months of conservative therapy have not been successful or when the symptoms have progressed in a short time period and interfere with the patient's usual activities.

Cervical Spine Fusion Surgery for Degenerative Disc Disease

Anterior cervical discectomy and fusion (ACDF) is the most commonly used decompressive procedure in the cervical spine and is used for the treatment of single level disc disease[4]. The disc is removed anteriorly; discs that are herniated either laterally or midline can be removed. The aim of the procedure is to remove pressure from the spinal nerves and to realign and stabilize the spinal concern. Bony material (either autograft or allograft) is placed into the intervertebral space in order to stimulate healing and fusion. A metal place is subsequently placed in order to stabilize the fusion site and to obviate the need for a post-operative brace.

An important and limiting complication of cervical spine fusion surgery is the development of DDD in adjacent discs[5-7]. Artificial intervertebral disc arthroplasty has been proposed as an alternative that might decrease the incidence of this complication.

Artificial Intervertebral Disc Arthroplasty

As an alternative to ACDF, artificial intervertebral disc arthroplasty (AIDA) has been proposed as a surgical treatment for patients with symptomatic cervical DDD [8, 9]. With AIDA, instead of placing bone in the intervertebral space, an artificial disc is placed instead. In contrast to ACDF, an anterior plate is not needed to stabilize the adjacent vertebra and an external brace is not needed either.

Since AIDA maintains the usual intervertebral disc space, it has been suggested that the usual movement and lordosis of the spine is more likely to be preserved. Maintenance of position and motion has been

suggested to decrease the risk of adjacent segment DDD that has been see with ACDF[8], although the clinical significance of these AIDA induced changes is not entirely clear [9, 10].

Artificial Cervical Discs

Three cervical artificial discs currently have Food and Drug Administration (FDA) approval. These include the ProDisc-C cervical disc, the Prestige ST Cervical Disc and the Bryan cervical disc, Medtronic.

The Prestige ST cervical disc is a metal on metal device. It is made of stainless steel and contains two components- a ball and a trough that articulate. It is attached to the cervical vertebrae with screws. It is manufactured from titanium ceramic composite material. A porous titanium plasma spray coating on the end plate surface facilitates bone in growth and long term fixation[11, 12].

The Pro-Disc –C cervical disc is a metal on polymer device. It has cobalt-chromium end plates with a central keel for anchorage to the vertebral bodies and a locking core of ultra high molecular weight polyethylene (UHMWPE) as a central polymer that provides a ball and socket articulation. In order to be compatible with tissue, the endplates are coated a titanium plasmapore.

The Bryan cervical disc is also a metal on polymer device. It is a single piece of a porous coated, clamshell shaped titanium endplates with a polycarbonate, polyurethane core.

All of the discs are indicated for use in skeletally mature patients for single level disc disease in levels C3 to C 7. Candidates for surgery are those who have failed conservative therapy and have evidence of symptomatic nerve root and or spinal cord compression as documented by patient symptoms and radiographically.

In conclusion, artificial cervical disc arthroplasty has been proposed as an alternative to ACDF for the treatment of single level symptomatic cervical degenerative disc disease. It has the theoretic advantage of a reduced risk of adjacent segment degeneration. Thus, the question is how the outcomes of AIDA compare with those of ACDF in patients with symptomatic cervical spine DDD.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: **The technology must have final approval from the appropriate government regulatory bodies.**

The Prestige® Cervical Disc (Medtronic Sofamor Danek, Memphis, TN) received FDA Premarket Approval (PMA) on July 16, 2007.

The ProDisc-C® (Synthes Spine Inc., West Chester, PA) received PMA clearance on December 17 2007.

The Bryan® Cervical Disc System (Medtronic Sofamor Danek, West Chester, PA) received PMA clearance on May 12, 2009.

TA Criterion 1 is met.

TA Criterion 2: **The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

The Medline database, Cochrane clinical trials database, Cochrane reviews database and Database of Abstracts of Reviews of Effects (DARE) were searched using the key words cervical disc or cervical vertebrae or replacement or prosthesis or artificial disc and also with the term cervical arthroplasty. The search was performed for the period from 1966 to July, 2009. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested form the device manufacturers. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

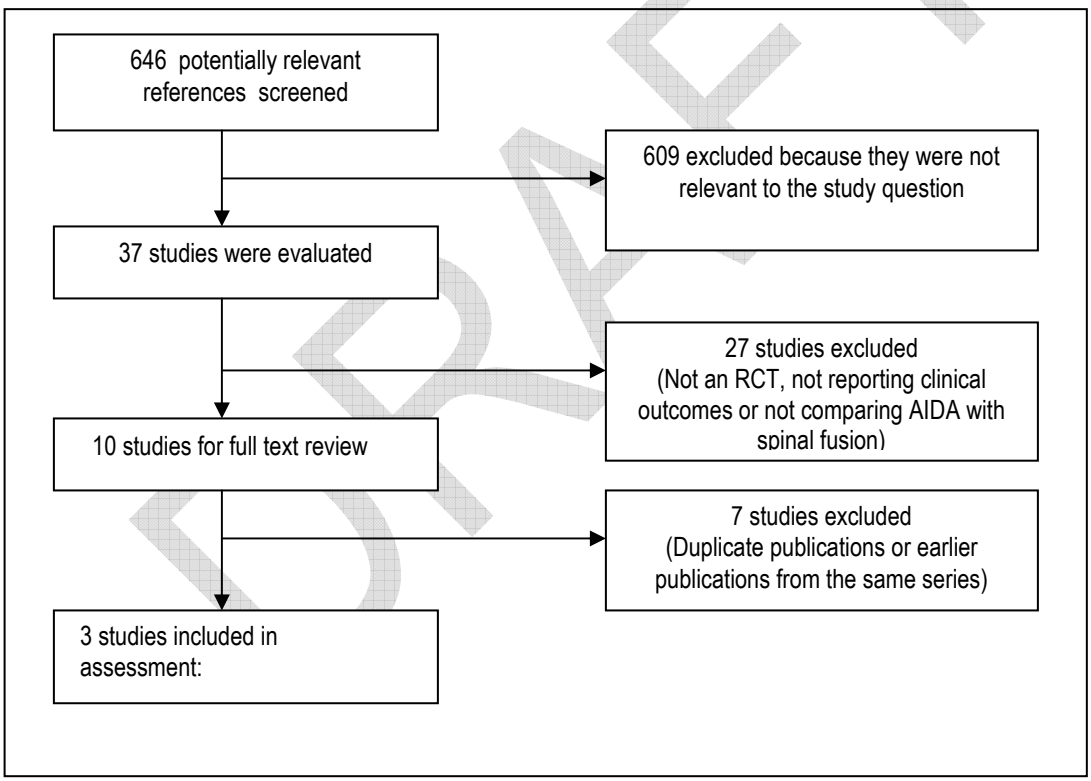
Inclusion criteria:

- Study had to compare AIDA with spinal fusion
- Study had to be a randomized trial
- Study had to measure clinical outcomes
- Included only humans
- Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes such as radiographic changes or surgical technique. They were also excluded if they were retrospective and/or if they were case series.

A total of 646 potentially relevant articles were identified. 609 were excluded for not addressing the research question. A total of 37 studies were evaluated. 27 were excluded. Reasons for exclusion included not being a randomized controlled trial (RCT), not reporting clinical outcomes or not comparing AIDA with spinal fusion. Of the remaining, seven were either duplicate publications or earlier publications from the same series. Of these, three randomized trials of FDA approved cervical disc devices that evaluated clinical outcomes were identified and are included in this review.

Figure 1: Selection of studies for inclusion in review



Details of the three randomized trials and the outcomes measured are described in Table 1. A description of the clinical outcomes evaluated in the trials follows.

Table 1: Randomized Trials of Cervical Disc Replacement Comparing Cervical Disc Arthroplasty with Anterior Cervical Decompression and Fusion

AUTHOR	N	Type of Disc	Inclusion Criteria	Mean Age	Length of follow-up	Outcomes Evaluated
Murrey, 2009[13].	209	ProDisc	Age 18-60 Symptomatic Cervical Disc Disease at one level C3-7 Unresponsive to non-operative treatment for at least 6 weeks NDI Score >15/50	42,1-43.5	24 months	Overall Success Neck disability index (NDI) Neurologic exam VAS Pain and intensity (neck and arm) VAS satisfaction Device Success Adverse events
Heller, 2009[14].	465	BRYAN	At least 21 Symptomatic Cervical Disc Disease at one level Unresponsive to non-operative treatment for at least 6 weeks	44.4-44.7	24 months	Overall Success Neck Disability Index Numeric Rating Scales for Neck and Arm Pain SF-36
Mummaneni, 2007[11].	541	Prestige	Age 18 and over Single level symptomatic DDD between C3 and C 7 and intractable radiculopathy, myelopathy or both	43.3-43.9	24 months	Overall Success Neck Disability Index SF-36 Neck pain and arm pain numeric rating scales Neurologic success

The primary clinical outcomes measured in all of these studies were the Neck Disability Index (NDI) and Overall Success. Additional outcomes include neurologic success, neck and arm pain, and Short Form 36 (SF-36) scores. The clinical outcomes are defined below.

The Neck Disability Index (NDI) is the primary outcome in these studies and is used to measure the effects of neck pain associated with activities of daily living. It includes ten questions that include neck pain intensity, personal care, reading, headaches, concentration, work, driving, sleeping and recreation. Total NDI score is calculated by adding the results and converting to a percentage from 0-100%. A lower score indicates less disability. NDI scores are compared pre and post-operatively to determine improvement. In addition, the change in the NDI at follow-up is also reported in some studies.

Neck Disability Index Success: Another measure of the NDI is the Neck Disability Index Success: Neck Disability Index Success is defined as a >15 point improvement in NDI from baseline. A 15 point improvement is chosen because it is thought to be of clinical significance.

Overall Success: Overall success is based on successful outcomes with NDI score (≥15 point improvement from pre to post operative score and maintenance or improvement in neurological status). In addition, 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.

Neurologic Success: Neurologic Success was based on postoperative maintenance or improvement in condition compared with the preoperative status. Indicators included motor function, sensory function and deep tendon reflexes.

SF-36: TheSF-36 is a self-administered test used to assess general health status. It measures specific health concepts related to physical function and limitations, social functioning and health perceptions. There are two scores- the physical component summary (PCS) and the mental component summary (MCS). The PCS score is based on physical functioning, role physical bodily pain and general health subscales. The MCS score is composed of the vitality, social functioning, emotional and mental health scales.

Post operative arm pain and neck pain: Neck and arm pain was measured post operatively. It was often measured using a Visual Analogue Score (VAS). Often the neck and arm pain measures were compared pre and post-operatively.

Level of Evidence: 1

TA Criterion 2 is met

TA Criterion 3: The technology must improve net health outcomes.

Each of the three randomized trials compared artificial cervical disc replacement to cervical fusion. In accordance with FDA regulations for the evaluation of new devices, each of the studies was compared to cervical fusion using a non-inferiority design. The goal, therefore, was to show that the new technology (cervical disc replacement) was not inferior to the established technology, and thus a one sided comparison was used. The secondary hypothesis for each of these trials was a superiority hypothesis and was designed to evaluate whether or not disc replacement might be superior to cervical fusion, and for this comparison a two-sided hypothesis was used.

The BRYAN cervical disc trial was published in 2009. This was a multicenter study where patients with single level cervical DDD were randomized to receive either the BRYAN cervical disc (n=242) or anterior cervical discectomy and fusion (n=221)[14]. The main study hypothesis was that the outcomes from disc replacement would be at least equivalent to fusion. 465 Patients were followed for two years. Initially, investigators and patients were blinded to the procedure. However, post-operatively, the investigational group was treated with a two week course of non steroidal anti-inflammatory drugs and was allowed to resume nonstrenuous activities as they pleased. Because of these post operative differences, "further blinding was not practical or ethical." At 24 month follow-up there was a 91,6% retention rate.

The primary clinical outcomes are listed in Table 2. The primary outcome was "overall success" which included the primary efficacy and safety measures. Overall success is described above. The second primary outcome was the Neck Disability Score. Additional outcomes included arm and neck pain, and SF-36 PCS and MCS scores.

Table 2: Summary of Outcomes at 24 months in the BRYAN Cervical Disc Arthroplasty with Anterior Cervical Decompression and Fusion Trial[14]

Outcome	Intervention Group (N=242)	Control Group (n=221)	One sided P value
Neck Disability Index (post-op)	16.2	19.2	0.025
Neck Disability Index Success (>15 point improvement	86%	78.9%	<0.001
Change in Neck Disability Index	-34.7	-30.6	0.03
Post-operative SF-36 PCS scale	47.9	46.3	0.15
Post-operative SF-36 MCS Scale	51.7	51.7	0.27
Neck Pain (numerical rating scale)	23.0	30.3	.009
Arm pain (numerical rating scale)	19.2	21.5	.19
Neurologic success	93.9%	90.2%	<0.001
Overall success	82.6%	72.7%	0.005
Implant related or implatnt/surgical procedure related Serious adverse events	1.7&	3.2%	NS

At 24 months, both groups had improvements in the clinical outcomes. Overall success in the intervention group was 82.6% compared with 72.7% in the fusion group (p=0.005). NDI scores were 16.2 in the intervention group and 19.2 in the control group (p=0.025). NDI success (defined as >15 point improvement in the NDI) was 86% in the intervention group versus 78.9% in the fusion group (p=0.001). Improvements in SF-36 scores were comparable, as were measures of neck and arm pain. Patients who received the artificial disc returned to work about two weeks earlier than those who had fusion.

Given that this was a non-inferiority trial, an as-treated analysis was the primary analysis (versus an intention to treat analysis). There were 12 patients in the study who were randomly assigned to receive the artificial disc but who received the control treatment because of anatomic or technique difficulties during the surgery. Another important limitation is that 117 patients were randomly assigned but declined participation once receiving the assigned treatment, many because of dissatisfaction with the assigned treatment.

Based on follow up of the measured clinical outcomes, the Bryan cervical disc appears to be safe and efficacious at two year follow-up.

The Prestige trial was published in 2007[11]. This was a multicenter trial in which 541 patients with single level cervical DDD were randomized to cervical disc arthroplasty with the Prestige disc (n=276) or cervical fusion (n=265). Participants were not blinded.

The main study hypothesis was that the outcomes from disc replacement would be at least equivalent to fusion. A secondary hypothesis was that disc replacement was superior to fusion. Participants were followed for two years.

The primary clinical outcomes are listed in Table 3. The primary outcome was "overall success" which included the primary efficacy and safety measures. Overall success is described above. The second primary outcome was the Neck Disability Index Score. Additional outcomes included arm and neck pain, and SF-36 PCS and MCS scores

Table 3: Summary of Outcomes at 24 months in the Prestige Trial[11] at 24 month follow-up

Outcome	**Intervention Group (n=276)**	**Control Group (N=265)**	**One sided P value**
Neck Disability Index Post-op	19.3	22.4	NS
Change in Neck Disability Index	-36	-33.6	NS
NDI success	Absolute Value not reported	Absolute Value not reported	.2815
Improvement in SF-36 PCS scale	13.1	11.8	NS
SF-36 MCS Scale	7.4	7.5	NS
Neck Pain	Absolute Value not reported	Absolute Value not reported	.38
Arm pain	Absolute Value not reported	Absolute Value not reported	.48
Neurologic Success	92.8%	84.3%	0.006
Overall success	79.3%	67.8%	0.005
Return to work time	45 days	61 days	0.094
Revision Surgeries	0	5	0.0277
Adverse Events	6.2%	4.2%	

Overall success at 24 months was actually higher in the intervention group than in the control group. The NDI scores and NDI success were not statistically significantly different. The rate of neurologic success was greater in the intervention group. SF-36 scores and neck pain were improved more in the intervention group. There were fewer secondary surgeries in the intervention group.

Based on two year follow up of the measured clinical outcomes, the Prestige cervical disc appears to be safe and efficacious at two year follow-up.

The ProDisc-C trial was published in 2009 and is the study upon which FDA approval was based. [13]. This was a multi-center study at 13 clinical sites. 209 patients were randomized to receive either the ProDisc artificial disc replacement (n=103) or ACDF (n=106). All participants had single level cervical disc disease that was nonresponsive to conservative treatment. All participants were blinded until after the surgery.

The main study hypothesis was that the outcomes from disc replacement would be at least equivalent to fusion. A secondary hypothesis was that disc replacement was superior to fusion. 209 Patients were followed for two years.

Table 4: Summary of Outcomes at 24 months in the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease[13]

Outcome	Intervention Group (N=106)	Control Group (n=103)	One sided P value
Neck Disability Index (post-op)	21.4	20.5	1.00
Neck Disability Index Success (>15 point improvement	79.8%	78.3%	0.467
Sf-36 Success Rate	79.2%	70%	0.0943
Percent with Improvement in baseline Sf-36 PCS scale	80.8%	70.4%	Not reported for subscale
Percent with improvement in baseline SF-36 MCS Scale	71.8%	68.9%	Not reported for subscale
VAS Neck Pain Intensity change from baseline	46 mm	43 mm	NS
VAS Arm pain intensity change from baseline	43 mm	44 mm	NS
20% improvement in nect or arm pain frequency at 24 months	87.9%	86.9%	1.0
Neurologic success	90.9%	88%	0.638
Overall success	72.3%	68.3%	0.0105

The 24 month results of the ProDisc study are described in Table 4. The primary outcomes of overall success and Neck Disability Index Success were comparable in the two groups. Overall success was 72.3 in the intervention group versus 68.3% in the control group. The results of the secondary outcomes were comparable. Fewer secondary surgeries were required in the intervention group. Few patients in the disc replacement group required narcotics at follow-up (10.1% vs 18.5%; p=0.073) . At 24 month follow-up, safety and efficacy were comparable in those who had disc replacement compared with those who got fusion.

In all three studies, the rate of adverse events was not inferior to those seen in the fusion group and were often less than those seen in the fusion group. Adverse events included device related complications, surgical complications and the need for secondary surgeries Study follow-up was not long enough to determine the effect of disc replacement versus surgery on the rate of development of DDD in adjacent discs.

The results of the three trials showed that cervical disc replacement was not inferior to cervical fusion based on two year clinical outcomes. The clinical outcomes evaluated are largely relevant. The NDI is an established scale that measures quality of life as impacted by neck pain. Neck and arm pain are also clinically significant. Neurologic success means that overall neurologic status cannot decline after the surgery. The SF-36 measures physical and mental functioning both pre and post operatively. Overall success is a stringent outcome and includes improvement in the NDI of a clinically significant level, maintenance or improvement of neurologic status, and the requirement for no adverse events or additional surgeries. However, the impact after two years of follow-up is not known.

A critically important question is how the risks and benefits of disc replacement will balance over the long term. Although the two year follow-up data are promising, they do not provide information about the long term impact of these procedures. The theoretic advantage of a decrease in the development of adjacent disc DDD has not been shown over the long term..

Thus, given the lack of information about the long term clinical impact of artificial cervical disc replacement, whether or not the technology ultimately improves net health outcomes is not known.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Cervical fusion is the standard of care for the treatment of symptomatic cervical DDD. All three of the RCTs of artificial disc replacement appropriately compare disc replacement to the standard of care, cervical fusion.

At two year follow-up, cervical disc replacement appears to be comparable to and not inferior to cervical fusion. It is plausible that cervical disc replacement will reduce the risk of future adjacent segment DDD, but this has not yet been shown. In addition, the long term effects of cervical disc replacement, including any possible long term benefits or future complications are not yet known.
Thus, although in the short term (two year follow up), cervical disc replacement has been shown to be not inferior to cervical fusion, and some clinical outcomes have been shown to even be improved, the impact of cervical disc replacement after two years is not known. Thus, it is not known whether or not the technology is as beneficial as any of the established alternatives.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, three randomized multi-center clinical trials have compared artificial cervical replacement to cervical spinal fusion, but have looked only at 24 month follow-up outcomes. Long term clinical outcomes have not yet been evaluated in any setting. Since an improvement in long term clinical outcomes has not yet been demonstrated in the investigational setting, it cannot be attainable outside the investigational setting.

TA Criterion 5 is not met.

CONCLUSION

In summary, three randomized trials have compared cervical disc replacement to spinal fusion. At two year follow-up, cervical disc replacement appears to be not inferior to fusion for several relevant clinical outcomes, and even superior for some clinical outcomes. However, longer term follow-up of these studies is not yet available but will provide important information about the long term benefits and risks of cervical

disc replacement. Given the uncertainty about the long term risks and benefits of cervical disc replacement, it is not known whether or not it improves health outcomes over the long term.

DRAFT RECOMMENDATION

It is recommended that cervical disc replacement as an alternative to spinal fusion does not meet CTAF criteria 3-5 for improvement in health outcomes.

October 28, 2009

This is the first assessment of this technology by CTAF.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

A recent assessment by the BCBSA TEC in August 2009 found that the use of "artificial intervertebral disc arthroplasty for the treatment of patients with cervical degenerative disc disease does not meet the TEC criteria".

Centers for Medicare and Medicaid Services (CMS)

There is no current national coverage determination for the use of Cervical Artificial Disc in the medicare population. Determination is made at the local medicare level. No specific local policies were noted for this technology.

California Orthopaedic Association (COA)

The COA has been invited to provide an opinion of this technology and to have a representative attend the meeting to provide testimony and participate in discussion.

California Association of Neurological Surgeons (CANS)

CANS has been invited to provide an opinion of this technology and to have a representative attend the meeting to provide testimony and participate in discussion.

Spinal Arthroplasty Society (SAS)

SAS has been invited to provide an opinion of this technology and to have a representative attend the meeting to provide testimony and participate in discussion.

National Institute for Health and Clinical Excellence (NICE)

NICE issued *Prosthetic intervertebral disc replacement in the cervical spine* guidance in November 2005. This document is available at: http://guidance.nice.org.uk/IPG143. NICE is currently conducting an update of the 2005 guidance.

ABBREVIATIONS USED IN THIS REVIEW

CTAF	California Technology Assessment Forum
DDD	Degenerative disc disease
ACDF	Anterior cervical discectomy and fusion
AIDA	Artificial intervertebral disc arthroplasty
FDA	Food and Drug Administration
UHMWPE	Ultra high molecular weight polyethylene
DARE	Database of Abstracts of Reviews of Effects
NDI	Neck disability index
VAS	Visual analog score
PCS	Physical component summary
SF-36	Short form 36
MCS	Mental component summary
RCT's	Randomized controlled trials

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