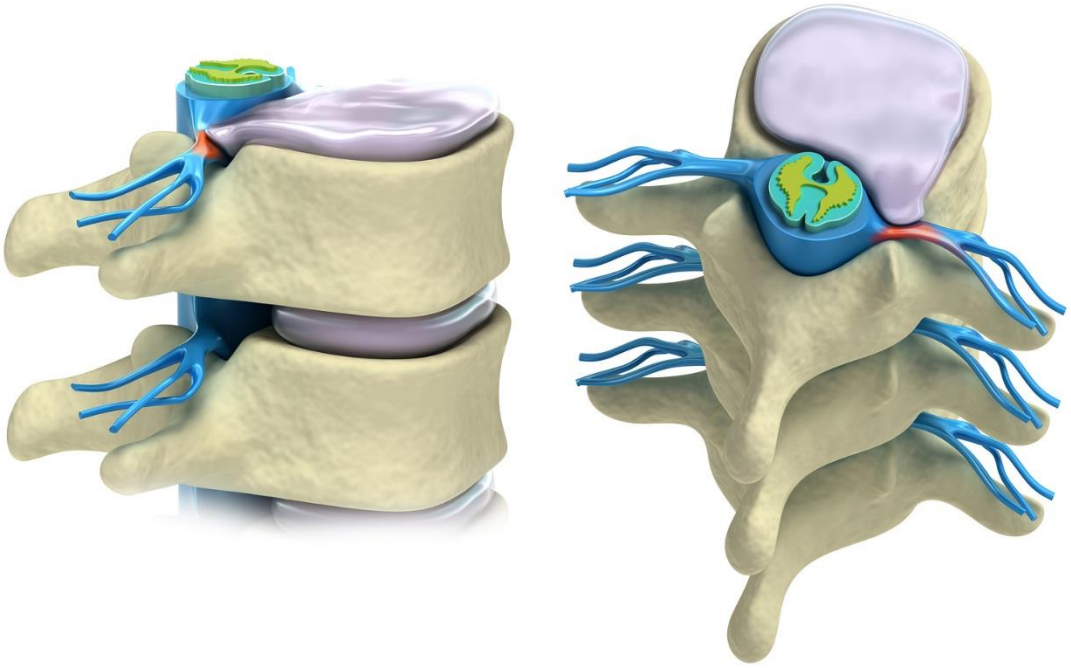
KCE REPORT 254S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CERVICAL AND LUMBAR TOTAL DISC REPLACEMENTS

SUPPLEMENT



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HEALTH TECHNOLOGY ASSESSMENT

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SUPPLEMENT

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COLOPHON

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APPENDIX REPORT

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1. HTA CORE MODEL ASSESSMENT ELEMENTS

This appendix presents the assessment elements from the following HTA Core Model® V2.1PublicDraft domains: CUR, TEC, SAF, EFF, ECO. For each, the section of the report where the answer to the question may be found is indicated.

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
HTA Core Model Domain: Health problem and current use of technology (CUR)				
Target Population	What is the target population in this assessment?	A0007	Section 1.1. Background, section 2.1.1. Population and condition	Section 1.1. Background, section 3.1.1. Population and condition
Target Population	How many people belong to the target population?	A0023	Section 1.1. Background, section 2.1.1. Population and condition	Section 1.1. Background, section 3.1.1. Population and condition
Target Condition	What is the disease or health condition in the scope of this assessment?	A0002	Section 1.1. Background, section 2.1.1. Population and condition	Section 1.1. Background, section 3.1.1. Population and condition
Target Condition	What are the known risk factors for the disease or health condition?	A0003	*Not addressed in the present report*	*Not addressed in the present report*
Target Condition	What is the natural course of the disease or health condition?	A0004	Section 1.1. Background, section 2.1.1. Population and condition	Section 1.1. Background, section 3.1.1. Population and condition
Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	A0005	Section 1.1. Background, section 2.1.1. Population and condition	Section 1.1. Background, section 3.1.1. Population and condition
Target Condition	What are the consequences of the disease or health condition for the society?	A0006	Section 1.1. Background	Section 1.1. Background
Target Condition	What aspects of the consequences / burden of disease are targeted by the technology?	A0009	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics
Current Management of the Condition	What are the differences in the management for different stages of the disease or health condition?	A0017	Section 2.1.2. Existing treatments	Section 3.1.2. Existing treatments
Current Management of the Condition	What are the other typical or common alternatives to the current technology?	A0018	Section 2.1.2. Existing treatments	Section 3.1.2. Existing treatments

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	A0024	*Not addressed in the present report*	*Not addressed in the present report*
Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	A0025	Section 2.2.1.7. Belgian recommendations of good practice for cervical disc replacement	Section 3.2.1.5. Belgian recommendations of good practice for lumbar disc replacement
Utilisation	For which health conditions and populations, and for what purposes is the technology used?	A0001	Section 2.3.2.2. Characteristics of patients undergoing Cervical TDR and comparison with patients undergoing a fusion	Section 3.3.2.2. Characteristics of patients undergoing Lumbar TDR and comparison with patients undergoing a fusion
Utilisation	How much are the technologies utilised?	A0011	Section 2.3. Current use	Section 3.3. Current use
Utilisation	What kind of variations in use are there across countries/regions/settings?	A0012	Section 2.3.2.3. Geographic variation of cervical TDR use	Section 3.3.2.3. Geographic variation of lumbar TDR use
Utilisation	Who decides which people are eligible for the technology and on what basis?	G0009	*Not addressed in the present report*	*Not addressed in the present report*
Utilisation	What is the phase of development and implementation of the technology and the comparator(s)?	B0003	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics
Utilisation	Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?	F0001	*Not addressed in the present report*	*Not addressed in the present report*
Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	A0020	*Not addressed in the present report*	*Not addressed in the present report*
Regulatory Status	What is the reimbursement status of the technology?	A0021	Section 2.2.1.8. Belgian reimbursement and regulation	Section 3.2.1.6. Belgian reimbursement and regulation
HTA Core Model Domain: Description and technical characteristics of technology (TEC)				
Features of the technology	What is this technology and the comparator(s)?	B0001	Section 2.2. Description and technical characteristics, Section 2.1.2. Existing treatments	Section 3.2. Description and technical characteristics, Section 3.1.2. Existing treatments
Features of the technology	What is the claimed benefit of the technology in relation to the comparators?	B0002	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	B0003	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics
Features of the technology	Who administers the technology and the comparators and in what context and level of care are they provided?	B0004	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics
Features of the technology	Are the reference values or cut-off points clearly established?	B0018	*Not addressed in the present report*	*Not addressed in the present report*
Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	A0020	*Not addressed in the present report*	*Not addressed in the present report*
Regulatory Status	What is the reimbursement status of the technology?	A0021	Section 2.2.1.8. Belgian reimbursement and regulation	Section 3.2.1.6. Belgian reimbursement and regulation
Investments and tools required to use the technology	What material investments are needed to use the technology?	B0007	Section 3.2. Description and technical characteristics, Section 2.2.1.8. Belgian reimbursement and regulation	Section 2.2. Description and technical characteristics, Section 3.2.1.6. Belgian reimbursement and regulation
Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	B0008	*Not addressed in the present report*	*Not addressed in the present report*
Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator?	B0009	Section 2.2. Description and technical characteristics, Section 2.1.2. Existing treatments	Section 3.2. Description and technical characteristics, Section 3.1.2. Existing treatments
Investments and tools required to use the technology	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?	B0010	Section 2.3.1.1. Data sources, section 2.4.2. Results on clinical effectiveness (Conclusions and Discussion), section 2.4.3. Results on safety (Conclusions and Discussion)	Section 3.3.1.1. Data sources, section 3.4.2. Results on clinical effectiveness (Conclusions and Discussion), section 3.4.3. Results on safety (Conclusions and Discussion)

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Training and information needed to use the technology	What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology?	B0012	*Not addressed in the present report*	*Not addressed in the present report*
Training and information needed to use the technology	What kind of training and information is needed for the personnel/carer using this technology?	B0013	*Not addressed in the present report*	*Not addressed in the present report*
Training and information needed to use the technology	What kind of training and information should be provided for the patient who uses the technology, or for his family?	B0014	*Not addressed in the present report*	*Not addressed in the present report*
Training and information needed to use the technology	What information of the technology should be provided for patients outside the target group and the general public?	B0015	*Not addressed in the present report*	*Not addressed in the present report*
Other	Who manufactures the technology?	A0022	Section 2.2. Description and technical characteristics	Section 3.2. Description and technical characteristics
HTA Core Model Domain: Safety (SAF)				
Patient safety	How safe is the technology in relation to the comparator(s)?	C0008	Section 2.4.3. Results on safety	Section 3.4.3. Results on safety
Patient safety	Are the harms related to dosage or frequency of applying the technology?	C0002	Section 2.4.3. Results on safety (multi-level)	Section 3.4.3. Results on safety (multi-level)
Patient safety	How does the frequency or severity of harms change over time or in different settings?	C0004	Section 2.4.3. Results on safety	Section 3.4.3. Results on safety
Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	C0005	Not addressed in the present report	Not addressed in the present report
Patient safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?	C0006	Not addressed in the present report	Not addressed in the present report
Patient safety	Are the technology and comparator(s) associated with user- dependent harms?	C0007	Not addressed in the present report	Not addressed in the present report

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Occupational safety	What kind of occupational harms can occur when using the technology?	C0020	Not addressed in the present report	Not addressed in the present report
Environmental safety	What kind of risks for public and environment may occur when using the technology?	C0040	Not addressed in the present report	Not addressed in the present report
Safety risk management	How does the safety profile of the technology vary between different generations, approved versions or products?	C0060	Not addressed in the present report	Not addressed in the present report
Safety risk management	Can different organizational settings increase or decrease harms?	C0061	Not addressed in the present report	Not addressed in the present report
Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	C0062	Not addressed in the present report	Not addressed in the present report
Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?	C0063	Not addressed in the present report	Not addressed in the present report
Safety risk management	How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)	C0064	Not addressed in the present report	Not addressed in the present report
Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?	B0010	Section 2.3.1.1. Data sources, section 2.4.2. Results on clinical effectiveness (Conclusions and Discussion), section 2.4.3. Results on safety (Conclusions and Discussion)	Section 3.3.1.1. Data sources, section 3.4.2. Results on clinical effectiveness (Conclusions and Discussion), section 3.4.3. Results on safety (Conclusions and Discussion)
HTA Core Model Domain: Clinical effectiveness (EFF)				
Mortality	What is the expected beneficial effect of the technology on mortality?	D0001	*Not addressed in the present report*	*Not addressed in the present report*
Mortality	What is the effect of the technology on the mortality due to causes other than the target disease?	D0003	*Not addressed in the present report*	*Not addressed in the present report*
Morbidity	How does the technology modify the effectiveness of subsequent interventions?	D0026	*Not addressed in the present report*	*Not addressed in the present report*
Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	D0005	Section 2.4.2. Results on clinical effectiveness	Section 3.4.2. Results on clinical effectiveness
Morbidity	How does the test-treatment intervention modify the magnitude and frequency of morbidity?	D0032	*Not addressed in the present report*	*Not addressed in the present report*

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	D0006	Section 2.4.2. Results on clinical effectiveness	Section 3.4.2. Results on clinical effectiveness
Test-treatment chain	Is there an effective treatment for the condition the test is detecting?	D0024	*Not addressed in the present report*	*Not addressed in the present report*
Change-in management	Does use of the test lead to improved detection of the condition?	D0020	*Not addressed in the present report*	*Not addressed in the present report*
Change-in management	How does use of the test change physicians' management decisions?	D0021	*Not addressed in the present report*	*Not addressed in the present report*
Change-in management	Does the test detect other potential health conditions that can impact the subsequent management decisions?	D0022	*Not addressed in the present report*	*Not addressed in the present report*
Change-in management	How does the technology modify the need for hospitalization?	D0010	Section 2.4.3. Results on safety	Section 3.4.3. Results on safety
Change-in management	How does the technology modify the need for other technologies and use of resources?	D0023	Section 2.4.3. Results on safety	Section 3.4.3. Results on safety
Function	What is the effect of the technology on patients' body functions?	D0011	Section 2.4.2. Results on clinical effectiveness (functional status)	Section 3.4.2. Results on clinical effectiveness (functional status)
Function	What is the effect of the technology on work ability?	D0014	*Not addressed in the present report*	*Not addressed in the present report*
Function	What is the effect of the technology on return to previous living conditions?	D0015	*Not addressed in the present report*	*Not addressed in the present report*
Function	How does the use of the technology affect activities of daily living?	D0016	Section 2.4.2. Results on clinical effectiveness (functional status)	Section 3.4.2. Results on clinical effectiveness (functional status)
Health-related Quality of life	What is the effect of the technology on generic health-related quality of life?	D0012	Section 2.4.2. Results on clinical effectiveness (quality of life)	Section 3.4.2. Results on clinical effectiveness (quality of life)
Health-related Quality of life	What is the effect of the technology on disease-specific quality of life?	D0013	*Not addressed in the present report*	*Not addressed in the present report*
Quality of life	Does the knowledge of the test result affect the patient's non- health-related quality of life?	D0030	*Not addressed in the present report*	*Not addressed in the present report*
Patient satisfaction	Was the use of the technology worthwhile?	D0017	Section 2.4.2. Results on clinical effectiveness (patient satisfaction)	Section 3.4.2. Results on clinical effectiveness (patient satisfaction)
Patient satisfaction	Is the patient willing to use the technology again?	D0018	*Not addressed in the present report*	*Not addressed in the present report*

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Patient safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?	C0006	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	What is the accuracy of the test against reference standard?	D1001	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?	D1002	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	What is the reference standard and how likely does it classify the target condition correctly?	D1003	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	What are the requirements for accuracy in the context the technology will be used?	D1004	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	What is the optimal threshold value in this context?	D1005	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	Does the test reliably rule in or rule out the target condition?	D1006	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	How does test accuracy vary in different settings?	D1007	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	What is known about the intra- and inter-observer variation in test interpretation?	D1008	*Not addressed in the present report*	*Not addressed in the present report*
Test accuracy	Is there evidence that the replacing test is more specific or safer than the old one?	D1019	*Not addressed in the present report*	*Not addressed in the present report*
Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes?	D0029	Section 2.4.4. Discussion	Section 3.4.4. Discussion
HTA Core Model Domain: Costs and economic evaluation (ECO)				
Preliminary remark: we did not produce any primary economic evaluation, the answers below refer to the systematic literature review.				
Resource utilization	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	E0001	Section 2.5.4. Results of the economic evaluations	Section 3.5.4. Results of the economic evaluations
Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	E0002	Section 2.5.4. Results of the economic evaluations	Section 3.5.4. Results of the economic evaluations
Resource utilization	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	E0009	Section 2.5.4. Results of the economic evaluations	Section 3.5.4. Results of the economic evaluations

Topic	Issue	Assessment element ID	Answer for Cervical total disc replacement	Answer for Lumbar total disc replacement
Measurement and estimation of outcomes	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?	E0005	Section 2.5.3.5. Quality of life effect, section 2.5.3.6. Other differential effects	Section 3.5.3.5. Quality of life effect, section 3.5.3.6. Other differential effects
Examination of costs and outcomes	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?	E0006	Section 2.5.4. Results of the economic evaluations (a.o. Table 7)	Section 3.5.4. Results of the economic evaluations (a.o. Table 15)
Characterising uncertainty	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?	E0010	Section 2.5.4. Results of the economic evaluations, section 2.5.5. Discussion	Section 3.5.4. Results of the economic evaluations, section 3.5.5. Discussion
Characterising heterogeneity	To what extent can differences in costs, outcomes, or 'cost effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?	E0011	Not addressed in the present report	Not addressed in the present report
Validity of the model(s)	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?	E0012	Section 2.5.4. Results of the economic evaluations, section 2.5.5. Discussion	Section 3.5.4. Results of the economic evaluations, section 3.5.5. Discussion

2. CURRENT USE OF TOTAL DISC REPLACEMENT

2.1. Cervical total disc replacement

2.1.1. INAMI – RIZIV billing codes for cervical surgery

Code	Label (Fr / Nl)	Key letter	Tariff (*)
(281094)-281105	Arthrodèse intercorporéale cervicale y compris le prélèvement du greffon / Arthrodesia tussen de cervicale wervellichamen, inclusief het nemen van de ent	N 625	€ 793.70
(281116)-281120	Cure chirurgicale d'une hernie discale cervicale / Heelkundige behandeling van een cervicale discushernia	N 625	€ 793.70

(Ambulatory) - (*) situation at 01/08/2015

2.1.2. Most frequent 3-digit ICD-9-CM codes of principal diagnosis in case of CTDR

Ranking	3 digit ICD 9 CM code		Number of stays	Percentage
1	722	INTERVERTEBRAL DISC DISORDERS	1585	80.18%
2	721	SPONDYLOSIS AND ALLIED DISORDERS	281	14.21%
3	723	OTHER DISORDERS OF CERVICAL REGION	76	3.84%
4	724	OTHER AND UNSPECIFIED DISORDERS OF BACK	10	0.51%
5	996	COMPLICATIONS PECULIAR TO CERTAIN SPECIFIED PROCEDURES	6	0.30%
6	839	OTHER, MULTIPLE, AND ILL-DEFINED DISLOCATIONS	4	0.20%
7	738	OTHER ACQUIRED DEFORMITY	3	0.15%
8	806	FRACTURE OF VERTEBRAL COLUMN WITH SPINAL CORD INJURY	3	0.15%
9	278	OVERWEIGHT, OBESITY AND OTHER HYPERALIMENTATION	1	0.05%
10	292	DRUG-INDUCED MENTAL DISORDERS	1	0.05%
11	Other		7	0.35%
TOTAL			**1977**	**100%**

Source: RHM – MZG 2008-2011

2.1.3. Five-digit ICD-9-CM codes of principal diagnosis Intervertebral Disc Disorder (722.xx) in case of CTDR

Ranking	5 digit ICD 9 CM code		Number of stays	Percentage
1	722.0	DISPLACEMENT OF CERVICAL INTERVERTEBRAL DISC WITHOUT MYELOPATHY	1001	50.63%
2	722.71	INTERVERTEBRAL DISC DISORDER WITH MYELOPATHY, CERVICAL REGION	256	12.95%
3	722.4	DEGENERATION OF CERVICAL INTERVERTEBRAL DISC	251	12.70%
4	722.91	OTHER AND UNSPECIFIED DISC DISORDER, CERVICAL REGION	57	2.88%
5	722.10	DISPLACEMENT OF LUMBAR INTERVERTEBRAL DISC WITHOUT MYELOPATHY	15	0.76%
6	722.52	DEGENERATION OF LUMBAR OR LUMBOSACRAL INTERVERTEBRAL DISC	3	0.15%
7	722.11	DISPLACEMENT OF THORACIC INTERVERTEBRAL DISC WITHOUT MYELOPATHY	1	0.05%
8	722.93	OTHER AND UNSPECIFIED DISC DISORDER, LUMBAR REGION	1	0.05%
TOTAL			**1585**	**80.18%**

Source: RHM – MZG data 2008-2011

2.2. Lumbar total disc replacement

2.2.1. INAMI – RIZIV billing codes for lumbar TDR

Code	Label (Fr / Nl)	Key letter	Tariff (*)
Procedure			
281654 - 281665	Arthrodèse ou vissage intercorporéal par voie antérieure, y compris le prélèvement éventuel du greffon / Arthrodesia of schroeven tussen de wervellichamen langs voor, inclusief het eventueel nemen van de ent	N 650	€ 825.45
Lumbar disc prosthesis before July the 1st, 2014			
735792* - 735803	Prothèse pour le remplacement d'un disque intervertébral lombaire total, pour l'ensemble des éléments / Prothese voor vervanging van een volledige lumbale tussenwervelschijf, voor het geheel van de samenstellende elementen		€ 2302.33
Lumbar disc prosthesis between July the 1st, 2014 and April the 1st, 2015.			
163015* - 163026	Prothèse pour le remplacement d'un disque intervertébral lombaire total, pour l'ensemble des éléments / Prothese voor vervanging van een volledige lumbale tussenwervelschijf, voor het geheel van de samenstellende elementen		€ 2302.33
Lumbar disc prosthesis from April the 1st, 2015.			
163015* - 163026	Prothèse pour le remplacement d'un disque intervertébral lombaire total, pour l'ensemble des éléments / Prothese voor vervanging van een volledige lumbale tussenwervelschijf, voor het geheel van de samenstellende elementen		€ 1800

(Ambulatory) - (*) situation at 01/08/2015

2.2.2. Most frequent 3-digits ICD-9-CM codes of principal diagnosis in case of LTDR

Ranking	3 digits ICD 9 CM code		Number of stays	Percentage
1	722	INTERVERTEBRAL DISC DISORDERS	1059	83.39%
2	721	SPONDYLOSIS AND ALLIED DISORDERS	151	11.89%
3	724	OTHER AND UNSPECIFIED DISORDERS OF BACK	44	3.47%
4	805	FRACTURE OF VERTEBRAL COLUMN WITHOUT MENTION OF SPINAL CORD INJURY	4	0.32%
5	738	OTHER ACQUIRED DEFORMITY	3	0.24%
6	996	COMPLICATIONS PECULIAR TO CERTAIN SPECIFIED PROCEDURES	3	0.24%
7	998	OTHER COMPLICATIONS OF PROCEDURES, NEC	2	0.16%
8	558	OTHER AND UNSPECIFIED NONINFECTIOUS GASTROENTERITIS AND COLITIS	1	0.08%
9	727	OTHER DISORDERS OF SYNOVIUM, TENDON, AND BURSA	1	0.08%
10	732	OSTEOCHONDROPATHIES	1	0.08%
11	Other		1	0.08%
TOTAL			**1270**	**100%**

Source: RHM – MZG data 2008-2011

2.2.3. Five-digits ICD-9-CM codes of principal diagnosis Intervertebral Disc Disorder (722.xx) in case of LTDR

Ranking	5 digits ICD 9 CM code		Number of stays	Percentage
1	722.0	DISPLACEMENT OF CERVICAL INTERVERTEBRAL DISC WITHOUT MYELOPATHY	2	0.16%
2	722.10	DISPLACEMENT OF LUMBAR INTERVERTEBRAL DISC WITHOUT MYELOPATHY	212	16.69%
3	722.51	DEGENERATION OF THORACIC OR THORACOLUMBAR INTERVERTEBRAL DISC	2	0.16%
4	722.52	DEGENERATION OF LUMBAR OR LUMBOSACRAL INTERVERTEBRAL DISC	641	50.47%
5	722.71	INTERVERTEBRAL DISC DISORDER WITH MYELOPATHY, CERVICAL REGION	1	0.08%
6	722.73	INTERVERTEBRAL DISC DISORDER WITH MYELOPATHY, LUMBAR REGION	28	2.20%
7	722.83	POSTLAMINECTOMY SYNDROME, LUMBAR REGION	15	1.18%
8	722.91	OTHER AND UNSPECIFIED DISC DISORDER, CERVICAL REGION	1	0.08%
9	722.93	OTHER AND UNSPECIFIED DISC DISORDER, LUMBAR REGION	157	12.36%
TOTAL			**1059**	**83.39%**

Source: RHM – MZG data 2008-2011

3. CLINICAL EFFECTIVENESS AND SAFETY OF TOTAL DISC REPLACEMENT

3.1. Common search strategy for cervical and lumbar total disc replacements

PICOProject number	
Project name	**Spine technologies**
Search question(s)	**Lumbar and cervical disc implants vs other techniques**
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)	***and related keywords***
P (patient)	
I (Intervention)	Lumbar and cervical disc implants
C (comparison)	Other techniques
O (outcome)	Morbidity, etc
S (settings)	**SR, >= 2006**

3.1.1. Search strategies

3.1.1.1. Medline @ Ovid

Date	**2014-10-9**		
Database	**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present**		
Search Strategy	**#**	***Query***	***Results***
	1	exp Total disc replacement/	**275**
	2	((disc? or disk?) adj3 (artificial or replacement or arthroplast* or prosthes* or implant*)).ab,ti.	**2326**
	3	1 or 2	**2368**
	4	arthroplasty, replacement/	**4520**
	5	Joint Prosthesis/	**9155**
	6	Metal-on-Metal Joint Prostheses/	**131**
	7	exp "Prostheses and Implants"/	**395 314**
	8	prosthesis design/	**37 781**
	9	prosthesis failure/	**22 053**
	10	prosthes*.ab,ti.	**64 186**
	11	implant*.ab,ti.	**285 068**
	12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	**580 445**
	13	intervertebral disc/	**11 170**
	14	intervertebral disc degeneration/	**1633**
	15	intervertebral disc displacement/	**15 886**
	16	cervical vertebrae/	**27 942**
	17	Lumbar vertebrae/	**39 879**
	18	(disc? or disk? or interspin* or spin*).ab,ti.	**489 837**
	19	13 or 14 or 15 or 16 or 17 or 18	**514 196**
	20	12 and 19	**24 395**
	21	3 or 20	**24 811**
	22	limit 21 to yr="2006 -Current"	**12 215**

	23	limit 22 to animals	**2649**
	24	limit 22 to humans	**8805**
	25	23 not 24	**2017**
	26	22 not 25	**10 198**
	27	**limit 26 to systematic reviews**	**285**
	28	randomized controlled trial.pt.	**396 972**
	29	controlled clinical trial.pt.	**90 468**
	30	randomized.ti,ab.	**338 373**
	31	placebo.ti,ab.	**167 112**
	32	clinical trials as topic/	**175 785**
	33	randomly.ti,ab.	**227 374**
	34	trials.ti.	**50 259**
	35	28 or 29 or 30 or 31 or 32 or 33 or 34	**942 420**
	36	exp animal/ not humans/	**4 075 570**
	37	35 not 36	**869 545**
	38	26 and 37	**761**
	39	**38 not 27**	**667**
Note	**Line 27: Export for systematic reviews** **Line 39: Export for RCT without systematic reviews** **Lines 28-37 : Cochrane RCT filter sensitivity and specificity**		

3.1.1.2. Embase @ Embase.com

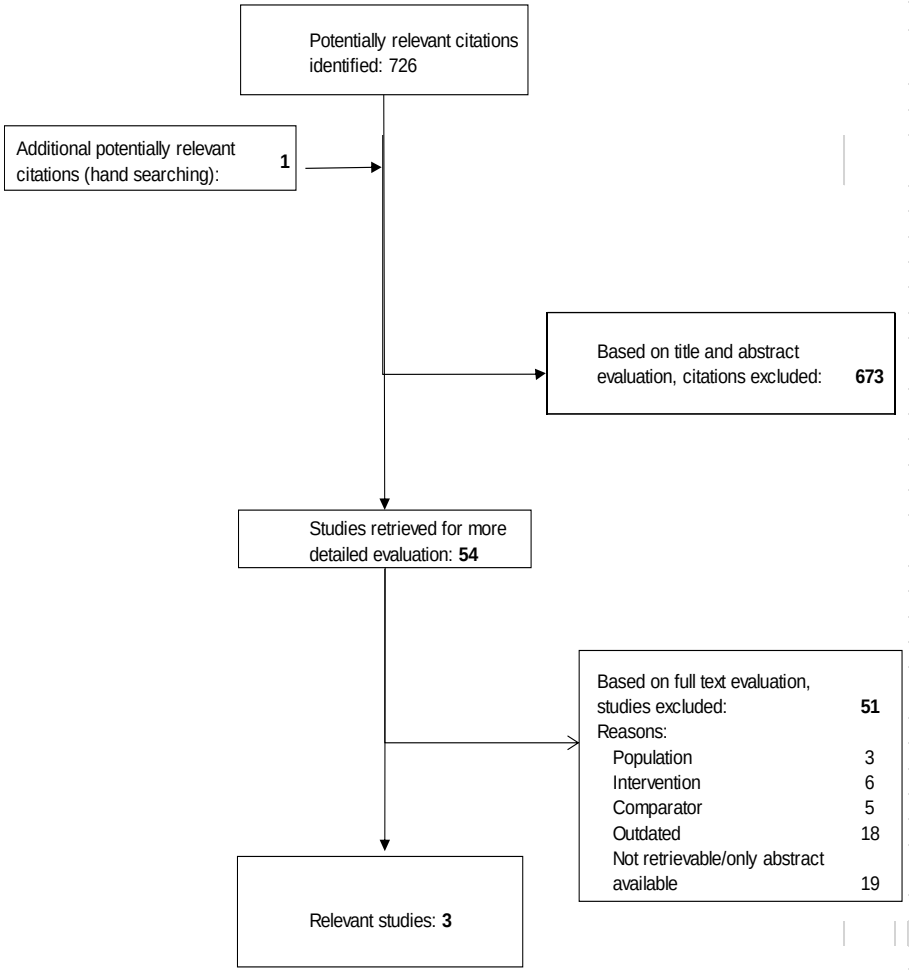
Date	**2014-10-9**		
Database	**Embase (Embase.com)**		
Search Strategy	**#**	***Query***	***Results***
	#1	'total disc replacement'/exp	**357**
(attention, for PubMed, check « Details »)	#2	((disc OR discs OR disk OR disks) NEAR/3 (artificial OR replacement OR arthroplast* OR prosthes* OR implant*)):ab,ti	**3080**
	#3	#1 OR #2	**3123**
	#4	'arthroplasty'/exp	**50 703**
	#5	'joint prosthesis'/exp	**48 183**
	#6	'metal on metal joint prosthesis'/exp	**202**
	#7	'orthopedic prostheses, orthoses and implants'/exp	**133 447**
	#8	'prosthesis'/exp	**166 830**
	#9	'prosthesis failure'/exp	**27 368**
	#10	prosthes*:ab,ti	**73 216**
	#11	implant*:ab,ti	**351 023**
	#12	'implant'/exp	**393 966**
	#13	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	**787 939**
	#14	'intervertebral disk'/exp	**11 011**
	#15	'intervertebral disk hernia'/exp	**19 028**
	#16	'intervertebral disk degeneration'/exp	**6314**
	#17	'cervical spine'/exp	**30 769**
	#18	'lumbar vertebra'/exp	**14 595**
	#19	disc:ab,ti OR discs:ab,ti OR disk:ab,ti OR disks:ab,ti OR interspin*:ab,ti OR spin*:ab,ti	**547 595**
	#20	#14 OR #15 OR #16 OR #17 OR #18 OR #19	**571 799**
	#21	#13 AND #20	**36 202**
	#22	#3 OR #21	**36 652**

	#23	#22 AND (2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)	**22 438**
	#24	[medline]/lim	**21 410 203**
	#25	#23 NOT #24	**10 477**
	#26	[cochrane review]/lim OR 'systematic review' OR 'meta analyse' OR [meta analysis]/lim OR [systematic review]/lim OR 'meta analyses' OR 'meta analysis' OR 'guideline' OR 'guidelines'	**592 124**
	#27	#25 AND #26	**408**
Note			

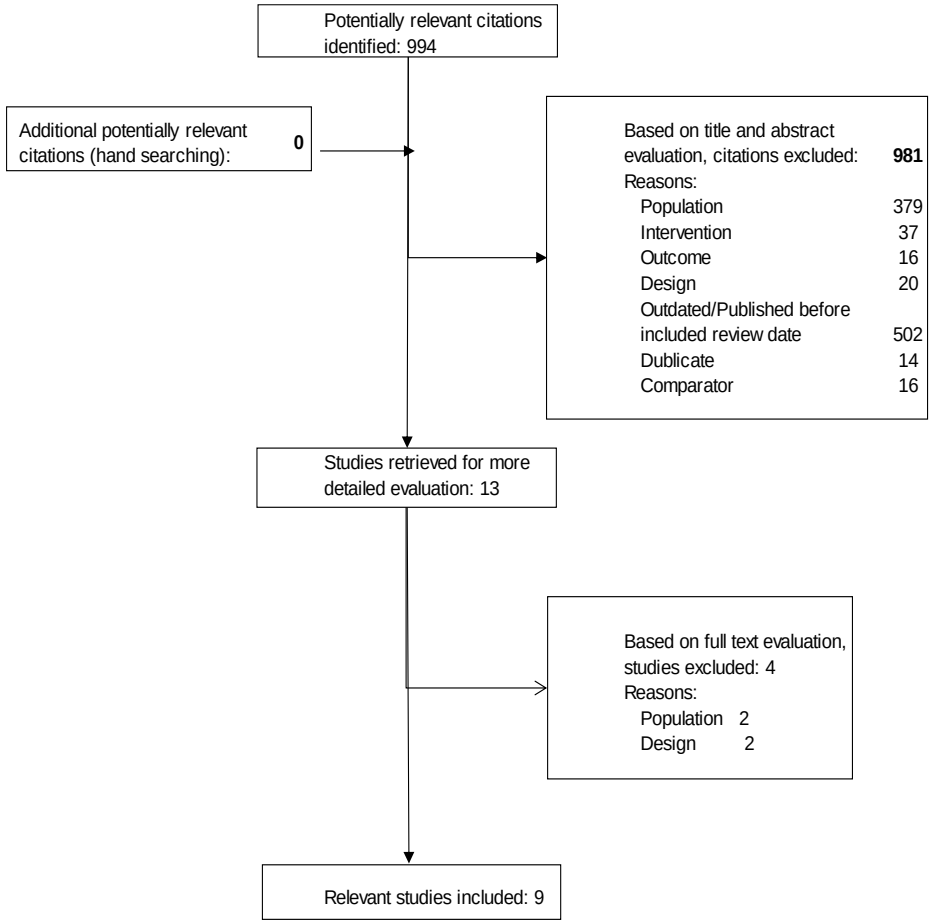
3.1.1.3. Cochrane Database of Systematic Reviews

Date	**2014-10-9**		
Database	**Cochrane**		
Search Strategy (attention, for PubMed, check « Details »)	**#**	***Query***	***Results***
	#1	MeSH descriptor: [Total Disc Replacement] explode all trees	**34**
	#2	((disc or discs or disk or disks) near/3 (artificial or replacement or arthroplast* or prosthes* or implant*)):ab,ti	**315**
	#3	#1 or #2	**319**
	#4	MeSH descriptor: [Arthroplasty, Replacement] explode all trees	**3200**
	#5	MeSH descriptor: [Joint Prosthesis] explode all trees	**1692**
	#6	MeSH descriptor: [Metal-on-Metal Joint Prostheses] explode all trees	**2**
	#7	MeSH descriptor: [Prostheses and Implants] explode all trees	**14 108**
	#8	MeSH descriptor: [Prosthesis Design] explode all trees	**1581**
	#9	MeSH descriptor: [Prosthesis Failure] explode all trees	**587**
	#10	prosthes*:ab,ti	**1843**
	#11	implant*:ab,ti	**11 921**
	#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	**23 876**
	#13	MeSH descriptor: [Intervertebral Disc Degeneration] explode all trees	**97**
	#14	MeSH descriptor: [Intervertebral Disc] explode all trees	**251**
	#15	MeSH descriptor: [Intervertebral Disc Displacement] explode all trees	**614**
	#16	MeSH descriptor: [Cervical Vertebrae] explode all trees	**758**
	#17	MeSH descriptor: [Lumbar Vertebrae] explode all trees	**2116**
	#18	(disc or discs or disk or disks or interspin* or spin*):ab,ti	**16 363**
	#19	#13 or #14 or #15 or #16 or #17 or #18	**17 188**
	#20	#12 and #19	**1044**
	#21	#3 or #20	**1163**
	#22	#21 Publication Year from 2006 to 2014	**684**
Note	**CDSR : 13** **DARE: 53** **HTA: 50** **Economic Evaluations: 34** **CENTRAL : 1014**		

3.1.2. Study flow of selection of HTAs and SRs for CTDR + LTDR



3.1.3. Study flow of selection of RCTs for CTDR and LTDR



3.2. Results for cervical total disc replacement

3.2.1. Evidence tables of systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Boselie 2012[1]	**SR and meta-analysis** **Funding:** Maastrict University Medical Centre, Netherlands **Primary studies included:** 2011; Coric, 2009; Heller, 2011; Kelly, 2010; Marzluff, 2010; McAfee, 2007; Mummaneni, 2007; Nabhan, 2010; Pettine, 2004; Porchet **Search date:** May 25th, 2011	**Eligibility criteria:** Patients (18 years of age or older), with symptomatic single level cervical degenerative disc disease of C3-C4, C4-C5, C5-C6, or C6-C7. Symptomatic was defined as the presence of radicular pain, myelopathy, or both, corresponding to the afflicted level. Duration of symptoms had to be at least six weeks (with the exception of progressive myelopathy, which requires earlier treatment) and there had to be an insufficient relief of symptoms with conservative therapy. **Exclusion criteria:** Patients with metabolic bone disease (e.g. osteoporosis), more than one pathological level, previous surgery of the cervical spine, inflammatory spinal arthritis, malignancy, or radiotherapy of the cervical spine region were excluded	**Intervention:** Single level anterior cervical discectomy with fusion (either by plate, cage, autograft, allograft material, or a combination) **Comparator:** Anterior cervical discectomy with the placement of an artificial cervical disc.	**Arm pain** at 3 months and at 12-24 months (VAS or NRS), n= 1346 (3 months) and n= 1310 (12-24 months) N=6: Significant difference between arthroplasty and fusion at three months and one to two years, in favour of arthroplasty (MD -2.18; 95% CI -3.68 to -0.68; MD -1.54; 95% CI -2.86 to -0.22, respectively) Clinical relevance was low, since the pooled difference in effect size was small (< 10% of the scale). **Neck pain** at 3 months and at 12-24 months (VAS or NRS), n= 1347 (3 months) and 1309 (12-24 months), N=6: No significant difference between arthroplasty and fusion at three months (MD -3.67; 95% CI -9.80 to 2.46) (random effects model was used owing to a large amount of heterogeneity caused by the extremely small SDs of one study)	**Revision surgery at index level:** 3 months (n=290 N=1): No significant difference between the two treatment groups (RR 0.31; 95% CI 0.01 to 7.47; P = 0.47) 12-24 months (n=1484, N=7): Significant difference between the two treatment groups in favour of arthroplasty (RR 0.39; 95% CI 0.23 to 0.64; P = 0.0002), only six of the seven studies were pooled because one study did not have events in neither of the groups **Secondary surgery at adjacent levels:** 3 months: (secondary surgery at one or both adjacent level(s), n= 290, N=1	AMSTAR 11/11

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		Note: An absolute maximum of 10% of the patients included in a study population to not meet these requirements was allowed. In the current review this primarily applied to the criterion 'previous surgery of the cervical spine', in which case we did not allow for any previous adjacent level fusions.		Significant difference between arthroplasty and fusion at 12-24 months in favour of arthroplasty (MD -3.12; 95% CI -4.69 to -1.28) Clinical relevance was low, since the pooled difference in effect size was small (< 10% of the scale). **Neck related functional status** at 3 months and at 12-24 months (NDI), n=1545 (3 months), n=1505 (12-24 months), N=6 Significant difference between arthroplasty and fusion at three months and one to two years, in favour of arthroplasty (MD -5.14; 95% CI -6.94 to -3.34; MD -2.79; 95% CI -4.73 to - 0.85, respectively) Clinical Relevance was low, since the pooled effect size was small (< 10% of the scale). **Patient satisfaction** (12-24 months): n=498, N=2 No significant difference between arthroplasty and fusion at one to two years (RR 1.06; 95% CI 1.00 to 1.12; P = 0.06)	No significant difference between the two treatment groups (RR 0.31; 95% CI 0.01 to 7.47; P = 0.47) 12-24 months: (secondary surgery at one or both adjacent level(s), n= 1431, N=6 No significant difference between the two treatment groups (RR 0.60; 95% CI 0.35 to 1.02; P = 0.06) **Mobility at the index level:** 3 months, n=1622, N=6 (only 4 studies pooled due to lack of SD reporting) Mobility was significantly higher in the arthroplasty group (MD 4.75; 95% CI 4.45 to 5.06; P < 0.00001)	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				Neurological status (% of participants with unchanged or improved neurological status) at 3 months (n=497, N=1) and at 12-24 months (n=1147, N=3) 3 months: No significant difference between the two treatment groups (RR 1.05; 95% CI 0.99 to 1.12; P = 0.09) 12-24 months: Significant difference between the two treatment groups in favour of arthroplasty (RR 1.05; 95% CI 1.01 to 1.09; P = 0.007) **Global health status** 3 months (SF36-PCS), n=440, N=1: Significant difference between the two treatment groups in favour of arthroplasty (MD 2.40; 95% CI 0.55 to 4.25) 3 months (SF 36- MCS), n=440, N=1: No significant difference between the two treatment groups (MD 1.80; 95% CI -0.10 to 3.70)	Note: Outcome was not suitable for depicting in a forest plot, since it gives no information about the actual amount of rotation in either group, therefore no direction of effect can be interpreted to be in favour of a treatment, (slight decrease in the fusion group not necessarily less favourable than a substantial increase in the arthroplasty group). Various studies reported an average (simply weighed by the number of patients) sROM of 6.8° (range 5.4° to 10°) in the arthroplasty group, versus 1.3° (range 0.3° to 2.5°) in the fusion group. Compared to the average sROM at baseline, which was 7.7° in the arthroplasty group versus 7.8°in the fusion group, there was a slight decrease in the arthroplasty group, and a substantial decrease in the fusion group. 12 -24 months: n=1622, N=6 (only 4 studies pooled due to lack of SD reporting)	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				12-24 months (SF36-PCS), n=950, N=3: Significant difference between the two treatment groups in favour of arthroplasty (MD 2.10; 95% CI 0.68 to 3.51) 12-24 months (SF 36-MCS), n=950, N=3: Significant difference between the two treatment groups in favour of arthroplasty (MD 1.46; 95% CI 0.10 to 2.82) Note: For all global health results clinical relevance was low, since the pooled effect size was small (< 10% of the scale).	Mobility significantly higher in the arthroplasty group (MD 6.90; 95%CI 5.45 to 8.35; P < 0.00001). Average sROM (simply weighed by the number of patients) in the arthroplasty group was reported to be 8.0° versus 0.9° in the fusion group. **Mobility at adjacent levels:** 3 months; n=1032, N=4; 12-24 months; n=1210, N=5 3 months: *Upper adjacent level:* Significant difference, with a slightly higher sROM in the arthroplasty group (MD 0.69°; 95% CI 0.16° to 1.21°). In absolute values the average sROM in the arthroplasty group was 9.6° versus 9.0° in the fusion group. *Lower adjacent level* No significant	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					difference between the two groups (MD -0.37°; 95% CI -1.04° to 0.29° 12-24 months: *Upper adjacent level:* sROM was significantly higher in the arthroplasty group (MD 0.53°; 95% CI 0.03° to 1.03°). In absolute values the average ROM for the arthroplasty group was 10.5° versus 10.2° in the fusion group. *Lower adjacent level:* No significant difference between the two groups (MD -0.81°; 95% CI -1.99° to 0.36°)	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Ren, 2013[2]	**SR and meta-analysis** **Funding:** Paper states that the authors did not receive funding	**Inclusion criteria:** Patients with single-level or two-level cervical spondylosis (symptomatic cervical disc disease)	**Intervention:** Cervical disc arthroplasty (CDA) **Comparator:**	**Functional Status:** Neck Disability Index (NDI): CDA had significantly greater improvement in NDI than ACDF > 48 months: (MD 5.49, 95 % CI 2.79–8.20; p<0.0001)	**Complications** Adjacent segment disease (ASD): No significant difference between the two treatment groups in rate of ASD > 48 months: CDA (6.4 %), ACDF (5.7 %) (OR	AMSTAR 8/11

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Primary studies included: 2013;Coric, 2013;Nunley, 2013;Zigler, 2011;Sasso, 2010;Burkus, **Search date:** March, 2013	Only trials that reported outcomes after a minimum of 48 months of follow-up were included **Exclusion criteria:** All other patients	Anterior cervical decompression and fusion (ACDF)	**Pain:** Neck pain (VAS): CDA had significantly greater improvement than ACDF (MD 5.42; 95 % CI 0.21–10.63; p = 0.04) Arm pain (VAS): CDA had significantly greater improvement than ACDF (MD 9.19; 95 % CI 6.57–11.81; p<0.00001) **Quality of life:** CDA significantly greater improvement in SF-36 PCS at > 48 months than ACDF (MD 1.91; 95 % CI 0.94–2.89; p = 0.0001) **Neurology** NS for "neurological success" between groups at > 48 months (OR 1.54, 95 % CI 0.91–2.63; p = 0.11) **Mobility** Four studies reported the mean flexion–extension ROM at the index level, but the SD could not be calculated. In each study, the ROM was significantly higher in patients who underwent CDA than in those who underwent ACDF.	0.95, 95 % CI 0.59–1.53; p = 0.83) Reoperation: Overall rate of reoperation > 48 months significantly lower in CDA (3.9 %) than ACDF (9.1 %) (OR 0.44, 95 % CI 0.22–0.89; p = 0.02) Rate of reoperation > 48 months for ASD was lower in patients who underwent CDA but this difference was not significant (OR 0.62, 95 % CI 0.34–1.13, I2 = 0 %; p = 0.12). HO > 48 months: One study reported bridging ossification in seven patients (17 %) who underwent CDA; a second study reported complete bridging ossification at the index level in six patients (6 %) who underwent CDA; a third study reported bridging ossification in three patients (3.2 %) who underwent CDA. HO was not reported in any patients who underwent ACDF. **Adverse events:** Dysphagia/dysphonia:	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					One study reported 22 ACDF patients (8.3 %) vs. 24 CDA patients (8.7%). Another study found one patients with dysphagia in the CDA group (2.4 %). A third study found one patients with dysphagia in the CDA group (0.9 %). Revision surgery: One study found there was no revision surgeries (0 %) in the CDA group compared with five revision surgeries in five in the ACDF group (1.9 %). Other adverse events: Another study reported 1 (3.1 %) implant loosening in a patient who underwent ACDF and no implant breakages or device failures had occurred in the CDA patients Finally, one study found (5.7 %) pseudarthrosis in patients who underwent ACDF.	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Verma, 2013[3]	**SR and meta-analysis** **Funding:** No funding received **Primary studies included:** 2011;Coric, 2011;Sasso, 2010; Burkus, 2009; Murrey, 2007; Nabhan, 2004; Porchet **Search date:** Not stated (studies up to 2011 are included)	**Inclusion criteria:** Patients with single-level or two-level degenerative cervical disc disease (myelopathy or radiculopathy) **Exclusion criteria:** All other patients	**Intervention:** Total disc arthroplasty (TDA) **Comparator:** Anterior cervical decompression and fusion (ACDF)		**Complications** Adjacent segment disease (ASD) at 2-5 years: Significant difference between the two treatment groups in rate of revision surgery for ASD for ACDF versus TDA in favour of TDA (OR=0.74; 95% CI 0.58-0.93, p=0.01) The significant difference disappears when only patients available for follow-up are included in the analysis (patients with ACDF have lower follow-up rates)	AMSTAR 5/11

3.2.2. Evidence tables of primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Cheng, 2009[4]	**RCT** **Funding:** Not stated **Setting:** Qilu Hospital of ShanDong University, China **Sample size:** 65 patients randomised: 31 patients received Bryan Cervical Disc TDR 34 patients received ACDF **Follow-up:** 1 week, 3 months, 6 months, 12 months and 24 months. Only statistical results for 12 and 24 months are provided	**Inclusion criteria:** Cervical radiculopathy or myolopathy resulting from disc herniation or stenosis at 2 contiguous levels from C-3 to C-7 that was unresponsive to non-operative treatment for at least 12 weeks **Exclusion criteria:** Exclusion criteria included: • presence of significant anatomical deformity • previous cervical procedure • severe osteoporosis • spinal infection	**Intervention:** **2-level** TDR with the Bryan cervical disc **Comparator:** **2-level** fusion (ACDF)	**Functional Status:** Neck Disability Index (NDI): 12 months: Significant difference in favor of TDR (12 vs. 18 in total score), p=0.030 24 months: Significant difference in favour of TDR (11 vs. 19 in total score), p=0.023 **Pain (VAS):** Neck pain: 12 months: no statistical value provided 24 months: Significant difference in favour of TDR (1.5 vs 2.6), p=0.012 Arm pain: 12 months: no statistical value provided 24 months: Significant difference in favour of TDR (1.4 vs 2.7), p=0.013 **Quality of life (SF-36 PCS):** 12 months: Significant difference in favour of TDR (49 vs. 46), p=0.033	**Other complications/adverse events:** • One patient had deep vein thrombosis in the Bryan cohort • One patient developed dysphagia in the ACDF cohort	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
				24 months: Significant difference in favour of TDR (50 vs. 45), p=0.013 **Mobility** 24 months: average flexion-extension in the Bryan group was 7.9° and in the fusion group 0.5° (no between group statistics provided)		

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Davis, 2013[5]	**RCT** **Funding:** Dr. Davis has received funding for this study from LDR Spine **Setting:** 24 centres in US **Sample size:** 330 patients randomised: 225 patients received Mobi-C TDR 105 patients received ACDF	**Inclusion criteria:** Diagnosis of DDD with radiculopathy or myloradiculopathy at 2 contiguous levels from C-3 to C-7 that was unresponsive to non-operative treatment for at least 6 weeks or demonstrated progressive symptoms necessitating immediate surgery Diagnosis had to be confirmed by imaging **Exclusion criteria:** Exclusion criteria included: - >2 vertebral levels requiring treatment	**Intervention:** **2-level** TDR with the Mobi-C cervical artificial disc **Comparator:** **2-level** fusion (ACDF)	**Functional Status:** Neck Disability Index (NDI): 24 months: NDI scores favoured arthroplasty; mean change was 37 (SD=20) in the TDR group and 30 (SD=19) in the fusion group. The difference from baseline between the two treatments was significant (p<0.05, using the unpaired t-test) 48 months: Significant difference favoring arthroplasty; mean change was 36.5 (SD=21.3) in the TDR group and 28.5 (SD=18.3) in the fusion group (p=0.0048, using the unpaired t-test) **Pain:** Neck pain (VAS):	**Subsequent surgical intervention:** 24 months: 7 patients (3.1%) in the arthroplasty groups and 12 patients (11.4%) in the fusion group required a subsequent surgical intervention. According to the authors this rate difference is statistically significant in favor of arthroplasty. 48 months: At 48 months, the cumulative percentage of patients who underwent subsequent surgeries at the index level remained significantly lower (p < 0.0001) for the	Questionable use of statistical methods to establish significant between group difference for "neurological success" (use of the Farrington-Manning test) We calculated a Chi-square statistics ourselves to find that the p-value is 0.752605. This result is not significant at p < 0.05.

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
	Follow-up: 24 and 48 months results	- prior surgery at operative levels or prior fusion at any level -disc height <3 mm -active malignancies -a BMI > 40 -smoking > one pack of cigarettes a day -daily use or history use of high dose steroids -known allergy to e.g. cobalt and chromium		24 months: Improvements in neck pain from baseline at 24-months were 54 (SD=25) in the TDR group and 53 (SD=29) in the fusion group. This is not a significant between group difference. 48 months: NS mean improvement in VAS neck pain score from baseline: 53 (SD=30) for the TDR group and 48 (SD=29) for the fusion group. Arm pain (VAS): 24 months: NS between group difference. Improvements in arm pain from baseline 35 (SD=29) in the TDR group and 34 (SD=38) in the fusion group. 48 months: The mean improvement in VAS arm pain score from baseline was similar (NS) between groups with 56 (SD=31) for TDR and 53 (SD=31) for fusion patients. **Quality of life (SF-12 PCS and MSC):** 24 months: Arthroplasty group: increased mean PCS score from baseline of 13.5 points, mean MSC score from baseline of 9.5 points.	TDR group at 4.0% (9 of 225 patients, with 10 surgeries) than for the fusion group at 15.2% (16 of 105 patients, 18 surgeries). **Adjacent segment disease (ASD):** 24 months: 13.1% of TDR patients and 33.3% of fusion patients had superior ASD whereas 2.9% of the TDR patients and 18.1% of the fusion patients had inferior ASD. This was a significant difference at both levels (p<0.03). 48 months: 64.7% of the fusion patients and 27.6% of the TDR patients had superior ASD. This is a significant difference (p < 0.0001). Results for the inferior levels were similar at 56.2% for the fusion group and 16.4% for the TDR group (p < 0.0001). **Dysphagia:** 24 months:	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
				Fusion group: increased mean PCS score from baseline of 10.5 points, increased mean MSC score from baseline of 7.2 points. Authors use unpaired t-test to compare change between treatments and concludes there is a significant difference for the PCS score ($p<0.05$) but NS for the MCS score ($p>0.05$) 48 months: Significant difference for PCS scores: SF-12 PCS scores was 13 (SD=12) for the TDR group and 10 (SD=12) for the fusion group at 48 months ($p < 0.05$). NS for the MCS score. **Neurology** 24 months: Significant difference between the two treatment groups in favour of arthroplasty with 5.6% of patients showing neurological deterioration in the arthroplasty group vs. 6.7% in fusion group (authors use the Farrington-Manning test to compare frequencies between groups and concludes there is a significant difference with $p<0.0001$). 48 months: NS (6.2% of TDR patients vs. 7.6% in fusion group) **Mobility**	9 patients (3.8%) in the arthroplasty groups and 8 patients (7.6 %) in the fusion group developing dysphagia as an adverse event. We calculated the p-value and found this was a non-significant difference (p-value is 0.165964) **Other complications/adverse events:** 24 months: Incidence rate of device-related adverse events were 16.7% (39/225) in the arthroplasty group and 34.3% (36/105) for the fusion patients. We calculated the p-value and found this was a significant difference (the Fisher exact test statistic value is 0.001072. The result is significant at $p < 0.05$). 48 months: No evidence was identified	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
				24 months: Fusion: mean ROM values < 1° for both treated segments in both lateral flexion/extension and lateral bending. TDR group: mean ROM was 10.1° (SD=5.9°) in flexion/extension and 5.6° (SD=3.3°) at the superior treated level. For the inferior treated level the ROM values were 8.3° (SD=5.3°) in flexion/extension and 5.4° (SD=3.3°) in lateral bending. 48 months: On average the TDR group maintained their flexion/extension and lateral bending compared to baseline.		

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Philips, 2013[6]	**RCT** **Funding:** NuVasive Inc. funds were received to support this trial **Setting:** 24 centres in US **Sample size:** 416 patients randomised: 224 patients received PCM cervical TDR 192 patients received ACDF **Follow-up:** 24 months	**Inclusion criteria:** -Diagnosis of single-level radiculopathy and/or myolopathy -Symptomatic at only 1-level C3-C4 through C7-T1 (inclusive) -Symptoms had to be radiographically confirmed showing either decreased disc height, or degenerative spondylosis on CT or MRI, or disc herniation **Exclusion criteria:** Exclusion criteria included: - prior failed cervical fusion -prior cervical trauma -cervical instability -congenital canal stenosis -facet joint pathology -malignancies -known allergy to device materials	**Intervention:** PCM Cervical disc replacement **Comparator:** ACDF with allograft and plate	**Functional Status:** Neck Disability Index (NDI): NDI scores significantly favoured arthroplasty; mean change in PCM group 21.8 vs. 25.5 in fusion group, p=0.029 **Pain:** Neck pain (VAS): NS between group difference (p=0.063) Arm pain (VAS): NS between group difference (p=0.152) **Quality of life (SF-36 PCS and MCS):** PCS: NS between group difference (p=0.2) MCS: NS between group difference (p=0.404) **Neurology** NS between group difference for “neurological success” (p=0.100) **Patient Satisfaction** VAS scores 82.8/100 mm (PCM group) vs. 81.4/100 MM in fusion group (p=0.007) **Mobility** Flexion/extension PCM group 5.7° (SD 3.9), fusion 0.8° (SD 0.8)	**Subsequent surgical intervention** PCM 5.2% (11/184), ACDF 5.4% (10/184) (NS) **Dysphagia** Significant difference: PCM mean VAS: 8.8 mm ACDF mean VAS: 12.1 mm (p=0.045) **Other adverse events** Implant or surgery related AEs: NS between groups: ACDF 7.4% (14/190) PCM 5.6% (12/214)	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Vaccaro, 2013[7]	**RCT** **Funding:** No funds received **Setting:** 18 investigational sites in US **Sample size:** 380 **Follow-up:** 24 months	**Inclusion criteria included:** 1-level SCDD between C3-C7, defined as neck or arm (radicular) pain, or functional or neurological deficit and radiographical confirmation (by CT, MRI, radiography etc.) of any of the following: -Herniated nucleus pulposos; -Radioculopathy or myolopathy; -Spondylosis (defined by the presence of osteophytes); or -Loss of disc height -Age between 18-60 yr -Failed at least 6 weeks of conservative treatments -Able to adhere to follow-up schedule (psychosocially, physically, mentally) **Exclusion criteria included:** ->one vertebral level requiring surgery	**Intervention:** Cervical Total Disc Replacement with the SECURE-C device **Comparator:** ACDF	**Functional Status:** Neck Disability Index (NDI): NS (superiority at NDI ≥ 25% impr.); SECURE C = 87.8%, Bayesian Credible Intervals (BCI) =(-3.2, 12.6) **Pain:** Neck pain (VAS): Significant difference (superiority at VAS ≥ 20 mm impr.) SECURE-C=98.4 %, Bayesian Credible Intervals=(0.9-21.0) Arm pain (VAS): Left arm: NS (superiority at VAS ≥ 20 mm impr.) SECURE-C=88.6% Right arm: NS (superiority at VAS ≥ 20 mm impr.) SECURE-C=82.7% **Quality of life (SF-36 PCS and MCS):** PCS: NS (superiority at ≥ 15% impr.) SECURE-C=62.6 MCS: NS (superiority at ≥ 15% impr.) SECURE-C=94.0% **Neurology** NS: 96% of SECURE-C had stable or improved neurological status vs. 94.9% of ACDF group **Patient Satisfaction**	**Subsequent surgical intervention** The percentage of patients experiencing secondary surgical interventions (revision, removal, reoperation, or supplemental fixation) at the index level was statistically lower for the combined (randomised and nonrandomised) SECURE-C group (2.5%) than the ACDF group (9.7%). **Adverse events** Significant difference in favour of arthroplasty: SECURE-C group had overall fewer adverse events: SECURE-C = 70.8% vs. ACDF 79.2% (% oof patients experiencing at least one adverse event over the course of 24 months) Adverse event rates for each event type were similar for both groups, except neck and upper extremity pain and index-level surgery, which were statistically lower for SECURE-C, and musculoskeletal	Trial is set up as a non-inferiority trial, it does not provide mean and SD values and could therefore not be incorporated in the updates of the meta-analysis (continuous outcomes)

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
		- prior fusion at adjacent levels -prior surgery at level to be treated -radiographical confirmation of facet joint disease -clinically compromised vertebral bodies at the affected level(s) due to current or past trauma -cervical instability, severe spondylosis, malignancies, pregnancy		Significant difference (superiority) in favour of arthroplasty: SECURE-C=99.7% , BCI=(2.9-17.8) **Mobility** Mean flexion-extension ROM in SECURE-C group =9.7° (no SD provided), 84.6 % of SECURE-C patients was within definition of "neurological success". In ACDF group 89.1% of patients experienced "radiographical fusion" (<2°flexion-extension ROM, presence of bridging trabecular bone, and ≤3 mm in translation)	(nonspinal; e.g. , arthritis, shoulder injury, epicondylitis, extremity fractures, knee ligament tears), which was statistically higher for SECURE-C. The rate of severe or life-threatening adverse events was similar for the combined SECURE-C (19.5%) and ACDF (23.6%) groups. The total number of patients having surgery-related adverse events was lower for the combined SECURE-C (5.5%) group than ACDF (12.5%) group (NS)	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Zhang, 2012[8]	**RCT** **Funding:** Chinese Medical Doctor Associations funds were received **Setting:** 3 large Chinese hospitals **Sample size:** 120	**Inclusion criteria:** Patients with symptomatic mild DDD at 1 cervical level, including disc herniation with radiculopathy caused by foraminal osteophytes, soft disc herniation, or myelopathy, who had not responded to at least 6 weeks of conservative treatment. **Exclusion criteria:** Patients with axial neck pain as a solitary symptom	**Intervention:** Cervical TDR using the BRYAN prosthesis **Comparator:** ACDF	**Functional Status:** Neck Disability Index (NDI): NS between group difference: Mean TDR= 14.89 (SD=2.90), Mean ACDF=15.25 (SD=3.77), p=0.584 **Pain:** Neck pain (VAS): Significant difference in favour of arthroplasty: Mean TDR=19.07 (SD=5.02), mean ACDF=21.45 (SD=4.85), p=0.013	**Subsequent surgical intervention** 1 patients in the TDR group (radiculopathy at adjacent segment) and 4 patients (3 had ASD and one had myelopathy) in the ACDF group had reoperations **Adverse events** No vascular or neurological complications in any of the groups	No ITT analysis, only patients who completed study were included in analysis

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
	Follow-up: 24 months	Patients with contraindications for TDR, including incompetent posterior elements, instability or severe facet arthrosis, insufficient cervical motion at the index level, bridging osteophytes, collapse of intervertebral disc space of more than 50% of normal height, and severe osteoporosis		Arm Pain (VAS): NS between group difference: Mean TDR= 16.20 (SD=3.79), Mean ACDF=17.34 (SD=4.76), p=0.166 **Mobility** Significant difference in favour of arthroplasty for flexion-extension ROM: Mean TDR=8.79° (SD=0.89), mean ACDF=0.79° (SD=0.63), p<0.001		

3.2.3. AMSTAR Quality appraisal of systematic reviews

SR Study ID	a priori" design provided?	Duplicate study selection ?	Comprehensive literature search?	Status of publication used as inclusion criteria?	List of included and excluded studies provided ?	Characteristics of included studies provided?	Scientific quality of included studies assessed and documented ?	Scientific quality of included studies appropriately used to formulate conclusions ?	Appropriate methods used to combine study finding?	Publication bias assessed?	Conflicts of interest reported ?	Total score
Boselie 2012[1]	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	11/11
Ren, 2013[2]	?	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	8/11
Verma, 2013[3]	YES	?	YES	YES	NO	YES	NO	NO	YES	NO	NO	5/11
Luo 2014[9]	?	YES	YES	NO	NO	YES	YES	NO	NO	NO	YES	5/11

3.2.4. Quality appraisal of primary studies

Cochrane risk of bias tool

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data

Domain	Support for judgement	Review authors' judgement
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

Reference	Random sequence generation	Allocation concealment	Blinding participants	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cheng, 2009[4]	Low risk	Unclear risk	High risk	High risk	High risk	Low risk	Low risk
Davis, 2013[5]	Low risk	Low risk	Low risk	High risk	High risk	Low risk	High risk
Philips, 2013[6]	Low risk	Low risk	High risk	High risk	High risk	Low risk	High risk
Vaccaro, 2013[7]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Zhang, 2012[8]	Low risk	Low risk	High risk	High risk	High risk	Low risk	Unclear risk

3.3. Results for lumbar total disc replacement

3.3.1. Evidence table of systematic review

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Jacobs, 2012[10]	**SR and meta-analysis** **Funding:** No external funding received **Primary studies included:** 2011; Gornet 2011; Hellum 2009; Berg 2008; Moreno 2008; Sasso 2007; Zigler 2005; Blumenthal **Search date:** review content assessed up-to-date March 6th, 2012	**Inclusion criteria:** Patients scheduled for surgery for chronic (lasting longer than 12 weeks) degenerative disc disease. **Exclusion criteria:** All other patients	**Intervention:** Total disc replacement **Comparator:** Any other treatment for lumbar degenerative disc disease	**TDR vs fusion:** **Back Pain:** VAS at 24 months: SD in favour of TDR: MD=5.22: (95% CI: 0.2 -10.3) **Leg Pain:** VAS at 24 months: NS **Overall improvement:** No meta-analysis could be performed (large variation in study criteria for overall improvement) **Patient Satisfaction:** VAS (continuous for patient satisfaction) at 24 months: SD in favour of TDR (patient satisfaction more prevalent in this group): OR=1.93 (95% CI: 1.36- 2.76) **Back-specific functional status:** Percentage of patients improved on Oswestry at 24 months: SD in favour of TDR: OR=1.45 (95% CI: 1.06- 1.98)	**TDR vs fusion:** **Radiological outcomes:** At 24 months ROM in the TDR group was comparable to ROM at preoperative status In the fusion group ROM was nearly zero **Complications:** **Thromboembolic complications:** One study reported two thromboembolic events in the TDR group and none in the fusion groups. Another study reported one cardiovascular event in the disc group and none in the fusion group. **Re-operations:** 24 months: NS **Neurological complications:** NS (reported in one study) **Adjacent segment degeneration:**	**AMSTAR 11/11**

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				Quality of life: No meta-analysis could be performed. Results from one study found a significant difference for TDR on the mental component score only in the short term (1.5 and 3 months). In the same study the difference on the physical component score was significant at every follow-up favouring TDR. **<u>TDR versus rehabilitation:</u>** **Back Pain:** 12 months: MD=14.0 mm (95% CI: 5.0 – 23.0) 24 months: MD= 12.3 mm (95% CI: 3.1 – 21.3) **Patient Satisfaction:** 24 months: SD in favour of TDR (patient satisfaction more prevalent in this group): OR 2.65 (95% CI: 1.42- 4.96) **Back-specific functional status:**	24 months: NS **Facet joint degeneration:** NS (check time-point in the study by Berg 2009) **<u>TDR versus rehabilitation:</u>** **Radiological:** No radiological parameters were measured (no implant motion, asd etc) **Complications:** Thromboembolic complications were reported for two patients with TDR (none in the rehab group) Differences in subsequent operations rates: NS	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				Patients improvement on Oswestry at 12 months: 8.9 points higher in the TDR group compared with rehab (95% CI: 4.77 – 13.03 points) Patients improvement on Oswestry at 24 months: 6.90 points higher in the TDR group compared with rehab (95% CI: 2.23 – 11.57 points)		

3.3.2. Evidence tables of primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Hellum (2012)[11] and Johnson (2013)[12] Companion papers to Hellum (2011)[13] reported in the review by Jacobs (2012)[10]	**RCT** **Funding:** Grants from South Eastern and the Western Norway Regional Health Authorities, from Haakon and Sigrun Oedegaards fund at the Norwegian Society of Radiology, and the Norwegian ExtraFoundation for Health and Rehabilitation **Setting:** 5 University Hospitals in Norway **Sample size:** • 173 patients randomised: • 86 patients randomised to TDR • 87 patients randomised to rehabilitation	Patients with a history of low back pain for at least one year, Oswestry Disability Index of at least 30 points, and degenerative changes in one or two lower lumbar spine levels	Surgery with disc prosthesis or multidisciplinary rehabilitation for 12-15 days	Primary results are described in the review by Jacobs (see above)	24 months: **ALD** ALD developed with similar frequencies (no significant difference) in patients who were (n = 59) and were not (n = 57) treated with surgery. Results are provided for each evaluation parameter and all results are non-significant, including the FA decrease in 1 patient (2%) both in the surgery group and the rehabilitation group.	High loss to follow-up, ALD analysis is based on 116 of the original 173 patients

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
	Follow-up: 24 months				**Movement:** Segmental movement in the sagittal plane and disc height were measured using distortion compensated roentgen analysis (DCRA) comparing radiographs in active flexion and extension. No significant change in sagittal plane movement between treatment groups were found	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
Zigler (2012)[14] and Zigler (2012)[15] **Companion papers to Zigler (2007)[16] reported in the review by Jacobs (2012)[10]**	**RCT** **Funding:** No funding **Setting:** 17 investigatioal sites across the United States **Sample size:** 286 **Follow-up:** 24 and 60 months	Patients 18-60 years Single-level DDD at L3–S1 with 1. Back and/or leg (radicular) pain; and 2. Radiographic confirmation of any 1 of the following by CT, MRI, diskography, plain film, myelography, and/or flexion/extension films: i. Instability ii. Decreased disc height iii. Scarring/thickening of anulus fibrosis; iv. Herniated nucleus pulposus; or v. Vacuum phenomenon.	**Intervention:** TDR with the Pro-Disc-L **Comparator:** Circumferential arthrodesis (fusion)	Results at 24 months are described in the review by Jacobs, 2012 **60 months:** **Oswestry score:** At 5 years, both treatment groups maintained significant improvements in the ODI score compared with baseline ($p < 0.0001$). The mean ODI score improvements for TDR patients were maintained from 2 to 5 years, whereas mean ODI improvements for fusion patients were similar to those for TDR patients at 5 years ($p = 0.4552$). **SF-36 PCS:** Both treatment groups had improvements in the SF-36 PCS at 2 and 5 years of follow-up, compared with	Results at 24 months are described in the review by Jacobs, 2012 **60 months:** **VAS pain:** Both TDR and fusion groups demonstrated significant improvements in VAS pain scores at 2 and 5 years posttreatment compared with baseline ($p < 0.0001$). The mean percentage improvements in VAS pain were similar in TDR and fusion patients at the 2- and 5-year follow-up visits. **VAS satisfaction:** At 5 years posttreatment,	Significant loss to follow-up after 60 months, 56/93 pt were evaluated in the fusion group and 137/183 pt in the TDR group Additionally, only 72.9 % of patients had complete radiographic data set

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
		Oswestry Low Back Pain Disability Questionnaire score≥40 Failed ≥ 6 mo of conservative treatment Psychosocially, mentally, and physically able to comply fully with protocol, including adhering to follow-up schedule and requirements, and filling out forms Willing to give written informed consent		baseline ($p < 0.0001$). The TDR patients experienced a greater but not significant improvements in SF-36 PCSs at 5 years ($p = 0.1677$). **Neurological success:** NS in neurological success between TDR and fusion patients (p=1.00), Of the patients who had neurological success at 2 years 90.5% of fusion patients and 93.0% of TDR patients had neurological success at 5 years. **Radiographic outcomes:** Six domains of radiographic outcomes were measured: no device migration p=0.5607 (NS but favours fusion) no device subsidence p=1.0000 (not seen in any of the treatment groups) disc height decrease ≤3 mm, p=0.0530 (NS but favours fusion) fusion status p=0.0767 (NS but higher in fusion group) no radiolucency p=1.0000 (not seen in any of the treatment groups) ROM p=0.0634 (NS but higher in TDR group) **Index level secondary surgery:** Secondary surgeries at the index level occurred in 9 fusion patients (12%) and 13 TDR patients (8%)	TDR patient satisfaction was similar to that at 2 years, whereas mean VAS satisfaction in fusion patients increased to a level that was similar to that in TDR patients (TDR: 78.3 ± 27.1, fusion: 78.1 ± 26.7, $p = 0.6199$). **Adjacent level degenerative changes:** Adjacent-level degeneration was characterized by a composite score including disc height loss, endplate sclerosis, osteophytes, and spondylolisthesis. Changes in ALD at 5 years were observed in 9.2% of TDR patients and 28.6% of fusion patients ($p = 0.004$). Among the patients without adjacent-level disease preoperatively, new findings of ALD at 5 years posttreatment were apparent in 6.7% of TDR patients and 23.8% of fusion patients ($p = 0.008$).	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Comments
				p= 0.048 (NS) **Adjacent level surgery:** Adjacent-level problems leading to secondary surgery was reported for 1.9% of TDR patients and 4.0% of fusion patients (p = 0.6819).		

3.3.3. AMSTAR Quality appraisal of systematic review

SR Study ID	a priori" design provided?	Duplicate study selection ?	Comprehensive literature search?	Status of publication used as inclusion criteria?	List of included and excluded studies provided ?	Characteristics of included studies provided?	Scientific quality of included studies assessed and documented ?	Scientific quality of included studies appropriately used to formulate conclusions ?	Appropriate methods used to combine study finding?	Publication bias assessed?	Conflicts of interest reported ?	Total score
Jacobs, 2012[10]	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	11/11

3.3.4. Quality appraisal of primary studies

See section 3.2.4 for Cochrane risk of bias tool description.

Reference	Random sequence generation	Allocation concealment	Blinding participants	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Hellum (2012)[11] and Johnson (2013)[12]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk
Zigler (2012)[14] and Zigler (2012)[15]	Low risk	Low risk	High risk	High risk	High risk	Low risk	Unclear risk

4. ECONOMIC EVALUATION OF TOTAL DISC REPLACEMENT

4.1. Common search strategy for cervical and lumbar total disc replacements

4.1.1. Search strategies

4.1.1.1. Medline @ Ovid

Database		Ovid MEDLINE(R) In Process & Other Non Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date			02/04/2015
Date covered			1946 to present
Search strategy	**#**	**Searches**	**Results**
	1	Economics/	26583
	2	"Costs and Cost Analysis"/	42182
	3	"Value of Life"/ec [Economics]	227
	4	exp Economics, Pharmaceutical/ or Economics, Medical/ or Economics, Hospital/ or Economics, Dental/ or Economics, Nursing/	26686
	5	(economic$ or cost or costs or costing or price$ or pricing or pharmacoeconomic$).ti,ab.	483404
	6	budget$.ti,ab.	20074
	7	cost-effectiveness.mp.	37658
	8	cost-utility.mp.	2734
	9	(cost-minimisation or cost-minimization).mp.	903
	10	or/1-9	547919
	11	limit 10 to letter	7507
	12	limit 10 to editorial	6414
	13	limit 10 to historical article	6030
	14	or/11-13	19879
	15	10 not 14	528040
	16	Animals/	5410936
	17	15 not 16	477239
	18	exp Total disc replacement/	287
	19	((disc? or disk?) adj3 (artificial or replacement or arthroplast* or prosthes* or implant*)).ab,ti.	2396
	20	18 or 19	2444
	21	intervertebral disc/	11022
	22	intervertebral disc degeneration/	1720
	23	cervical vertebrae/	27838
	24	Lumbar vertebrae/	39786
	25	or/21-24	72082
	26	Arthroplasty, Replacement/	4510
	27	25 and 26	353
	28	20 or 27	2496
	29	limit 28 to (editorial or historical article or letter)	74
	30	28 not 29	2422
	31	17 and 30	77
	32	limit 31 to yr="2006 -Current"	**65**
Note		mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier.	

4.1.1.2. Embase @ Embase.com

Database		Embase	
Date			02/04/2015
Date covered			No restriction
Search strategy	**#**	**Searches**	**Results**
	#1	'cost benefit analysis'/exp	66396
	#2	'cost effectiveness analysis'/exp	104648
	#3	'cost utility analysis'/exp	5985
	#4	'cost minimization analysis'/exp	2625
	#5	'cost control'/exp	51257
	#6	'cost of illness'/exp	14628
	#7	'health care cost'/exp	214197
	#8	'pharmacoeconomics'/exp	169729
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	471577
	#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 AND ([editorial]/lim OR [letter]/lim OR [note]/lim)	79818
	#11	#9 NOT #10	391759
	#12	'total disc replacement'/exp	403
	#14	((disc OR discs OR disk OR disks) NEAR/3 (artificial OR replacement OR arthroplast* OR prosthes* OR implant*)):ab,ti	3190
	#15	'intervertebral disk'/exp	11809
	#16	'intervertebral disk hernia'/exp	19577
	#17	'intervertebral disk degeneration'/exp	6601
	#18	'cervical spine'/exp	31604
	#19	'lumbar vertebra'/exp	15064
	#20	#15 OR #16 OR #17 OR #18 OR #19	73544
	#21	'arthroplasty'/exp	53390
	#22	#20 AND #21	793
	#23	#12 OR #14 OR #22	3560
	#24	#12 OR #14 OR #22 AND ([editorial]/lim OR [letter]/lim OR [note]/lim)	173
	#25	#23 NOT #24	3387
	#26	#11 AND #25	94
	#27	#26 AND [medline]/lim	49
	#28	#26 NOT #27	45
	#29	#28 AND [2006-2015]/py	**44**
Note			

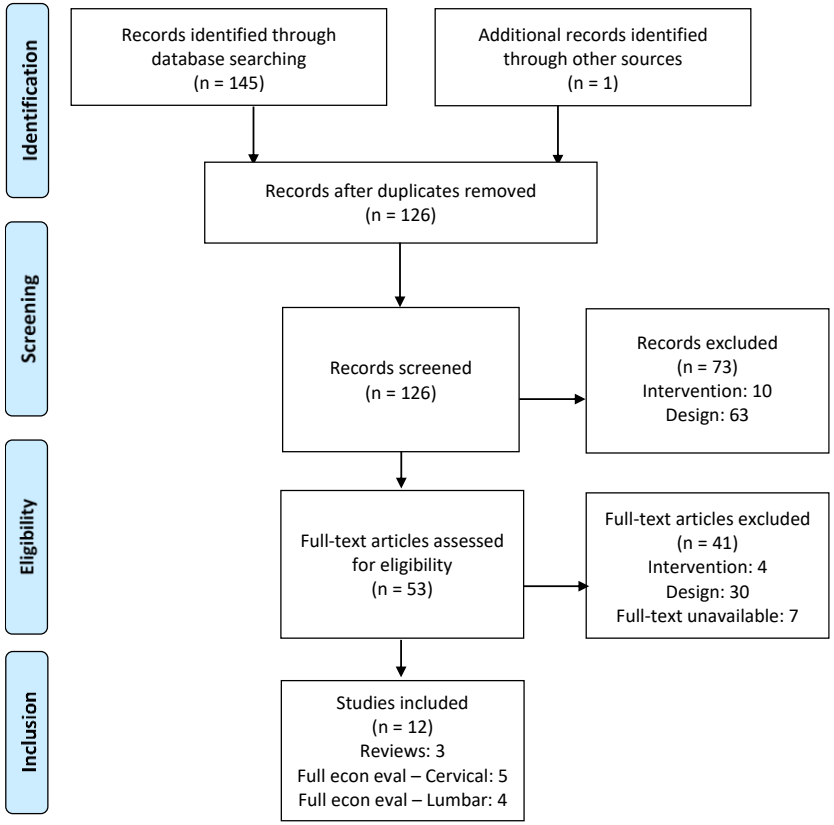
4.1.1.3. CRD HTA and CRD NHS EED

Database		CRD HTA and CRD NHS EED	
Date			02/04/2015
Date covered			No restriction
Search strategy	**#**	**Searches**	**Results**
	1	MeSH DESCRIPTOR Total disc replacement EXPLODE ALL TREES IN NHSEED,HTA	8
	2	((disc? or disk?) adj3 (artificial or replacement or arthroplast* or prosthes* or implant*)) IN NHSEED, HTA	45
	3	#1 OR #2	45

	4	MeSH DESCRIPTOR intervertebral disc EXPLODE ALL TREES IN NHSEED,HTA	14
	5	MeSH DESCRIPTOR intervertebral disc degeneration EXPLODE ALL TREES IN NHSEED,HTA	14
	6	MeSH DESCRIPTOR cervical vertebrae EXPLODE ALL TREES IN NHSEED,HTA	58
	7	MeSH DESCRIPTOR lumbar vertebrae EXPLODE ALL TREES IN NHSEED,HTA	172
	8	#4 OR #5 OR #6 OR #7	227
	9	MeSH DESCRIPTOR arthroplasty, replacement EXPLODE ALL TREES IN NHSEED,HTA	417
	10	#8 AND #9	18
	11	#3 OR #10	45
	12	(#11) FROM 2006 TO 2015	**36**
Note			

4.1.2. Study flow of selection of economic evaluations

The electronic searches returned 145 citations in total (65 in Medline(OVID), 44 in Embase and 36 in CRD HTA & CRD NHS EED). One additional publication was identified via manual search. After exclusion of 20 duplicates, 126 unique citations were left. The flow chart of the selection process is presented below.



4.2. Data extraction sheets for cervical total disc replacement

Ament JD, Yang Z, Nunley P, Stone MB, Kim KD. Cost effectiveness of Cervical Total Disc Replacement vs Fusion for the Treatment of 2 Level Symptomatic Degenerative Disc Disease. JAMA Surg, 2014.[17]		
Sponsor(s) of the study		University of California and Spine Institute of Louisiana. This work was supported in part by LDR Medical. LDR Medical had a role in the collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication, but not in the design and conduct of the study.
Country, currency, price year		USA, 2012 US dollar
Research question		What is the cost-effectiveness of cervical total disc replacement versus anterior cervical discectomy and fusion for 2-level degenerative disc disease?
Analytic technique		Decision analytic model – Markov model (Cycle length: 6 weeks)
Study design		Cost-utility analysis
Perspective		Societal (including direct medical and productivity costs)
Time horizon		2 years (as for the companion RCT form Davis et al., 2013)
Discounting		Costs: 3%, Outcomes: 3%
Interventions compared		Cervical total disc replacement (CTDR) Anterior cervical discectomy and fusion (ACDF)
Population		Median age of the patients: 45 years Patients with two-level symptomatic cervical degenerative disc disease
COST	**Items included**	Direct medical costs: initial surgery, complications, medications, ancillary services Productivity costs
	Measurement/valuation	Medical costs: 2012 Medicare reimbursement rates Productivity costs: Human capital approach
	Data sources	Relevant codes directly collected from institutional billing data
OUTCOME	**Endpoints/health states**	Health states: mild disability, moderate disability, severe disability, crippled, bed-bound, death Endpoints: post-surgical complications (supplemental fixation, revision, reoperation, device removal)
	Health states valuation	ACDF: transition probabilities across the 5 health states (excluding mortality) derived from the companion RCT and split into 4 time segments: 0-6 weeks, 6 weeks-6 months, 6 months-1year, 1 year-2 years.

		Post-surgical complications derived from companion RCT for the 4 time periods.	
	Treatment effect/extrapolation	CTDR: transition probabilities across the 5 health states (excluding mortality) derived from the companion RCT and split into 4 time segments: 0-6 weeks, 6 weeks-6 months, 6 months-1year, 1 year-2 years. Post-surgical complications derived from companion RCT for the 4 time periods. Extrapolations: - In sensitivity analysis: transition probabilities for years 3-4 and over = probabilities in years 1-2 observed in RCT - Complication rates: not explained/not clear	
	Utility assessment	Mild disability (0.855), moderate disability (0.685), severe disability (0.609), crippled (0.547), bed-bound (0.475)	
	Data sources	Rates and probabilities: observations from companion RCT Utilities: SF-12 collected during companion RCT, transformed to SF-6D utilities	
UNCERTAINTY	**Sensitivity analysis**	Deterministic one-way	
	Scenario analysis	Time horizon (1 to 10 years) Perspective (Health care payer)	
	Generalisability	Other populations (specific cohorts of patients, patients aged <45 years)	
Assumptions		Post-surgical complication rates are time-dependant but do not vary according to what health state patients transitioned from.	
RESULT	**Base-case**	CTDR more costly (incremental costs $2139 per patient) and more clinically effective (0.087 QALY gained per patient) than ACDF. ICER CTDR vs. ACDF: $24 594 per QALY	
	Sensitivity analysis	Costs (+/- 20%): if value of CTDR device decreases, CTDR becomes more cost-effective Complication rates (+/- 20%) Utilities (values from the 95% CI): if value of mild disability decreases, CTDR becomes less cost-effective	
	Scenario analysis	Time horizon	CTDR less cost-effective with 1 year time horizon CTDR is dominant if time horizon >4 years
		Perspective	Under the health care perspective, the ICER increases to $100 257 per QALY
		Subgroups	CTDR more cost-effective in most disabled patients (i.e. bedbound and crippled) CTDR more cost-effective in <45 years patients (but also cost-effective in those >45 years)
Conclusions		CTDR is a highly cost-effective treatment option for 2-level cervical disc disease, from a societal perspective. After 4 years, CTDR dominates ACDF.	

	Despite the impact of the input parameter variations shown in the sensitivity analyses, with the exception of the value placed on the minimal disability health state, the ICER value stays below the threshold of $50 000 per QALY in each instance, affirming the stability of the result that CTDR is a cost-effective treatment option.
Remarks	The study refers to reoperation rates in general, with no distinction between reoperation at the index or at the adjacent level.

Lewis DJ, Attiah MA, Malhotra NR, Burnett MG, Stein SC. Anterior surgical management of single level cervical disc disease: a cost effectiveness analysis. Spine, 2014.[18]		
Sponsor(s) of the study		University of Pennsylvania and Baylor College of Medicine. No funds were received in support of this work. No conflict of interest reported.
Country, currency, price year		USA, 2014 US dollar
Research question		What is the cost-effectiveness of 5 surgical approaches to treat single level cervical disc disease?
Analytic technique		Decision analytic model – decision tree (TreeAgePro)
Study design		Cost-utility analysis
Perspective		Health Care Payers (though a societal perspective is reported)
Time horizon		5 years (latest time point available for all 5 options in the literature)
Discounting		Not reported (0%?)
Interventions compared		1. ACDF with autograft 2. ACDF with allograft 3. ACDF with intervertebral cervical 4. Cervical total disc replacement (CTDR) 5. ACD (without fusion)
Population		Adult patients with radiculopathy secondary to one-level symptomatic cervical disc disease
COST	**Items included**	Direct medical costs: initial surgery including implants, OP follow-up, follow-up complications
	Measurement/valuation	-
	Data sources	Medicare reimbursement codes, hospital costs (DRGs), literature
OUTCOME	**Endpoints/health states**	Endpoints: perioperative complications (up to 30 days post initial operation), follow-up complications (same level or adjacent level reoperations, from day 31 up to 60 months after initial surgery).
	Health states valuation	-

	Treatment effect/extrapolation	**Probability (Standard deviation)**	**Perioperative complication**	**Late reoperation – index level**	**Late reoperation – adjacent level**
		1. ACDF with autograft	0.117 (0.008)	0.049 (0.037)	0.054 (0.038)
		2. ACDF with allograft	0.036 (0.004)	0.032 (0.152)	0.043 (0.114)
		3. ACDF with spacer	0.033 (0.004)	0.037 (0.065)	0.043 (0.069)
		4. Cervical total disc replacement	0.020 (0.002)	0.026 (0.039)	0.023 (0.065)
		5. ACD (without fusion)	0.045 (0.004)	0.019 (0.198)	0.023 (0.132)
		Rates of perioperative complications, index level reoperation and adjacent level reoperation derived for the 5-year period for each procedure investigated. No extrapolation needed.			
	Utility assessment	**Mean utility (Standard deviation)**	**Successful surgery with no complication**	**Perioperative complication**	**Late reoperation**
		1. ACDF with autograft	1 (assumption)	0.870 (0.023)	0.915 (0.167)
		2. ACDF with allograft	1 (assumption)	0.827 (0.044)	0.915 (0.167)
		3. ACDF with spacer	1 (assumption)	0.838 (0.049)	0.915 (0.167)
		4. Cervical total disc replacement	1 (assumption)	0.842 (0.043)	0.915 (0.167)
		5. ACD (without fusion)	1 (assumption)	0.805 (0.034)	0.915 (0.167)
	Data sources	Rates and probabilities: literature review and meta-analyses Utilities: literature review			
UNCERTAINTY	**Sensitivity analysis**	Probabilistic (on probabilities and costs, not clear for utilities)			
	Scenario analysis	No			
	Generalisability	No			
Assumptions					
RESULT	**Base-case**	Incremental analysis (comparison of all 5 scenarios together): ACD without fusion dominates all other surgical options. All other options are more expensive and produce less QALYs than ACD without fusion.			
	Sensitivity analysis	No			
	Scenario analysis	No			

Conclusions	"The results of our decision analytic model indicate that at 5 year post operation, ACD is superior in both effectiveness and costs to ACDF (with autograft, allograft, or spacer) and CTDR for the management of single-level cervical disc disease."
Remarks	Utilities for pre-operation not reported. Only the impact of complications is thus accounted for in utility computations.

McAnany SJ, Overley S, Baird EO, Cho SK, Hecht AC, Zigler JE, Qureshi SA. The 5 year cost effectiveness of anterior cervical discectomy and fusion and cervical disc replacement: a Markov analysis. Spine, 2014.[19]		
Sponsor(s) of the study		Mount Sinai Medical Centre and Texas Health Research Institute. No fund received for this work. Paid consultancy activities from the authors are reported.
Country, currency, price year		USA, 2010 US dollar
Research question		Given the demonstrated non-inferiority of CTDR versus ACDF, what is the cost-effectiveness of ACDF and CTDR for the treatment of single-level cervical degenerative disc disease?
Analytic technique		Decision analytic model – Decision tree (TreeAge Pro)
Study design		Cost-utility analysis
Perspective		Health care payer
Time horizon		5 years
Discounting		Costs: 3%, Outcomes: 3%
Interventions compared		Cervical total disc replacement (CTDR) Anterior cervical discectomy and fusion (ACDF)
Population		Assumed population aged 40 years old, presenting with an acute disc herniation with associated myelopathy / radiculopathy, with an operative indication after failed conservative therapy
COST	**Items included**	Direct medical costs
	Measurement/valuation	Based on the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilisation Project (using ICD9 codes) for inpatient costs, and on Medicare reimbursement rates for physician services
	Data sources	Observations in databases: DRG reimbursements, professional fees, Medicare reimbursement rates
OUTCOME	**Endpoints/health states**	Health states: (1) well after primary surgery, (2) non-operative complication, (3) well after reoperation, (4) complication after reoperation, (5) adjacent segment reoperation, (6) death Endpoints: complications and reoperations
	Health states valuation	

	Treatment effect/extrapolation	**Rate per procedure per year**	**CTDR**	**ACDF**	
		Non-operative complications	0.023	0.042	
		Reoperations – index level	0.011	0.028	
		Reoperations – adjacent level	0.011	0.013	
		Complication after reoperation	0.50 (assumption)	0.50 (assumption)	
	Utility assessment	**Utilities**	**CTDR**	**ACDF**	
		Preoperative disc herniation	0.54	0.54	
		Well after primary surgery	0.72	0.72	
		Reoperation	0.43	0.43	
		Non-operative complication, complication after revision: 60% of the utility of the "well after surgery" health state.			
	Data sources	Rates and probabilities: literature reviews, expert opinion Utilities: based on the results from the ProDisc-C trial from Zigler et al.[20] SF-36 data collected at 6 weeks, 3, 6, 12, 18, 24 and 60 months post-surgery (ACDF or CTDR), conversion to SF-6D data. Baseline utilities for preoperative single-level degenerative disc disease was extrapolated based on the raw SF-36 data from the trial.			
UNCERTAINTY	**Sensitivity analysis**	Deterministic one-way			
	Scenario analysis	No			
	Generalisability	No			
Assumptions		A patient can only enter into the revision state once			
RESULT	**Base-case**	Over 5 years	**CTDR**	**ACDF**	**Incremental**
		Costs	$102 274	$119 814	- $ 17 540
		QALYs	2.84	2.81	0.03
		ICER			CTDR dominant over ACDF
	Sensitivity analysis	<u>All sensitivity analyses performed at a cut-off of $50 000 / QALY</u> CTDR costs (Base-case: $16 500): if cost > $20 500, ACDF becomes more cost-effective ACDF costs (Base-case: $22 700): if cost < $18 600, ACDF becomes more cost-effective CTDR utility well after primary surgery (Base-case 0.72): if utility < 0.713, ACDF becomes more cost-effective			

	ACDF utility well after primary surgery (Base-case 0.72): if utility > 0.747, ACDF becomes more cost-effective CTDR complication rate (Base-case: 2.30%): if rate > 4.37%, ACDF becomes more cost-effective ACDF complication rate (Base-case: 4.20%): if rate < 2.20%, ACDF becomes more cost-effective CTDR index-level reoperation rate (Base-case: 1.1%): if rate > 27%, ACDF becomes more cost effective CTDR adjacent-level reoperation rate (Base-case: 1.1%): if rate > 10.5%, ACDF becomes more cost-effective
Scenario analysis	-
Conclusions	"CTDR was found to be the dominant strategy because it was less costly and more effective at 5 years than ACDF." "The model was particularly sensitive to the costs and utilities of CTDR, and CTDR was the dominant strategy only over a relatively narrow range." "The model is unable to predict the long-term survival of either implant, and catastrophic failure requiring revision would change the relative effectiveness of the procedures."
Remarks	

Qureshi SA, McAnany S, Goz V, Koehler SM, Hecht AC. Cost effectiveness analysis: comparing single level cervical disc replacement and single level anterior cervical discectomy and fusion: clinical article. J Neurosurg Spine, 2013.[21]	
Sponsor(s) of the study	Authors' affiliation is Mount Sinai Medical Centre. Some authors are consultant for device companies. No explicit mention of the funding source.
Country, currency, price year	USA, 2010 US dollar
Research question	What is the cost-effectiveness of cervical CTDR and ACDF in the treatment of symptomatic single-level cervical disc disease unresponsive to appropriate conservative management?
Analytic technique	Cost-utility analysis
Study design	Decision analytic model – Decision tree (TreeAge Pro)
Perspective	Health care payer
Time horizon	20 years
Discounting	Costs: 3%, Outcomes: 3%
Interventions compared	Cervical total disk replacement (CTDR) Anterior cervical discectomy and fusion (ACDF)
Population	Assumed population aged 45 years old, presenting with single-level cervical degenerative disk disease with radiculopathy that failed to respond to appropriate conservative management.

COST	**Items included**	Direct medical costs		
	Measurement/valuation	Based on the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilisation Project (using ICD9 codes) for inpatient costs, and on Medicare reimbursement rates for physician services.		
	Data sources	Observations in databases: Nationwide Inpatient Sample (DRG, ICD), Medicare reimbursement rates (procedures)		
OUTCOME	**Endpoints/health states**	ST complications (pseudarthrosis and hardware failure), LT complication (adjacent segment degeneration), revisions		
	Health states valuation	-		
	Treatment effect/extrapolation	**Rate per procedure per year**	**CTDR**	**ACDF**
		Pseudarthrosis and hardware failure	1% (not clear)	5%
		Adjacent segment degeneration	1.5% (not clear)	3%
		Extrapolations: all rates and figures constantly applied for 20 years (?), though no explanation reported.		
	Utility assessment		**CTDR**	**ACDF**
		Cervical disc disease	0.7 (assumption)	0.7 (assumption)
		Well after primary surgery	0.9	0.8
		Reoperations	0.85	0.75
		Adjacent level DDD	0.7	0.7
	Data sources	Rates and probabilities: literature reviews. Utilities – Cervical disc disease: as no studies assigned a specific utility factor to cervical disc disease, utilities reported in the literature for arthritis of any joint (0.7) and neck pain (0.7) were used. Utilities: based on the review of 4 RCTs and 1 meta-analysis: Burkus et al., 2010 (Prestige trial),[22] Coric et al., 2011 (Kineflex-C trial),[23] Heller et al., 2009 (Bryan trial),[24] Murray et al., 2009 (ProDisc-C)[25] and McAffee et al., 2012[26]		
UNCERTAINTY	**Sensitivity analysis**	Deterministic one-way		
	Scenario analysis	No		
	Generalisability	No		
Assumptions		“CTDR prosthesis survival assumed to be 20 years (as for hip prosthesis), although no follow-up longer than 6 years is available”		
RESULT	**Base-case**	Over a lifetime	**CTDR**	**ACDF**	**Incremental**
		Costs	$11 987	$16 823	- $4836

	QALYs	3.94	1.92	2.02
	ICER			CTDR dominates ACDF
Sensitivity analysis	All sensitivity analyses performed at a cut-off of $50 000 / QALY			
	CTDR prosthesis survival time (= time horizon)	Threshold value: 9.75 years, below which ACDF is more cost-effective than CTDR If prosthesis survival time (base-case 20 years) is > 11 years, CTDR is cost-effective If CTDR 1-year failure rate (base-case 1%) is >29%, ACDF becomes more cost-effective		
	CTDR costs	If CTDR cost (base-case not reported) is > $17 000, ACDF becomes more cost-effective		
	Utilities	If CTDR utility well after surgery (base-case 0.9) is < 0.796, ACDF is more cost effective Using $50 000 WTP threshold, CTDR is more cost-effective if CTDR utility is ≥ 0.81 ACDF is more cost-effective if its utility is > 0.908 (base-case 0.8)		
	LT CTDR failure	CTDR long-term threshold failure rate: 30.8% per year, above which ACDF is more cost effective		
	Revision	For the reference case, a patient who demonstrates primary hardware failure is as likely to have revision CTDR as revision ACDF No threshold value determined		
Scenario analysis	No			
Conclusions	"Our reference case showed that CTDR has the potential to be a more cost-effective strategy for the treatment of cervical disc disease than ACDF. Findings in the reference case are extrapolated based on the assumption that a CTDR prosthesis will survive for 20 years and result in better function than that obtained with ACDF." "Longer-term follow-up is necessary to confirm durability and function of CTDR prostheses to establish cost-effectiveness."			
Remarks				

Warren D, Andres T, Hoelscher C, Ricart Hoffiz P, Bendo J, Goldstein J. Cost utility analysis modeling at 2 year follow up for cervical disc arthroplasty versus anterior cervical discectomy and fusion: A single center contribution to the randomized controlled trial. International Journal of Spine Surgery, 2013.[27]					
Sponsor(s) of the study		Authors' affiliation is NYU Hospital for Joint Diseases. But no explicit mention of the funding source.			
Country, currency, price year		USA, US dollar (costing year not reported)			
Research question		What is the cost-effectiveness of cervical total disc replacement versus anterior cervical discectomy and fusion for 1-level degenerative disc disease?			
Analytic technique		Piggy-back economic evaluation (based on the patients from 1 centre enrolled in the ProDisc-C trial – Murray et al, 2009)			
Study design		Cost-utility analysis			
Perspective		Health care payer			
Time horizon		Costs: limited to the index hospitalisation period Outcomes: 2 years (as for the companion RCT)			
Discounting		Not reported			
Interventions compared		Cervical total disk replacement (CTDR) Anterior cervical discectomy and fusion (ACDF)			
Population		Patients from the ProDisc-C IDE study (one centre only) 28 patients aged 41 years on average with single-level cervical radiculopathy, without adjacent segment degeneration or prior fusion			
COST	**Items included**	Direct medical costs incurred during the index hospitalisation only. Outpatient health care resource used or long-term complications (reoperations) are not accounted for.			
	Measurement/valuation	Resourced consumption obtained from RCT observations. Valuations via Medicare reimbursement rates and Medicare physician fee schedule.			
	Data sources	Medicare fees			
OUTCOME	**Endpoints/health states**				
	Health states valuation	Piggy-back economic evaluation			
	Treatment effect/extrapolation	No extrapolation			
	Utility assessment		**CTDR, n=18 (SD)**		**ACDF, n=10 (SD)**
			From SF-36	***From NDI***	***From SF-36***	***From NDI***

	Baseline	0.51 (0.12)	0.50 (0.10)	0.47 (0.10)	0.49 (0.1)
	Year 1	0.68 (0.17)	0.65 (0.12)	0.72 (0.13)	0.61 (0.21)
	Year 2	0.68 (0.16)	0.64 (0.11)	0.71 (0.13)	0.70 (0.10)

	Data sources	Utilities: Neck Disability Index and SF-36 data collected during companion RCT at different time intervals (preoperative and 6, 12, 18 and 24 months post-treatment). NDI and SF-36 transformed into utilities via SF-6D (at 12 and 24 months only).
UNCERTAINTY	**Sensitivity analysis**	No
	Scenario analysis	No
	Generalisability	No
Assumptions		

RESULT	**Base-case**	Over 2 years (Own computations, see remark)	**CTDR, n=18 (SD)**	**ACDF, n=10 (SD)**	**Incremental**
		Costs	$13 171 (106)	$16 162 1337)	- $2991
		QALYs – SF-36	0.32 (0.26)	0.47 (0.30)	- 0.15
		QALYs – NDI	0.27 (0.2)	0.37 (0.23)	- 0.10
		ICER – SF-36			$19 940
		ICER – NDI			$29 910
	Sensitivity analysis	No			
	Scenario analysis	No			
Conclusions		“The ICER suggests that the non-significant added benefit via ACDF comes at a reasonable cost.” “Overall, based on our patients at a 2-year time point, we demonstrate that ACDF delivers similar outcomes at a greater relative cost, though the cost-utility (cost/QALY) values appear to be in favour of ACDF.”			
Remarks		Methodologically not sound study. - The research question of the study is to compare CTDR vs ACDF. However the ICER is computed the opposite way in the study: ACDF vs CTDR. For consistency within our review, ICER reported here were transformed to CTDR vs. ACDF. - Time horizon for costs and outcome data collection is not identical -> health resources consumed and costs should be collected for the entire time horizon. - Apparently one mistake in the computation of the NDI ICER -> our own ICER computation is reported - The costing year is not reported. Only the word “current year” is reported. - No discounting - Only costs from the index hospitalisation are accounted for		

	- No sensitivity analysis is performed, though incremental efficacy is non-significant In the south-west quadrant, lower costs are possible, but at the expense of lower benefits. Again, we can calculate an ICER, although this now refers to a cost saving per unit of effect lost, which is again measured as the slope of the line from the origin to the point.

4.3. Data extraction sheets for lumbar total disc replacement

Johnsen L, Hellum C, Storheim K, Nygaard O, Brox JI, Rossvoll I, Ro M, Andresen H, Lydersen S, Grundnes O, Pedersen M, Leivseth G, Olafsson G, Borgstrom F, Fritzell P. Cost effectiveness of total disc replacement versus multidisciplinary rehabilitation in patients with chronic low back pain: a Norwegian multicenter RCT. Spine, 2014.[28]	
Sponsor(s) of the study	Not industry sponsored. Jönköping län grant funds and the South Eastern Norway Regional Health Authority and EXTRA funds from the Norwegian Foundation for Health and Rehabilitation, through the Norwegian Back Pain Association funds were received in support of this work.
Country, currency, price year	Norway, 2012 Euros (converted based on 1 euro 2012 = 6.7 Norwegian krone 2006)
Research question	To evaluate the cost-effectiveness of total disc replacement (LTDR) versus multidisciplinary rehabilitation (MDR) in patients with chronic low back pain (CLBP).
Analytic technique	Cost-utility analysis
Study design	Piggy-back economic evaluation (RCT from Hellum et al., 2011[13] using ProDisc II)
Perspective	Societal (including direct medical, productivity and caregivers costs)
Time horizon	2 years (as for the companion RCT)
Discounting	No discounting applied. Justified by the short-term time horizon.
Interventions compared	Lumbar total disc replacement (LTDR) Multidisciplinary rehabilitation (MDR)
Population	Mean patient age: 41 years (both arms) Patients with chronic low back pain (>1 year) and with 1 or 2-level lumbar degenerative disc disease
COST – **Items included**	Index treatment, other hospital care, primary care, patients' private costs Costs due to loss of production both for the patient and their relatives
COST – **Measurement/valuation**	Medical and caregiver costs: resources used collected from the RCT, from diaries prospectively completed by the patients, and from a top-down approach (MDR). Productivity costs: Human capital approach.

	Data sources	RCT observations				
OUTCOME	**Endpoints/health states**	QALY (Piggy-back econ eval: post-surgical complication rate after LTDR in the RCT: 7.4%)				
OUTCOME	**Health states valuation**					
OUTCOME	**Treatment effect/extrapolation**	No extrapolation				
OUTCOME	**Utility assessment**	(SD=standard deviation)	**LTDR, n=86 (SD)**		**MDR, n=86 (SD)**	
			EQ-5D	***SF-6D***	***EQ-5D***	***SF-6D***
		Baseline	0.291 (0.297)	0.555 (0.086)	0.266 (0.296)	0.548 (0.081)
		Year 2 (visual inspection of Fig 1)	0.67	Not available	0.55	Not available
OUTCOME	**Data sources**	RCT observations Utilities: EQ-5D collected during companion RCT at different time intervals (baseline, 3, 6, 12 and 24 months post-treatment)				
UNCERTAINTY	**Sensitivity analysis**	Probabilistic				
UNCERTAINTY	**Scenario analysis**	Utility instrument (SF-6D collected during companion RCT) Per-protocol analysis (base-case is Intention-to-treat) Perspective (excluding caregivers costs)				
UNCERTAINTY	**Generalisability**	No				
Assumptions						
RESULT	**Base-case**	At 2 years follow-up	**LTDR (SD)**	**MDR (SD)**	**Incremental**	
		Costs	€87 622 (58 351)	€74 116 (58 237)	€13 505 (95% CI -€4440–€31 452)	
		QALYs (EQ-5D)	1.29 (0.53)	0.95 (0.52)	0.34 (95% CI 0.18–0.5)	
		ICER			€39 748 (95% CI €15 990–€65 645)	
		LTDR more clinically effective than MDR at 2 years (statistically significant). LTDR more costly than MDR at 2 years (not statistically significant).				
RESULT	**Sensitivity analysis**	Probability LTDR is cost-effective at Norwegian WTP threshold (kr 500 000 or €74 600): 90%				
RESULT	**Scenario analysis**	Utility instrument	At 2 years follow-up	**LTDR (SD)**	**MDR (SD)**	**Incremental**
			QALY (SF-6D)	1.33 (SD 0.21)	1.22 (SD 0.18)	0.11 (95% CI 0.05–0.17)

		ICER LTDR vs. MDR: €128 328 (95% CI €51 329–€219 907) per QALY Probability LTDR is cost-effective at Norwegian WTP threshold (kr500 000 or €74 600): 40%, thus LTDR no longer cost-effective
	Per-protocol analysis	LTDR not cost-effective
	Excluding caregivers costs	Probability LTDR is cost-effective increases
Conclusions	In this study, LTDR was cost-effective compared with MDR after 2 years when using EQ-5D for assessing QALYs gained and a WTP of €74 600 (kr500 000/QALY). However, it was not superior when the SF-6D was used, so the results should be interpreted with caution.	
Remarks	Scenario analysis including only direct medical costs was not performed	

Parkinson B, Goodall S, Thavaneswaran P. Cost effectiveness of lumbar artificial intervertebral disc replacement: driven by the choice of comparator. ANZ J Surg, 2013.[29] **Medical Services Advisory Committee. Review of interim funded service: Artificial intervertebral disc replacement lumbar. Canberra: Medical Services Advisory Committee (MSAC), 2011.[30]**	
Sponsor(s) of the study	CHERE and ASERNIP-S, project funded by the Australian Department of Health and Ageing. The project is part of the HTA process for the MSAC.
Country, currency, price year	Australia, 2011 Australian dollar
Research question	To conduct an economic evaluation of lumbar total disc replacement (LTDR) compared with lumbar fusion.
Analytic technique	Cost-utility analysis
Study design	Decision analytic model – Markov model (Cycle length: 1 month) Utilities evaluation: based on the RCT from Berg et al., 2009[31]
Perspective	Health Care Payers
Time horizon	2 years
Discounting	No discounting applied as “short-term horizon”
Interventions compared	Lumbar total disc replacement (LTDR) Posterolateral fusion (PLF) Posterior lumbar interbody fusion (PLIF)

		Note: comparisons with other types of fusion are performed (Anterior lumbar interbody fusion (ALIF), Combined fusion (COMB) which is a combination of PLF and PLIF, Circumferential fusion (CIRC)). However the final outcome reported for those techniques is not the EQ-5D such that ICERs for those techniques cannot be computed.
Population		Patients suffering from significant axial back pain and/or radicular (nerve root) pain, secondary to disc degeneration or prolapse, who have failed conservative treatment.
COST	**Items included**	Pre-surgery workup, initial surgery, post-surgery follow-up, re-operation costs
	Measurement/valuation	National claims database (more representative of resource use in clinical practice compared to RCTs).
	Data sources	Number of fusions and LTDR performed: analysis of Medicare Benefits Schedule (MBS) claims data 2005-2010. Resources used: initial surgery from MBS, consumables and pre- and post-surgery form expert opinion. Hospitalisation costs: AR-DRG.
OUTCOME	**Endpoints/health states**	Health states: successful surgery, failed surgery, re-operation (replacement to either AIDR or fusion), removal without replacement, supplementation (additional instrumentation without removal of the implant), revision (modifications of the implant without removal of the entire implant), other re-operation (not involving the implant, such as decompression). Endpoint: QALY
	Health states valuation	From the companion paper of Berg et al., 2009[31]
	Treatment effect/extrapolation	From the companion paper of Berg et al., 2009[31]
	Utility assessment	

	LTDR (SD), n=80	Fusion PLIF or PLF (SD), n=72
Baseline	0.42 (0.31)	0.36 (0.33)
Year 1	0.71 (0.28)	0.68 (0.27)
Year 2	0.67 (0.33)	0.69 (0.25)

	Meaning of the values reported in ( ) obtained from Fritzell et al., 2011
	Data sources	Systematic review of 4 RCT and meta-analyses for rates: CHARITE trial by Blumenthal., 2005,[32] ProDisc-L trial by Zigler., 2007,[16] CHARITE, ProDisc-L or Maverick trial by Berg et al., 2009[31] and FlexiCore trial by Sasso et al., 2008[33] Utilities: EQ-5D values reported in the RCT from Berg et al., 2009[31]
UNCERTAINTY	**Sensitivity analysis**	Deterministic one-way: QALYs gained with LTDR (varied over its 95% confidence interval), exclusion of the costs of reoperations, the proportion of fusion patients requiring BMP (varied from 0 to 60%), the length of stay in hospital (hospitalisation costs with LTDR was assumed to be equal to that with fusion).
	Scenario analysis	Different QALY computations (no baseline risk adjustment)
	Generalisability	No

Assumptions

Only one re-operation is considered, following which patients enter the 'successful surgery post re-operation' state.

Deaths from complications or other causes were not considered.

Re-operations at adjacent or multiple levels were not considered as these are infrequent and currently there is little evidence of differences in adjacent segment degeneration between LTDR and fusion.

RESULT

Base-case

Over 2 years	**LTDR**	**PLF**	**Incremental**
Costs	$23 117	$22 310	$807
QALY	1.32	1.33	- 0.01
ICER TRD versus PLF: PLF dominates			
Over 2 years	**LTDR**	**PLIF**	**Incremental**
Costs	$23 117	$27 757	- $4640
QALY	1.32	1.33	- 0.01
ICER LTDR versus PLF: $598 794 (QALYs difference appears thus to be -0.0077, rounded to -0.01)			

Utilities were adjusted for differences at baseline.

Sensitivity analysis

- Most sensitivity analyses generate similar results to the base-case results. Results were most sensitive to variations in the QALY assumptions.
- If upper CI for QALY gains with LTDR (in favour of LTDR):
  ICER LTDR vs. PLF: $1463
  ICER LTDR vs. PLIF: LTDR dominates
- If lower CI for QALY gains with LTDR (against LTDR):
  ICER LTDR vs. PLF: PLF dominates
  ICER LTDR vs. PLIF: $8181 (in south-west quadrant, i.e. LTDR less costly and less effective)

Scenario analysis

If QALYs are unadjusted for difference in baseline	**LTDR**	**PLF / PLIF**	**Incremental**
QALY	1.25	1.16	0.10
ICER LTDR versus PLF: $8443 ICER LTDR versus PLIF: LTDR dominates			

Conclusions

The incremental cost-effectiveness depends on the comparator, and further research is required before any firm conclusions can be drawn.

Remarks	In the south-west quadrant, lower costs are possible, but at the expense of lower benefits. Again, we can calculate an ICER, although this now refers to a cost saving per unit of effect lost, which is again measured as the slope of the line from the origin to the point. In this study, ICERs are also reported for other clinical outcomes. Although relevant to the patients, only the ICERs per QALY gained are retained here as this outcome summarises all aspects of the impact of an intervention. We further limit the review to this outcome (and LY gained if available), for reasons of comparability across the studies. Only point estimate results are presented. Uncertainty is not accounted for. Short-term time horizon, while longer-term costs are most likely to occur for both treatment arms.

Fritzell P, Berg S, Borgstrom F, Tullberg T, Tropp H. Cost effectiveness of disc prosthesis versus lumbar fusion in patients with chronic low back pain: randomized controlled trial with 2 year follow up. Eur Spine J, 2011.[34]		
Sponsor(s) of the study		Study sponsored by industry: DePuySpine, Syntheses, Medtronic. One co-author of the economic evaluation is the first author of the clinical results from the companion RCT.
Country, currency, price year		Sweden, 2006 Swedish Crown (SEK), in 2006 1 Euro = 9.26 SEK
Research question		What is the cost effectiveness of disc prosthesis versus lumbar fusion in patients with chronic low back pain?
Analytic technique		Cost-utility analysis
Study design		Piggy-backed economic evaluation based on the RCT from Berg et al., 2009[31]
Perspective		Societal and Health Care Payer
Time horizon		2 years
Discounting		No discounting (not clearly reported)
Interventions compared		Lumbar total disc replacement (LTDR, with Charité, Prodisc or Maverick) Posterior lumbar discectomy and fusion (= posterolateral fusion or posterior lumbar interbody fusion)
Population		Patients (aged 21-55) who had suffered at least 12 months from discogenic low back pain in one or two motion segments between L3 and S1 and in whom nonspecific conservative treatment had been tried and failed.
COST	**Items included**	Direct medical costs: preoperative radiographic examinations, index hospitalisation, complications and follow-up. Direct non-medical costs: travel, shopping, house cleaning (included in societal perspective only). Indirect costs: work absenteeism (included in societal perspective only).
	Measurement/valuation	Stockholm Spine Center costs and national drug lists.
	Data sources	Prospective data collection alongside the companion RCT (Berg et al., 2009[31]).

		Data collected at 1, 3, 6, 12, 18 and 24 months post index hospitalisation.
OUTCOME	**Endpoints/health states**	Endpoint: QALY
	Health states valuation	From the companion paper of Berg et al., 2009[31]
	Treatment effect/extrapolation	From the companion paper of Berg et al., 2009[31] Reoperation rates (at 2 year): 10% LTDR versus 36% Fusion Implant removal rate (at 2 year): 0% LTDR versus 28% Fusion
	Utility assessment	

	LTDR, n=80	**Fusion, n=72**
Baseline	0.43	0.38
Year 1	0.71	0.68
Year 2	0.68	0.69

The baseline values reported here are different from those reported in the companion paper (0.43 for LTDR and 0.38 for fusion here instead of 0.42 and 0.36 respectively in Berg et al., 2009), no explanation is provided.

The LTDR year 2 value reported here is different from the value reported in the companion paper (0.68 here instead of 0.67 in Berg et al., 2009), no explanation is provided.

OUTCOME	**Data sources**	Prospective data collection alongside the companion RCT (Berg et al., 2009[31]). Data collected at baseline and at 12 and 24 months post index hospitalisation.
UNCERTAINTY	**Sensitivity analysis**	Probabilistic sensitivity analysis for data uncertainty Univariate sensitivity analyses: exclusion of reoperation costs
	Scenario analysis	Discounting rate at 3% (not clear if applied to both costs and outcomes)
	Generalisability	Discussed
Assumptions		The authors did not compare the costs or the cost-effectiveness of each specific implants/procedures used separately as they did not consider it probable that any procedure would produce relevantly different results in a 2-year period.
RESULT	**Base-case**	

Over 2 years	**LTDR (SD)**	**Fusion (SD)**	**Incremental (95% CI)**
QALY	0.41	0.40	0.01 (non-significant)
Costs – Societal	SEK 599 560 (400 272)	SEK 685 919 (422 903)	SEK -86 359 (-214 332 to 45 605)
Costs – HCP	SEK 147 750 (73 408)	SEK 170 746 (58 290)	SEK -22 995 (-43 055 to -1202)
Mean ICER LTDR versus Fusion – Societal: LTDR dominant although no significant QoL improvement.			

	Net benefit approach with a SEK 500 000 (€54 000) WTP threshold – Societal = Threshold * Inc QALY – Inc Cost = SEK 91 359 (-73 643 to 249 114)

Costs in Euro	LTDR (SD)	Fusion (SD)	Incremental (95% CI)
Costs – Societal	€64 747 (43226)	€74 073 (45670)	€ -9326 (-23 146 to 4925)
Costs – HCP	€15 956 (7927)	€18 439 (6295)	€ -2483 (-4650 to -130)

Accumulated QALYs over two years were calculated using the area under the curve (AUC).

AUC using values reported in this article – own computations: LTDR 0.405, Fusion 0.405 -> no difference.

AUC using values reported in Berg et al., 2009: LTDR 0.420, Fusion 0.435 -> LTDR less effective.

Sensitivity analysis	If exclusion of reoperation costs: - Societal perspective: no change - HCP perspective: cost difference between groups no longer significant, incremental cost is SEK -7611 (-24 783 to 11 992) or € -822 (-2676 to 1295)
Scenario analysis	If discounting at 3%: No change.
Generalisability	"One surgeon (SB) performed the index operation in 80% of the patients, and it is possible that patient selection, although there were strict inclusion and exclusion criteria to balance this, and surgical skills play a role, for which reasons the results achieved in this study therefore may not be generally replicable elsewhere."
Conclusions	Societal costs showed no significant difference when compared with LTDR and instrumented lumbar fusion after 2 years. From a healthcare perspective, fusion was significantly more costly, mainly due to a high reoperation rate in this group. It was not possible in this study to determine whether LTDR or fusion was more cost-effective for society within the 2-year time frame, although LTDR was associated with less costs and a very small gain in quality of life. The point estimate of the ICER was located in the southeast quadrant of the cost-effectiveness plane indicating a possible advantage for LTDR, but the probabilistic analysis using bootstrapping showed widespread distribution of the ICERs in all four quadrants why it therefore not significantly favoured either procedure. The minimal gain of 0.01 EQ-5D units (on a one-point scale) after 2 years makes it practically impossible to conclude that LTDR was associated with a higher gain in QALYs compared with fusion, even though there was also a non-significant (societal) or significant (HCP) cost difference in favour of LTDR.
Remarks	Net benefit is defined as NB = k Q-C, where k is the WTP for a QALY, Q is the incremental QALYs, and C is the incremental cost. A positive NB suggests treatment is cost-effective (depending on uncertainty, here confidence intervals), while a negative NB suggests the opposite.

REFERENCES

1. Boselie TF, Willems PC, van Mameren H, de Bie R, Benzel EC, van Santbrink H. Arthroplasty versus fusion in single-level cervical degenerative disc disease. Cochrane Database of Systematic Reviews. 2012;9.
2. Ren C, Song Y, Xue Y, Yang X. Mid- to long-term outcomes after cervical disc arthroplasty compared with anterior discectomy and fusion: a systematic review and meta-analysis of randomized controlled trials. Eur Spine J. 2014;23(5):1115-23.
3. Verma K, Gandhi SD, Maltenfort M, Albert TJ, Hilibrand AS, Vaccaro AR, et al. Rate of adjacent segment disease in cervical disc arthroplasty versus single-level fusion: meta-analysis of prospective studies. Spine. 2013;38(26):2253-7.
4. Cheng L, Nie L, Zhang L, Hou Y. Fusion versus Bryan Cervical Disc in two-level cervical disc disease: a prospective, randomised study. International orthopaedics. 2009;33(5):1347-51.
5. Davis RJ, Kim KD, Hisey MS, Hoffman GA, Bae HW, Gaede SE, et al. Cervical total disc replacement with the Mobi-C cervical artificial disc compared with anterior discectomy and fusion for treatment of 2-level symptomatic degenerative disc disease: a prospective, randomized, controlled multicenter clinical trial: clinical article. Journal of neurosurgery. Spine. 2013;19(5):532-45.
6. Papanastassiou ID, Phillips FM, Van Meirhaeghe J, Berenson JR, Andersson GB, Chung G, et al. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. Eur Spine J. 2012;21(9):1826-43.
7. Vaccaro A, Beutler W, Peppelman W, Marzluff JM, Highsmith J, Mugglin A, et al. Clinical outcomes with selectively constrained SECURE-C cervical disc arthroplasty: Two-year results from a prospective, randomized, controlled, multicenter investigational device exemption study. Spine. 2013;38(26):2227-39.
8. Zhang X, Zhang X, Chen C, Zhang Y, Wang Z, Wang B, et al. Randomized, controlled, multicenter, clinical trial comparing BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion in China. Spine. 2012;37(6):433-8.

9. Luo J, Huang S, Gong M, Dai X, Gao M, Yu T, et al. Comparison of artificial cervical arthroplasty versus anterior cervical discectomy and fusion for one-level cervical degenerative disc disease: a meta-analysis of randomized controlled trials. Eur. J. Orthop. Surg. Traumatol. 2014.
10. Jacobs W, Van der Gaag NA, Tuschel A, de Kleuver M, Peul W, Verbout AJ, et al. Total disc replacement for chronic back pain in the presence of disc degeneration. Cochrane Database of Systematic Reviews. 2012;9.
11. Hellum C, Berg L, Gjertsen Ø, Johnsen LG, Neckelmann G, Storheim K, et al. Adjacent level degeneration and facet arthropathy after disc prosthesis surgery or rehabilitation in patients with chronic low back pain and degenerative disc: second report of a randomized study. Spine. 2012;37(25):2063-73.
12. Johnsen LG, Brinckmann P, Hellum C, Rossvoll I, Leivseth G. Segmental mobility, disc height and patient-reported outcomes after surgery for degenerative disc disease: a prospective randomised trial comparing disc replacement and multidisciplinary rehabilitation. The bone & joint journal. 2013;95-B(1):81-9.
13. Hellum C, Johnsen LG, Storheim K, Nygaard OP, Brox JI, Rossvoll I, et al. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. BMJ (Clinical research ed.). 2011;342:d2786.
14. Zigler JE, Delamarter RB. Five-year results of the prospective, randomized, multicenter, Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential arthrodesis for the treatment of single-level degenerative disc disease. Journal of neurosurgery. Spine. 2012;17(6):493-501.
15. Zigler JE, Glenn J, Delamarter RB. Five-year adjacent-level degenerative changes in patients with single-level disease treated using lumbar total disc replacement with ProDisc-L versus circumferential fusion. Journal of neurosurgery. Spine. 2012;17(6):504-11.
16. Zigler J, Delamarter R, Spivak JM, Linovitz RJ, Danielson GO, Haider TT, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine. 2007;32(11):1155-62; discussion 63.
17. Ament JD, Yang Z, Nunley P, Stone MB, Kim KD. Cost-effectiveness of cervical total disc replacement vs fusion for the treatment of 2-level symptomatic degenerative disc disease.[Erratum appears in JAMA Surg. 2014 Dec;149(12):1295]. JAMA Surg. 2014;149(12):1231-9.
18. Lewis DJ, Attiah MA, Malhotra NR, Burnett MG, Stein SC. Anterior surgical management of single-level cervical disc disease: a cost-effectiveness analysis. Spine. 2014;39(25):2084-92.
19. McAnany SJ, Overley S, Baird EO, Cho SK, Hecht AC, Zigler JE, et al. The 5-year cost-effectiveness of anterior cervical discectomy and fusion and cervical disc replacement: a Markov analysis. Spine. 2014;39(23):1924-33.
20. Zigler JE, Delamarter R, Murrey D, Spivak J, Janssen M. ProDisc-C and anterior cervical discectomy and fusion as surgical treatment for single-level cervical symptomatic degenerative disc disease: five-year results of a Food and Drug Administration study. Spine. 2013;38(3):203-9.
21. Qureshi SA, McAnany S, Goz V, Koehler SM, Hecht AC. Cost-effectiveness analysis: comparing single-level cervical disc replacement and single-level anterior cervical discectomy and fusion: clinical article. J Neurosurg Spine. 2013;19(5):546-54.
22. Burkus JK, Haid Jr RW, Traynelis VC, Mummaneni PV. Long-term clinical and radiographic outcomes of cervical disc replacement with the prestige disc: Results from a prospective randomized controlled clinical trial - Presented at the 2009 joint spine section meeting. Journal of Neurosurgery: Spine. 2010;13(3):308-18.

23. Coric D, Nunley PD, Guyer RD, Musante D, Carmody CN, Gordon CR, et al. Prospective, randomized, multicenter study of cervical arthroplasty: 269 patients from the Kineflex|C artificial disc investigational device exemption study with a minimum 2-year follow-up: clinical article. J Neurosurg Spine. 2011;15(4):348-58.
24. Heller JG, Sasso RC, Papadopoulos SM, Anderson PA, Fessler RG, Hacker RJ, et al. Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion: clinical and radiographic results of a randomized, controlled, clinical trial. Spine (Phila Pa 1976). 2009;34(2):101-7.
25. Murrey D, Janssen M, Delamarter R, Goldstein J, Zigler J, Tay B, et al. Results of the prospective, randomized, controlled multicenter Food and Drug Administration 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. Spine J. 2009;9(4):275-86.
26. McAfee PC, Reah C, Gilder K, Eisermann L, Cunningham B. A meta-analysis of comparative outcomes following cervical arthroplasty or anterior cervical fusion: results from 4 prospective multicenter randomized clinical trials and up to 1226 patients. Spine (Phila Pa 1976). 2012;37(11):943-52.
27. Warren D, Andres T, Hoelscher C, Ricart-Hoffiz P, Bendo J, Goldstein J. Cost-utility analysis modeling at 2-year follow-up for cervical disc arthroplasty versus anterior cervical discectomy and fusion: A single-center contribution to the randomized controlled trial. International Journal of Spine Surgery. 2013;7(1):e58-e66.
28. Johnsen LG, Hellum C, Storheim K, Nygaard OP, Brox JI, Rossvoll I, et al. Cost-effectiveness of total disc replacement versus multidisciplinary rehabilitation in patients with chronic low back pain: a Norwegian multicenter RCT. Spine. 2014;39(1):23-32.
29. Parkinson B, Goodall S, Thavaneswaran P. Cost-effectiveness of lumbar artificial intervertebral disc replacement: driven by the choice of comparator. ANZ J Surg. 2013;83(9):669-75.
30. Medical Services Advisory Committee. Review of interim funded service: Artificial intervertebral disc replacement - lumbar. Report. 2011. Canberra: Medical Services Advisory Committee (MSAC) PUB: Medical Services Advisory Committee (MSAC) Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1090.1/$File/1090.1_Final_Report.pdf
31. Berg S, Tullberg T, Branth B, Olerud C, Tropp H. Total disc replacement compared to lumbar fusion: a randomised controlled trial with 2-year follow-up. European spine journal. 2009;18(10):1512-9.
32. Blumenthal S, McAfee PC, Guyer RD, Hochschuler SH, Geisler FH, Holt RT, et al. A prospective, randomized, multicenter Food and Drug Administration Investigational Device Exemptions study of lumbar total disc replacement with the CHARITE(trademark) artificial disc versus lumbar fusion - Part I: Evaluation of clinical outcomes. Spine. 2005;30(14):1565-75.
33. Sasso RC, Foulk DM, Hahn M. Prospective, randomized trial of metal-on-metal artificial lumbar disc replacement: Initial results for treatment of discogenic pain. Spine. 2008;33(2):123-31.
34. Fritzell P, Berg S, Borgstrom F, Tullberg T, Tropp H. Cost effectiveness of disc prosthesis versus lumbar fusion in patients with chronic low back pain: randomized controlled trial with 2-year follow-up. Eur Spine J. 2011;20(7):1001-11.