Agenda for Spine Section Executive Committee Meeting
March 11, 2009
Phoenix,AZ

Members Present:

Guests:

The meeting was called to order by Dr. Resnick at

1. Secretary's report M. Groff
    a. Update of email list and contact info
    b. Review and approval of minutes
    c. Review EC grid
2. Treasurer's Report C. Wolfla
    a. Review and approve budget
3. Committee Reports
    a. Annual Meeting C. Kuntz/ P. Matz
    b. CPT J. Cheng
    c. Exhibits P. Mummanneni
    d. Future sites I. Kalfas/P Mummaneni
    e. World Spine E. Benzel
    f. Research and Awards P. Gerszten
    g. Education Mike Wang
    h. Guidelines M. Kaiser
    i. Outcomes Z. Ghogawala
    j. Peripheral nerve TF A. Maniker
    k. Publications L. Holly
    l. Public Relations M. Steinmetz
    m. Membership Marg. Wang
    n. Washington Committee R. Heary
    o. Fellowships P. Mummanini
    p. Web Site J. Chang
    q. CME E. Mendel
    r. Nominating Committee J. Alexander
    s. Rules and Regs T. Choudhri
    t. Newsletter M. Steinmetz/ J. Cheng
    u. ASTIM G. Trost
    v. NREF Z. Gokoslan/E. Woodard
    w. AANS PDP K. Foley/ P. Johnson
    x. Young Neurosurgeons comm. E. Potts
    y. FDA drugs and devices J. Alexander
    z. FDA Disabillity G. Trost
    aa. Inter-Society Liaison M. Rosner

4. New Business
    a) Meeting invitations to CNS and AANS Presidents
    b) Outcomes Registry
    c) Section Lectureships at AANS annual meeting - funding
    d) Inter-society liason (Ondra)
    e) Fellowship match coordination with NASS
    f) Stipend for award winners
    g) Officer nominations

5. Old Business
    a) Membership dues structure
    b) Spine Section Meeting Management
    c) Future sites – site survey
    d) History Project
    e) Endowment fund
    f) Job description for Business Administrator

There being no further business the meeting was adjourned at

Respectfully submitted, Michael W. Groff, Secretary.

Executive Committee

Officers and Committee Chairs

JOINT SECTION ON DISORDERS OF THE SPINE & PERIPHERAL NERVES

September 2008

Position	2004-05	2005-06	2006-07	2007-2008	2008-2009
Chair	G. Rodts	R. Heary	C. Branch	J. Alexander	D. Resnick
Chair Elect	R. Heary	C. Branch	J. Alexander	D. Resnick	C. Shaffrey
Immediate Past Chair	R. Haid	G. Rodts	R. Heary	C. Branch	J. Alexander
Secretary	C. Branch	D. Resnick	D. Resnick	D. Resnick	M. Groff
Treasurer	T. Ryken	T. Ryken	C. Wolfla	C. Wolfla	C. Wolfla
Members at Large	D. Kim R. Apfelbaum J. Alexander	J. Alexander D. Kim K. Foley	D. Kim K. Foley G. Trost	K. Foley G. Trost C. Shaffrey	G. Trost M. McLaughlin E. Zager
Ex-Officio Members	Z. Gokaslan	Z. Gokaslan	C. Shaffrey G. Rodts	R. Haid E. Woodard P. Johnson	J. Hurlbert J. Knightly
Annual Meeting Chair	C. Shaffrey	M. Groff	M. McLaughlin	J. Hurlbert	C. Kuntz
Scientific Program Chair	M. Groff	M. McLaughlin	J. Hurlbert	C. Kuntz	P. Matz
Exhibit Chair	M.McLaughlin	J. Knightly	J. Knightly	J. Knightly P. Mummaneni	P. Mummaneni
Future Sites	J. Alexander	J. Alexander	I. Kalfas	I. Kalfas	I. Kalfas P. Mummaneni
Education Committee Chair	J. Hurlbert	J. Hurlbert	C. Kuntz	M. Groff P. Matz	Mike Wang
CME Representative	T. Ryken	T. Ryken	E. Mendel	E. Mendel	E. Mendel
Newsletter	L. Khoo	J. York	M. Groff	M. Groff	M. Steinmetz K. Eichholz
Rules and Regulations Chair	D. DiRisio	D. DiRisio	T. Choudhri	T. Choudhri	T. Choudhri
Nominating Committee Chair	R. Haid	R. Rodts	R. Heary	C. Branch	J. Alexander
Research and Awards Committee Chair	J.Guest	C. Wolfla	P. Gerszten	P. Gerszten	P. Gerszten
Publications Committee Chair	C. Dickman	C. Dickman	M. Wang	M. Wang	L. Holly
Web Site Committee Chair	C. Wolfla	C. Wolfla	J. Cheng	J. Cheng	J. Cheng
Guidelines Committee Chair	D. Resnick	P. Matz	P. Matz	P. Matz M. Kaiser	M. Kaiser
Membership Committee	G. Trost	G. Trost	Z. Gokaslan	Z. Gokaslan Marg. Wang	Marg. Wang
Outcomes Committee Chair	P. Gerszten	M. Kaiser T. Choudhri	M. Kaiser	M. Kaiser Z. Ghogawala	Z. Ghogawala
CPT Committee	W. Mitchell	W. Mitchell R. Johnson	R. Johnson	J. Cheng	J. Cheng
Peripheral Nerve Task Force Chair	R. Midha	E. Zager	E. Zager	E. Zager	A. Maniker
Washington Committee	P. McCormick	R. Rodts	R. Heary	J. Alexander/R. Heary	R. Heary
FDA drugs and devices					J. Alexander

Section Rep.,P.A.C.	S. Ondra	S. Ondra	S. Ondra	Z. Gokaslan	Z. Gokaslan
Public Relations	C. Kuntz T.Choudhri	C. Kuntz T. Choudhri	T. Choudhri	M. Steinmetz M	. Steinmetz
Fellowships		J. Alexander	P. Mummaneni	P. Mummaneni	P. Mummaneni
NREF Advisory Board			J. Guest	J. Guest	Z. Gokaslan E. Woodard
AANS PDP Representative			M. Groff	M. Groff	P. Johnson K. Foley
Young Neurosurgeons Representative				H. Aryan	E. Potts D. Sciubba
AMA Impairment				G. Trost	G. Trost
ASTM				G. Trost	G. Trost
Inter- Society Liaison				S. Ondra M. Rosner	M. Rosner

Minutes for Spine Section Executive Committee Meeting
September , 2008
Orlando, FL

Members Present: Michael Groff, Paul Matz, Tanvir Chourdri, Michael Wang, Langston Holley, Joe Cheng, Peter Gerszten, San Sciubba, Ziya Gokaslan, Allen Maniker, Marjorie Wang, Chris Shaffrey, Dan Resnick, Praveen Mummaneni, Pat Johnson, Chris Wolfla, Ehud Mendel

Guests: Troy Tippett, Engelbreit, Orrico, Dave Addelson Presedent elect CNS

The meeting was called to order by Dr. Resnick at 8:12 AM

1. Secretary's report M. Groff
    a. Review and approval of minutes
    b. Update of email list and contact info
    c. Review EC grid
    d. Informational items
2. Treasurer's Report C. Wolfla
    a. Review and approve budget
    b. Review financials who are the money managers can we move money around, no. Total assets are growing. We depend on annual meeting for liquidity. Financially healthy in spite of market changes.
    c. History project needs to go on the books
    d. Industry support for fellowship. Troy Tippit we are re inventing the wheel NREF does this already. However, we have little control over what happens with NREF funds. We disburse $140K / year in fellowship funding. However, only $6K is funded by the section directly. Motion to accept the proposal by Dr. Wolfla found on p247 of the agenda with the addition that the funds are unrestricted fund for education and fellowship awards.
    e. Guest: Troy Tippit reports on recent meeting with NASS including Drs. Branch, Baker, Fajwackei. He feels that Neurosurgery and the spine community need to do a better job of communicating with one voice. NASS considering a Washington presence. CMS to define Never events to include post-op infection and DVT. He would like the section to encourage NASS to pursue a lobbying effort with a physical presence in Washington. MOC and outcomes should be coordinated with NASS.
    f. Guest: Dr. Addelson meeting svc working well. Guidelines leadership appreciated and recognized. Education and direction – continuing education at all levels.
3. Committee Reports
    a) Annual Meeting C. Kuntz/ P. Matz

Financials are in place. Meeting highlights course Steve Ondra on COE. Steve Phurroughs from CMS will likely be on the program. This is the 25th anniversary of the

section. Scientific program content will emphasis clinical trials, spine care in different health systems. Paul McCormick honored guest.

b) CPT J. Cheng

Costs are rising CTP is declining. SRS spine, Cervcial TDA. CMS should not look at data from younger (non-medicare age) pts. This argument does not work.
Trying to avoid bundling of adc and arthodesis. This should not have been reevaluated in 2010.
CMS looks at growth of code > 10% per year if so the reimbursement is cut
NCD BMP, arthoplasty,, multilevel fuson, IDET
BC/BS TEC assessments. Need more manpower to address these reports.
NASS has a library of responses to these non-coverage actions. WE should formalize a relationship with them. Formulate a steering committee.
Praveen will go to Washington State or interface with Jens Chapman
ACR appropriateness study limited imaging available via a consensus document. ACR has invited neurosurgery to sit on their committee. Marjorie and Langston, Tanvier nominated to that committee

Intraoperative sterotactice guidance
Facet injections
Wellpoint

BC/BS PQRI - like quality improvement project. Require participation in a registry, perhps the MOC registry. QIW Jack Knightly, Chris Wolfla,

c) Exhibits P. Mummanneni

Prospectus has been sent. Heary rates should be revisited for booth space.

d) Future sites I. Kalfas/P Mummaneni

Sites are being evaluated in light of our size and a membership survey.

e) World Spine E. Benzel

f) Research and Awards P. Gerszten

Dr. Gerszten's successor should be identified.

g) Education Mike Wang

See attached.

h) Guidelines M. Kaiser

Tumor section will co-fund guidelines with us. Thoracolumbar guidelines still organizational. Paul's guidelines have been approved and will go to JNS.

i) Outcomes Z. Ghogawala

See attached.

j) Peripheral nerve TF A. Maniker

Last Klein speaker sorted out. Will continue to invite international speakers. Would like to continue to have speaker at AANS meeting because that is where more peripheral nerve people are.

k) Publications L. Holly

Expedited review of Annual Meeting solicited paper has not been working.

l) Public Relations M. Steinmetz

Spine section strongly encourages a PR FTE in the Washington office

m) Membership Marg. Wang

Reaching out to ortho. Ad in Spine. Eblast with CSRS.

n) Washington Committee R. Heary

o) Fellowships P. Mummanini
CAST all applications are in
p) PAC representative Z. Gokoslan
This position will be retired.
q) Web Site J. Chang
We have new content. Flash card of the week. Annual meeting video dowloads of plenary session. We have eblast ability. Bloging Member data base is running.
r) CME E. Mendel

s) Nominating Committee J. Alexander
We need a treasurer, Presedent elect, member at large. Need 90 days before section meeting. Chris to help Report forthcoming.
t) Rules and Regs T. Choudhri (no report)
u) Newsletter M. Steinmetz/ C. Eicholz
v) ASTM G. Trost
w) NREF Z. Gokoslan/E. Woodard
they were not accepted.
x) AANS PDP K. Foley/ P. Johnson
y) Young Neurosurgeons comm. E. Potts (no report)
z) FDA drugs and devices J. Alexander
MD/Society/Industry relationships discussed with respect to managing any potential conflict.
aa)AMA Impairment G. Trost (no report)
bb) Inter-Society Liaison M. Rosner
SRS meeting to define liaison role. Possible guest presentations at our meeting. Joint pre-meeting symposium complex spine. Sept 2009 One month away from CNS. Shaffreee to formalize it.

4. New Business
a) Volunteer for WA state evidence report response
b) History project – need interviewers
c) Endowment fund
d) WA state evidence report response
e) CMS NCD fusion BMP, HAC s/p spine fusion
f) Questionable practice
5. Old Business
a) Review LFTF project
b) Review Video cost estimate
c) Contribution to Washington Committee $75K, unanimous
d) Response to HTA
e) Kline Lecture
f) Mission Statement
g) Job description for Business Administrator -

There being no further business the meeting was adjourned at 12:00PM

Respectfully submitted, Michael W. Groff, Secretary.

UBS

UBS Financial Services Inc.
1200 Harbor Boulevard
Weehawken, NJ 07086-6791

For Quarter Ending 12/31/08

ACCOUNT PROFILE

Financial Advisor:	BODOLAY, JOHN L 847-277-2129
Program:	PACE[SM] Multi Advisor Program
PACE Risk Profile Summary:	Moderate
Investment Time Horizon:	More than 10 years (several market cycles)
Negative Performance Comfort:	Up to three consecutive down quarters

Prepared for:

AMERICAN ASSOCIATION OF
NEUROLOGICAL SURGEONS
CNS SECTION ON DISORDERS OF
THE SPINE
5500 MEADOWBROOK INDSTRL CT
ROLLING MEADOWS, IL 60008-3800

026685 004203 54

Your Branch Office and Financial Advisor:

UBS Financial Services Inc.
BARRINGTON, IL
BODOLAY, JOHN L 847-277-2129
847-277-2100

GS-08240 -25-I- -D0-4-1601091902

Enclosed please find your PACE Portfolio Review for the most recent quarter. This report represents only your PACE investments and does not take into account other holdings at UBS. It is our goal to provide you with portfolio reporting that is comprehensive yet easy to understand. Please review this report carefully. Contact your Financial Advisor if your financial situation, investment objectives or investment restrictions have changed, or if you have any questions.

UBS Financial Services Inc. and some affiliates receive fees in connection with services delegated to them by the transfer agent to certain affiliated funds in PACE. In PACE, the amount of such fees may vary depending on the arrangement between the transfer agent and the affiliated funds. PACE mutual fund investments are sold by prospectus only. This Portfolio Review must be accompanied or preceded by a current prospectus for each mutual fund held in the account. The prospectus contains details about each mutual fund including risks, charges and expenses, and should be read carefully before you invest or send money. Available to you at no additional charge is a current PACE Disclosure Document which describes the PACE program and the PACE program fee. Please contact your Financial Advisor if you would like to receive a copy.

MA026685

INVESTMENT SUMMARY

December 31, 2008

Below you will find a brief commentary on the financial markets for the most recent quarter as well as a summary of your PACE portfolio's performance since its inception.

Financial Market Summary

Most major equity indices had losses in the fourth quarter, typically between -20% to -30%. Many investors retreated to the relative safety of U.S. Treasuries, and that sector provided among the best returns in the quarter. The U.S. economy was declared officially to be in recession, as the banking system and housing market remained weak, with individuals and institutions borrowing and spending less. The government's report on third quarter GDP was negative (-0.5%), echoing the most recent negative report, which was for 4Q07. Jobs were lost at an increasing rate in 2008, with almost half of the year's 2.6 million job loss occurring in the last three months of the year. The Fed lowered interest rates to almost zero during the quarter, in an attempt to loosen up lending and help stabilize financial markets. After the cut, the dollar began to give up some of its recent-month gains against the euro. Developed countries around the world were facing their own recessions, rate cuts and stimulus packages, while stocks in many emerging market economies were down more than 50% in 2008. Many commodities went from boom to bust in 2008, as the economy soured. Oil fell by more than $100 a barrel from July to December, taking pressure off gas prices and helping restrain inflation.

Investment Performance[1]

12/31/03 - 12/31/08	Return (%)	Std Dev[3]
PACE Portfolio	-0.39	10.81
Comparative Index[5]	1.16	9.00
Custom Index[5]	1.36	8.54
CPI[6]	2.48	1.97
TBills	3.10	0.43

	Dollar Value
Initial Investment as of 12/26/03	$600,325.44
Beginning Value for Performance 12/31/03	606,312.81
Net Contributions & Withdrawals[2] since 12/31/03	-39,694.27
Investment Results since 12/31/03	-31,142.17
Ending Value	$535,476.37

Comparative Index: 18.00% Russell 1000 Value, 15.00% Russell 1000 Growth, 16.50% Russell Midcap Growth, 10.50% MSCI EAFE Net, 39.50% Barclays Intermediate Aggrega, 0.50% TBills

Custom Index: 51.00% Wilshire 5000, 40.00% BC Aggregate, 9.00% MSCI EAFE Net

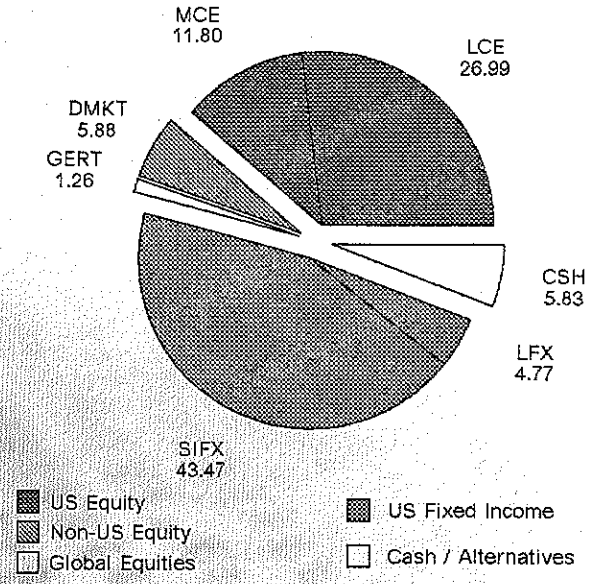
* Returns for periods greater than one year are annualized
Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

ASSET ALLOCATION

December 31, 2008

This section compares your current portfolio allocation to the Client Target Allocation for your portfolio. It also highlights information that you should consider as you evaluate your portfolio, such as whether your portfolio has moved out-of-balance relative to your Client Target Allocation. If you wish to rebalance or make other adjustments to your allocation, please call your Financial Advisor and he or she will make any necessary adjustments for you at no additional charge.

Current Holdings



Allocation Watch	
Portfolio Out-of-Balance vs. Client Target:[7]	Yes
Client Target Allocation Has Changed:[8]	Yes
Client Holdings Outside of your Risk parameters:[9]	No
Automatic Rebalancing Engaged:[10]	No
* Change in the Investor Profile:[11] Moderately Conservative to Moderate	Yes

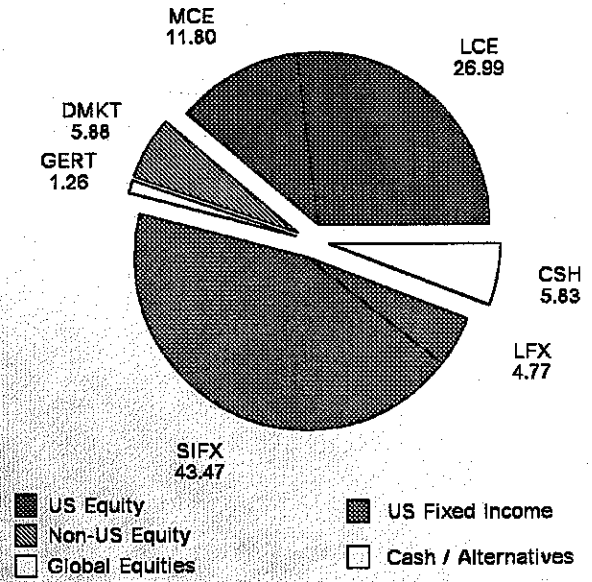
Allocation Comparison

Asset Class and Investment Style		Client Target (%)	Current Holdings (%)	Dollar Value
US Equity				
LCE	**Large Cap Equity**	**33.00**	**26.99**	**$144,518.04**
	Large Cap Value *(EHSTX, PZFVX)*	18.00	11.92	$63,842.23
	Large Cap Growth *(NFEAX, JDCAX)*	15.00	11.84	63,389.63
	Large Cap Core *(ITHAX)*	0.00	3.23	17,286.18
MCE	**Mid Cap Equity**	**16.50**	**11.80**	**$63,198.76**
	Mid Cap Growth *(LACAX, TEGAX)*	16.50	11.80	63,198.76
	SubTotal	49.50	38.79	$207,716.80
Non-US Equity				
DMKT	**Developed Markets**	**10.50**	**5.88**	**$31,463.59**
	Developed Markets *(NIVAX)*	10.50	5.88	31,463.59
	SubTotal	10.50	5.88	$31,463.59
Global Equities				
GERT	**Global Equity REIT**	**0.00**	**1.26**	**$6,727.10**
	Global Equity REIT *(IGLAX)*	0.00	1.26	6,727.10
	SubTotal	0.00	1.26	$6,727.10

Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

ASSET ALLOCATION
December 31, 2008

Current Holdings



Allocation Watch	
Portfolio Out-of-Balance vs. Client Target:[7]	Yes
Client Target Allocation Has Changed:[8]	Yes
Client Holdings Outside of your Risk parameters:[9]	No
Automatic Rebalancing Engaged:[10]	No
Change in the Investor Profile:[11] Moderately Conservative to Moderate	Yes

Allocation Comparison (continued)

Asset Class and Investment Style		Client Target (%)	Current Holdings (%)	Dollar Value
US Fixed Income				
SIFX	**Short/Intermediate Fixed**	**39.50**	**43.47**	**$232,813.24**
	Sh/Int Core *(PTTAX)*	39.50	43.47	232,813.24
LFX	**Long Fixed**	**0.00**	**4.77**	**$25,519.83**
	Long Governments *(PRTNX)*	0.00	4.77	25,519.83
	SubTotal	39.50	48.24	$258,333.07
Cash / Alternatives				
CSH	**Cash**	**0.50**	**5.83**	**$31,235.81**
	Cash	0.50	5.83	31,235.81
	SubTotal	0.50	5.83	$31,235.81
PACE Portfolio		100.00	100.00	$535,476.37

Please refer to the Individual Fund Performance page for more information.

Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

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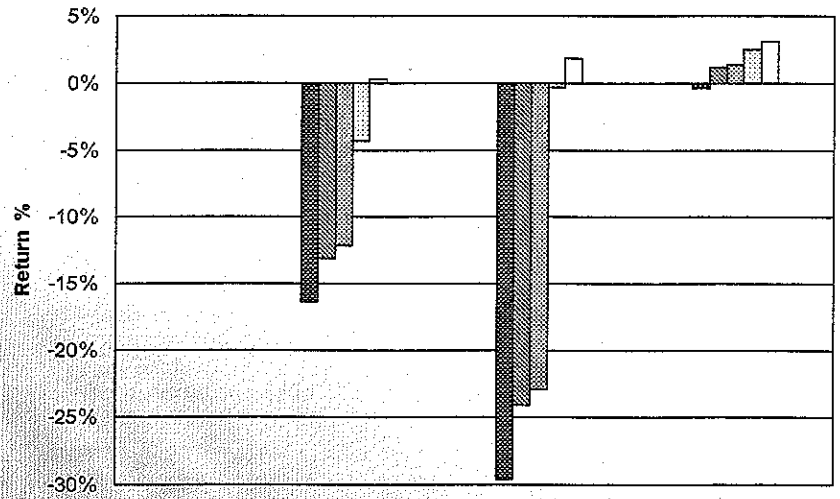
PERFORMANCE SUMMARY

December 31, 2008

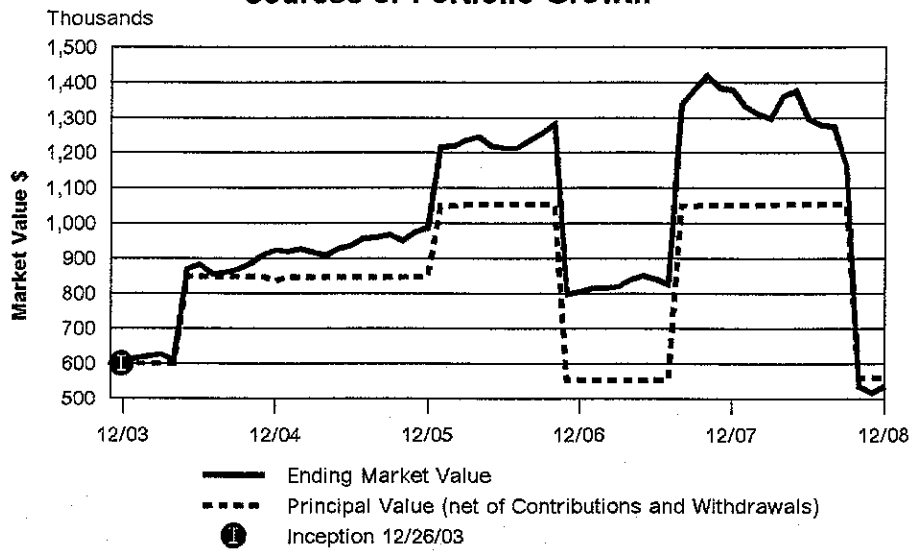
The graph on the left summarizes the performance of your portfolio for the current quarter, year to date, and the past full year. The graph on the right illustrates the sources of your portfolio's growth in dollar terms since inception. Although it is important to evaluate your portfolio's performance over multiple time periods, we believe the greatest emphasis should be placed on the longer period returns.

Performance Analysis



	Quarter 09/30/08 - 12/31/08	Year 12/31/07 - 12/31/08	Period* 12/31/03 - 12/31/08
PACE Portfolio[1]	-16.38	-29.57	-0.39
Comparative Index[5]	-13.04	-24.13	1.16
Custom Index[5]	-12.15	-22.90	1.36
CPI[6]	-4.33	-0.34	2.48
TBills	0.25	1.80	3.10

Sources of Portfolio Growth



	Quarter 09/30/08 - 12/31/08	Period* 12/31/03 - 12/31/08	Since Inception 12/26/03 - 12/31/08
Beginning Market Value	$1,160,069.61	$606,312.81	$600,325.44
Net Contributions[2]	-494,126.34	-39,694.27	-39,694.27
Investment Results	-130,466.90	-31,142.17	-25,154.80
Ending Market Value[1]	$535,476.37	$535,476.37	$535,476.37

* Returns for periods greater than one year are annualized
Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

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INDIVIDUAL FUND PERFORMANCE[1]

December 31, 2008

Below, the returns of the mutual funds currently held in your portfolio are compared to the appropriate comparative index for each fund's investment style. Performance figures for the most recent quarter and trailing one year are shown on the left. Performance as of the end of the month in which you invested in each fund is shown on the right.

Investment Style / Fund Name	Quarter 09/08-12/08		Year 12/07-12/08		Since Investment in Fund			Asset Class Index[2]	Client Target %	Current Holdings %
	Fund Return	Comp. Index %	Fund Return	Comp. Index %	Invest Date*	Fund Return	Comp. Index %			
Sh/Int Core								**BC Bond Intermediate Aggregate**	**39.50**	**43.47**
PIMCO TOTAL RETURN FUND CLASS A *(PTTAX)*	5.31	3.58	4.78	4.86	12/03	4.79	4.43		39.50	43.47
Large Cap Value								**Russell 1000 Value**	**16.00**	**11.92**
EATON VANCE LARGE CAP VALUE FUND CLASS A *(EHSTX)*	-29.61	-22.18	-41.34	-36.85	11/06	-18.06	-19.01		0.00	6.99
JOHN HANCOCK CLASSIC VALUE FUND CLASS A *(PZFVX)*	-32.20	-22.18	-51.54	-36.85	01/05	-14.32	-4.36		9.00	4.93
Large Cap Growth								**Russell 1000 Growth**	**15.00**	**11.84**
COLUMBIA MARSICO FOCUSED EQUITIES FUND CLASS A *(NFEAX)*	-26.57	-22.79	-43.94	-38.44	01/05	-6.05	-5.01		7.00	7.67
JANUS ADVISER FORTY FUND CLASS A *(JDCAX)*	-32.68	-22.79	NA	NA	02/08	-46.51	-31.88		8.00	4.17

* The investment dates and the funds shown may differ if you have changed the funds in which you are invested over time. The date shown reflects the end of the month in which the fund was either purchased or transferred into the program. An "NA" will appear if you have not been invested in a particular fund for the full month, quarter and/or the entire year displayed above.

Funds with a market value of less than $100.00 at the current quarter end date are not included on this page.

Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

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INDIVIDUAL FUND PERFORMANCE[1]

December 31, 2008

Investment Style Fund Name	Quarter 09/08-12/08 Fund Return	 Comp. Index %	Year 12/07-12/08 Fund Return	 Comp. Index %	Since Investment in Fund Invest. Date*	 Fund Return	 Comp. Index %	Asset Class Index[5]	Client Target %	Current Holdings %
Large Cap Core								**Russell 1000**	**0.00**	**3.23**
HARTFORD CAPITAL APPRECIATION FUND CL A *(ITHAX)*	-37.70	-22.48	-54.56	-37.60	11/06	-24.96	-17.58		0.00	3.23
Mid Cap Growth								**Russell Midcap Growth**	**16.50**	**11.80**
COLUMBIA ACORN FUND CLASS A *(LACAX)*	-32.31	-27.36	-44.55	-44.32	12/03	-1.28	-2.33		5.50	4.09
TOUCHSTONE MID CAP GROWTH FUND CLASS A *(TEGAX)*	-32.48	-27.36	-44.33	-44.32	12/03	-2.44	-2.33		11.00	7.71
Developed Markets								**MSCI EAFE Net**	**10.50**	**5.88**
ING INTERNATIONAL VALUE FUND CLASS A *(NIVAX)*	-25.44	-19.95	-43.73	-43.38	12/03	1.87	1.66		10.50	5.88
Global Equity REIT								**NAREIT Equity**	**0.00**	**1.26**
ING GLOBAL REAL ESTATE FUND CLASS A *(IGLAX)*	-35.20	-38.80	-45.46	-52.96	02/06	-15.10	-15.18		0.00	1.26
Long Governments								**Barclays Gov - L.T.**	**0.00**	**4.77**
PIMCO REAL RETURN FUND CLASS A *(PRTNX)*	-5.33	17.92	NA	NA	02/08	-12.29	19.29		0.00	4.77

* The investment dates and the funds shown may differ if you have changed the funds in which you are invested over time. The date shown reflects the end of the month in which the fund was either purchased or transferred into the program. An "NA" will appear if you have not been invested in a particular fund for the full month, quarter and/or the entire year displayed above.

Funds with a market value of less than $100.00 at the current quarter end date are not included on this page.

Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

MA026688

QUARTERLY PORTFOLIO RETURNS

December 31, 2008

This report summarizes your PACE portfolio's total market value, net contributions/withdrawals, and gross and net returns (after all fees) for each quarter since inception. Net return is calculated after the deduction of fund management fees and operating expenses and the PACE Program Fee. Your portfolio's net return is shown for each quarter and calendar year.

Quarter Ending	Year Ending	Market Value ($)	Net Contributions & Withdrawals ($)[2]	PACE Portfolio Gross Return Quarter (%)	PACE Portfolio Gross Return Year (%)	PACE Portfolio Net Return[1] Quarter (%)	PACE Portfolio Net Return[1] Year (%)
12/26/03 - 03/31/04		625,332.84	52.10	4.26		4.16	
06/30/04		883,418.27	249,517.77	0.62		0.52	
09/30/04		868,646.09	-1,091.69	-1.43		-1.55	
12/31/04		923,519.22	-11,385.00	7.75		7.65	
	2004				**11.42**		**10.95**
03/31/05		917,412.95	9,060.60	-1.54		-1.64	
06/30/05		937,544.37	-2.61	2.30		2.19	
09/30/05		966,921.34	944.21	3.13		3.03	
12/31/05		987,836.86	973.73	2.16		2.06	
	2005				**6.12**		**5.70**
03/31/06		1,234,995.23	205,401.96	3.88		3.79	
06/30/06		1,212,839.80	10.88	-1.69		-1.79	
09/30/06		1,256,915.33	0.00	3.71		3.63	
12/31/06		804,508.38	-500,899.01	4.78		4.71	
	2006				**10.99**		**10.60**
03/31/07		818,806.57	371.40	1.78		1.73	
06/30/07		843,129.58	612.42	2.97		2.89	
09/30/07		1,379,697.38	496,641.51	2.44		2.36	
12/31/07		1,377,427.60	1,254.39	-0.16		-0.25	
	2007				**7.18**		**6.87**
03/31/08		1,297,552.83	1,026.26	-5.80		-5.87	
06/30/08		1,296,404.76	966.77	-0.09		-0.16*	
09/30/08		1,160,069.61	976.38	-10.52		-10.58*	
12/31/08		535,476.37	-494,126.34	-16.38		-16.48*	
	2008				**-29.57**		**-29.82**
Rate of Return for 12/31/03 - 12/31/08 (Time-Weighted)				**-0.39**		**-0.75**	

* Your portfolio's performance has triggered your down quarter tolerance threshold indicated on the Account Profile section of the coverpage of this report.
Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

MA026688

QUARTERLY PORTFOLIO RETURNS

December 31, 2008

Quarter Ending	Year Ending	Market Value ($)	Net Contributions & Withdrawals ($)[2]	PACE Portfolio Gross Return		PACE Portfolio Net Return[1]	
				Quarter (%)	Year (%)	Quarter (%)	Year (%)
Rate of Return Since Inception for 12/26/03 - 12/31/08 (Time Weighted)				-0.19		-0.55	

*Returns for periods greater than one year are annualized.

* Your portfolio's performance has triggered your down quarter tolerance threshold indicated on the Account Profile section of the coverpage of this report.
Please refer to the Portfolio Review Reference Guide on the last page for all footnotes.

PORTFOLIO REVIEW REFERENCE GUIDE

In our attempt to provide you with the highest quality information available, we have compiled this report using data obtained from recognized statistical sources and authorities in the financial industry. While we believe this information to be reliable, we cannot make any representations regarding its accuracy or completeness.
Since markets change, one of the ongoing services you receive through PACE is the periodic update of your recommended allocation. We encourage you to review the current recommendation for your PACE portfolio and contact your Financial Advisor should you desire further clarification or wish to act on this information.
Please keep this guide on hand for footnote descriptions as you review your Quarterly Portfolio Review.

Performance

1. To be consistent with your portfolio's Comparative Indexes, performance measurement starts at the end of the month in which you invested and is presented on a time-weighted basis. Additionally, your portfolio's return since inception is shown on the page entitled "Quarterly Portfolio Returns." Except for since inception returns, all other portfolio and index calculations are as of month-end for all periods shown. Returns for periods greater than one year are annualized.

   Performance has been calculated after the deduction for fund management fees and operating expenses, but before the deduction of the net PACE Program Fee and reflects reinvestment of dividends. Additionally, performance net of all fees is shown on the page entitled "Quarterly Portfolio Returns." These fees will reduce your actual portfolio returns. Past performance does not guarantee future results.

   Time Weighted Rate of Return - A measure of the compound rate of growth in a portfolio. Because this method eliminates the distorting effects created by inflows of new money, it is used to compare the returns of investment managers. When calculating, the effect of varying cash inflows is eliminated by assuming a single investment at the beginning period and measuring the growth or loss of market value to the end of that period.

2. PACE Program fees paid from sources other than your PACE account are treated as a contribution. A PACE Program Fee rebate that is not reinvested is treated as a withdrawal. UBS Financial Services Inc. receives shareholder servicing and other service fees related to the purchase and sale of Non-affiliated Funds. Beginning September 2000, UBS Financial Services Inc. may share a portion of such fees with its Financial Advisors. The amount of such fees paid to UBS Financial Services Inc., and therefore Financial Advisors, may vary depending on the arrangement between UBS Financial Services Inc. and the Non-Affiliated Funds.

3. Standard Deviation is a statistical measure of the variability of investment returns. For example, for a portfolio with an average annual return of 10% and a standard deviation of 15%, two thirds of the time the portfolio's individual annual returns ranged from -5% to +25%. If an "NA" appears, one full year of data is required before standard deviation measures are statistically valid.

4. The entire period over which performance is measured, starting at the end of the first calendar month after initial investment.

Comparative, Custom, and Subclass Indexes

5. The Comparative Index for your overall PACE portfolio is a blended index comprised of indexes representing the subclasses corresponding to your Client Target Allocation. They are the following: Large Company Equity = Russell 1000 Stock Index; Small Company Equity = Russell 2500 Stock Index; Short/Intermediate Fixed = Barclays Intermediate Govt/Credit Bond Index; Long-Term Fixed = Barclays Govt/Credit Bond Index; Balanced = 60% SP500 Index/40% Barclays Govt/Credit Bond Index; Municipal Fixed = Barclays Muni Bond Index; International Equity = MSCI EAFE net Index; International Fixed = Citigroup World Govt Bond Index; and cash equivalents are represented by the 90-day Treasury Bills Index . If you change your Client Target Allocation, your Comparative Index will change in step with changes to your Client Target Allocation.

   The Custom Index is an optional index selected by you which may consist of a blend of up to twelve indexes and an option of adding or subtracting an annualized return value.

   Client Objective - Client Objective is an optional annualized return objective selected by you. In establishing this objective, you should make sure that it is consistent with your tolerance for risk.

   The indexes are not adjusted for any fees or expenses and reflect reinvestment of dividends and interest. For a description of indexes, please contact your Financial Advisor.

6. Consumer Price Index for Urban Wage Earners and Clerical Workers-U.S. City Average, All Items. Based on monthly data published by the U.S. Department of Labor. The CPI for the most recent month is estimated due to the delayed release of CPI data by the U.S. Government. Therefore, CPI for the most recent month is assumed to be equal to the CPI for the previous month. This may understate or overstate CPI performance for the current quarter, but generally has a negligible impact over longer periods of time.

   The CPI + % is an optional index that, if selected, will replace the standard CPI measure on your Review if elected. This index consists of the CPI return plus an absolute annualized return selected by you.

Asset Allocation

7. Portfolio Out-of-Balance vs. Client Target - A portfolio is considered to be out-of-balance if any one fund has deviated more than 5% points from its designated Client Target Allocation. If you have selected automatic rebalancing, your current portfolio allocation should always be within balance at quarter-end.

8. Client Target Allocation has Changed - This indicates your client target has changed during the previous quarter. If you change your Client Target Allocation, your Comparative Index will change in step with changes to your Client Target Allocation.

9. Client Holdings Outside of your Risk parameters - Indicates whether your Client Holdings Allocation is outside of your risk parameters specified by your responses to the Investor Profile Questionnaire. If the indication is "Yes", you will receive an Alert page as part of this review, please discuss your Client Holdings Allocation with your Financial Advisor.

10. Automatic Rebalancing Engaged - Indicates whether you have selected automatic rebalancing to a Client Target Allocation. For taxable accounts, rebalancing or other adjustments may create taxable events.

11. Change in the Investor Profile - Based on updated information you have provided we have updated your Investor Profile.

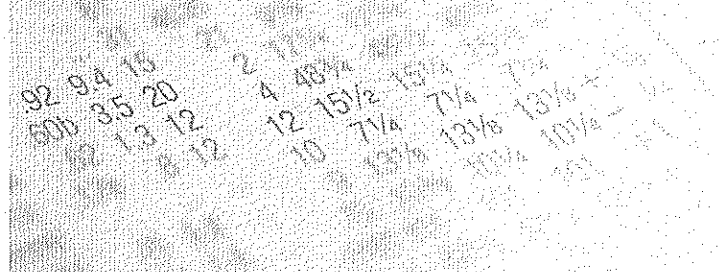
IMPORTANT NOTICE REGARDING YOUR TRADE CONFIRMATIONS FOR REBALANCING TRANSACTIONS

You currently receive individual trade confirmations from UBS for all mutual fund trading activity in your UBS Personalized Asset Consulting and Evaluation Program (PACE) account(s). This includes all trades that are executed in connection with any of the auto service features (auto rebalancing, auto purchase and auto redemption) in your PACE account, which you may elect when participating in the UBS PACE Program.

In response to feedback we received from our clients and Financial Advisors, we have enhanced the PACE program to reduce the number of trade confirmation mailings that you receive in connection with auto-services transactions and simplify your financial recordkeeping. After February 15, 2009, we will no longer be sending you individual trade confirmations for the mutual fund trading activity resulting from the auto service features of your PACE investments. Alternatively, as permitted under applicable regulations, auto service trades executed in your PACE investments will be reported to you in your monthly UBS account statement(s) for the month during which the auto service occurred. Please note that this feature is limited to auto-services transactions only. Trade confirmations for all other activity in your PACE investment will be mailed to you upon completion of each transaction.

Please be advised that if you have more than one PACE account, you will receive separate notifications for each account.

You are not required to elect this monthly delivery feature in order to participate in PACE. If you have any questions regarding this change, or if you wish to continue to receive individual trade confirmations in connection with the auto service features of your PACE investment, please contact your UBS Financial Advisor.



92 9.4 15
500 35 20
12 1.3 12
9 12
2
4 46¾
12 15½ 15¼
10 7¼ 7¼
13⅛ 13⅛
10¼ 10¼

American Association of Neurological Surgeons

5550 Meadowbrook Drive
Rolling Meadows, IL 60008

member services: 888.566.AANS
phone: 847.378.0500
fax: 847.378.0600
web: www.AANS.org
www.NeurosurgeryToday.org

January 20, 2009

Christopher Wolfla, MD
Department of Neurosurgery
9200 W. Wisconsin Ave.
Milwaukee, WI 53226

Dear Doctor Wolfla:

The enclosed financial statements for the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves are for the Quarter Ended December 31, 2008, and comparative information for the Quarter Ended December 31, 2007.

After your review of the financial statements, if you have any questions, please do not hesitate to contact me at 847-378-0561 or rpc@aans.org.

Sincerely,

Rebecca Calloway-Blyth
Section Accountant

Enclosures

Cc: Daniel K. Resnick, MD
James R. Bean, MD
P. David Adelson, MD
Paul C. McCormick, MD
Laurie Behncke
Ronald W. Engelbreit

AANS/CNS Section on Disorders of the Spine
Statement of Financial Position
As of December 31, 2008

	Current Year 12/31/08	Prior Year 12/31/07
ASSETS		
Checking & Short Term Investments	$459,902	$668,696
Accounts Receivable, net of Allowance for Uncollectible Accounts	40,735	32,500
Prepaid Expenses	12,398	12,398
Long-Term Investment Pool, at Market	1,555,441	1,382,522
TOTAL ASSETS	$2,068,476	$2,096,116
LIABILITIES AND NET ASSETS		
Liabilities		
Deferred Dues	54,100	56,200
Total Liabilities	**$54,100**	**$56,200**
Net Assets		
Unrestricted	$2,144,822	$1,922,406
Unrestricted - Fellowships	$85,000	
Net Revenue (Expense)	(215,446)	117,511
Total Net Assets	**$2,014,376**	**$2,039,916**
TOTAL LIABILITIES AND NET ASSETS	$2,068,476	$2,096,116

AANS/CNS Section on Disorders of the Spine
Statement of Activities
For the Six Months Ending December 31, 2008

	FY '07 Final	FY '08 Final	YTD FY '08	YTD FY '09	FY '09 Budget
REVENUES					
Membership Dues	55,975	53,925	27,375	24,150	49,500
Mailing List Sales	1,475	885	885	1,180	
Fellowship/Award Sponsorship	129,390	174,000	90,000	60,000	177,000
Miscellaneous Revenue	108				
Contributions for Operating Expenses	9,368	7,405	3,106	3,941	7,847
Annual Meeting Revenue	915,425	961,534			961,675
TOTAL REVENUES & SUPPORT	1,111,741	1,197,749	121,366	89,271	1,196,022
EXPENSES					
Audio Visual	1,011	1,888	1,561	1,491	2,000
Bank Fee	484	518	230	322	502
Contributions & Affiliations	75,000	75,000			75,000
Decorating	594			205	250
Food & Beverage	3,636	3,626	1,301	3,399	5,000
Fellowships	140,092	144,507			188,500
Grants	500,000				
Honoraria & Awards	300				
Marketing & Advertising					
Office & other Supplies	229	543	354	199	600
Photocopy	0	1		0	50
Postage & Distribution	1,214	1,058	545	698	1,500
Printing/Typesetting					
Speaker Expenses					
Telephone	2	11		451	50
Volunteer Travel	1,462	1,188	1,188	60	1,500
Website	3,192	5,521	3,021	2,013	15,500
Staff Coordination	9,461	7,405	3,106	3,941	7,977
Guidelines Development	15,948				33,600
Spine Section History Project				7,968	50,000
Annual Meeting Expense	583,402	616,907	40,000	40,000	632,465
TOTAL EXPENSES	1,336,028	858,173	51,307	60,747	1,014,494
Investment Earnings	154,713	(32,160)	47,451	(243,970)	84,838
NET REVENUE	(69,574)	307,416	117,511	(215,446)	266,366

AANS/CNS Section on Disorders of the Spine
Annual Meeting
For the Six Months Ending December 31, 2008

	FY '07 Final	FY '08 Final	YTD FY '08	YTD FY '09	FY '09 Budget
Revenues					
Misc Contribs: Unrestricted		302,000			285,000
Registration Fees	228,175	271,359			263,125
Exhibitor Fees	407,800	382,200			407,500
Exhibitor Sponsorship Revenue	274,500				
Special Event Revenues	4,950	5,975			6,050
Total Revenues	915,425	961,534			961,675
Expenses					
Scientific Program	199,851	208,701			255,998
Social Events/General	138,139	164,674			183,251
Exhibit Program	49,121	46,813			53,411
Advanced Registration	33,882	40,131			43,305
Annual Meeting Promotion	65,360	61,390			74,550
On-Site Coordination	12,757	15,081			17,600
Annual Meeting Planning Cmte		117			4,350
Staff Coordination	110				130
Miscellaneous Expenses	84,225	80,000	40,000	40,000	80,000
Total Expenses	583,445	616,907	40,000	40,000	712,595
Net Excess (Loss)	331,980	344,627	(40,000)	(40,000)	249,080

AANS/CNS SECTION ON DISORDERS OF THE SPINE

NOTES TO FINANCIAL STATEMENTS

December 31, 2008

General & Administrative

Telephone – Budget $50, Actual $451

The Telephone expenses from the CNS meeting were more than anticipated.

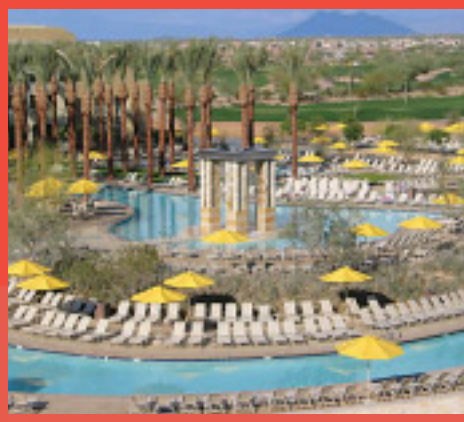
PRELIMINARY PROGRAM

25th Annual Meeting of the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves

Silver Anniversary

The Backbone of Spinal Surgery: Evidence, Appraisal, and Advocacy

March 11 – March 14, 2009
JW Marriott Desert Ridge Resort & Spa
Phoenix, Arizona



ADVANCE REGISTRATION DEADLINE MONDAY, FEBRUARY 9, 2009!

American Association of Neurological Surgeons

MEETING HIGHLIGHTS

- **Obtain up to 18.50 credits in Category 1 CME credit towards the AMA Physician's Recognition Award (PRA). An additional 8 credits are available through optional programming.**
- **Choice of eight Special Courses, including two special symposia for Nurses, Nurse Practitioners and Physician Assistants/ Physician Extenders.**
- **Three Luncheon Symposia.**
- **Scientific Sessions and Special Courses presented by leading experts from both neurosurgery and orthopedic spinal and peripheral nerve surgery subspecialties.**
- **Presentation of over 175 Oral Platform, Oral Poster and Digital Poster Abstracts.**
- **Honored Guest and Meritorious Award Recipient – Paul C. McCormick, MD.**

MEETING PURPOSE

The purpose of the 2009 AANS/CNS Section on Disorders of the Spine & Peripheral Nerves Annual Meeting is to provide continuing medical education to neurosurgeons, orthopedic surgeons, spine care specialists, fellows, residents, physician assistants/physician extenders and nurse clinicians involved in the practice of spine and peripheral nerve surgery. Education is provided in the form of didactic lectures, special courses demonstrating neurosurgical techniques, exhibits presenting the newest instruments and information, and digital posters providing the latest information regarding clinical laboratory advances in neurological surgery.

Welcome

The AANS/CNS Section on Disorders of the Spine and Peripheral Nerves invites you to the 2009 Annual Meeting, March 11-14, at the JW Marriott Desert Ridge Resort & Spa in Phoenix, Arizona. This year's twenty-fifth anniversary meeting promises to deliver maximum educational value as we explore the theme: *The Backbone of Spinal Surgery: Evidence, Appraisal, and Advocacy.*

Eight Special Courses are available, highlighting contemporary neurosurgical and non-surgical approaches, essential practice management solutions and critical patient advocacy issues. Two of these Special Courses are designed specifically for nurses, nurse practitioners and physician assistants/physician extenders.

Three Luncheon Symposia are available on Friday afternoon. These courses cover topics ranging from complication avoidance to treatment of spine tumors.

Our Scientific Sessions explore the past, present and future of spine and peripheral nerve surgery to help attendees examine what we've learned as a specialty and build on these experiences for the future.

This high-impact scientific program will be set against the backdrop of one of Phoenix's most luxurious resorts, the JW Marriott Desert Ridge Resort & Spa. This 316-acre resort features a unique architectural design incorporating the elements of nature – fire, water, earth and sky – and each guest room features a balcony or patio overlooking wildflower gardens, swimming pools, lakes and waterways plus golf course or mountain views.

The JW Marriott Desert Ridge Resort & Spa also offers endless opportunities for recreation and respite, from the bentgrass greens of the desert-style Palmer Signature golf course to an outdoor massage on one of Revive Spa's private balconies. And the whole family will love the more than four acres of shimmering waterways and miles of hiking and biking trails.

Join us for an outstanding educational program and exciting exhibition highlighting the latest neurosurgical products, and enjoy all the tranquility that awaits you at the JW Marriott Desert Ridge Resort & Spa. We look forward to seeing you in Phoenix!

Sincerely,

Daniel K. Resnick, MD
Chairperson

Charles Kuntz, IV, MD
Annual Meeting Chairperson

Paul G. Matz, MD
Scientific Program Chairperson

DATES TO REMEMBER

Who Should Attend
Educational sessions are geared toward neurosurgeons, orthopedic surgeons, spine care specialists, fellows, residents, physician assistants/ physician extenders, and nurse clinicians, and are applicable to the practice of spine and peripheral nerve surgery.

February 9, 2009
Advance Registration Discount and Housing Deadline.

February 9–16, 2009
Contact Laser Registration for any Housing questions.

February 16, 2009
Cancellation Deadline
$100 processing fee will be charged for written cancellations received by February 16. No refunds given after this date.

February 16, 2009
Course and symposia tickets will be refunded in full until this date. No refunds given after this date.

February 17, 2009
Any changes to hotel reservations must be made directly with hotel from this date forward.

PRELIMINARY PROGRAM AT-A-GLANCE

Wednesday, March 11, 2009

8:00 AM – 6:00 PM
Registration

8:00 AM - 6:00 PM
Speaker Ready Room

1:30 – 5:30 PM
Special Courses I – VI

6:00 – 8:00 PM
Opening Reception

Thursday, March 12, 2009

6:00 AM – 6:00 PM
Registration

6:00 AM – 6:00 PM
Speaker Ready Room

6:30 – 7:00 AM
Continental Breakfast

7:00 AM – 12:30 PM
Scientific Session I

9:00 AM – 7:00 PM
Exhibit Hall Open

9:30 – 10:15 AM
Beverage Break
***What's New* Sessions**

12:30 – 1:25 PM
Lunch
***What's New* Sessions**

1:25 – 5:15 PM
Scientific Session II

3:00 – 3:45 PM
Beverage Break
***What's New* Sessions**

5:15 – 6:45 PM
Reception in the Exhibit Hall

Friday, March 13, 2009

6:00 AM – 5:00 PM
Registration

6:00 AM – 5:00 PM
Speaker Ready Room

6:30 – 7:00 AM
Continental Breakfast

7:00 AM – 12:15 PM
Scientific Session III

9:00 AM – 12:00 Noon
Exhibit Hall Open

9:30 – 10:15 AM
Beverage Break
***What's New* Sessions**

12:15 – 12:30 PM
Annual Business Meeting

12:30 – 2:30 PM
Luncheon Symposium I – III

1:30 – 5:30 PM
Special Course VII & VIII

Saturday, March 14, 2009

6:00 AM – 12:30 PM
Registration

6:00 AM – 12:30 PM
Speaker Ready Room

6:30 – 7:00 AM
Continental Breakfast

7:00 – 8:20 AM/
10:25 AM – 12:30 PM
Scientific Session IV

8:20 – 9:40 AM
David Cahill Memorial Controversies Sessions

9:00 AM – 12:00 Noon
Exhibit Hall Open

9:40 – 10:25 AM
Beverage Break
***What's New* Sessions**

**Hours and schedule are subject to change.*

WEDNESDAY, MARCH 11, 2009 MEETING AGENDA

Please note: All courses and faculty are preliminary and subject to change. Seating is limited for all Special Courses and Lunch Symposia. Register Today!

Wednesday, March 11

1:30 – 5:30 PM
Special Course I - Coding Update and Review

Additional $200 for medical registrants. Includes lunch.

Directors: Robert R. Johnson, II, Joseph S. Cheng

Faculty: John J. Knightly, Peter D. Angevine, Karin R. Swartz, Justin Brown, R. Patrick Jacob

Course Description: This course will provide up-to-date information on current issues in spine coding. Coding scenarios will be reviewed for the correct coding of routine as well as complex spinal procedures.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Recognize the newest changes in CPT coding for spine.
- Review the methodology for correct spine coding.
- Identify specific difficult coding scenarios and bring clarity to the coding process.

1:30 – 5:30 PM
Special Course II - New Developments in Arthroplasty

Additional $200 for medical registrants. Includes lunch.

Directors: Regis W. Haid Jr., Praveen V. Mummaneni

Faculty: Vincent C. Traynelis, William R. Taylor, Stephen Papadopoulos, Kevin T. Foley, Rick Sasso, Richard G. Fessler

Course Description: The focus of this course is to review the indications and contraindications of Cervical and Lumbar Arthroplasty. The results of IDE studies, as well as longer term follow up will be discussed. Complications, revisions and reoperations will be examined. A comparison between arthroplasty and arthrodesis will be elucidated. Different devices, the tribology, and biomechanics will be reviewed.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Have an understanding of the indications and contraindications for arthroplasty.
- Discuss the associated complications and management strategies for them.
- Gain a better understanding of the biology and biomechanics of the devices.

1:30 – 5:30 PM
Special Course III - Biomechanics: Its Use in Surgical Decision Making

Additional $200 for medical registrants. Includes lunch.

Directors: Edward C. Benzel, Richard P. Schlenk, Marc Eichler

Faculty: Lars Gilbertson, PhD

Course Description: This course seeks to use biomechanics as a foundation for decision making in complex spinal surgery. The course will review the biomechanics in lumbar spinal disease and also review the biomechanics associated with implants.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the biomechanical foundations of clinical decision making.
- Understand the biomechanical theory associated with spinal implants including motion sparing devices.
- Understand the clinical application of biomechanical theory.

1:30 – 5:30 PM
Special Course IV - Pediatric Craniocervical

Additional $200 for medical registrants. Includes lunch.

Directors and Faculty: Douglas L. Brockmeyer, Francesco T. Mangano

Course Description: This course will serve as a symposium for those with an interest in pediatric craniocervical abnormalities and disease. It seeks to examine issues related to management of pediatric craniocervical disease including surgical and non-surgical treatment, complication management, and disease pathophysiology.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Discuss appropriate management of complex pediatric craniospinal disorders.
- Discuss appropriate research strategies to further the care of patients with craniospinal disorders.
- Understand the mechanism involved in the pathophysiology and progression of pediatric craniocervical disease.

1:30 – 5:30 PM
Special Course V - Surgical Management of the Aging Spine: Deformity, Stenosis, Listhesis, Disc

Additional $200 for medical registrants. Includes lunch.

Directors: Charles L. Branch, Jr., Gregory R. Trost

Faculty: Tyler R. Koski, Michael P. Steinmetz, Darryl J. Dirisio

Course Description: This course seeks to examine degenerative spinal disease from the perspective of aging. It will look at basic spinal pathology and determine what effects diseases of the aging play on surgical and non-surgical management of the spine.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Determine which diseases of the aging (e.g. osteoporosis) may profoundly affect treatment of degenerative spinal conditions.
- Determine how diseases of the aging shift treatment protocols for degenerative spinal diseases.
- Discuss modification that may be employed for the surgical management of the aging spine.

1:30 – 5:30 PM
Special Course VI - Evaluation and Management of the Patient with a Spinal Infection

Special Course for Nurses, Nurse Practitioners and Physician Assistants/Physician Extenders.

Additional $110 for medical registrants. Includes lunch.

Directors: R. John Hurlbert, Andrea L. Strayer, MSN, CNRN, ACNP, Erin Villard, RN, MN, ACNP

Faculty: Andrew N. Nemecek, Christopher Bono, Tina Lisman, PAC, Peg Black, NP, Joseph S. Cheng, Allan Levy

Course Description: This course will provide practical, current didactic information on spine infection with particular emphasis on prevention, risk factors, evaluation, surgical and non-surgical decision making and management as well as discussion on future trends. Interactive case presentations will illustrate treatment and care considerations. Expert advanced practice nurse, physician assistant, and neurosurgeon faculty will explore the challenges of caring for this complex patient population.

THURSDAY, MARCH 12, 2009 MEETING AGENDA

Wednesday, March 11 continued

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Discuss current trends, possible future scenarios, and current preventive evidence for surgical site infections.
- Describe clinical evaluation including use of laboratory and imaging studies.
- Analyze non-surgical and surgical decision making and management.

Physician attendees will not be awarded CME credit for this course. Nursing contact hours will be provided through AANN. The American Association of Neuroscience Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Physician Assistants/Physician Extenders will receive credit for attendance. Each physician assistant/physician extenders will need to contact his or her individual membership association and certification board to determine the requirements for accepting credits. All attendees will receive a confirmation of attendance.

6:00 – 8:00 PM
Opening Reception

Thursday, March 12

6:30 – 6:55 AM
Case Presentations
Moderators: Frank LaMarca, Ryan Jewell

6:55 – 7:00 AM
Introductory Remarks and Meeting Announcements
Daniel K. Resnick

7:00 – 8:55 AM
Scientific Session I - Past Evidence: Lessons Learned, Dealing with the Aging Spine

Moderators: Charles Kuntz, IV, Paul G. Matz, Philip Weinstein

Session Description: This Scientific Session will review the history of the Joint Section on its 25th Anniversary with attention to the reasons for development of a professional subspecialty society. It will also examine how aging affects the treatment of common spine and peripheral nerve maladies. Senior surgeons will give their perspectives on the treatment of spine and peripheral nerve disorders and the affects of aging.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the history and evolution of the spine section.
- Evaluate the current treatment of common cervical and lumbar degenerative spine disorders.
- Understand how aging affects treatment of spine disorders.
- Understand how aging affects treatment of peripheral nerve disorders.

7:00 AM
History of the Spine Section: 25 Years of Growth
Stewart B. Dunsker

7:20 AM
Cervical Disease: Treating Spondylotic Myelopathy
Mark N. Hadley

7:40 AM
Treatment of Spondylolisthesis in the Osteoporotic Spine
Vincent C. Traynelis

8:00 AM
Management of Geriatric Spinal Deformity
Christopher I. Shaffrey

8:20 AM
Lessons Learned in 30 Years of Peripheral Nerve Surgery and the Influence of Aging
John E. McGillicuddy

8:40 AM
Panel Discussion
Stewart B. Dunsker, Mark N. Hadley, Vincent C. Traynelis, Christopher I. Shaffrey, John E. McGillicuddy

8:55 AM
Presidential Address -
The Backbone of Spinal Surgery - Evidence, Appraisal, and Advocacy
Daniel K. Resnick

9:10 AM
Meritorious Award Winner
Paul C. McCormick

Meritorious Award Presentation
The Nature and Use of Evidence in Spinal Surgery

9:30 – 10:15 AM
Beverage Break with Exhibitors

What's New Session I
Moderator: Daniel M. Sciubba

10:15 AM – 12:30 PM
Oral Platform Presentations I
Moderators: Robert F. Heary, Ira M. Goldstein

12:30 – 1:25 PM
Lunch with Exhibitors

What's New Session II
Moderator: Eric A. Potts

1:25 – 1:30 PM
Meeting Announcements

1:30 – 3:00 PM
Scientific Session II - Present Appraisal: New Trials and Their Implications

Moderators: Andrew T. Dailey, Peter C. Gerszten

Session Description: This Scientific Session will critically review the clinical trials for the treatment of spinal metastasis that have been published over the last few years. The results of these trials will be summarized and critically evaluated in reference to implications for practice. This session will also look at new treatments and new technologies and examine ways for the practitioner to gauge the utility of a treatment.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Critically evaluate the methodology (including study design and analysis) used in the clinical trials discussed.
- Discuss the results of the clinical trials that were reviewed.
- Distill how those clinical trials will affect similar patients seen in the practitioner's clinical practice.
- Critically appraise new treatments and technologies with attention to the likelihood for success and failure.

1:30 PM
Review of Randomized Controlled Trials
Zoher Ghogawala

1:45 PM
Critical Appraisal of Results
Michael G. Kaiser

2:00 PM
Clinical and Economic Implications for Treatment
Neill M. Wright

2:15 PM
Appraising New Treatments: Nerve Transfer
Allen H. Maniker

2:30 PM
Successes and Pitfalls in Gauging New Technology
J. Patrick Johnson

2:45 PM
Panel Discussion
Zoher Ghogawala, Michael G. Kaiser, Neill M. Wright, Allen H. Maniker, J. Patrick Johnson

3:00 – 3:45 PM
Coffee Break with Exhibitors

What's New Session III
Moderator: James P. Burke

FRIDAY, MARCH 13, 2009 MEETING AGENDA

Thursday, March 12 continued

3:45 – 5:15 PM
Oral Poster Presentations I
Moderators: John J. Knightly, Langston Holly

Oral Poster Presentations II
Moderators: Marjorie C. Wang, Larry T. Khoo

5:15 – 6:45 PM
Reception with the Exhibitors

Friday, March 13

6:30 – 6:55 AM
Case Presentations
Moderators: Laurence D. Rhines, Patrick R. Pritchard

6:55 – 7:00 AM
Meeting Announcements

7:00 – 8:00 AM
Scientific Session III (Part 1) - Present Appraisal: The Tethered Cord from Child to Adult from Asymptomatic to Symptomatic

Moderators: Christopher E. Wolfla, Mark McLaughlin

Session Description: This Scientific Session will critically review the natural history of the tethered cord syndrome as it develops in children and moves to adulthood. The session will examine the treatment of tethered cord in asymptomatic and minimally symptomatic adults and reflect on the merits of different treatment options. New directions in the treatment of adult tethered cord syndrome will be discussed.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the natural history of tethered cord syndrome.
- Critically evaluate treatment options in adults with asymptomatic or minimally symptomatic tethered cord.
- Appraise new treatment alternatives for tethered cord syndrome in adults.

7:00 AM
Natural History of Tethered Cord Syndrome: From Pediatric to Adult
Francesco Mangano

7:15 AM
Treatment of Minimally or Asymptomatic Adult Tethered Cord Syndrome
Philip Weinstein

7:30 AM
New Horizons in Treating Adult Tethered Cord Syndrome
Charles Kuntz, IV

7:45 AM
Panel Discussion
Francesco Mangano, Philip Weinstein, Charles Kuntz, IV

8:00 – 9:00 AM
Scientific Session III (Part 2) - Future Advocacy: What the Future Holds for Neural Injury

Moderators: Eric L. Zager, James S. Harrop

Session Description: This Scientific Session will critically examine controversial issues in patients with acute spinal cord injury from the standpoint of surgical therapy and neurocritical care. The session will also explore the current status of functional restoration with regard to stem cells and robotics. Neural regeneration through the clinical use of pleuripotential progenitor (stem) cells will be critically evaluated The session will explore the feasibility of functional restoration through the used of robotics.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Critically evaluate options for decompression of the spine with respect to appropriate timing.
- Understand and evaluate the current status of critical care treatment of the patient with spinal cord injury.
- Discuss the future direction of neural stem cell therapy for spinal cord injury.
- Appraise the use of robotics for functional restoration of neural injury.

8:00 AM
Cervical Spinal Cord Contusion: Early Decompression or Not?
Michael P. Steinmetz

8:12 AM
Early ICU Therapy Controversies: Reduction, Steroids, Hypertensive Therapy, Hypothermia
Michael Y. Wang

8:24 AM
Neural Repair Through Stem Cells: Reality or Dream?
Michael G. Fehlings

8:36 AM
Functional Restoration Through Robotics
James M. Ecklund

8:48 AM
Panel Discussion
Michael P. Steinmetz, Michael Y. Wang, Michael G. Fehlings, James M. Ecklund

9:00 – 9:30 AM
Fellowship Awards and Updates
Joseph S. Cheng

9:30 – 10:15 AM
Coffee Break with Exhibitors

***What's New* Session IV**
Moderator: Maxwell Boakye

10:15 AM – 12:15 PM
Oral Platform Presentations II
Moderators: Eric J. Woodard, Gregory R. Trost

12:15 – 12:30 PM
Annual Business Meeting
Daniel K. Resnick

12:30 PM
Lunch on your own

12:30 – 2:30 PM
Luncheon Symposium I - Revision Spine Surgery and Management of Complications

Additional $200 for medical registrants. Includes lunch.

Directors: Timothy C. Ryken, Michael W. Groff

Faculty: Patrick W. Hitchon, Michael G. Fehlings, Robert F. Heary, Christopher J. Barry, Kurt M. Eichholz

Course Description: This course will provide state-of-the-art information on complication avoidance and revision spine surgery techniques. Senior surgeons will review their clinical experience and lessons learned. Extensive interactive case presentations will illustrate treatment and care considerations and explore complication avoidance algorithms and revision spine surgery techniques.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand management strategies and operative techniques for complication avoidance.
- Discuss the management of routine as well as complex postsurgical cervical, thoracic, and lumbosacral nonunion and deformity.
- Review treatment options for adjacent segment disease, recurrent disk herniation, and failed fusion and arthroplasty as well as failed fracture treatment.

FRIDAY, MARCH 13, 2009 MEETING AGENDA

Friday, March 13 continued

12:30 – 2:30 PM
Luncheon Symposium II – Neurosurgeon as CEO: Business Aspects of Spinal Surgery

Additional $200 for medical registrants. Includes lunch.

Directors: Iain H. Kalfas, Eric J. Woodard

Faculty: ?????????????????????????????????????? ??????????????????

Course Description: This course will examine neurosurgery from the philosophy of the small business operation. It will review the basics of revenue generation, transactions with third-party payors, marketing, and operations including management of expenses and personnel.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the mechanisms of revenue generation as well as critically examine future scenarios to change in revenue generation.
- Critically examine operations including costs, personnel, efficiency.
- Discuss different management paradigms for small business.

12:30 – 2:30 PM
Luncheon Symposium III – Treatment of Primary and Metastatic Spine Tumors

Additional $200 for medical registrants. Includes lunch.

Directors: Ehud Mendel, Ziya L. Gokaslan

Faculty: Mark H. Bilsky, Peter C. Gerszten, Laurence D. Rhines, Jean-Paul Wolinsky, Daryl R. Fourney, Meic H. Schmidt, Dean Chou

Course Description: This course will review the natural history and management of primary and metastatic spinal tumors. Radiographic imaging, intervention strategies, and treatment algorithms will be reviewed. Surgical treatment including approaches will be discussed. Extensive interactive case presentations will illustrate treatment and care considerations and explore the challenges of caring for this complex patient population.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the significance of tumor biology in considering management options.
- Review the indications and techniques for management of primary and metastatic spinal tumors.
- Discuss surgical approaches and techniques for tumor resection and spinal reconstruction.

1:30 – 5:30 PM
Special Course VII – Peripheral Nerve Exposures and Nerve Repair Techniques

Complimentary to Section Resident Members.

Additional $200 for medical registrants. Includes lunch.

Directors: Allen H. Maniker, Robert J. Spinner

Faculty: Robert L. Tiel, Eric L. Zager, Allan J. Belzberg, John E. McGillicuddy, Rajiv Midha

Course Description: This course will demonstrate the common exposures to peripheral nerves in the upper extremity and common techniques used for peripheral nerve reconstruction. It is targeted to practicing surgeons, senior residents and fellows.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the pertinent and practical surgical anatomy of the brachial plexus and peripheral nerves in the upper limb as related to common nerve injuries, nerve entrapments, and other nerve disorders.
- Review common techniques utilized in the reconstruction of peripheral nerves (direct repair, grafting, nerve transfers, and nerve conduits).
- This course will prepare residents for written board examinations and young neurosurgeons for oral board examinations.

1:30 – 5:30 PM
Special Course VIII – Evaluation and Management of the Spine Trauma Patient

Special Course for Nurses, Nurse Practitioners and Physician Assistants/Physician Extenders.

Additional $110 for medical registrants. Includes lunch.

Directors: Gregory R. Trost, Andrea L. Strayer, MSN, CNRN, ACNP, Erin Villard, RN, MN, ACNP

Faculty: Richard P. Schlenk, Fran Feldkamp, PA, Michael P. Steinmetz, Marc Eichler, Denise Brost, NP, Connie Marple, NP

Course Description: This course will provide practical, current didactic information on spine trauma with particular emphasis on update on medical therapies and intensive care after a complete injury; radiographic interpretation and classification schemes; facet fractures, ligamentous injury and upper cervical spine injuries. Interactive case presentations will illustrate treatment and care considerations. Expert advanced practice nurse, physician assistant, and neurosurgeon faculty will explore the challenges of caring for this complex patient population.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Analyze current evidence regarding steroid therapy and hypothermia after SCI.
- Describe radiographic evaluation following spinal trauma and classification of fracture types.
- Describe radiographic evidence as well as care considerations for facet fractures, ligamentous injury, and upper cervical spine including odontoid fractures.
- Discuss ICU care considerations following a complete SCI.

Physician attendees will not be awarded CME credit for this course. Nursing contact hours will be provided through AANN. The American Association of Neuroscience Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Physician Assistants/Physician Extenders will receive credit for attendance. Each physician assistant/physician extenders will need to contact his or her individual membership association and certification board to determine the requirements for accepting credits. All attendees will receive a confirmation of attendance.

SATURDAY, MARCH 14, 2009 MEETING AGENDA

Saturday, March 14

6:30 – 6:55 AM
Case Presentations
Moderators: Brian R. Subach, Kurt M. Eichholz

6:55 – 7:00 AM
Meeting Announcements

7:00 – 8:20 AM
Scientific Session IV - Future Advocacy: CMS, the Spine, and Spine Care in Alternative Health Systems

Moderators: Kevin T. Foley, William E. Krauss

Session Description: This Scientific Session will critically examine the cost of treating spine and peripheral nerve disease from the perspective of CMS. It will then explore the treatment of spine and peripheral nerve disease in other health care systems: the military, the Canadian healthcare system, the Japanese healthcare system.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Understand the role of CMS in critically evaluating the outcomes from spine and peripheral nerve disease.
- Critically evaluate whether CMS "Never events" are really completely preventable.
- Discuss the way spine and peripheral nerve disease is treated from the perspective of different healthcare systems.

7:00 AM
CMS and Spine: CMS and the Cost of Spinal Degenerative Disease
Steve Phurroughs, MD, MPA

7:20 AM
Are All CMS "Never" Events Really Never Events?
John O'Toole

7:32 AM
Lessons from the Military System
Michael K. Rosner

7:44 AM
Lessons from the Canadian System
R. John Hurlbert

7:56 AM
Lessons from the Japanese System
Junichi Mizuno

8:08 AM
Panel Discussion
Steve Phurroughs, MD, MPA, John O'Toole, Michael K. Rosner, R. John Hurlbert, Junichi Mizuno

8:20 – 9:40 AM
David Cahill Memorial Controversies Sessions
Spine and Peripheral Nerve

Moderators: Joseph T. Alexander, Robert E. Isaacs

Session Description: This Scientific Session will involve a debate presentation format. Controversial clinical management decisions will be presented. Experts will argue their perspectives with regard to the management scenarios for difficult spine and peripheral nerve cases.

Learning Objectives: *Upon completion of this course, participants should be able to:*

- Critically evaluate the utility of correcting geriatric spinal deformities.
- Understand treatment options for the patient with asymptomatic cervical stenosis who has spinal cord abnormalities on MRI.
- Critically evaluate the utility of fusion for recurrent lumbar disc herniation.
- Discuss with MIS leads to better outcomes.

8:20 AM
Geriatric Scoliosis: Surgical Correction or Nonoperative Management
Faculty: Christopher E. Wolfla vs. Tyler R. Koski

8:40 AM
Asymptomatic Cervical Stenosis with Signal Change: Treat or No Treat
Faculty: Regis W. Haid Jr. vs. Michael W. Groff

9:00 AM
Recurrent Disc: Fuse or No Fusion
Faculty: Volker K. Sonntag vs. Charles L. Branch, Jr.

9:20 AM
MIS Outcomes: Better or Not
Faculty: Edward C. Benzel vs. Richard G. Fessler

9:40 – 10:25 AM
Coffee Break with Exhibitors

***"What's New"* Session V**
Moderator: Tanvir Choudhri

10:25 – 11:00 AM
Mayfield Awards/Presentations
Moderator: Praveen Mummaneni

11:00 AM – 12:30 PM
Oral Poster Presentations III
Moderators: Nicholas Theodore, Patrick R. Pritchard

Oral Poster Presentations IV
Moderators: Peter D. Angevine, John C. Liu

12:30 PM
Meeting Adjourns

CME CREDIT

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Congress of Neurological Surgeons and the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves. The Accreditation Council for Continuing Medical Education (ACCME) accredits the CNS to sponsor continuing medical education for physicians.

US Physicians

The CNS designates this educational activity for a maximum of 26.50 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity. The same number of Category 1 Credits awarded will be applied toward the Continuing Education Award in Neurosurgery.

**A maximum of 18.50 AMA PRA Category 1 Credits™ may be earned for scientific sessions only.*

Physician Assistant/ Physician Extender CME Credit

Physician Assistant/Physician Extenders will receive credits for attendance at the general Scientific Program and for any optional events attended. Each physician assistant/ physician extender should contact his or her individual membership association and certification board to determine the requirements for accepting credits. All attendees will receive a Confirmation of Attendance.

Additional CME Credits can be earned by attending the following:

Special Courses
Attendees will receive a maximum of four (4) *AMA PRA Category 1 Credits™* for each eligible half-day Special Course. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Luncheon Symposium
Attendees will receive a maximum of two (2) *AMA PRA Category 1 Credits™* for each eligible Luncheon Symposium. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Posters
Physicians may claim *AMA PRA Category 2 Credit™* directly from the AMA for preparing a poster presentation, which also includes the published abstracts. Physicians may claim them on their AMA PRA certificate application or apply directly to the AMA for an *AMA PRA Category 2 Credit™* certificate.

Physicians may claim *AMA PRA Category 2 Credit™* for viewing scientific posters.

Physicians should self-claim credit on their AMA PRA certificate application form.

SOCIAL EVENTS AND GENERAL INFORMATION

Opening Reception

Wednesday, March 11
6:00 – 8:00 PM

Take in spectacular views of the mountains and watch the sunset while enjoying a wonderful array of food and refreshments as you network with old friends and new colleagues at the Opening Reception. The reception will be held at the JW Marriott Desert Ridge Resort & Spa. Each medical attendee and spouse/guest registered for the meeting will receive one complimentary ticket. Resort casual attire is recommended for this event.

Reception with the Exhibitors

Thursday, March 12
5:15 – 6:45 PM

Join us for this special event in the exhibit hall! Attendees will have the opportunity to interact with exhibiting companies while enjoying pre-dinner cocktails and hors d'oeuvres with colleagues. Each medical attendee and spouse/guest* registered for the meeting will receive one complimentary ticket. Business casual attire is recommended for this event.

**Please note: Due to liability and security issues, children under 18 years of age are not permitted on the exhibit floor at any time.*

Golf

Don't miss this opportunity to play one of Arizona's top-rated golf courses! The Wildfire Golf Club at the JW Marriott Desert Ridge Resort & Spa features two unique courses sure to challenge golfers of all skill levels.

The Palmer Signature Course is a desert-style, par 72 course of tournament length, 7,145 yards, with generous fairways and large, bentgrass greens. It has four to six tee boxes on every hole,

challenging all levels of golfing skill. The 415-yard, par 4, 6th is Palmer's signature hole, with the beautiful Camelback Mountain as the backdrop.

The Faldo Championship Course is a par 71 course offering a slight variation from the typical Sonoran Desert-theme courses. Nick Faldo designed this course to be different from other Arizona layouts, to have rhythm and flow and with more bark than bite. The surrounding mountains, century-old saguaro cacti and 106 sand bunkers provide a spectacular setting and are reminiscent of the Australian sandbelt courses.

Golf Registration: Golf participants can sign up individually or as a foursome by calling (888) 705-7775. The $199 per person fee includes green fees and golf cart (equipped with the latest GPS Technology). Club rental is available on a first-come, first-served basis at $60 per set plus tax and includes two sleeves of golf balls. Shoe rental is also available at $20 per pair plus tax. Reservations may be made up to 30 days in advance.

Area Attractions and Tour Information

Phoenix offers a host of opportunities for adventure and relaxation. Enjoy a romantic hot air balloon ride for two, or a desert jeep tour and horseback riding for the whole family. To obtain more information or make reservations for Phoenix area attractions and tours, please visit the city's official website at www.PhoenixCVB.org or contact any member of the JW Marriott Desert Ridge Resort & Spa Concierge Team at (480) 293-5000. It is best to make arrangements in advance. The concierge team will be available to assist you on site as well.

Children's Program and Child Care Services

Kokopelli Kids is a full-service children's recreation program for JW Marriott Desert Ridge Resort & Spa guests ages 4-12. Each day is designed to provide maximum enjoyment for all participants. Counselors plan each day according to the ages and interest of the children enrolled. Activities include computer learning, arts and crafts, sports, swimming, Native American folklore, musical games and much more. Full and half day programs are available and each day offers a new theme, from sports to space to the wild west. Contact the resort concierge at (480) 293-5000 for additional information.

The AANS/CNS Section on Disorders of the Spine and Peripheral Nerves is not affiliated with nor is it endorsing the services of the company listed below; however, the following company is identified by the resort for in-room childcare:
All About Nannies, Inc.
(480) 948-3901
allaboutnanniesinc.com
For more details, contact the resort concierge at (480) 293-5000.

Evaluations

The Annual Meeting evaluation process is a key component in providing cutting-edge programming at the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting. Medical registrant feedback on the quality and diversity of the program helps to determine future annual meeting programming. Your voice is important and your opinions are valued!

Speaker Ready Room

The Speaker Ready Room will be available Wednesday, March 11 through Saturday, March 14. All speakers and abstract presenters should visit the Speaker Ready Room prior to their presentations.

No Smoking Policy

Smoking is not permitted at any official AANS/CNS Section on Disorders of the Spine and Peripheral Nerve Annual Meeting events.

LIST OF EXHIBITORS

Aesculap Implant Systems
Allen Medical Systems
Amedica Corp.
American Association of Neurological Surgeons
Anspach Companies
Anulex Technologies, Inc.
Apatech, Inc.
ArthroCare Corporation
Biomet Spine
Cervitech, Inc.
Congress of Neurological Surgeons
DePuy Spine, a Johnson & Johnson Company
DFine, Inc.
Elliquence, LLC
Globus Medical
Impulse Monitoring, Inc.
Integra
K2M, Inc.
LANX Inc.
Medtronic
Nutech Medical, Inc.
NuVasive
Orthofix, Inc.
Orthovita, Inc.
Ossur Americas
Osteotech, Inc.
PainDx, Inc. (Formerly NDA, Inc.)
Paradigm BioDevices Inc.
Paradigm Spine
Physician's Choice Consulting
PhysIOM
Pioneer Surgical Technology
Priority Consult, LLC
Regent Surgical Health
RSB Spine
Salient Surgical Technologies, Inc.
SeaSpine, Inc.
Signus Medical, LLC
Spinal Elements
Spine Surgical Innovation
Spine Wave
SpineFrontier, Inc.
Synthes Spine
TeDan Surgical Innovations
Trans1, Inc.

Preliminary as of 10/24/2008

EXHIBIT PRODUCTS & SERVICES

Don't miss the Exhibit Hall at the 2009 Annual Meeting of the AANS/CNS Section of Disorders of the Spine and Peripheral Nerves. Exhibitors value this time to learn from you, establish the individual needs of your practice, and share trends in their specialties. It's also a great opportunity for you to learn more about the latest technological advances in spinal neurosurgery.

Your preferred exhibitors encourage you to stop by their booths for one-on-one discussions, hands-on product demonstrations or to catch a glimpse of the many exciting new products and services available for show at this year's Annual Meeting.

Exhibit Hall Features

The Exhibit Hall, located in the Grand Canyon Ballroom Salons 1-8, will feature:

- More than 50 exhibiting companies displaying state-of-the-art equipment, products and services.
- **Lunch in the Exhibit Hall*:** Plan to spend your Thursday lunch break mingling with exhibitors between *What's New* presentations.
- **Cocktail Reception:** Join us Thursday evening for another great social networking opportunity! Take this time to browse the aisles of the Exhibit Hall and visit your favorite companies or perhaps encounter some fresh faces on the exhibit floor, all while enjoying cocktails and hors d'oeuvres.
- **E-mail Café:** Stay in touch with home and the office through this complimentary attendee service.
- **Digital Posters:** This state-of-the-art format lets attendees browse abstracts enhanced by photos and video. The digital format also makes it easy to search for abstracts by author or topic.
- ***What's New* Sessions:** Join the crowd during daily breaks and Thursday lunch as speakers share the latest in cutting-edge research and technology.

Exhibit Hours

Thursday, March 12
9:00 AM – 7:00 PM

Friday, March 13
9:00 AM – 12:00 Noon

Saturday, March 14
9:00 AM – 12:00 Noon

Beverage Break and *What's New* Session Hours

Thursday, March 12
9:30 – 10:15 AM
12:35 – 1:25 PM*
3:00 – 3:45 PM

Friday, March 13
9:30 – 10:15 AM

Saturday, March 14
9:40 – 10:25 AM

**Lunch in the Exhibit Hall is complimentary to all medical attendees and guests ages 18 and older.*

SPECIAL THANKS TO OUR SPONSORS!

Ambassadors:

Neurosurgical Education Ambassador
Biomet Spine

Power of Networking Ambassador
Stryker

Partners:

Neurosurgical Leadership Partner
Medtronic

Resident Education Partner
DePuy Spine, a Johnson & Johnson Company

Benefactor:
Synthes Spine

Supporters:
Anulex Technologies, Inc.
ArthroCare
Integra
NuVasive
TranS1

As of October 24, 2008

REGISTRATION & HOUSING INFORMATION

Registration and Housing Deadline: February 9, 2009

Register today using one of these three methods:

Online:

www.spinesection.org

- Internet booking is available 24 hours a day, seven days a week.
- Credit card only.
- Receive ***immediate*** Registration & Housing Confirmation.

Fax:

US and Canada (866) 805-5721
International (514) 228-3162

- Credit card only.
- Allow ***seven business days*** for a Registration & Housing Confirmation.
- Type or print all information on the registration/housing form in black ink.
- AANS/CNS/Laser Registration is not responsible for faxes not received due to mechanical failure or circumstances beyond our control.

Mail:

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves
Annual Meeting
c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967

- Credit card or check only (no wire transfers).
- Allow seven business days for a Registration Confirmation.
- Checks must be drawn on a US bank in US dollars.
- Checks will be processed electronically. If you do not want your check processed electronically, please choose a different payment method. Checks for registration and hotel reservation must be made separately.

Make check payable to:
AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting.

Registration Cancellation/Refunds

Requests for registration and housing cancellations must be made in writing and sent to:

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves
Annual Meeting
c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967

Cancellation requests received by 5:00 PM EST on or before Monday, February 16, will receive a full refund less a $100 processing fee. There will be no refunds for cancellation requests received after this date. (No refunds will be given for no-shows.)

Course and symposia tickets will be refunded in full until 5:00 PM EST on Monday, February 16. No refunds will be processed after this date.

Registration Information

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting registrations will not be processed without a valid credit card or check. Space in Special Courses and Luncheon Symposiums will not be reserved without payment.

Speaker Registration

Complimentary registration will not be provided for one-day speakers. All speakers must register at the applicable registration rate.

Spouse/Guest Registration

The Guest registration fee provides each individual with a ticket to the Opening Reception on Wednesday evening and the Cocktail Reception on Thursday evening. The fee also allows access to the Exhibit Hall and daily continental breakfasts with the medical registrants served from 6:30 – 7:45 AM. Advance registration is encouraged.

Child Registration

Although there is no registration fee, children under 18 years of age should register for the Annual Meeting to receive a badge. Registered children receive a ticket to the Opening Reception on Wednesday evening and a daily continental breakfast served from 6:30 - 7:45 AM. Children under the age of 18 are not allowed on the exhibit floor.

Americans with Disabilities Act/Special Needs and Requests

The AANS/CNS Section on Disorders of the Spine and Peripheral Nerves wishes to take the necessary steps to ensure that no individual with a disability is excluded, denied services, segregated or otherwise treated differently than other individuals because of the absence of auxiliary aids and services.

If you require any of the auxiliary aids or services identified in the Americans with Disabilities Act in order to attend any AANS/CNS Section on Disorders of the Spine and Peripheral Nerves programs, or have any special needs requests, such as food allergies, please contact Laser Registration at DSPN@Laser-Registration.com. Please provide any requests to Laser Registration **at least 30 days prior** to the Annual Meeting to guarantee accommodation.

Scooter and wheelchair rentals are available by contacting Scootaround Inc. at their toll-free hotline: (888) 441-7575. You can also submit a rental inquiry on the web at www.scootaround.com.

Questions

If you have questions, contact:
Laser Registration
By Phone: (866) 298-0802
US and Canada
By Phone: (514) 228-3077 – International
E-mail: DSPN@Laser-Registration.com

IMPORTANT DATES TO REMEMBER

February 9, 2009
Advance Registration Discount and Housing Deadline.

February 9 - 16, 2009
Contact Laser Registration for any Housing questions.

February 16, 2009
Cancellation Deadline
$100 processing fee will be charged for written cancellations received by February 16. No refunds given after this date.

February 16, 2009
Course and symposia tickets will be refunded in full until this date. No refunds given after this date.

February 17, 2009
Any changes to hotel reservations must be made directly with hotel from this date forward.

HOUSING & TRAVEL INFORMATION

HOUSING DEADLINE – FEBRUARY 9, 2009, 5:00 PM EST.

Hotel Accommodations

The JW Marriott Desert Ridge Resort & Spa offers luxury accommodations and amenities your whole family is sure to enjoy, from fine dining to a host of recreation opportunities. This 316-acre luxury resort in the Sonoran Desert features a unique architectural design incorporating the four elements of nature – fire, water, earth and sky. **This hotel has a smoke-free policy.**

Resort Amenities:

- Deluxe guest rooms with patios or balconies overlooking wildflower gardens, swimming pools, lakes and waterways plus golf course or mountain views.
- Four acres of turquoise pools and shimmering waterways.
- WildFire Golf Club featuring two on-site 18-hole golf courses.
- Stunning, two-story spa oasis, featuring signature treatments that combine ancient rituals with cutting-edge techniques.
- Eight-court tennis center.
- Desert botanical garden.
- Four fine-dining restaurants, two cafés, a lounge and a spa bistro.

Hotel Cancellations or Changes

Through February 9, 2009, 5:00 PM EST

- All changes and cancellations must be made through Laser Registration.
- Rooms are not transferable.
- Refunds for deposits will be issued by Laser Registration.

February 9 - 16, 2009

- Contact Laser Registration for any Housing questions.

Beginning February 17, 2009

- All changes and cancellations must be made directly with the hotel. Should you not arrive on the scheduled day of your reservation, your room will become available for resale at 6:00 AM the following morning and the advance deposit will be retained by the hotel.

Hotel Cancellation Policy

Deposits are refundable only if hotel receives notification of cancellation at least 7 days prior to your scheduled arrival date.

Transportation to the Resort

Shuttle Service

SuperShuttle provides shuttle service between Phoenix Sky Harbor International Airport and the JW Marriott Desert Ridge Resort & Spa. Collect your luggage and go to the outer island marked "VAN SERVICE." A uniformed Guest Service Representative will arrange SuperShuttle transportation to your destination. Call SuperShuttle at (602) 244-9000, 24 hours in advance of your departure for return reservations, or simply stop by the resort concierge and ask them to make a SuperShuttle reservation for you. Fare information is available at www.supershuttle.com.

Car Service

Transtyle sedans are readily available to take you between the Phoenix Sky Harbor International Airport and the JW Marriott Desert Ridge Resort & Spa. Rate information is available at www.transtyle.com. Although recommended, advance reservations are not necessary. Call (480) 948-6131 for further information and to make reservations.

REGISTRATION FORM

REGISTRATION INFORMATION

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting registrations will not be processed without a valid credit card or check. Space in Special Courses or Luncheon Symposiums will not be reserved without payment.

ONSITE REGISTRATION HOURS

Wednesday, March 11
8:00 AM – 6:00 PM
Thursday, March 12
6:00 AM – 6:00 PM
Friday, March 13
6:00 AM – 5:00 PM
Saturday, March 14
6:00 AM – 12:30 PM

WHAT'S INCLUDED IN THE REGISTRATION FEE?

Medical Registration includes the following:

- Daily Continental Breakfasts.
- Daily Beverage Breaks.
- Daily Scientific Sessions.
- Entrance to the Exhibit Hall.
- One ticket to Wednesday Opening Reception.
- One ticket to Thursday Lunch with Exhibitors.
- One ticket to Thursday Reception with Exhibitors.

Spouse/Guest Registration includes the following:

- Daily Continental Breakfasts with medical attendees.
- Daily Scientific Sessions.
- One ticket to Wednesday Opening Reception.
- One ticket to Thursday Reception with Exhibitors.
- Entrance to the Exhibit Hall.

Questions

If you have questions, contact:
Laser Registration
By Phone: US and Canada
(866) 298-0802
By Phone: International
(514) 228-3077
E-mail:
DSPN@Laser-Registration.com

Advance Registration Deadline: February 9, 2009.

Please print or type:

Last Name _____ First Name _____ Suffix _____

Credentials _____

Organization _____

Address _____

City _____ State _____ Zip Code _____

Country _____

Phone _____ Fax _____

E-mail Address _____

Spouse/Guest Name (if applicable: please print name as it will appear on badge). _____

Child Name(s) and age _____

Member ID (found on mailing label) _____

Meeting Registration Fees

Registration Category	Received on or Before February 9, 2009	Received After February 9, 2009
Spine Section Member (101S)	❑ $450	❑ $550
NASS Member (102S)	❑ $450	❑ $550
Non-Member (104S)	❑ $500	❑ $600
Resident (105S)	❑ $300	❑ $400
Nurse (106S)	❑ $300	❑ $400
Physician Assistant (107S)	❑ $300	❑ $400
Spouse/Guest (108S)	❑ $100	❑ $130
Child (109S)	❑ $0	❑ $0
Subtotal for Registration Fee Section		**$**

REGISTRATION FORM

METHOD OF PAYMENT

❑ Business or Personal Check

Check # _____

❑ Visa ❑ Master Card ❑ American Express

_____
Credit Card Number

_____
Expiration Date

_____
Name (exactly as it appears on card)

_____
Signature (I authorize Laser Registration to charge my credit card for the total amount due and acknowledge the registration cancellation policies that are in effect.)

_____
Address

_____
City/State/Zip Code

PAYMENT INSTRUCTIONS

ONLINE – Visit www.spinesection.org and complete an online Advance Registration Form using a credit card for payment. The online registration form is the most immediate and secure method of registration.

MAIL – Please make check payable in US dollars and drawn on a US bank to:
AANS/CNS Section on Disorders of the Spine and Peripheral Nerves
Mail to: c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967
Checks will be processed electronically. If you do not want your check processed electronically, please choose a different payment method. Checks for registration and hotel reservation must be separate.

FAX – If you are paying by credit card, fax this form to US (866) 805-5721 or International (514) 228-3162.

REGISTRATION CANCELLATION/REFUNDS
Requests for registration cancellation must be made in writing and sent to:
AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting
c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967
Cancellation requests received by 5:00 PM EST on or before Monday, February 16, will receive a full refund less a $100 processing fee. There will be no refunds for cancellation requests received after this date. No refunds will be given for no-shows.

Course and symposia tickets will be refunded in full until 5:00 PM EST on Monday, February 16. No refunds will be processed after this date.

_____
Medical Registrant's Full Name (please print)

Special Courses and Luncheon Symposium

Special Courses and Luncheon Symposium titles are subject to change.

Special Course I – Coding Update and Review
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $200 (020S) *(Includes Lunch)* — $ _____

Special Course II – New Developments in Arthroplasty
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $200 (021S) *(Includes Lunch)* — $ _____

Special Course III – Biomechanics: Its Use in Surgical Decision Making
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $200 (022S) *(Includes Lunch)* — $ _____

Special Course IV – Pediatric Craniocervical
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $200 (023S) *(Includes Lunch)* — $ _____

Special Course V – Surgical Management of the Aging Spine: Deformity, Stenosis, Listhesis, Disc
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $200 (024S) *(Includes Lunch)* — $ _____

Special Course VI – Evaluation and Management of the Patient with a Spinal Infection
Special Course for Nurses, Nurse Practitioners and Physicians Assistants
Wednesday, March 11, 1:30 – 5:30 PM — ❑ Medical Registrant $110 (025S) *(Includes Lunch)* — $ _____

Special Course VII – Peripheral Nerve Exposures and Nerve Repair Techniques
Friday, March 13, 1:30 – 5:30 PM — ❑ Resident/Fellow $0 (025R) *(Includes Lunch)*
❑ Medical Registrant $200 (026S) *(Includes Lunch)* — $ _____

Special Course VIII – Evaluation and Management of the Spine Trauma Patient
Special Course for Nurses, Nurse Practitioners and Physicians Assistants
Friday, March 13, 1:30 – 5:30 PM — ❑ Medical Registrant $110 (027S) *(Includes Lunch)* — $ _____

Luncheon Symposium I – Revision Spine Surgery and Management of Complications
Friday, March 13, 12:30 – 2:30 PM — ❑ Medical Registrant $200 (026S) *(Includes Lunch)* — $ _____

Luncheon Symposium II – Neurosurgeon as CEO: Business Aspects of Spinal Surgery
Friday, March 13, 12:30 – 2:30 PM — ❑ Medical Registrant $200 (023S) *(Includes Lunch)* — $ _____

Luncheon Symposium III – Treatment of Primary and Metastatic Spine Tumors
Friday, March 13, 12:30 – 2:30 PM — ❑ Medical Registrant $200 (024S) *(Includes Lunch)* — $ _____

Subtotal for Special Courses/Luncheon Symposium Section $

Social Event

Reception with Exhibitors

Thursday, March 12, 2009, 5:15 – 6:45 PM — ❑ _____@ $100 (042S) — $ _____

Note: One (1) ticket is included in the registration fee for each medical registrant and spouse/guest. Use this to order additional tickets. Children under the age of 18 are not allowed on the exhibit floor.

Subtotal for Social Event Section $

GRAND TOTAL $

HOUSING FORM

PAYMENT INSTRUCTIONS

ONLINE – Visit www.spinesection.org and complete using a credit card for payment. The online registration and housing form is the most immediate and secure method of registration, and housing reservation.

MAIL – Please make check payable in US dollars and drawn on a US Bank to AANS/CNS Laser Registration – Housing and Travel Services. Checks for registration and hotel reservation must be separate. Mail to:

AANS/CNS Section on Disorders of
the Spine and Peripheral Nerves
c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967

FAX – If you are paying by credit card, fax this form to (US) (866) 805-5721 or (International) (514) 228-3162.

Hotel Cancellations or Changes

Through February 9, 2009, 5:00 PM EST

- All changes and cancellations must be made through Laser Registration.
- Rooms are not transferable.
- Refunds for deposits will be issued by Laser Registration.

February 9 - 16, 2009

- Contact Laser Registration for any Housing questions.

Beginning February 17, 2009

- All changes and cancellations must be made directly with the hotel.

Should you not arrive on the scheduled day of your reservation, your room will become available for resale at 6:00 AM the following morning and the advance deposit will be retained by the hotel.

Hotel Cancellation Policy
Deposits are refundable only if hotel receives notification of cancellation at least 7 days prior to your scheduled arrival date.

Important Housing Information

Support the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves by booking your hotel room for the Annual Meeting by one of the methods listed on the housing form. In order to obtain the necessary meeting and exhibit space at the hotel, the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves must commit to a minimum number of guest rooms. If that commitment is not fulfilled, the Section will incur significant financial penalties and have difficulty obtaining sufficient meeting space in the future. Unfortunately, this can have a major impact on the member services and programs that the Section is able to offer in the future. We appreciate your commitment to the Section by staying at the Official Meeting Hotel.

HOUSING DEADLINE: FEBRUARY 9, 2009

All hotel reservations must be accompanied by the first night's room rate in order to confirm your accommodations. At check-in, a credit card or cash deposit is required for final payment.

Last Name _____ First Name _____

Address _____

City _____ State _____ Zip Code _____

Phone _____ Fax _____

E-mail Address _____

❑ I will be sharing this room with another attendee (non-family).

Reservation Information

Accommodation and Rates (check accommodation type)

Standard Guest Room ❑ $361 Single/Double* ❑ $381 Triple* ❑ $401 Quad*

For Suite availability, please contact Laser Registration at
(866) 298-0802 or (514) 228-3077 or E-mail dspn@laser-registration.com

* Above rates are subject to 12.27% state and local taxes per night.

A portion of the room rate will be utilized to cover the cost of registration and housing services. These special rates are only available until the February 9, 2009 cut-off date. The AANS/CNS Section on Disorders of the Spine and Peripheral Nerves cannot guarantee the availability of this rate after the cut-off date. Check-in time is 4:00 PM; check-out time is 11:00 AM. Rates are effective (3) days prior to and (3) days after the official meeting dates of March 11 – March 14, 2009. Confirmation for dates other than official meeting dates, made prior to the cut-off date, will be based on availability.

JW Marriott Desert Ridge Resort & Spa will make every effort to honor specific requests; however, they reserve the right to provide alternate accommodations when necessary. Note: All rooms are non-smoking.

Special Requests (check all that apply)

❑ One King Bed ❑ Two Double Beds ❑ Handicap Accessible Room

❑ Other _____

Arrival Date: _____ Departure Date: _____

Number of Rooms Needed: _____ Number of People in Party: _____

Method of Payment

A deposit of one night's room is required. Payment can be made by check, money order, or credit card. If paying by check, please make check payable to AANS/CNS Laser Registration - Housing and Travel Services. Mail to:

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting
c/o Laser Registration
1200 G Street NW, Suite 800
Washington DC 20005-3967

❑ Business or Personal Check Check #_____

* Checks will be processed electronically. If you do not wish to have your check processed electronically, please choose a different payment method. Checks for registration and hotel reservation must be separate.

❑ VISA ❑ MasterCard ❑ American Express

Credit Card Number _____ Expiration Date _____

Name (exactly as it appears on card) _____

Signature (I authorize Laser Registration to charge my credit card for the deposit due and acknowledge the cancellation policies that are in effect.) _____

Address _____

City/State/Zip Code _____

SAVE THE DATE!

Rosen Shingle Creek Resort
Orlando, Florida

Orlando, Florida • February 17–20, 2010

26th Annual Meeting of the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves

Thank you to our 2009 Annual Meeting Sponsors:

Neurosurgical Education Ambassador – Biomet Spine
Power of Networking Ambassador – Stryker
Neurosurgical Leadership Partner – Medtronic
Resident Education Partner – DePuy Spine, a Johnson & Johnson Company

Benefactor:
Synthes Spine

Supporters:
Anulex Technologies, Inc. – ArthroCare – Integra – NuVasive – TranS1

American Association of Neurological Surgeons

Congress of Neurological Surgeons
Education and Innovation

AANS/CNS Section on Disorders of the Spine and Peripheral Nerves
10 N. Martingale Road, Suite 190
Schaumburg, IL 60173-2294
847 240 2500

2009 AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting **Phoenix, AZ** **March 11 - 14, 2009** **General Exhibit Sales Report**		**2009 Budget**
Total Booth Space Sold $423,600		$407,500
Total Payment Received	$446,600	
Total Square Feet Sold 11,700		
Total NEW Exhibitors	24	
Total Exhibitors – Revenue Generating 70		
Total Island Exhibitors	7	
Total Cancellations	6	
Total Cancellation Refunds Paid	$18,200	
Total Cancellation Fees $3,000		
Total Reduction Refunds	0	
Total Reduction Refunds Paid $0		
Total Reduction Fees	$0	
Total Complimentary Booths	2	
Total Exhibit Revenue	$426,600	$407,500

Plus (2) comp booths – AANS and CNS.

2009 AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting **Phoenix, AZ** **March 11 - 14, 2009** **General Sponsorship Sales Report**		**2009 Budget**
Total Sponsorship Opportunities Sold $337,500		$285,000
Total NEW Sponsors	1	
Total Sponsors 13		
Total Supporter Sponsors	8	
Total Benefactor Sponsors	1	
Total Partner Sponsors	1	
Total Ambassador Sponsors	3	
Total Payment Received	$337,500	$285,000

2009 AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Annual Meeting

EXHIBIT SALES & SPONSORSHIP REPORT
(As of 3/6/09)

Exhibits:

- We have sold **11,700** square feet of revenue-generating exhibit space to **72** exhibiting companies (inclusive of the AANS and CNS booths/comp).
- This total includes 24 new exhibiting companies and 7 island exhibitors.
- Total exhibit booths sold = 117 out of 120 available 10'x10' booths.
- The floorplan also includes two complimentary exhibits for AANS and CNS.

Sponsorships:

- We have 13 confirmed sponsors, representing 21 sponsorship opportunities (detail below).

Exhibiting Company	2009 Corporate Support Contribution/Level	2009 Corporate Support Opportunity
Aesculap	Supporter	What's New Sessions
Anulex	Supporter	What's New Sessions
ArthroCare	Supporter	What's New Sessions
Biomet Spine	Ambassador - Neurosurgical Education	**Neurosurgical Education Ambassador** Program Book Digital Poster Center Scientific Sessions
DePuy Spine	Partner - Resident Education	**Resident Education Partner** YNS Dinner First 25 Residents Special Course Reg. & What's New Sessions
Integra	Supporter	Badge Lanyards
K2M	Supporter	General Annual Meeting Sponsorship
Medtronic	Ambassador - Neurosurgical Leadership	**Neurosurgical Leadership Partner** Chairman's Dinner Meritorious Award Hotel Key Cards
Nuvasive	Supporter	Annual Meeting Bags & What's New Sessions
Spine Wave	Supporter	What's New Sessions
Stryker	Ambassador -Power of Networking	**Power of Networking Ambassador** Opening Reception Reception W/ Exhibitors
Synthes	Benefactor	General Annual Meeting Sponsorship
Trans1	Supporter	What's New Sessions

Subject: FW: Dinners at the Spine Section meeting
Date: Thursday, January 29, 2009 2:47 PM
From: Regina N. Shupak <rns@1CNS.ORG>
To: Groff, MD Michael mgroff@bidmc.harvard.edu

Dear Dr. Groff,

Nice talking with you this afternoon.

The Executive Committee Meeting date and time noted below is based on the 2008 date and time.

Let us know if you would like it changed at all.

Thank you, Regina.

From: Jacqueline M. Bellan
Sent: Thursday, January 29, 2009 1:42 PM
To: mgroff@bidmc.harvard.edu
Cc: Regina N. Shupak
Subject: RE: Dinners at the Spine Section meeting

Dr. Groff,
Below is a schedule of the meetings and dinners you requested. Please note that all events will take place on the property of the JW Marriott Desert Ridge Hotel & Spa.

Executive Committee Dinner
Tuesday, March 10, 2009
7:00 – 10:00 PM
Location: Roy's (Ohana Room)

Executive Committee Meeting
Wednesday, March 11, 2009
7:00 AM – 1:00 PM
Location: TBD

Opening Reception
Wednesday, March 11, 2009
6:00 – 8:00 PM
Location: Sage Court

Chairman's Dinner
Thursday, March 12, 2009
7:00 – 10:00 PM
Location: Meritage Steakhouse

Chair Advisory Council Meeting
Friday, March 13, 2008
3:30 – 5:30 PM
Location: Desert Suite I

Chair Advisory Council Reception & Dinner
Friday, March 13, 2008
7:00 – 7:45 PM Reception with Exhibitors
7:45 – 10:00 PM Dinner
Location: Ristorante Tuscany

Young Neurosurgeon Dinner
Friday, March 13, 2008
7:00 – 10:00 PM
Location: Wildflower AB

Please let me know if you have further questions or any concerns.

Jackie Bellan
Senior Meeting Services Coordinator

Congress of Neurological Surgeons
10 North Martingale Road
Suite 190
Schaumburg, IL 60173
Phone: 847-240-2500
Fax: 847-240-0804
Mail to: jmb@1cns.org <mailto:jmb@1cns.org>
Visit us on line at: www.cns.org <file:///C:/Documents%20and%20Settings/jmb/Application%20Data/Microsoft/Signatures/www.cns.org>
Mark your calendar now for the 2009 CNS Annual Meeting, October 24-29, 2008 in New Orleans, Louisiana!

From: Michael Groff [mailto:mgroff@bidmc.harvard.edu]
Sent: Wed 1/28/2009 9:50 PM
To: Regina N. Shupak
Subject: Dinners at the Spine Section meeting

Regina,

Can you send me the date, time and place for all the dinners at the upcoming meeting in Phoenix? Do we have the Chairman's advisory Committee meeting on the schedule?

Thanks,

mike

AANS/CNS SECTION ON DISORDERS OF THE SPINE AND PERIPHERAL NERVES

American Association of Neurological Surgeons

A Section of the
American Association of Neurological Surgeons
and
Congress of Neurological Surgeons

CONGRESS OF NEUROLOGICAL SURGEONS 1951
ERUDITIO OBSERVANTIA SOCIETAS
Education and Innovation

Laurie L. Behncke
Executive Director
The Congress of Neurological Surgeons
10 North Martingale Road
Schaumburg, IL 60173

30 October 2008

Dear Ms. Behncke:

On behalf of the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves, I would like to thank you and the Congress of Neurological Surgeons for excellent management of the Section's Annual Meeting over the last three years.

Based on this very positive relationship, the Section formally requests a proposal from the Congress of Neurological Surgeons for continuation of Annual Meeting management services for the 2010, 2011, and 2012 Section Annual Meetings.

The Section Executive Committee sincerely hopes that the Congress of Neurological Surgeons will look favorably on this request. If possible, I request that this proposal be forwarded to Section Chair Daniel Resnick, MD, by February 14, 2009, for discussion at the Section Executive Committee meeting in March.

If you need any additional information, please feel free to contact me at your convenience.

Sincerely,

Christopher E. Wolfla

Christopher Wolfla, MD
Treasurer

AMERICAN ASSOCIATION OF
NEUROLOGICAL SURGEONS
THOMAS A. MARSHALL, *Executive Director*
5550 Meadowbrook Drive
Rolling Meadows, IL 60008
Phone: 888-566-AANS
Fax: 847-378-0600
info@aans.org

President
JAMES R. BEAN, MD
Lexington, Kentucky

CONGRESS OF
NEUROLOGICAL SURGEONS
LAURIE BEHNCKE, *Executive Director*
10 North Martingale Road, Suite 190
Schaumburg, IL 60173
Phone: 877-517-1CNS
FAX: 847-240-0804
info@1CNS.org

President
P. DAVID ADELSON, MD
Pittsburgh, Pennsylvania

December 8, 2008

Barbara J. Brown
Data Analyst, Office of Medical Policy & Tech Assessment
WellPoint, Inc.
4553 La Tienda Drive
Thousand Oaks, California 91362

Submitted Via Email: **Technology.Compendium@WellPoint.com**

Subject: BCBSA Draft Policy: 7.01.108 Artificial Intervertebral Disc: Cervical Spine
WellPoint Draft Policy: SURG.00055 Artificial Intervertebral Discs

Dear Ms. Brown:

On behalf of the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves, we appreciate the opportunity to comment on the above referenced draft coverage policies regarding the topic of Artificial Intervertebral Discs for the national Blue Cross and Blue Shield Association (BCBSA) and WellPoint. Submitted by Joseph S. Cheng, MD, MS, a member of the AANS and CNS Coding and Reimbursement Committee, this represents the collective opinion of organized neurosurgery's board-certified physicians.

We have attached our detailed review and comments on the attached questionnaire form, and as you will see, we do not agree with the proposed position statement that artificial intervertebral discs are considered investigational and not medically necessary in the treatment of degenerative disc disease of the spine.

The AANS and CNS appreciate the opportunity to collaborate in this process and offer these comments and we look forward to our continued relationship to further improve patient access to quality medical care. In the meantime, if you have any questions about our response, please contact us.

Sincerely,

James R. Bean

P. David Adelson

James R. Bean, MD, President
American Association of Neurological Surgeons

P. David Adelson, MD, President
Congress of Neurological Surgeons

WASHINGTON OFFICE
KATIE O. ORRICO, *Director*
725 Fifteenth Street, NW, Suite 500 Washington, DC 20005
Phone: 202-628-2072 Fax: 202-628-5264 E-mail: korrico@neurosurgery.org

Daniel K. Resnick, MD, Chair
AANS/CNS Section on Disorders of the Spine
and Peripheral Nerves

Attachment: WellPoint, Inc., Medical Policy Questionnaire

cc: Joseph S. Cheng, MD, MS, Member, AANS/CNS Coding and Reimbursement Committee
Gregory J. Przybylski, MD, Chairman, AANS/CNS Coding and Reimbursement Committee

AANS/CNS Staff Contact:

Catherine Jeakle Hill
Senior Manager, Regulatory Affairs
AANS/CNS Washington Office
725 15th Street, NW
Suite 500
Washington, DC 20005
Phone: 202-628-2072
Fax: 202-628-5264
Email: chill@neurosurgery.org

WellPoint, Inc.
Medical Policy Questionnaire

November 25, 2008

WellPoint, Inc. incorporates input from physicians practicing in relevant clinical areas along with other sources such as the peer-reviewed published medical literature, technology assessments, evidence-based consensus statements, and evidence-based guidelines from nationally recognized professional medical specialty societies as part of our process for developing and maintaining medical policies and clinical UM guidelines and on behalf of a national healthcare association (“”Association”) to support their processes for developing and maintaining medical policies.

We are currently reviewing the topic of **Artificial Intervertebral Discs**. We are requesting your expert opinion regarding this topic and have developed a series of relevant questions presented in the table below.

We have designed our process to help you avoid duplication of effort in reviewing various entities’ medical policies, with the goal of reducing your administrative burden. At the same time, your feedback and the feedback we receive from others on this topic will be shared with non-WellPoint entities, the Association and its constituents. This will allow your input to be considered as WellPoint, Inc. formulates its medical policy positions, which affect the more than 35 million members enrolled in our plans, by even broader audience on behalf of the Association and the many millions of Americans whose health care benefits are provided by its member plans.

Attached are ***two (2) draft versions*** of the policy, **7.01.108 Artificial Intervertebral Disc: Cervical Spine (file name CVDI - 701108 - ArtDisc-Cerv.pdf)** and the second is labeled **SURG.00055 Artificial Intervertebral Discs (file name SURG.00055 WP 10-22-2008 CoDr.doc).** The first policy addresses artificial intervertebral discs of the cervical spine only. The second policy addresses artificial intervertebral discs of the cervical and lumbar spine.

***Your input is being requested on both versions*.** Please use the questionnaire labeled **7.01.108 Artificial Intervertebral Disc: Cervical Spine** to complete your response to the Association draft and the *separate* questionnaire for your response regarding the second policy draft labeled **SURG.00055 Artificial Intervertebral Discs** to correspond to your response.

We will carefully review your responses to the questions below and we welcome additional insights you provide on this topic. Please be sure to:

- **Answer all questions**
- **Complete the conflict of interest section**
- **Complete the demographic information and release statement on the following page**
- **Provide peer-reviewed literature citations when changes to a policy position are suggested**

Thank you for supporting our process to maintain medical necessity determinations consistent with the principles of evidence-based medicine by providing your expertise, guidance and input.

Please complete the information on the following page.

Please return your comments to: Barbara Brown at technology.compendium@wellpoint.com on or before December 23, 2008.

The following information is needed for this review.

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Your input will be shared with the applicable medical policy committee(s) when this topic is presented. Please indicate if WellPoint, Inc. may release any or all of the following points of information to the committee(s) and non-WellPoint entities, including a national Association.

	Yes	No	Comments
Your Board Certification	X		
Name of your Academic/Hospital Affiliation(s)	X		
Your Name	X		

Policy Number: 7.01.108 Policy Title: Artificial Intervertebral Disc: Cervical Spine Definitions of Medically Necessary and Investigational included in Exhibit I			
	Yes	**No**	**Comments**
General questions:			
Is the **POLICY POSITION** clear and supported by the medical evidence in the peer reviewed medical literature? If no, please comment.		X	Current medical evidence indicates that there is sufficient evidence to conclude that using artificial discs in the cervical spine is equivalent to fusion surgery. This position is supported by the Washington State Health Care Authority during its 2008 health technology assessment in addition to an independent panel, convened to review the assessment for Washington State on October 17, 2008, which voted to cover cervical artificial intervertebral discs. In addition, medical evidence to indicate that the use of cervical artificial intervertebral discs is medically necessary and not considered investigational if supported by the findings and policies of other insurance carriers such as Aetna (Clinical Policy Bulletin: Intervertebral Disc Prostheses. Policy Number: 0591 (Last Review: 05/23/2008)). The available studies had sufficient power for their study design, consistent multicenter protocols, homogeneous investigational and control groups, and the patients enrolled were representative of the intended medical population. As well, the outcomes were validated and included independent radiographic assessments.
Is the **RATIONALE** clear and does it accurately reflect the currently available medial evidence? If no, please comment.		X	The rationale provided in "7.01.108 Artificial Intervertebral Disc: Cervical Spine" does not accurately reflect the current available medial evidence. The first criticism was that 2 years of follow-up is not adequate to evaluate long-term results, in particular any effect of the device on adjacent-level disc degeneration, device durability, adverse events, and revisability. Although it is preferable to have longer periods of data analysis than 2 years, the 2 year period is a reasonable amount of time for follow up in clinical studies before a procedure is accepted as non-investigational. Follow up of 2 years is considered the standard in our clinical studies. However, artificial cervical discs have been in reported clinical use for almost 20 years with approximately 23,000 artificial cervical discs implanted so far, with the majority outside of the United States (Pracyk 2005, ECRI 20007). The published results are favorable, such as the Prestige Cervical Disc

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	Yes	No	Comments
			(previously known as the Bristol Cummins' artificial cervical joint) which was first implanted 17 years ago (Cummins 1998). At 5 years, they were able to follow-up with 18 of the original 20 patients, and noted that the device was stable and mobile and did not report issues related to disc degeneration, device durability, or adverse events. Robertson in 2004 published four year follow up results, noting that in the 12 patients available from the Prestige I study, the device continued to function and adjacent level disease was not present with clinical improvement in patient function and quality of life. Patel in 2007 reported 5-9 year follow-up for 31 patients who had the Prestige artificial disc placed between 1998 and 2002 and noted that all but one patient maintained motion of the artificial disc with no instances of device failure or adverse events. Delamarter in 2007 reported up to 4 year follow-up on 30 patients from the ProDisc-C U.S. IDE study noting clinical improvement. He also noted that motion was maintained, no evidence of adjacent segment degeneration, and no device-related complications. Bertagnoli in 2008 also reported up to 4 years of follow-up for 73 patients using the ProDisc-C artificial cervical disc noting that range of motion was maintained in over 90% of the patients and that there were no device-related complications or re-operations that were required. The Bryan Cervical Disc has been reported to have been implanted in over 15,000 times worldwide (FDA 2007). Goffin in 2006 reported the 4-year results for 69 single level procedures with the Bryan Cervical Disc noting that 61 of 69 patients had an excellent/good result and that motion was preserved in 83% of the patients and that only 3 of 69 developed some adjacent level degeneration at 4-years. This can be compared to the prior studies indicating a prevalence of 2.9% per year with an overall incidence of 25.6% in cervical fusion patients based on survivorship analysis (Hilibrand 1997, 1999). The second criticism was that the study was not blinded, and that the investigators and patients knew which procedure had been performed, which has potential to bias outcome assessments. Although a bias may be introduced, it would be impractical to

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	Yes	No	Comments
			double blind a surgeon regarding an implant that is to be surgically placed. While blinded studies are statistically valid and an ideal goal for pharmaceutical studies, it is not something that can be achieved in device studies. In addition, post-operative care and imaging will allow the patient to become aware of their device as it would not be feasible to blind the radiographic review as the device would be clearly identifiable on x-rays. The third and final criticism was that some experimental patients had increased pain of the neck (6.2% vs. 0.8% at 2 years) and arm (9.4% and 5.8%) after the procedure, and that these findings merit additional investigation for their clinical relevance. This finding is unusual and does not reflect the majority of the other published reports noting that artificial intervertebral disc arthroplasty is a good alternative to anterior cervical fusions in patients with cervical spondylosis and degenerative disc disease (Acosta 2005, Anderson 2007, Smucker 2006, Phillips 2005, Anderson 2004, Pracyk 2005, Bertagnoli 2005). As well, there are a number of smaller studies showing that cervical arthroplasty is safe and at as effective as cervical fusions in those patients who had similar surgical indications to ACDF such as radiculopathy and myelopathy (Brown 2006, McAfee 2004). In the three large randomized clinical trials, there were consistent evidence that artificial cervical discs were statistically noninferior to the standard ACDF, with non-statistically significant improvements in neurologic status and the neck disability index (NDI) in the patients receiving the artificial cervical discs. The authors of the Wellpoint draft policy also noted that the FDA has required the Prestige disc manufacturer to conduct a 7-year post-approval clinical study of the safety and function of the device, and a 5-year enhanced surveillance study of the disc to more fully characterize adverse events in a broader patient population. This statement by the FDA does not indicate any negative concerns related to the device as this statement would seem to indicate, as otherwise the Prestige disc would not have been approved by the FDA, but rather a continued evolution of the FDA process.

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			Since the enactment of the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, the Center for Devices and Radiological Health (CDRH) has been developing new protocols for postmarket surveillance to monitor the performance of marketed medical devices. As the medical devices today are vastly different from those used 30 years ago, "The postmarket system that we set up 30 years ago is not designed to deal with all of the new things that are happening today in the device industry" as noted by CDRH Director Daniel Schultz, M.D..
Is the **DESCRIPTION** clear and accurate? If no, please comment.	X		
Specific questions regarding the Policy determination:			
Therapeutic Interventions: • The policy indicates artificial intervertebral discs of the cervical spine are considered **investigational** for treatment of disorders of the cervical spine, including degenerative disc disease. - Do you agree? - If no, please comment and cite literature to support.		X	We do not agree with the policy indicating that artificial intervertebral discs of the cervical spine are considered investigational for treatment of disorders of the cervical spine, including degenerative disc disease. This conclusion is not consistent with the favorable results from the available published literature, nor does it indicate the prevailing clinical opinion among neurosurgeons and orthopedic spine surgeons. On September 8, 2006, our American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and the AANS/CNS Section on Disorders of the Spine and Peripheral Nerves submitted a letter to the FDA in support of a favorable consideration for cervical disc arthroplasty. In addition to the comments as noted above, the follow references are cited for support from the literature. Aetna Clinical Policy Bulletin: Intervertebral Disc Prostheses. Policy Number: 0591 (Last Review: 05/23/2008) (http://www.aetna.com/cpb/medical/data/500_599/0591.html) Bertagnoli R. Single level ProDisc-C Total Disc Replacment up to four years follow-up, Number 145. North American Spine Society, October 15-18, 2008, Toronto, Canada. Cheng JS, Liu F, Komistek RD, Mahfouz MR, Sharma A, Glaser D. Comparison of Cervical Spine Kinematics Using a Fluoroscopic Model for Adjacent Segment Degeneration. Journal of Neurosurgery - Spine, 7(5):509-

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			513. Nov 2007. Cummins B, Robertson J and Gill S. Surgical experience with an implanted artificial cervical joint, J Neurosurg 1998, 88: 943-948. Delamarter R, Bradhan B, Kanim L, et al. Cervical disc replacement: over 3-4 prospective randomized clinical outcomes and range of motion follow-up with the Prodisc-C prosthesis, Number 64. North American Spine Society, October 23-27, 2007, Austin, TX. ECRI Institute, Emerging Technology (TARGET) Evidence Report, Artificial intervertebral disc replacement (AIDR) for symptomatic cervical disc disease, 2007. Food and Drug Administration, Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee, Office of Surveillance and Biometrics, Design of Condition of Approval Studies and Smith & Nephew Birmingham Hip Resurfacing (BHR) System, P040033, September 8, 2005. Food and Drug Administration, Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee, Medtronic Sofamor Danek Bryan Cervical Disc, P060023, July 17, 2007. Food and Drug Administration, Center for Devices and Radiologic Health, Division of Post-market Surveillance, Office of Surveillance and Biometrics, Guidance for Industry and FDA staff – Procedures for Handling Post-approval Studies Imposed by PMA Order, August 1, 2007. Food and Drug Administration, Center for Devices and Radiologic Health, Post-approval studies, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm Goffin J, Casey A, Kehr P, Liebig K, et al. Preliminary clinical experience with the Bryan Cervical Disc Prosthesis, Neurosurgery 2002, 51: 840-847. Goffin J, van Loon J, van Calenbergh F. Cervical arthroplasty with the Bryan Disc: 4-

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	Yes	**No**	**Comments**
			and 6-year results, Cervical Spine Research Society, November 30-December 2, 2006, Palm Beach, FL. Hilibrand AS, Carlson GD, Palumbo MA, et al.: Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical athrodesis. J Bone Joint Surg 81-A:519-528, 1999. Lee CK, Langrana NA. A review of spinal fusion for degenerative disc disease: need for alternative treatment approach of disc arthroplasty? Spine J. 2004 Nov-Dec;4(6 Suppl):173S-176S. Liu F, Cheng JS, Komistek RD, Mahfouz MR, Sharma A. In Vivo Evaluation of Dynamic Characteristics of the Normal, Degenerative, Fused, and Disc Replacement Cervical Spines. Spine, 32(23): 2578–2584. Nov 1, 2007. Mummaneni, et al. Journal of Neurosurgery Spine. 2007 Mar; 6(3):198-209. Clinical and Radiographic Analysis of Cervical Disc Arthroplasty Compared with Allograft Fusion: A Randomized Controlled Clinical Trial. Office of the Inspector General, Department of Health and Human Services, Review of the Food and Drug Administration's Handling of Adverse Drug Reaction Reports, A-15-98-50001, December 1999. http://www.oig.hhs.gov/oas/reports/phs/c9850001.pdf Papadopoulos S. The Bryan Cervical Disc System, Neurosurg Clin N Am 2005, 16: 629-36. Patel N, Robertson J, Metcalf N and Gill S. Long-term follow-up of patients treated with the Prestige Artificial Disc at a Single Center, Congress of Neurological Surgeons, September 15-20, 2007, San Diego, CA. Pracyk J and Traynelis V. Treatment of the painful motion segment: Cervical arthroplasty, Spine 2005, 30 (16S): S23-32. Robertson J and Metcalf N. Long-term outcome after implantation of the Prestige I disc in an end-stage indication: 4-year results from a pilot study, Neurosurg Focus 2004, 3:

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	Yes	**No**	**Comments**
			E10. Washington State Health Care Authority, Health Technology Assessment, HTA Final Report Artificial Discs Replacement, ADR, September 19, 2008,
• Do you consider artificial intervertebral discs of the cervical spine **medically necessary**? If yes, - Are there any specific criteria which would be useful in selecting appropriate patient populations?	X		We would recommend that the indications for use of cervical disc arthroplasty follow the inclusion criteria from the large scale clinical trials used for FDA approval. That would include the application of this procedure to skeletally mature patients with cervical spine disease at C3-C7 necessitating a single-level decompression via an open anterior approach, and used for patients with intractable pain, radiculopathy, and/or myelopathy associated with radiographic studies showing a herniated cervical disc or cervical spondylosis and osteophytes.
- Are there any specific clinical or patient characteristics for when artificial intervertebral discs of the cervical spine are not appropriate? - Please comment and cite literature to support.	X		We would recommend that clinical or patient characteristics for which the artificial intervertebral disc is not appropriate include patients with cervical instability (sagittal plane translation >3.5mm, sagittal plane angulation >20°), facet joint pathology, osteoporosis, cancer, and infection. The literature supporting this is as indicated in the large scale clinical trials.
• Are there additional indications for artificial intervertebral discs of the cervical spine beyond those discussed in the document? - If yes, please comment and cite literature to support.		X	
• Is there evidence to support one type of artificial disc over another (i.e., ProDisc-C® and Prestige ST Cervical Disc)? - If yes, please comment and cite literature to support.		X	
• Is the use of artificial intervertebral discs of the cervical spine safe and efficacious in the treatment of degenerative disc disease? - If yes, please comment and cite literature to support.	X		The available large multicenter prospective randomized IDE studies have concluded that disc arthroplasty is a safe and reasonable alternative to anterior cervical fusion in the treatment of degenerative disc disease in selected patients as described by the study inclusion criteria over a clinically meaningful time point as defined by the FDA. Mummaneni in 2007 reported statistical noninferiority for disc arthroplasty versus ACDF in all three primary outcome variables (Neck Disability Index (NDI), neurological status, and functional spinal unit height (FSU)) and for the overall success composite

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	Yes	No	Comments
			outcome with the neurological status noting statistical superiority. Arthroplasty patients showed preservation of motion with retention of sagittal angular motion of over 7 degrees and also a 2-point greater improvement in the Neck Disability Index (NDI). Although it was not statistically significant, there was an overall success with better SF-36 at 12 and 24 months associated with a greater relief of neck pain and earlier return to work in the arthroplasty group. There were no serious associated adverse events and no cases of implant failure or migration, along with a lower rate of revision surgeries including a lower rate of supplemental fixation and of re-operations at the adjacent segment. Murrey reported a prospective, randomized, controlled trial of 209 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive Prodisc-C or ACDF with plate and allograft with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that Prodisc-C is not inferior to ACDF 2 years after surgery in Overall Success, the study's primary endpoint. Heller reported a prospective, randomized, controlled trial of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive Bryan Cervical Disc or Atlantis Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that the cervical disc replacement maintained segmental motion at 24 months after implantation and was associated with improved NDI Success (superiority), improved clinical outcomes, and 13 days faster return to work compared to ACDF patients. Statistical superiority in Overall Success (study's primary endpoint) was demonstrated at 24 months.
***Improved Patient Outcomes*:** • Is there adequate evidence to demonstrate that the use of artificial intervertebral discs of the cervical spine provide significant improvements in clinical outcomes *compared to the available alternatives?*		X	The current studies indicate that cervical disc arthroplasty is a safe and reasonable alternative to anterior cervical fusion with equivalent clinical outcomes. The main impetus for motion preservation is adjacent segment degeneration and disease, and this benefit is gained in the setting of equivalent post-operative improvements in clinical outcomes between cervical disc arthroplasty as compared to the available alternatives (cervical fusion).

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	Yes	**No**	**Comments**
• Is there *peer-reviewed literature,* other than that cited in the policy, to demonstrate improved patient outcomes due to the use of artificial intervertebral discs of the cervical spine? If so, please cite.	X		Yes, and these references are as cited above in the responses to the previous questions.
Is there *other information* you feel is relevant regarding the *medical necessity* of this technology?		X	
***Conflict of Interest*:** Do you have now, or have you had previously, any commercial or research relationship with any company or program which provides or markets products dealing with artificial intervertebral discs? If so, please disclose that relationship.		X	

EXHIBIT I

Medically Necessary Definition

"Medically Necessary" are procedures, treatments, supplies, devices, equipment, facilities or drugs (all services) that a medical practitioner, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- in accordance with generally accepted standards of medical practice; and
- clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and
- not primarily for the convenience of the patient, physician or other health care provider; and
- not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, national physician specialty society recommendations and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors.

Investigational Definition

The term "investigational" means that the medical policy does not meet the Technology Evaluation Criteria.

This means any procedure, treatment, supply, device, equipment, facility or drug (all services), are determined NOT to:

- have final approval from the appropriate government regulatory body; or
- have the credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community which permits reasonable conclusions concerning the effect of the procedure, treatment, supply, device, equipment, facility or drug (all services) on health outcomes; or
- improve the net health outcome; or
- be as beneficial as any established alternative; or
- show improvement outside the investigational settings.

Policy Number: SURG.00055 Policy Title: Artificial Intervertebral Discs			
Definitions of Medically Necessary and Investigational included in Exhibit I			
	Yes	**No**	**Comments**
General questions:			
Is the **POLICY POSITION** clear and supported by the medical evidence in the peer reviewed medical literature? If no, please comment.		X	The policy position blends in cervical and lumbar disc arthroplasty, which leads to incorrect assumptions. Cervical and lumbar arthroplasty and their investigational studies should not be conflated, as there are substantial anatomic and procedural differences. The Centers for Medicare and Medicaid Services (CMS) have issued a national non coverage determination for lumbar artificial disc replacement for the Medicare population over sixty years of age, but this does not apply to cervical artificial discs. The Category III codes for the cervical disc arthroplasty is incorrect in the policy, as the Federal Register (November 2008) indicates that CPT 22856/22561/22564 is included with appropriate RVU valuations.
Is the **RATIONALE** clear and does it accurately reflect the currently available medial evidence? If no, please comment.		X	We do not agree with the rationale by the authors of the Artificial Intervertebral Discs draft policy, Document #SURG.00055 (10/22/2008), and do not feel that it accurately reflects the current available medial evidence. Regarding the Charité Artificial Disc, they noted that although the Charité disc had a higher success rate than the BAK cage in its clinical IDE trial, this difference would not have met traditional criteria for a superiority trial. While hypothetically correct, in that a non-inferiority design (as compared to a superiority trial) could result in the Charite with a d=0.15, i.e. 95% confidence interval, could allow a 15% worse result when compared to BAK and still meet non-inferiority criteria, this has not been shown to be the case. The FDA has requested a 10% difference for a non-inferiority study, and the results were sufficient to allow approval of the Charité Artificial Disc. The authors of the Wellpoint draft policy also note that the randomized controlled trial for the Charité Artificial Disc had several methodological issues that made it difficult to interpret the results. Their first concern was that the analysis showed non-inferiority compared to BAK fusion using the composite measure of success, but did not show statistically significant superiority in most outcome measures. However, it should be noted that a non-inferiority trial is a common

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			and accepted study method for device trials, and that superiority trials are not the standard of IDE trials. As well, a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. In the referenced study, there was evidence that the efficacy of lumbar artificial discs, as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction was comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery. The overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving the Charité Artificial Disc and 48% of those receiving the lumbar fusion. The results suggest that 24 month outcomes for lumbar artificial discs were similar to lumbar fusion for degenerative disc disease. The rationale that utilizing a trial designed and analyzed as a noninferiority trial was done so in order to establish a less stringent standard for demonstrating efficacy than a standard clinical trial and that such trials are often employed when there is some margin of acceptable inferiority of a new technology in its principal outcome indicates a negative bias and misunderstanding of what is reasonably acceptable and feasible in clinical device trials. Issues such as unilateral cross over, ability to blind, among others have led to the use of non-inferiority as the base hypothesis in surgical and device trials and have been shown in other large scale non-device surgical studies such as the SPORT trial looking at lumbar disc herniation and disease. As well, fusion has been associated with a notable success rate in control cases and given the disease process being studies. The fusion success rate would be a difficult endpoint for cervical arthroplasty to exceed supporting the rationale for a non inferiority study design rather than a superiority design. There was also a second concern that there was a lack of a prespecified analysis plan, unexplained closure of the data base before

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			all patients reached completion, and lack of intent-to-treat analysis that may cast some doubt on the analysis. Although these were not addressed in the available papers, these variables were not an inherent part of the published peer reviewed work nor integral to the conclusions by the artificial disc study authors. Although additional and more rigorous trials of the outcomes of the use of an artificial disc in the treatment of DDD are needed, this same statement regarding the need for more rigorous trials and outcomes may be made for the majority of medical and surgical care currently available. This would then also apply to the general comments noted by the Wellpoint authors in extrapolating comments from Bertagnoli (2006) in that the authors cautiously recommend the use of artificial disc replacement in the treatment of chronic discogenic low back pain, in the study by Chung (2006) noting that future efforts need to be directed toward the evaluation of a larger number of patients with longer follow-up, and Freeman (2006) in that larger, well designed prospective randomized controlled trials with longer follow-up are needed. These general disclaimers and statements for future work were not meant to indicate that the technology and procedure remains experimental and outside the armamentarium of a general spine surgery practice. As well, it should be noted that cervical disc arthroplasty is quite different than lumbar disc arthroplasty. Concerns were raised in that the PMA was contingent upon a seven year post approval study to evaluate long-term safety and effectiveness of the Prodisc-C and the Prestige cervical disc. This has been addressed in the preceding question regarding the FDA requests and that this does not indicate a device rejection or experimental status, but rather the changing landscape in the FDA and in the area of medical devices. As well, although the Wellpoint document indicates that studies such as by Nabhan (2007) note that the loss of segmental motion was significantly higher in the ACDF group and that significant pain reduction was observed in the neck and arm postoperatively, it would seem that there were attempts to mitigate these positive results by noting comments such as "the

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			study was small and that larger studies with longer follow up are warranted". The issues raised which were postulated to cloud the conclusions such as that the trial was unblinded (double blinding is near impossible to do in a surgical study) and the 4% cohort withdraw rate which is not unexpected in this type of clinical trial. Also, although it was acknowledged that the investigational group reported better neurological success, concern was raised that the investigators provided no detail how the neurological status was measured and evaluated, despite the fact that the same argument was not made regarding the prior negative comments regarding artificial cervical discs and the comments accepted. This would seem to indicate a bias toward accepting negative data regarding surgical treatment while calling into question the positive outcomes.
Is the **DESCRIPTION** clear and accurate? If no, please comment.	X		
Specific questions regarding the Policy determination:			
Therapeutic Interventions: • The policy indicates that the use of artificial intervertebral discs is investigational in the treatment of cervical and lumbar degenerative disc disease. Do you agree? - If no, please comment and cite literature to support.		X	We do not agree with the policy indicating that artificial intervertebral discs of the spine are considered investigational for treatment of disorders of the spine, including degenerative disc disease. This conclusion is not consistent with the favorable results from the available published literature, nor does it indicate the prevailing clinical opinion among neurosurgeons and orthopedic spine surgeons. In addition to the comments as noted above, the follow references are cited for support from the literature. Food and Drug Administration (FDA). Clinical review for PMA (P040006) Charité artificial disc, DePuy Spine Inc (report on the Internet). Edited, United States Department of Health & Human Services, 2004. Food and Drug Administration (FDA). In-depth statistical review for expedited PMA (P040006) Charite artificial disc, DePuy Spine Inc (report on the Internet). Edited, United States Department of Health & Human Services, 2004. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED). Prosthesis intervertebral disc (report on the Internet). Edited, 2004.

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			Food and Drug Administration (FDA). New device approval: PRESTIGE cervical disc system - P060018 [report on the Internet]. Edited, 2007. Food and Drug Administration (FDA). New device approval: ProDisc-C total disc replacement - P070001 [report on the Internet]. Edited, 2007. Food and Drug Adminstration (FDA) Executive Summary, Bryan Cervical Disc. Edited, 2007. Washington State Department of Health, Center for Health Statistics, Comprehensive Hospitalization Abstract Reporting System (2005-2007). Edited. Abd-Alrahman, N.; Dokmak, A. S.; and Abou-Madawi, A.: Anterior cervical discectomy (ACD) versus anterior cervical fusion (ACF), clinical and radiological outcome study. Acta Neurochir (Wien), 141(10): 1089-92, 1999. Amit, A., and Dorward, N.: Bryan cervical disc prosthesis: 12-Month clinical outcome. British Journal of Neurosurgery, 21(5): 478-484, 2007. Anderson, P. A., and Rouleau, J. P.: Intervertebral disc arthroplasty. Spine, 29(23):2779-86, 2004. Bartels, R. H.; Donk, R.; van der Wilt, G. J.; Grotenhuis, J. A.; and Venderink, D.: Design of the PROCON trial: a prospective, randomized multi-center study comparing cervical anterior discectomy without fusion, with fusion or with arthroplasty. BMC Musculoskelet Disord, 7: 85, 2006. Bertagnoli, R.; Duggal, N.; Pickett, G. E.; Wigfield, C. C.; Gill, S. S.; Karg, A.; and Voigt, S.: Cervical total disc replacement, part two: clinical results. Orthop Clin North Am, 36(3): 355-62, 2005. Bertagnoli, R., and Kumar, S.: Indications for full prosthetic disc arthroplasty: a correlation of clinical outcome against a variety of indications. Eur Spine J, 11 Suppl 2:S131-6, 2002.

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	Yes	**No**	**Comments**
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• If you consider artificial intervertebral discs medically necessary in the treatment of cervical and lumbar degenerative disc disease: - Are there any specific criteria which would be useful in selecting appropriate patient populations?	X		The indications would be symptoms attributed to cervical or lumbar degenerative disc disease including signs of neurological compression. Artificial disc replacement is a potential alternative to spinal fusion in patients and intended to preserve motion at the involved spinal level to decrease stresses on adjacent segment structures and the risk of adjacent segment disease. This would also be based on the inclusion criteria of the patients enrolled in the clinical IDE studies.
- Are there any specific contraindications which would be useful in identifying patients for whom artificial intervertebral discs is not appropriate?	X		We would recommend that clinical or patient characteristics for which the artificial intervertebral disc is not appropriate include patients with spinal instability (sagittal plane translation >3.5mm, sagittal plane angulation >20°), facet joint pathology, osteoporosis, cancer, and infection. The literature supporting this is as indicated in the large scale clinical trials.
• The FDA approval for these devices is contingent upon 5-7 year follow up studies. o Do you think the current literature is sufficient to support use of artificial intervertebral discs?	X		This statement by the FDA does not indicate any specific negative concerns related to the devices as this question would seem to indicate, as otherwise the artificial cervical and lumbar discs would not have been approved by the FDA. This is a continued evolution of the FDA process with the Center

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			for Devices and Radiological Health (CDRH) developing new protocols for postmarket surveillance to monitor the performance of marketed medical devices.
***Improved Patient Outcomes*:** • Is there adequate evidence to demonstrate that the use of artificial intervertebral discs provide significant improvements in clinical outcomes compared to cervical or lumbar fusion?	X		The rationale for this has been provided in the prior questions.
• Is there *peer-reviewed literature,* other than that cited in the policy, to demonstrate improved patient outcomes due to the use of artificial intervertebral discs? If so, please cite.	X		The citations for this literature have been provided in the previous questions.
Is there *other information* you feel is relevant regarding the *medical necessity* of this technology?		X	
***Conflict of Interest*:** Do you have now, or have you had previously, any commercial or research relationship with any company or program which provides or markets products dealing with artificial intervertebral discs? If so, please disclose that relationship.		X	

EXHIBIT I

Medically Necessary Definition

"Medically Necessary" are procedures, treatments, supplies, devices, equipment, facilities or drugs (all services) that a medical practitioner, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- in accordance with generally accepted standards of medical practice; and
- clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and
- not primarily for the convenience of the patient, physician or other health care provider; and
- not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, national physician specialty society recommendations and the views of medical practitioners practicing in relevant clinical areas and any other relevant factors.

Investigational Definition

The term "investigational" means that the medical policy does not meet the Technology Evaluation Criteria.

This means any procedure, treatment, supply, device, equipment, facility or drug (all services), are determined NOT to:

- have final approval from the appropriate government regulatory body; or
- have the credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community which permits reasonable conclusions concerning the effect of the procedure, treatment, supply, device, equipment, facility or drug (all services) on health outcomes; or
- improve the net health outcome; or

- be as beneficial as any established alternative; or
- show improvement outside the investigational settings.

NCD Response for Cervical Artificial Discs

J.S. Cheng, MD, MS

On behalf of the NASS/AANS/CNS, we appreciate the opportunity to comment on the recently released Centers for Medicare and Medicaid Services (CMS) posting of potential national coverage determination (NCD) topics. In particular, this comment is in regards to artificial cervical discs. CMS has noted that: *"Artificial cervical discs are being developed in an effort to treat symptomatic degenerative disc disease more effectively. The goal of this type of technology is to maintain spinal motion following anterior discectomy, to reduce the incidence of degeneration of adjacent disc levels of the spine (adjacent-segment disease), and to permit more rapid return to normal activity. Is the evidence adequate that this procedure results in improved health for the Medicare population?"*

The current evidence regarding artificial cervical discs is adequate and shows that this procedure results in improved health outcomes in the patients receiving this procedure, however the majority of patients are not in the Medicare population. Given this, we do not recommend CMS offering a National Coverage Decision based on the evidence currently available. We feel that any comment by CMS given the insufficient data in the Medicare population would only allow third-party insurers to refuse authorization of these procedures, and limit the availability of this procedure despite the number of studies indicating the improvement in our patient's health.

We understand that there is a concern regarding the overutilization of these technologies and a misperception that it is without a net health benefit, and would like to address this. Spinal spondylosis, including cervical degenerative disease and spondylosis is a common problem in the United States and associated with aging (Emery 2001). This due to the avascular nature of the spinal disc and as it loses proteoglycans, such as chondroitin sulfate, and moisture it is unable to repair itself and becomes inelastic with microfissures and associated disc herniations resulting in settling and collapse of the disc space. This change in the disc space results in abnormal spinal motion patterns and further leads to anatomical changes in the formation of osteophytic spurs and can be associated with impingement of nerve roots or the spinal cord. This is a common radiographic finding with 60% of people over the age of 40 showing evidence of cervical degenerative disc disease and spondylosis, and by age 65, almost 95% of men and 70% of women have such changes. However, this results in a significant adverse affect on the health of our citizens, with over 5 million US adults disabled by spine-related disorders and a number of these patients being good candidates for surgery. This is frequently performed in relation to their symptoms, such as cervical radiculopathy which may manifest as arm pain, weakness, or paresthesias, along with cervical myelopathy, which may present with gait or balance difficulties, arm or leg weakness, along with arm or hand numbness.

The initial treatment for cervical spondylosis and degenerative disease is not surgery. Rather, patients undergo initial management with pharmacological agents such as NSAID's, analgesics, or muscle relaxants, and supplemented with physical therapies such as strength training, stretching, massage, or manipulation therapies. If the patient symptoms related to their disease persists or worsens, then

additional treatment including biofeedback or cognitive therapies may be added along with interventional procedures such as epidural steroid injections, facet deinnevation, or trigger point injections. Other alternative therapies may also be used by these patients such as intradiscal radiotherapy or acupuncture. However, these are not panaceas for this disease process with patients having spine problems showing an overall higher medical costs with reports of over $80 billion dollars a year spent on non-surgical management of spinal disorders and the pain and symptoms related to this (Brook 2008). This can be contrasted to the $570 million that CMS paid in professional fees in 2007 for the entire field of neurosurgery (cranial and spinal), which represents less that ¾ of 1% of what has been spent on non-surgical treatment. Non-surgical treatments have resulted in an increase in expenditures of 65% (adjusted for inflation) from 1997 to 2005. Unfortunately despite this, this is still associated with a significant physical function limitation and decrease in the activities of daily living as self-reported by patients, with 24.7% noting such problems causing issues related to their mental health, physical functioning, work or school limitations, and social limitations.

This debilitating degeneration disease was first noted by Bailey and Casamajor in 1911 when they first described osteo-arthritis of the cervical spine. Further work in this area was performed by Stookey in 1928 in describing how these patients are also affected by the associated herniations of cervical discs with compression of spinal cord and nerves. Clarke and Robinson in 1956 noted that this was not a static problem, but rather that disease and symptom progression was common, albeit gradual. However, improvement was rare and prognosis was generally poor. This was further supported by Lees and Turner in 1963, who described a lengthy clinical course for cervical spondylosis with long periods of non-progressive disability. To confound the issue further, cervical spondylotic radiculopathy and myelopathy symptoms may resolve with time, which may explain the current controversy in how best to manage this disease process. However, cervical spondylosis and associated myelopathy remains the most common cause of nontraumatic spastic paraparesis and quadriparesis, and represents 23.6% of these severely disabled and medically needy patients .

It is this unacceptable result of the natural history of this disease that has lead to the development of surgical treatments and techniques. Bucy in 1947 had initial attempts to treat this disorder with a laminectomy with transdural approach, but with results which were not satisfactory. Further refinement in techniques by Frykholm in 1951 or Mayfield in 1955 with hemifacetectomies also did not result in significant health improvements, until an anterior approach was developed by Cloward in 1953 and further refined by Smith and Robinson in 1958. This technique has been further refined and improved upon in medicine with the advent of graft material and instrumentation, leading to anterior cervical discectomy and fusions being the current definitive surgical treatment (Irwin 2005). Typically, the patients in whom surgery would be indication are those that have failed 6 months of conservative therapy, are unable to perform their activities or daily living due pain or neurological symptoms, persistent or progressive axial neck pain despite conservative treatment, or significant pain from stenosis. In these patients, surgery has resulted in the resolution of symptoms in 80-100% of those treated (Xie 2007, Yue 2005). It is this improvement that has resulted in the skyrocketing use of this procedure, especially as more surgeons are trained in this technique as noted that in 1988-90 with 26,000 procedures which has grown to 124,000 procedures per year in 1999.

Although surgery has now improved on the patient's health as compared to their natural history of their disease, it is not without its own drawbacks. Chief amongst these are concerns regarding adjacent segment spondylosis which has been reported to occur at a rate of 2.9% per year with an overall incidence of 25.6% based on survivorship analysis. This has been felt to be related to variables related to the patients underlying clinical disease along with iatrogenic and lifestyle choices, but also related to the fusion construct itself as related to the biomechanical alterations of a functioning joint. This has lead to the advent of artificial intervertebral disc arthroplasty as an alternative to anterior cervical fusions in patients with cervical spondylosis and degenerative disc disease (Acosta 2005, Anderson 2007, Smucker 2006, Phillips 2005, Anderson 2004, Pracyk 2005, Bertagnoli 2005). These studies were limited, and showed that cervical arthroplasty was at least as effective as cervical fusions and without any significant complications in those patients who had similar surgical indications to ACDF such as radiculopathy and myelopathy (Brown 2006; McAfee 2004). There are reports that the patients with cervical arthroplasty having an improved post-operative course given that it does not use an anterior cervical plates or orthoses, and with a shorter recovery period due to not using bone grafts (Traynelis 2007, Goffin 2006). As well, cervical disc arthroplasty has been associated with maintaining cervical disc height, along with lordosis and motion at the index and at the adjacent cervical spine levels (Sears 2006). This has been postulated to reduce the risk of adjacent level degeneration (Traynelis 2007) and improve the force/load transfer to the adjacent cervical levels (Phillips & Garfin 2005). This has been shown in a number of biomechanical models, which show that there is altered adjacent segment kinematics in patients or spines with a fusion, but as these are biomechanical studies, they do not portend to establish clinical relevance (Anderson 2007, Phillips 2005, Wigfield 2002). It is only in the recent past that further development of available tools to study cervical spine kinematics in a clinical setting has been developed and this shows that there is preserved adjacent segment kinetics in patients with an arthroplasty (Cheng 2007).

Cervical disc arthroplasty is a technology that has final approval from the appropriate governmental regulatory bodies, with the Prestige ST Cervical Disc receiving FDA marketing approval on July 16, 2007 and the ProDisc™-C Total Disc receiving a premarketing application (PMA) approval on December 17, 2007 and further FDA marketing approval on December 22, 2007. In addition, the Bryan Cervical Disc received an approvable decision by an FDA advisory panel on July 17, 2007 but has not received a final marketing approval. These devices have similar indications for use in skeletally mature patients with cervical spine disease at C3-C7 necessitation a single-level discectomy. These devices are implanted via an open anterior approach, similar to that of an ACDF, and used for symptoms similar to an ACDF for patients with intractable pain, radiculopathy, and/or myelopathy associated with radiographic studies showing a herniated cervical disc or osteophytes. In addition, the scientific evidence has permitted us to conclude that this procedure and technology has a net benefit on the health outcomes on our patients. Criticism has been raised regarding the non-inferiority design of the available randomized controlled clinical trials, and how such a study design does not provide sufficient evidence insufficient to support conclusions as it does not establish statistical superiority. However, this is confusing the science behind device studies with those from other disciplines, much as the criticisms from BC/BS TEC Assessment (http://www.bcbs.com/blueresources/tec/tec-assessments.html) about the non-blinded nature of these studies as it would be physically impossible to double blind a surgeon regarding an implant that is to be

surgically placed. As well, there are a number of studies that have addressed the concerns regarding the technology in improving the net health outcome and that this procedure has been shown to be as beneficial as any established alternatives, such as the ACDF. This is not a device to be frequently used in Medicare age patients, with the average population being young with patients in their mid-40's. Although these were non-inferiority study and not designed to show a net health benefit with statistical superiority, it should be noted that better results in regarding to the neurological variable along with overall success has been established. Mummaneni in 2007 had reported results in which the overall outcomes were similar between the groups receiving anterior cervical fusion versus arthroplasty, with the arthroplasty patients showing preservation of motion with retention of sagittal angular motion of over 7 degrees, along with a 2-point greater improvement in the Neck Disability Index (NDI). There were issues in that they were unable to show that variables such as Functional spinal unit (FSU) height reached predetermined levels, but it should be noted that they had difficulty due to anatomical interference and that alternate determinations were made without the FSU height included. Although it was not statistically significant, there was an overall success with better SF-36 at 12 and 24 months associated with a greater relief of neck pain and earlier return to work in the arthroplasty group. There were no serious associated adverse events and no cases of implant failure or migration, along with a lower rate of revision surgeries ($p = 0.0277$) including a lower rate of supplemental fixation ($p = 0.0031$) and of re-operations at the adjacent segment ($p = 0.0492$). As well, data is slowing developing that shows that this improvement is attainable outside the investigational settings, but it should be noted that this is hampered by the lack of support of payors regarding approving new technologies in their patients.

In regards specifically to the Medicare population, which is considered to be patients over the age of 65 or those with permanent disabilities, there are only small numbers of patients who have fallen into this category in the prior studies. Prior IDE studies included patients only within the ages of 18-60, and along with their exclusion criteria which excludes patients with severe disabilities and comorbidities, this does not capture patients within the Medicare population. The study by Mummaneni did include patients with cervical arthroplasty up to age 72, and had fusion control patients up to age 73, this was a very small number of patients and data on this subgroup will not be able to show any statistical significance. We feel that it is important to understand that this is different than concluding that there is insufficient data to justify the use of cervical arthroplasty in the Medicare population, and render a national coverage determination based on this "backwards logic". In addition, the studies are well designed but for answering the hypothesis at hand regarding patient safety and surgical outcome, and does not delve into trying to answering the questions regarding radiographic evidence of adjacent-segment degeneration, wear debris in the disc space, or clinical relevance of secondary surgical procedures. These questions have been addressed and positively concluded in various biomechanical studies, and shared as conference presentations, posters, and abstracts, and are not routinely included in a clinical paper. As such, this also would be unfair criticisms of this technology and procedure. However, we support and encourage further research endeavors into cervicaldisc arthroplasty in Medicare age patients along with further long term follow-up in regards to patient outcomes and adverse events, with recommendations to present this data to the CMS for consideration.

Our societies are committent to the welfare of our patients, and are working to achieve this by evaluating new procedures and devices based on the strength of available scientific evidence, length of follow up for long term results, studies that are independent and free from bias, and with results applicable to the general population. In addition, we are also evaluating these based on the magnitude of the positive health effect and cognizant of the costs of new technologies with needing to establish an improvement over existing technology or procedures along with its comparison to similar available technologies. However, we understand the ramifications of "jumping to conclusions" either way. A well intended, but misinformed negative NCD by CMS will have significant ramifications in the ability of the citizens of the United States in obtaining the healthcare they need and deserve. Given this, we recommend that we continue to support the use of cervical arthroplasty and continue to work towards the improvement of the health care of our patients.

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15. Mummaneni, et al. Journal of Neurosurgery Spine. 2007 Mar; 6(3):198-209. Clinical and Radiographic Analysis of Cervical Disc Arthroplasty Compared with Allograft Fusion: A Randomized Controlled Clinical Trial. [Medtronic Funded, PRESTIGE® Cervical Disc* (Medtronic)]

    This was a prospective, randomized, controlled trial of 541 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive PRESTIGE® Cervical Disc or ATLANTIS® Cervical Plate with allograft (ACDF) and followed up at 3 and 6 weeks, 3, 6, 12 and 24 months. The results noted that the PRESTIGE® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with improved neurological status (superiority), improved clinical outcomes, and a reduced rate of secondary surgeries compared to ACDF. Superiority in overall success (study endpoint) was demonstrated at 24 months in the PRESTIGE® Cervical Disc cohort.

16. Heller, et. Al. Abstract, 2007 North American Spine Society Annual Meeting. Comparison of BRYAN® Cervical Disc Arthroplasty with Anterior Cervical Decompression and Fusion: Clinical and Radiographic Results of a Randomized Controlled Clinical Trial. [Medtronic Funded, BRYAN® Cervical Disc (Medtronic)]

    This was a prospective, randomized, controlled trial of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or Atlantis ® Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that the BRYAN® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with improved NDI Success (superiority), improved clinical outcomes, and 13 days faster return to work compared to ACDF patients. Statistical superiority in Overall Success (study's primary endpoint) was demonstrated at 24 months in the BRYAN® Cervical Disc cohort.

17. Murrey, et. Al. Abstract, 2007 Cervical Spine Research Society Annual Meeting. Twenty-four month results from the prospective, randomized, multi-center IDE Trial of PRODISC-C® vs. ACDF. [PRODISC-C®, Synthes Spine]

    This was a prospective, randomized, controlled trial of 209 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive PRODISC-C® or ACDF with plate and allograft with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that Prodisc-C® is "not inferior" to ACDF 2 years after surgery in Overall Success, the study's primary endpoint.

18. Sasso, et. Al. J Spinal Disord Tech. Vol. 20, Number 7, Oct. 2007. Clinical Outcomes of BRYAN® Cervical Disc Arthroplasty: a Prospective, Randomized, Controlled, Multi-Center Trial With 24-month Follow-up. [BRYAN® Cervical Disc, Medtronic]

    This was a prospective, randomized, controlled trial of 115 patients from 3 U.S. IDE study sites for the BRYAN® Cervical Disc IDE Study Subset of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results noted that the BRYAN® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with statistically superior scores in Neck Disability Index, Neck Pain, and SF-36 PCS 24 months after surgery.

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    This was a prospective, randomized, controlled trial of 55 patients consisting of 27 PRESTIGE® II Cervical Disc with 28 iliac crest autograft fusion and with 2-year follow up with most of the outcome measures tending to favor the PRESTIGE® II Cervical Disc, and with the PRESTIGE® II Cervical Disc maintaining motion at treated level without adjacent segment compromise.

20. Hacker, et al. Journal of Neurosurgery Spine 2005 Dec; 3:424-28. Cervical Disc Arthroplasty: A Controlled Randomized Prospective Study With Intermediate Follow Up Results. [Medtronic Funded, BRYAN® Cervical Disc, Medtronic]

    This was a prospective, randomized, controlled trial of 46 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft with follow up of 3 and 6 weeks, 3,6,12 and 24 months. The results show that all patients reported in this study had reached a minimum of 1-year follow up with no device related complications and with equivalent results in releif of arm and neck pain seen in both study groups. The treatment parameters other than OR time were similar with no serious neurological or systemic complications observed and preserved motion was revealed in all BRYAN® Cervical Disc-treated patients.

21. Coric, et al. Journal of Neurosurgery Spine, 2006 Jan, Vol 4:31-35. Prospective Rrandomized Controlled Study of the BRYAN® Cervical Disc: Early Clinical Results from a Single Investigational Site. [Medtronic Funded, BRYAN® Cervical Disc, Medtronic]

    This was a prospective, randomized, controlled trial of 33 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft and follow up of 3 and 6 weeks, 3, 6, 12, 24 months. The results noted that at mean follow up at time of report of 19 months, there was no device

relateed complications and had similar improvements seen in both study groups. The BRYAN® Cervical Disc patients demonstrated maintenance of motion at treated level.

22. Nabhan, et al. Eur Spine J, 2007 Mar; 16(3):423-30. Disc Replacement Using PRODISC-C® versus Fusion: A Prospective Randomized and Controlled Radiographic and Clinical Study. [PRODISC-C®, Synthes Spine]

    This was a prospective, randomized, controlled trial of 25 patients with cervical disc herniation who were randomized to receive either a PRODISC-C® or ACDF. Radiostereometric analysis was used to quantify intervertebral motion immediately and at 3, 6, 12 and 24 weeks. Clinical results were judged using VAS and neuro examination. Motion decreased in both groups over time, however, the loss of segmental motion was significantly higher in the ACDF group. Significant pain reduction was observed in both groups ($p>0.05$). The cervical spine disc prosthesis preserves cervical spine segmental motion within the first 6 months after surgery. Clinical results were the same as early results of ACDF.

23. Anderson, et al. Journal of Neurosurgery, 2004. Comparison of Simulator-Tested and Retrieved Cervical Disc Prostheses. [BRYAN® Cervical Disc, Medtronic].

    This sudy compared wear/debris of human explanted BRYAN® Cervical Discs and PRESTIGE® Cervical Discs to wear/debris from discs tested on a spine simulator. Simulator predicted adequate wear for prostheses out to 40 years and human explants exhibited less wear than predicted by simulators (5 to 10 fold).

24. Anderson, et al. The Spine Journal, 2004. The BRYAN® Cervical Disc: Wear Properties and Early Clinical Results. [BRYAN® Cervical Disc, Medtronic]

    This was an in vitro study to assess the BRYAN® Cervical Disc's wear properties and clinical results with an in vitro mechanical testing in a caprine animal model and in a prospective European human trial. In vitro wear averaged approximately 1.76% by weight at 10M cycles and 18% by weight at 40 million cycles. Wear debris were present in periprosthetic tissues without inflammatory response in animals. 90% of European trial patients had satisfactory results.

25. Bertagnoli, et al. Journal of Neurosurgery, 2005. Early Results After PRODISC-C® Cervical Disc Replacement [PRODISC-C®, Synthes Spine]

    This was a case series with follow up at 3, 6, and 12 months and looking at radiographic examination (ROM), ODI, and VAS. At 12 months 63.6% patients completely satisfied, 36.4% satisfied, and 0% unsatisfied.

26. Bertagnoli, et al. Ortho. Clin N. Am., 2005. Cervical Disc Replacement:Part II Clinical Results. [PRODISC-C®, Synthes]

This was a case series of 27 patients with follow up at 3 and 6 wks, 3, 6, 12 months looking at NDI, VAS, ROM, and other clinical parameters. At 12 months it was noted that 52% completely satisfied, 36% satisfied, 12% unsatisfied.

27. Cummins, et al. Journal of Neurosurgery, 1998. Surgical Experience with an Implanted Artificial Cervical Joint. [BRISTOL-CUMMINS DISC]

    This is a retrospective cohort study looking at the surgical experience with the implantation of movable stainless-steel joints in 20 patients. Joint motion was determined by measuring the distance between cervical spine segments during flexion/extension. Follow up 3-65 months. No patients required additional motion segment surgery. Radiography did not demonstrate fusion at the treated level in any patient. Adjacent segment joint degeneration was absent. 16 of 20 patients reported improvement in pain relief. Three patients were considered failures because pain persisted or worsened. Complications were attributed to poor screw placement, incompatible screws, one-size-fits-all implants, and manufacturing errors. Stainless steel appears to suitable for this joint replacement design. With appropriate modification of sizes, this joint is shown to be capable of stability and motion and deserves further clinical evaluation.

28. Datta, et al. J Spinal Disord Tech, Vol. 20, Number 1, Feb. 2007. Sagittal Split Fractures in Multilevel Cervical Arthroplasty Using a Keeled Prosthesis [PRODISC-C®, Synthes Spine]

    This is a case report of a 34-year old male with a 2-level cervical spondylosis unresponsive to nonoperative care for 24 months. FDA compassionate use granted for treatment with Prodisc - C® at C5-6 and C6-7 levels The PRODISC-C® was inserted successfully at the C6-7 level. Following that, during use of a keeled osteotome at the C5-6 level, a loss of resistance was felt and radiographic imaging revealed a sagittal split fracture of the C6 vertebral body with no instability or loose fragments observed. Insertion of the PRODISC-C® at C5-6 was performed as planned. Postoperative radiographic evaluation revealed a fracture of the C5 vertebral body that was not detected during surgery. The patient had immediate relief of his preoperative symptoms and eventual relief of neck pain related to the fracture. The author concludes that this adverse event may be attributed to the keeled design of the prosthesis, as well as the need for chisel cutting before and during insertion of the prosthesis.

29. Dmitriev, et al. SPINE, 2005. Adjacent Level Intradiscal Pressure and Segmental Kinematics Following Cervical Arthroplasty. [PCM®, Cervitech, Inc.]

    This is a laboratory study looking at intradiscal pressure at levels adjacent to an arthroplasty. In 10 cadavers, similar adjacent level IDP's were recorded between TDR and intact spine in all loading conditions ($p<.05$). Segment above both arthrodesis groups had higher intradiscal pressure at adjacent level above ($p<.05$).

2004

Early Clinical Results

Following Cervical

Arthroplasty

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

22

Case Series Assess in vivo safety and

efficacy of the BRYAN®

Cervical Disc for the

treatment of cervical

DDD

22 single-level; 4 bi-level

Radiculopathy, n = 18

Myelopathy, n = 8

Outcome measures

SF-36

NDI

Radiological evaluation of segmental sagittal rotation

using quantitative motion analysis software

Mean follow up = 1-year

Significant differences (preop vs. postop) seen in NDI scores

Improvement trend seen in SF-36 PCS scores

Mean ROM at 1-year = 7.77°± 4.7°

Return-to-work summary

100% of patients receiving Workers Comp. returned to work

100% of radiculopathy patients working preoperatively returned to work

(mean = 3.2 months)

80% (n = 4) of radiculopathy patients receiving disability income returned

to work

20% (n = 1) of radiculopathy patients unable to return to work because of

unrelated cardiac problems

100% of myelopathy patients working preoperatively returned to work (mean

= 2 months)

Goffin Abstract presented

at the 2007

Cervical Spine

Research Society

Annual meeting

Cervical Arthroplasty with

the BRYAN® Cervical Disc:

4- and 6-year results

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

78

Prospective,

concurrently enrolled,

multi-center trial

Long-term, postmarket

follow-up report from

multi-center, prospective

clinical trial with the

BRYAN® Cervical Disc

that began in 2000 and

concluded in 2004

69 single-level patients at 4-year follow-up

9 bi-level patients at 4-year follow-up

10 single-level patients at 6-year follow-up

Outcome measures: Odom's Criteria and postoperative

radiographic evidence of motion maintenance

4-year Odom's Criteria Outcomes for 1-level patients:

41 = excellent

20 = good

6 = fair

2 = poor

4-year Odom's Criteria outcomes for bi-level patients:

5 = excellent

3 = good

1 = poor

4-Year Radiographic Outcomes

"...motion was preserved in 57 single-level patients..."

"...only 5 single-level patients and one bi-level patients lost motion due to

paravertebral ossification. Anti-inflammatory medication was only only rarely

used at the time all o fthese patients with 4-year follow-up were operated on."

"for the bi-level group, motion was preserved at the cranial level in all patients

and at the caudal level in 6 patients”

6-year Radiographic Outcomes

...motion was preserved in 9 of the 10 cases”

Goffin Neurosurgery

2002

Preliminary Clinical

Experience with the

BRYAN® Cervical Disc

Prosthesis

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

60

Prospective,

Concurrently Enrolled,

Multi-center Trial

Assess the effectiveness

of the BRYAN® Cervical

Disc ability to treat single

level cervical DDD:

Provide relief of

neurologic symptoms

Improve patient ability

to perform acts of daily

living

Decrease pain

Maintain segmental

stability and motion

60 single-level patients

Outcome measures

Pain

Neurologic function

Radiographic range of motion

Clinical success at 1-year was 90%

Evidence of anterior and/or posterior migration was seen in one patient and

suspected in a second

No evidence of spondylotic bridging across the treated disc space

Mean ROM at 1-year was 9.0°± 5.0°

No devices explanted or surgically revised

Goffin SPINE

2003

Intermediate Follow

Up after Treatment of

Degenerative Disc Disease

with the BRYAN® Cervical

Disc Prosthesis: Single-

Level and Bi-Level

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

103

Prospective,

Concurrently Enrolled,

Multi-center Trial

Assess the effectiveness

of the BRYAN® Cervical

Disc ability to treat single

and bi-level cervical DDD:

Provide relief of

neurologic symptoms

Improve patient ability

to perform acts of daily

living

Decrease pain

Maintain segmental

stability and motion

60 single-level patients

43 bi-level patients

Outcome measures

Pain

Neurologic function

Radiographic range of motion

Follow up summary

Clinical success for both studies exceeded 85% acceptance criteria at 1-year

Average ROM

9.0°± 4.9°, single-level at 2 years

7.4°± 5.1°, bi-level at 1 year

No device failures or explants

Procedure is safe and patients recover quickly

Goffin Seminars in Spine

Surgery

2006

Complications of Cervical

Disc Arthroplasty

SAFETY and

DURABILITY

BRYAN® (Medtronic),

PRODISC-C®

(Synthes Spine),

PRESTIGE® LP

(Medtronic),

CERVIDISC, and PCM®

(Cervitech, Inc.)

Cervical Discs

Case Reviews Report possible

complications,

likely reasons for

complications, and

potential preventative

measures for

complications in cervical

disc arthroplasty

The authors reported their own as well as other

surgeons' complications with cervical arthroplasty

reported in peer-reviewed literature.

Unlike their lumbar cousins, cervical discs have a higher degree of

consistency with regard to surgical indications.

Intraoperative risks are not terribly different from an ACDF

Early postoperative and intermediate complications may be prevented by

meticulous surgical decompression, proper endplate preparation, adequate

stability at the bone-implanrt interface, and use of proper postoperative

medications.

The majority of patients with paravertebral ossification remain mobile at 2

and 4-year follow up on dynamic plain flexion/extension radiographs.

Long-term wear testing results have been favorable and up to this point no

clinical study has identified a significant osteolytic process following cervical

arthroplasty.

Jensen SPINE

2005

Bone Ingrowth in Retrieved

BRYAN® Cervical Disc

Prosthesis

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

Explant Analysis Assess bone ingrowth

in retreived BRYAN®

Cervical Discs

2 chimpanzees implanted at C3-C4

BRYAN® Cervical Disc retrieval and interbody fusion

performed 3-months postop

2 humans implanted with BRYAN® Cervical Disc

Retreival and interbody fusion performed at 8 and 10

months

All BRYAN® Cervical Disc implants had stable fixation on preoperative

radiographic examination and upon removal

Chimpanzee ingrowth ranged from 10%-50%

Human ingrowth was 30.1%

Results comparable to hip and knee arthroplasty ingrowth rates of 10%-30%

Johnson Neurosurgical Focus

2004

Sagittal Alignment and the

BRYAN® Cervical Artificial

Disc

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

13

Case Series Evaluate cervical spine

radiographs to determine

sagittal alignment in

patients who underwent

one or two level

arthroplasty with the

BRYAN® Cervical Disc

13 patients, 16 BRYAN® Cervical Discs

Preoperative and postoperative radiographs were

obtained

Standard measuring techniques were used to determine

spinal curvature

Patients undergoing 1-level disc replacement had a 4.7 degree mean

reduction in lordosis

Patients undergoing two-level disc replacement had no signficant changes in

sagittal alignment

Lafuente Journal of Bone and

Joint Surgery

2005

The BRYAN® Cervical

Disc Prosthesis as an

Alternative to Arthrodesis

in the Treatment of

Cervical Spondylosis: 46

Consecutive Cases

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

46

Case Series Assess BRYAN® Cervical

Disc as an alternative

to arthrodesis in the

treatment of cervical

spondylosis

46 single-level patients treated with BRYAN® Cervical Disc

C3-C7

Radiculopathy, 80%

Myelopathy, 20%

Outcome measures

VAS

SF-36

NDI

Radiological evaluation

1-year follow up

Highly significant differences (preop vs. postop) found at 1 year

VAS ($z = 6.42$, $p<0.0001$)

SF-36 MCS ($z = -5.02$, $p<0.0001$)

SF-36 PCS ($z = -5.00$, $p<0.0001$)

NDI ($z = 7.03$, $p<0.0001$)

BRYAN® Cervical Disc seems reliable and safe in the treatment of cervical

spondylosis

Leung Neurosurgery

2005

Clinical Significance of

Heterotopic Ossification in

Cervical Disc Replacement

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

Prospective,

Multi-center Trial

Investigate incidence

of HO in cervical disc

replacement, identify

associated risk factors

for HO, and to examine

relationship of HO to

clinical outcomes

Patient data obtained from European Consortium

HO defined by McAfee scale 12 months postop

Odom's criteria and SF-36

17.8% of patients experienced some HO

6.7% of patients experience d grade 3 or 4 HO

Male patients and older patients were associated with development of HO

Mehren Spine, Vol. 31, Nu.

24, 2006

Heterotopic Ossification in

Total Cervical Artificial Disc

Replacement

CLINICAL RESULTS PRODISC-C®

Synthes Spine

54

Prospective

multicenter trial

Evaluate rate of HO

following insertion of

PRODISC-C®

McAfee HO Grading Scale Grade 0 = 26

Grade 1 = 6

Grade 2 = 30

Grade 3 = 8

Grade 4 = 7

Nabhan Eur Spine J (2007)

16:423-430

Disc replacement using

Pro Disc -C® versus fusion:

a prospective randomised

and controlled radiographic

and clinical study

CLINICAL RESULTS PRODISC-C®

Synthes Spine

33

Prospective,

randomized,

controlled study

Compare clinical and

radiographic outcomes

of patients with 1-level

symptomatic soft disc

herniation treated with

PRODISC-C® or ACDF

Neck and arm pain VAS scores and RSA motion analysis

at 3, 6, 12, and 24 weeks postoperatively

"…significant reduction of neck and arm pain without statistical difference

between the two groups…"

"...motion decreases over time in the presence of both disc replacement with

PRODISC-C® or ACDF….However, the loss of segmental motion is significantly

higher in the ACDF group..."

Parkinson Journal of

Neurosurgery

2005

Cervical Arthroplasty

Complicated by Delayed

Spontaneous Fusion

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

Case Report Assess BRYAN® Cervical

Disc to treat cervical

radiculopathy at C5-C6

55-year-old female underwent single-level BRYAN®

Cervical Disc placement at C5-C6

Postop dyamic imaging demonstrated loss of motion at

treated level

Patient suffered persistent neck pain

Arm pain resolved slowly

Osseous fusion observed across disc interspace

posterior to prosthesis at 17 months

Spondylotic lipping at C4-5 and C6-7 appeared to have

progressed on radiographic examination

Complication explained to patient who then stated she was happy with her

present degree of pain relief and declined further intervention

Precise reason for phenomenon is unclear

This is an exceedingly rare complication

Pickett Journal of

Neurosurgery

2006

Complications with

Cervical Arthroplasty

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

74

Prospective Case

Series

Determine incidence

and distribution

of perioperative

complications with

BRYAN® Cervical Disc

96 discs implanted in 74 patients Perioperative complication rate was 6.2% per treated level

1 retropharyngeal hematoma developed and had to be evacuated

3 cases of worsened neurological complications

1 case of intraoperative migration

1 case of postoperative migration with segmental kyphosis

1 postoperative severe segmental kyphosis was revised with custom-made

lordotic BRYAN® Cervical Disc

2 cases of heterotopic ossification and spontaneous fusion

1 partial dislocation seen in a patient with preoperative segmental

hypermobility

25% of patients reported neck and arm pain in late postoperative time points

Postoperative trend of kyphotic C2-7 curvature observed

Pickett Neurosurgical Focus

2004

Effect of a Cervical Disc

Prosthesis on Segmental

and Cervical Spine

Alignment

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

14

Case Series Assess the impact of the

BRYAN® Cervical Disc on

sagittal alignment of the

treated motion segment

and the overall cervical

spine (C2-C7)

14 BRYAN® Cervical Disc patients for whom early

(<6 months) and late (6-24 months) follow up were available

Static and dynamic radiographs measured by hand and

computer to determine:

Angles formed by the endplates of the natural disc

preoperatively

Angles formed by the shells of the implanted prosthesis

Angle of the FSU

C2-C7 Cobb angle

NDI

SF-36

BRYAN® Cervical Disc shell angle in neutral position became kyphotic

Mean change = -3.8°

Mean ROM at late follow up = 8.25°

FSU angles became became significantly more kyphotic postoperatively

Mean change = -6.0°

Cobb angles did not change significantly

Overall sagittal balance of the cervical spine was preserved

Pickett SPINE Kinematic Analysis

Following Cervical

Arthroplasty

SAFETY and

DURABILITY

BRYAN® Cervical Disc

Medtronic

20

Case Series Assess the biomechanical

profile of the cervical

spine following

arthroplasty

20 patients underwent 1 or 2-level BRYAN® Cervical Disc

implantation to treat DDD with radiculopathy and/or

myelopathy

Lateral films obtained at intervals up to 2 years

postoperatively

Neutral

Flexion

Extension

Kinematic parameters assessed using quantitative

motion analysis software

Sagittal rotation

Horizontal translation

Change in disc height

Center of rotation (COR)

Mean ROM at 2-year follow up = 7.8°

Kinematic parameters were not significantly altered following surgery

COR was most frequently located posterior and inferior to the center of the

disc space

BRYAN® Cervical Disc reproduced the preoperative kinematics of the cervical

spine

Pimenta The Spine Journal

2004

Clinical Experience with

the New Artificial Cervical

PCM® (Cervitech) Disc

CLINICAL RESULTS PCM®

Cervitech, Inc.

53

Case Series Pilot study with 53

patients in which 82

arthroplasties were

performed with the

PCM® cervical disc

1-year follow up

VAS

NDI

TIGT

Radiographic examination

90% patients had good to excellent results by 3 months

Robertson Journal of

Neurosurgery

2005

Assessment of Adjacent-

Segment Disease in

Patients Treated with

Cervical Fusion or

Arthroplasty: a Prospective

2-year study

ADJACENT

SEGMENT

DEGENERATION

BRYAN® Cervical Disc

Medtronic

232

Prospective 2-year

Study from Two

Independent Clinical

Studies

Compare incidence

of radiologically

documented changes and

symptomatic adjacentsegment

disease after

single-level anterior

cervical discectomy and

subsequent fusion or

athroplasty

Each study required serial radiography preoperatively

and at 24 months, as well as serial clinical evaluations

documenting adverse events, neurologic status, and

SF-36 results

- 74 BRYAN® Cervical Disc patients

- 158 AFFINITY® Cage patients

All serial radiographs and clinical data were examined by

authors for evidence of new adjacent-segment DDD

Fusion was associated with significant increase in x-ray film-based changes of

adjacent-segment disease (p=0.009)

Incidence of symptomatic adjacent-level DDD was statistically greater than

that in the group treated with the artificial disc (p=0.018)

Fusion patients required a statistically greater number of medical treatments

related to episodic symptoms of neck, shoulder, and arm pain attributed to

new disc disease (p=0.001)

Robertson Neurosurgical Focus

2004

Long-term Outcome

after Implantation of the

PRESTIGE® I Cervical Disc

in an End-Stage Indication:

4-Year Results from a Pilot

Study

CLINICAL RESULTS PRESTIGE® Cervical

Disc*

Medtronic

*FDA Approved 15

Pilot Study Assess long-term

performance of the

PRESTIGE® I Cervical Disc

in patients with endstage

cervical disease

15 patients, end-stage cervical disc disease

4-year follow up

Outcome measures

- SF-36

- NDI

- Neurological evaluation

- Radiological evaluation

NDI and SF-36 showed good improvement, especially considering the endstage nature of the disease

Radiographic analysis showed to PRESTIGE® I Cervical Disc maintained motion at 3 and 4 years postoperatively

Sekhon Journal of Clinical Neuroscience

2003

Two-Level Disc Placement for Spondylotic Cervical Myelopathy

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

Case Report Assess BRYAN® Cervical Disc for treatment of cervical radiculopathy at two adjacent levels

Implantation of BRYAN® Cervical Disc in 38-year-old woman with radiculopathy at C5-6 and C6-7

11-month follow up: no complications, patient's pain was resolved, films showed maintenance of motion and adequate cord decompression, no ectopic bone formation or osteophytes

Sekhon Journal of Neurosurgery

2005

Cervical Arthroplsty after

Fusion: 24 Discs in 15

Patients

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

15

Case Series Evaluate potential role

of cervical arthroplasty

in patients who have

already undergone

posterior cervical

foraminotomy or anterior

cervical interbody fusion

15 patients; 24 discs

6 previous posterior foraminotomy

9 previous anterior interbody fusions

Average follow up, 24 months

Good results in all cases as reflected by a 6.4 point improvement in arm pain

and neck pain VAS scores

Sekhon Neurosurgical Focus

2004

Cervical Arthroplasty

in Management of

Spondyloytic Myelopathy:

18-Month Results

CLINICAL RESULTS BRYAN® Cervical Disc

Medtronic

11

Case Series In vivo implantation of

BRYAN® Cervical Disc to

study its effectiveness

in treating spondylotic

myelopathy, preserving

range of motion, and

decelerating adjacentsegment

degeneration

11 patients

7 single level

4 bi-level

73% treated at either C5-6 or C6-7

Mean follow up = 18.4 months

Outcome measures

Nurick Grade

Oswestry NDI

Radiological evaluation

91% had good or excellent outcome

No major complications

1 spontaneous fusion observed at 17-month follow up, no further intervention

required

1 patient had transient worsening of preoperative pain symptoms along with

worsening of preoperative focal kyphosis

Improvement in Nurick Grade by 0.91 grades (p<0.001)

Improvement in Oswestry NDI by 41.5 percentage points (p<0.001)

This technique offers an excellent outcome in the short to medium term, but

longer follow up is warranted

Sekhon SPINE

2007

Magnetic Resonance

Imaging Clarity of the

BRYAN® , PRODISC-C®,

PRESTIGE® LP, and PCM®

Cervical Arthroplasty

Devices

MATERIAL

AFFECT ON MRI

ASSESSMENT

BRYAN® (Medtronic),

PRODISC-C®

(Synthes Spine),

PRESTIGE® LP

(Medtronic) , and

PCM® (Cervitech, Inc.)

Cervical Discs

20

Prospective,

Randomized,

Controlled, with

Double-blinded

Review

Compare postoperative

imaging characteristics of

the 4 currently available

cervical arthroplasty

devices at the level of

implantation and at

adjacent levels.

Preoperative and postoperative MRI scans of 20 patients

who had undergone cervical arthroplasty were assessed

for imaging quality. Five cases for each the BRYAN®,

PRODISC-C®, PRESTIGE® LP, and PCM® Cervical Disc

devices were analyzed. Six blinded spinal surgeons

scored sagittal and axial T2-weighted images using the

Jarvik 4-point scale.

The BRYAN® and PRESTIGE® LP Cervical Disc devices allowed satisfactory

visualization of the canal, exit foramina, cord, and adjacent levels after

arthroplasty. Visualization was significantly impaired in all PCM® and PRODISC-C®

cases at the operated level in both the spinal canal and neural foramina. At

the adjacent levels, image quality was statistically poorer in the PCM® and

PRODISC-C® than those of PRESTIGE® LP and BRYAN® Cervical Discs. Devices

containing non-titanium metals (cobalt-chrome-molybdenum alloys) prevent

accurate postoperative assessment with MRI at the surgical and adjacent levels

Sekhon Journal of Spinal

Disord Tech

2005

Reversal of Fusion with

a Cervical Arthroplasty

Prosthesis

SAFETY and

EFFECTIVENESS

BRYAN® Cervical Disc

Medtronic

Case Report Assess effectiveness

of BRYAN® Cervical

Disc in replacing a

failed arthrodesis

(pseudarthrosis) and

treating postoperative

bi-lateral radiculopathy at

the lower adjacent level

38-year-old male with radiculopathy underwent an ACDF

with plate fixation at level C5-C6

Developed radiculopathy at C6-C7 level 2 months after

surgery

Removal of fusion device at C5-C6 and subsequent

arthroplasty performed with BRYAN® Cervical Disc at

C5-C6 and C6-C7 levels

At discharge for second surgery, patient's neck pain and hand symptoms

improved and he had motion demonstrable on radiologic imaging

Sekhon Operative

Neurosurgery

2005

Cervicothoracic Junction

Arthroplasty after Previous

Fusion for Adjacent

Segment Degeneration:

Case Report

SAFETY and

EFFECTIVENESS

BRYAN® Cervical Disc

Medtronic

Case Report Case report 25-year-old female underwent two-level ACDF

Developed shoulder pain, neck pain, arm pain, and

parasthesia 18 months after surgery

MRI showed accelerated degeneration and neural

compression at C4-C5 and C7-T1 disc spaces

Previous fusion device was removed and arthroplasty

subsequently performed with BRYAN® Cervical Disc at

C4-C5 and C7-T1 levels

At discharge there was complete resolution of arm symptoms and reduction

in neck pain, and a reduction in the amount of pain medication she was taking

Shim** J Spinal Disord Tech,

Vol. 20, Number 6,

Aug. 2007

Posterior Avulsion Fracture

at Adjacent Vertebral

Body During Cervical

Disc Replacement with

Prodisc -c®

CLINICAL RESULTS PRODISC-C®

Synthes Spine

Case Report Case report on potential

complication with

Prodisc -c®

32-year-old male

Radiculopathy unresponsive to nonoperative care for

2 months

Treated with Prodisc -c® at C6-7 level

Following use of mallet to completely insert keel cutting chisel, copious bleeding occurred. The posterior central vertebral bodies of C6 and C7 were found to be fractured and avulsed bony fragments were displaced posteriorly compressing the spinal cord and had to be removed. The PRODISC-C® was inserted as planned and the patient recovered without neurological deficit. The author concludes that this adverse event may be attributed to the keeled design of the prosthesis, as well as the need for chisel cutting before and during insertion of the prosthesis.

Wigfield SPINE

2002

Frenchay Artificial Cervical

Joint: Results from a

Two-Year Pilot

CLINICAL RESULTS PRESTIGE® Cervical

Disc*

Medtronic

*FDA Approved

15

Case Series Assess safety, clinical

stability, and capacity of

a cervical intervertebral

disc prosthesis for

preserving motion in

the spine of patients

with DDD

15 patients/2-year follow up

Inclusion: Radiculopathy and/or myelopathy

Radiologically confirmed cervical disc herniation or

posterior osteophytes

Patients must have previous adjacent-level surgical

or congenital spinal fusion or radiologic evidence of

adjacent-level DDD

Outcome measures: SF-36, NDI, European Myelopathy

Score (EMS), and VAS

Motion was maintained and intervertebral disc height was re-established in all cases

Procedure considered safe for experienced spine surgeons to perform

Device was stable with no dislocation of components or screw backouts

Two screws broke, but without any consequences

Improvements in assessment scores were noted

Device maintained motion

Meticulous attention must be paid to surgical technique to maximize chances for good results

Wigfield Journal of Neurosurgery 2002

Influence of an Artificial Cervical Joint Compared with Fusion on Adjacent-Level Motion in the Treatment of Cervical DDD

ADJACENT SEGMENT DEGENERATION

PRESTIGE® Cervical Disc*

Medtronic

*FDA Approved

Case Series Report motion at

surgically treated and

adjacent levels after

ACDF and cervical

arthroplasty

12 BRISTOL™ Disc patients

13 ACDF patients

12-month follow up

Assess radiographic changes in adjacent level vertebral

angulation in flexion/extension

Arthroplasty maintains normal motion at treated and adjacent levels

ACDF results in increased motion at adjacent levels

Levels demonstrating increased motion appeared normal on preoperative

Radiographs

September 28, 2008

Kerry N. Weems, Acting Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Attention: CMS-1385-FC
Mail Stop: C4-26-05
7500 Security Blvd.
Baltimore, MD 21244-1850

Dear Mr. Weems:

On behalf of the North American Spine Society (NASS), (insert societies), we appreciate the opportunity to comment on the recently released CMS posting of potential National Coverage Determination (NCD) topics. In particular, our comments refer to the following four proposed NCD topics: 1) Bone Morphogenetic Proteins (BMP), 2) lumbar fusion for degenerative disc disease, 3) artificial cervical discs, and 4) vertebroplasty (VP) and kyphoplasty (KP).

The Medicare national coverage decision process is potentially a very powerful tool to define and regulate quality health care. At its best it can encourage critical analysis of the medical literature and the practice of evidenced based medicine. It can support best treatment options, limit unsubstantiated care and direct and stimulate needed research. At its worst, however, it can restrict individual patient treatment options and decisions based upon physician experience and be applied inappropriately and in unintended ways especially by non-Medicare insurance carriers.

Three areas of concern need to be highlighted. First, the study population for an NCD must be clearly defined. For example, spinal fusion is a procedure performed for a wide variety of diagnoses ranging from fracture to spinal deformity to disc degeneration. Each sub-group has different treatment indications and different levels of evidence. An NCD should clearly identify to whom it does and does not apply. The specific recommendation should not be expanded without careful consideration to dissimilar groups of patients with different diagnoses.

Second, an NCD focuses on the Medicare population (over age 65 or patients with permanent disabilities). Modern medicine realizes that individual patient physiology is a better metric for determining care, than a patient's age. When NCDs are based on age, (for example, non coverage over the age of 65) there should be a mechanism for individual consideration for atypical cases (For example, the 68 year old marathon runner, or the 22 year old paraplegic).

Finally, when evaluating the literature, many studies do not specifically include or target the Medicare population. Such research should not be summarily dismissed in the NCD

process. It does require, however, careful analysis to determine if and when the study conclusions can be extrapolated to Medicare population. Similarly,studies done primarily in the Medicare population may be applicable to younger non-Medicare patients.

A task force composed of members of the above societies was convened to review the proposed NCD topics. The medical evidence, as well as some pending publications and some research in progress, was reviewed and summarized for each topic. Each topic was then evaluated using three criteria:

1. Strength of the evidence
2. Relevance to the Medicare population
3. Likelihood that an NCD will improve the quality of spine care

Using these criteria, we have attempted to rank the topics in order of importance to patients. CMS NCD proposed topics in order of importance to Medicare patients:

1. BMP
2. VP/KP
3. Multilevel fusions
4. Cervical TDA

We have also taken the liberty of suggesting additional topics for NCD consideration in the future, which may be beneficial for CMS to consider. Those topics are as follows:

1. pulsed radiofrequency facet rhizotomy
2. moderate sedation
3. spinal orthosis
4. dynamic spinal fixation
5. interspinous distraction
6. intraoperative spinal monitoring

Bone Morphogenetic Protein (BMP)

CMS Proposed Topic-
"Members of the BMP family are potentially useful as therapeutics in areas such as spinal fusion. BMP-2 and BMP-7 have been shown in clinical studies to beneficial in the treatment of a variety of bone-related conditions including delayed union and non-union. BMP-2 and BMP-7 have received Food and Drug Administration (FDA) approval for human clinical uses. Certain off-label uses in cervical spine fusion may be associated with life-threatening complications. Is the evidence adequate to demonstrate health improvements in the Medicare population?"

Task Force Comments

Since FDA approval of rhBMP-2 (Medtronic) in 2002, BMPs have been widely used during spine fusion. The initial indication for BMP (rhBMP-2), based upon a premarket

study by ( ) was as a bone graft substitute for use during anterior lumbar interbody fusion at (levels) performed in conjunction with an interbody titanium cage (LT cage-Medtronic). Its use in anterior lumbar spine surgery has expanded to treat multiple levels of pathology and to include interbody devices from different manufacturers and devices of varying compositions (metal, bone and synthetic substances). Its "off-label" use has also been extended to posterior lumbar spine applications such as posterolateral fusion (PSF) or transforaminal interbody fusion (TLIF), and, to a much lesser extent, cervical spine applications have been reported. We will briefly review the evidence and comment on each of these uses

Anterior Lumbar Spine

Multiple studies, both basic science (list) and clinical (list), have substantiated the use of rhBMP-2 as a substitute for iliac crest bone graft (ICBG) in anterior lumbar interbody fusion. Equivalent fusion rates for have been demonstrated in a randomized prospective trial comparing anterior interbody fusion with either BMP or ICBG at (levels) in conjunction with titanium interbody cages. Multiple case series have also demonstrated its effectiveness (list). BMP has been shown to be safe (ref) and eliminates the need for a separate incision to obtain bone graft and its associated morbidity. Despite its high product cost, BMP has also been shown to be cost effective through more rapid mobilization, decreased hospital stay and more rapid return to work (check source for accuracy). The majority of these studies were done in younger patients and do not specifically address the Medicare population. Younger patients with strong, non-osteoporotic bone are required for fixation of the interbody titanium cage. There is no evidence to suggest that the BMP would be less safe or less effective in an older patient. Indeed, bone quality and not age may be a more important factor to consider when pathology permits a choice between anterior or posterior approach to achieve spinal fusion.

Posterior Lumbar Spine

While the body of literature evaluating BMPs in posterior spine fusion is somewhat limited by its relatively recent clinical availability, the literature is growing rapidly and includes a number of high quality studies. We have included some discussion of studies still in the editorial review process in order to demonstrate an appropriate response to CMS staff's expressed concern that ongoing critical evidence development should be undertaken once new technologies reach clinical practice. Several general issues are important in the evaluation of this literature. Firstly, variations in the specific BMP used, as well as dose, concentration, and carrier for each BMP may significantly affect risks or benefits. The studies evaluating high dose rhBMP-2 (40 mg, 2.0 mg/ml), lower dose rhBMP-2 (12 mg, 1.5 mg/ml), and rhBMP-7 all contribute to our overall understanding of biologics in lumbar fusion, but cannot necessarily be considered interchangeably. Secondly, the initial experience suggests that risks and benefits may differ based upon site (lumbar versus cervical) and application technique (PSF versus TLIF).

Posterolateral Spine Fusion (PSF)

The most significant available body of evidence examines the use of rhBMP-2 in posterolateral lumbar fusion. In 2002, Boden reported on a pilot study comparing

rhBMP-2 (40mg, 2.0 mg/ml) and iliac crest bone graft (ICBG) which suggested better fusion rates in the rhBMP-2 patients (Boden, S., Spine 2002; 27(21):2396-408). This led to an FDA approved randomized controlled IDE trial for rhBMP-2 and a compression resistant matrix (CRM) versus ICBG in single level posterolateral fusion. Two-year results from two centers participating in the IDE trial for rhBMP-2 (40 mg, 2.0 mg/ml) in single level posterolateral fusion have been reported (Dimar, J., Spine: Vol. 31, Number 22, pp 2534-2539). This subset of the RCT indicates better fusion rates, equivalent clinical outcomes and no increase in complications with rhBMP-2 versus ICBG. It is important to note that the dose/concentration of rhBMP-2 used in this study (40 mg, 2.0 mg/ml) was significantly greater than the dose/concentration (12 mg. 1.5 mg/ml) in the clinically available Infuse Bone Graft™ product (rhBMP-2/ACS). This raises the question of whether similar fusion rates will be achieved with the product in clinical use, but also affords a test of safety for posterolateral fusion, as complications were not seen with the much higher dose IDE protocol. A second published study from the same IDE trial data reports that the use of rhBMP-2 offsets, at least in part, the adverse effect of cigarette smoking on lumbar fusion rate (Glassman, S, Spine: Vol. 32, Number 15, pp 1693-1698). The complete IDE trial data set has been presented at national meetings, but is not yet published.

Several case series reports have been published on the use of clinically available Infuse Bone Graft™ (rhBMP-2 12 mg, 1.5 mg/ml) in an off-label posterolateral fusion application. One study examines the combination of rhBMP-2/ACS and ICBG, reporting better fusion rates at 2 years postoperatively as compared to ICBG alone (Singh, K., J Spinal Disord Tech 2006;19(6):416-423.). Another study reports on rhBMP-2/ACS in combination with several non-ICBG bone graft extenders, including local bone, demineralized bone matrix and bone bank bone (Glassman, S., Spine J 2007; 7:44-9). This study report fusion rates equal to or better than ICBG in single and multilevel posterolateral fusion cases. Neither study identifies complications related to the use of rhBMP-2/ACS. An additional study examines repeated exposures to rhBMP-2 without evident adverse consequences (Carreon, L., Spine. 2008 Feb 15;33(4):391-3.). An IDE pilot study comparing rhBMP-2 (12 mg, 1.5 mg/ml) combined with a ceramic bulking agent versus iliac crest bone graft in posterolateral lumbar fusion has been undertaken. It has been presented and is in editorial review (Bae H, Spine J 2007:7;IS-163S).

Most recently, a non-industry sponsored RCT comparing Infuse Bone Graft™ (rhBMP-2/ACS) versus ICBG in patients over 60 years of age has been completed. The study examines clinical outcomes, fusion success, and directly measured economic parameters. Initial perioperative cost data from this RCT demonstrated an increased initial cost for the hospital, but a net savings for the payer over a 3-month period with the use of rhBMP-2/ACS (Glassman, S., Spine J., 2008 (8), pp 443-448). The two-year data revealed similar HRQOL outcomes, but better fusion on CT scan, fewer complications, lower revision rate and lower overall cost in the rhBMP-2/ACS group. This two-year RCT data has been presented, and received the Outstanding Paper Award, at the International Meeting for Advanced Spine Techniques (IMAST) in 2008. The study has been accepted for publication in SPINE, but has not yet reached its publication date. Despite this, the

CMS staff may want to consider these data because they so directly address the issues raised in the proposed NCD topic question.

The literature assessing rhBMP-7 (OP-1) in posterolateral spine fusion, also suggests safety, and probable efficacy, based on an RCT comparing rhBMP-7 and ICBG in single level fusion for degenerative spondylolisthesis (Vaccaro, A., Spine 2005; 30:2709-16.). This study resulted in FDA approval of OP-1 putty, through the HDE process, as an alternative to ICBG in compromised patients. An additional small RCT comparing rhBMP-7 and ICBG in instrumented posterolateral fusion revealed equivalent radiographic success, however nonunion was detected at exploration in 4 of 7 patients (Kanayama, M., Spine 2006; 31:1067-74.).

Transforaminal Lumbar Interbody Fusion (TLIF)

A second common off-label application for rhBMP is in Transforaminal Lumbar Interbody Fusion (TLIF). No Level 1 data exists regarding the role of BMP in TLIF surgery. Several case series have been reported with variable findings. Two initial studies reported high fusion rates and minimal complications using rhBMP-2 for open and minimally invasive TLIFs (Schwender, J., J Spinal Disord Tech 2005 Feb;18 Suppl:S1-6., Villavicencio A., J Neurosurg Spine 2005;3(6):436-443.). Subsequently, concerns have been raised regarding the risk of heterotopic bone formation associated with the use of rhBMP-2 in TLIF. Conflicting evidence includes a prospective CT analysis which documented asymptomatic heterotopic bone in 20% of cases (Joeseph, V., Spine 2007 Dec 1;32(25):2885-90.), and a report of 5 patients seen at a referral center with heterotopic bone and radiculopathy (Wong DA, Spine J. 2007 Nov 21. [E-pub ahead of print]). Whether the risk for symptomatic heterotopic bone formation is dependent upon surgical technique, rhBMP-2 dose or any other surgical variable remains undetermined. No data regarding the use of rhBMP-7 in TLIF are available.

Cervical Spine

Notwithstanding its off-label status, the use of bone morphogenic protein, in the anterior cervical spine is considered controversial. This status derives primarily from two clinical observations. First, high fusion (bone healing) rates, in the absence of BMP, with stand-alone allograft have been consistently reported in the literature for both anterior discectomy and corpectomy constructs. Thus, the need for an iliac crest autograft substitute or replacement may have a limited role in comparison to the lumbar spine. Second, the use of BMP in the anterior cervical spine has been reported to be associated with higher than usual rates of soft-tissue swelling, dysphagia, and respiratory complications.

There is conflicting evidence regarding the safety and incidence of soft-tissue complications with BMP use in the anterior cervical spine. In a retrospective study of 200 patients who underwent anterior cervical discectomy with a PEEK spacer and low dose BMP, an incidence of dysphagia of 7 percent was reported [1]. In contrast, Shields et al [2] reported 23 percent complication rate among 151 patients who underwent anterior cervical surgery with high-dose BMP. Complications included postoperative hematomas or readmission for swallowing difficulty or airway distress.

In a retrospective comparative study, another group found a significantly higher incidence and severity of dysphagia in twenty-two patients in whom BMP was used compared to twenty-four in whom allograft alone was used to effect an anterior cervical discectomy and fusion [3]. Similarly, Smucker et al [4] found a statistically significantly higher rate of so-called "swelling events" with use of BMP in sixty-nine patients compared to 165 non-BMP controls who underwent anterior cervical spine surgery. Indeed, higher level evidence exists. In a prospective randomized controlled comparison of thirty-three patients who underwent anterior cervical discectomy and fusion with BMP or allograft, Baskin et al [5] reported no device-related complications. In contrast, Butterman [6] performed a non-randomized, prospective comparison of patients undergoing anterior cervical discectomy and fusion with iliac crest autograft or low-dose BMP. He reported a 50 percent rate of dysphagia in the BMP group versus a 14 percent rate in the iliac crest group.

Provided that close observation of a patient's airway is maintained, perhaps with a planned postoperative intubation interval, off-label BMP use in the anterior cervical spine may have some role as a salvage maneuver in complex cases in which the fusion environment is substantially challenged, such as in the treatment of established nonunions, unusually long multi-level defects, or osteomyelitis [7, 8]. As peri-esophageal and tracheal inflammation is less likely with posterior application, BMP also may have some role in the posterior cervical spinal fusions in highly select cases [9].

In summary, the current limited data suggest that there is persistent controversy regarding the use of BMP in the anterior cervical spine. The data suggest that its routine use for elective anterior cervical spine surgery does not seem to be warranted. While appropriate dosage has been proposed as a primary factor to ensure safety, the current literature is conflicted regarding this issue.

There is an overwhelming paucity of data evaluating the use of BMP in the posterior cervical spine, making any recommendation regarding its routine use difficult.

Summary - BMP

While the indications for the use of BMPs in spinal surgery in the Medicare population are not fully defined, substantial evidence exists supporting the efficacy and cost effectiveness of BMP in the anterior lumbar interbody fusion. Moderate and increasing evidence is being developed for its use in posterolateral fusions compared to ICBG. Posterolateral fusion, in conjunction with decompression for stenosis or deformity correction, in spondylolisthesis, or degenerative scoliosis, is the most common spinal fusion technique performed in the Medicare population. The Professional Society Coalition Task Force believes that BMP is a reasonable and safe alternative to ICBG in anterior interbody lumbar fusion. For posterior spinal fusion, there is moderate and increasing evidence that BMP is also beneficial. We also believe that ongoing additional investigation will contribute to refinements in dose, carriers and site specific applications for these valuable biologic technologies. In the anterior cervical spine, the evidence is

limited and there remain unanswered safety concerns and we do not support its broad use except in ongoing research trials.

Recommendations- BMP

1. **Anterior Lumbar Fusions- Recommend coverage in Medicare and non-Medicare patients without severe osteoporosis.**

2. **Posterior/Lateral Lumbar Fusion- Delay decision pending publication of pending literature.**

3. **Posterior Interbody Fusion- Literature is insufficient to make recommendation. Further study should be encouraged.**

4. **Anterior Cervical Spine- Do not recommend coverage except in research trials due to the lack of literature and safety concerns. Further study should be encouraged.**

5. **Posterior Cervical/Thoracic Spine- Literature is insufficient to make recommendation. Further study should be encouraged.**

Cervical BMP References

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Vertebroplasty and Kyphoplasty

CMS Proposed Topic-
"Vertebroplasty and kyphoplasty are radiologic procedures for the treatment of the intense pain caused by vertebral compression fracture in patients whose pain has been refractory to medical management or other therapy. Vertebroplasty and kyphoplasty involve the intraosseous injection of acrylic cement under local anesthesia and fluoroscopic guidance to control the pain of vertebral fractures associated with osteoporosis, tumors, and trauma. Typically, vertebroplasties are performed in an outpatient setting, while kyphoplasty typically requires hospital admission. Is the evidence adequate to demonstrate health benefits from pain reduction in selected patients?"

Task Force Comments

Vertebroplasty (VP) and kyphoplasty (KP) are procedures performed for conditions that are common in the Medicare population, specifically patients over the age of 65. Approximately 35% of women in the US 65 years or older have osteoporosis. Vertebral compression fracture (VCF) is the most common complication of this condition and more than 700,000 new vertebral compression fractures occur every year in the United States alone. These fractures account for more than 100,000 hospital admissions and close to $1.5 billion in annual costs.

Although most patients with VCF are asymptomatic or minimally symptomatic, a significant number of patients have sufficient pain to limit activity, resulting in decreased quality of life and disability. VCF may also lead to progressive spinal deformity, and the incidence of additional fractures is increased in patients with an incident VCF. They may be associated with other systemic conditions, including metastatic disease and chronic steroid use.

Conventional treatment for VCF is designed to alleviate symptoms, and includes analgesic medications, a variety of bracing alternatives, and modification of activity. Some patients do experience improvement in their symptoms over time, with medical treatment. Failure of medical management often results in the option of a percutaneous surgical procedure being offered. However, the severity of a patient's pain and the associated disability are the determining factors for whether a trial of medical management is warranted.

Percutaneous vertebral augmentation (PVA) is a minimal access procedure which restores strength to the fractured vertebra by the injection of polymethylmethacrylate (PMMA). Vertebroplasty (PV) and kyphoplasty (KP), a variation of vertebroplasty, have

become increasingly popular as a treatment alternative for VCF. Leading experts from many major insurance carriers have reviewed the body of scientific literature available and concluded that coverage for these procedures is warranted.

The following conditions are considered indications for this procedure, provided the affected vertebra has not been extensively destroyed and the patient's medical condition permits treatment:

1) osteoporotic vertebral compression fractures that have not responded to medical treatment including bracing, rest, analgesics, with incapacitating pain that may preclude mobilization in a previously mobile patient;
2) osteolytic vertebral metastasis or myeloma with severe back pain related to vertebral body destruction without cortical involvement; and
3) painful vertebral hemangioma

Percutaneous vertebroplasty is contraindicated in patients with local infection, spinal cord compression, destruction of the posterior wall of the vertebral body and severe degrees of vertebral body collapse; certain other medical conditions, such as coagulopathies, may preclude the procedure.

Results from the current studies evaluating vertebroplasty and kyphoplasty for treatment of both VCF related to osteoporosis and metastatic disease point to consistent and dramatic reduction in pain, typically within one day of the procedure. Other significant outcomes include decreased analgesic use and improvement in physical function or disability scale scores (Bouza et al 2006).

The most consistently raised issue in recent TEC assessments relates to the nature of studies, specifically the lack of comparative, blinded randomized clinical trials, and the use of subjective measures of pain and activity as outcome measures. The literature has consistently described pain relief, measured by VAS score, in a large percentage of patients treated with PVA (Bouza et al 2006; Eck et al 2008; Hulme et al 2006). Furthermore, pain relief is durable. Similar clinical benefits are noted in both VP and KP (Eck et al 2008).

The majority of the studies published on PVA are in the form of prospective consecutive case series or retrospective studies (Eck et al 2008). The retrospective studies include large numbers of patients whose quality of life is reportedly substantially improved with PVA intervention (Bouza et al 2006; Eck et al 2008; Hulme et al 2006).

The most commonly reported complications following PVA were cement leaks perioperatively or subsequent fractures in the first year post procedure. Cement (PMMA) leaks are commonly quoted at around 9% of treated osteoporotic vertebrae and slightly higher for metastatic fractures. Most leaks involve the disc or perivertebral soft tissues and are most commonly clinically asymptomatic (Hulme et al 2006). New fractures of remote and adjacent vertebrae in most studies occurred in frequency equivalent to the

general osteoporotic population that had one previous vertebral fracture (Hulme et at 2006).

Recognizing the limitations of the current literature, and balancing that with the clinical benefits described in large numbers of patients according to the retrospective studies, the following summary comments are provided:

1. PVA is a reasonable treatment option for managing vertebral compression fractures related to osteoporosis or metastatic disease.

2. Multiple studies indicate that both procedures are safe and efficacious in the treatment of osteoporotic and pathological vertebral compression fractures. The most common complication is extravasation of cement, which is of no consequence in most patients.

3. Many prospective consecutive case series indicate that PVA improves pain and function. There are no large long term randomized clinical trials comparing PVA with the natural history of VCF. In fact there exist no quality studies of the natural history of vertebral compression fractures.

4. Both VP and KP have similar clinical results and can be performed on an outpatient basis.

5. Kyphoplasty is significantly more expensive than vertebroplasty without a proven value added benefit.

Despite the lack of randomized clinical trials, the consistency of the findings regarding a large improvement in pain and function indicates that both vertebroplasty and kyphoplasty are effective in the treatment of pain due to vertebral fractures. VP is reasonable and necessary by producing immediate improvement in a patient's quality of life, primarily through the alleviation of pain and rapid return to ambulation. KP is equally as effective, but at a substantially greater cost. NASS encourages CMS to focus on best patient care by continuing coverage for patients with these minimally-invasive treatments that have been safely and successfully performed on thousands of patients across the United States, typically providing patients with immediate relief from pain and an independence from reliance on narcotics.

In summary, the benefits of vertebroplasty and kyphoplasty far outweigh any risks and the risks of conservative therapy, and the success rates are consistently high. These procedures are effective by producing immediate improvement in a patient's quality of life, primarily through the alleviation of pain and rapid return to ambulation. The value added benefit of KP over VP has not been demonstrated.

Recommendations- Vertebroplasty/Kyphoplasty

1. **VP- Recommend coverage in Medicare and non-Medicare patients for osteoporotic VCF**

2. **KP- Recommend coverage in Medicare and non-Medicare patients for osteoporotic VCF**

3. **VP and KP- Recommend coverage in Medicare and non-Medicare patients for osteolytic vertebral metastasis, myeloma and vertebral hemangioma**

4. **There is no added value of KP over VP and CMS hospital and outpatient payment policy should be equivalent for the two procedures.**

Vertebroplasty / Kyphoplasty References

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Multi-level Lumbar Fusion for Degenerative Disc Disease

CMS Proposed Topic-

"For certain patients, a two level spinal fusion may be an effective treatment for debilitating back pain from two degenerated lumbar discs. Multilevel fusion as a primary treatment for low back pain from degenerated discs is a controversial topic in spine medicine. However, lumbar fusion of three or more levels of the low back as a primary treatment for back pain is rarely recommended, and many surgeons recommend against it in all cases of multilevel degenerative disc disease. Is the evidence adequate to specify groups that do and do not benefit from the lumbar fusion procedure?"

Task Force Comments

Our primary concern with regard to the proposed NCD topic on multilevel lumbar fusion revolves around the difficulty in clearly defining the population in question. We agree that there is no high quality or even consistent lower quality evidence indicating that multilevel (3 or more level) fusion is effective as a treatment for isolated back pain without neurological deficit, deformity, or stenosis. Evidence to definitively support or

refute the efficacy of such procedures is not likely to be available in a reasonable timeframe because these procedures are uncommonly performed in any patient population. According to MedPar data, a grand total of 688 such multilevel procedures with a primary diagnosis of degenerative disc disease were performed in the United States during 2007 (out of approximately 57,000 fusions performed for degenerative disease). Given difficulties with the fidelity of administrative databases, it is likely that the true incidence is even lower due to failure to code for associated diagnoses. Furthermore, when such procedures are performed, they are more likely performed in an elective fashion on younger patients. These are "boutique" procedures that are not typically performed in the over age 65 Medicare or Medicaid population.

Answerable questions must be used as the basis for reasoned debate when policy decisions are proposed. For example, at the 2006 MCAC meeting on lumbar fusion, the published MCAC question, similarly described as fusion for isolated low back pain in the Medicare population, was not able to be addressed. The majority of data reviewed by the speakers, and much of the panel discussion, addressed the utilization of lumbar fusion in completely different patient populations. Nonetheless, the panel was required by procedure to vote on the atypical use of fusion for low back pain in the Medicare population, as this was the specific MCAC question. As there was no evidence relevant to the Medicare or Medicaid population, the panel was forced to conclude that such procedures were not supported by high quality evidence. This conclusion, supported by a draft Tech Report, has been published and used to inappropriately limit access to lumbar fusion in other populations.

It is also imperative that multi-level fusion procedures for isolated axial LBP or axial LBP without neural compression are not confused with multilevel fusion procedures that are performed for the purposes of deformity correction, correction of instability, or following destabilizing decompressive procedures in the elderly. There is substantial evidence indicating that the use of fusion in such situations improves functional outcome. In particular, data from the SPORT study, which has been presented and published since the 2006 MCAC meeting, provides high quality evidence supporting the benefit of lumbar fusion in appropriately selected patients (Weinstein JN, N Engl J Med 2007;356;22:2257-2270). Also, consistent with the CMS call for evidence development surrounding lumbar fusion in the Medicare population (Schafer J, Spine 2007;32(22):2403-2404.), several studies examining the role of single and multilevel fusion in older patients have now been published, or are awaiting publication (Glassman SD, Spine J 2007;7(5):547-551, Okuda S, J Bone Joint Surg Am. 2006 Dec;88-A(12):27142720, Glassman SD, Spine J. E-pub 2008, Bridwell K, SRS 2008, Ghogowala, Benzel, etc).

We welcome any and all opportunities to discuss the appropriate use of multilevel fusion in the Medicare population. We agree that demonstration of benefit for lumbar fusion, or any surgical intervention, limited to simple cases and idealized populations is not ultimately sufficient to predict value in standard clinical practice. We believe that additional and ongoing evidence development is critical to guide appropriate resource utilization in the Medicare population. It is our assertion that identification of the most

specific and relevant question for analysis is critical in order to maximize the utility of the subsequent analysis.

Recommendations- Multi-level (3 or more levels) Lumbar Fusion for Degenerative Disc Disease

1. **For DDD without deformity or instability (isolated axial LBP or axial LBP without neural compressionaxial)- Do not recommend coverage in Medicare and non-Medicare patients**

2. **For DDD with deformity, extensive decompression or instability- Recommend coverage in Medicare and non-Medicare patients**

Artificial Cervical Discs

CMS Proposed Topic-
"Artificial cervical discs are being developed in an effort to treat symptomatic degenerative disc disease more effectively. The goal of this type of technology is to maintain spinal motion following anterior discectomy, to reduce the incidence of degeneration of adjacent disc levels of the spine (adjacent-segment disease), and to permit more rapid return to normal activity. Is the evidence adequate that this procedure results in improved health for the Medicare population?"

Task Force Comments-

Spinal spondylosis and cervical degenerative disease are a common problem in the United States and associated with aging (Emery 2001). This is due to the avascular nature of the spinal disc and as it loses proteoglycans, such as chondroitin sulfate, and moisture it is unable to repair itself and becomes inelastic with microfissures and associated disc herniations resulting in settling and collapse of the disc space. This change in the disc space results in abnormal spinal motion patterns and further leads to anatomical changes in the formation of osteophytic spurs and can be associated with impingement of nerve roots or the spinal cord. This is a common radiographic finding, with 60% of people over the age of 40 showing evidence of cervical degenerative disc disease and spondylosis, and by age 65, almost 95% of men and 70% of women have such changes. While most radiographic changes are asymptomatic, a significant number (over 5 million) of US adults are disabled by spine-related disorders and a portion of these patients are good candidates for surgery.

The initial treatment for cervical spondylosis and degenerative disease is not surgery. Rather, patients undergo initial management with pharmacological agents such as NSAIDs, analgesics, or muscle relaxants, and supplemented with physical therapies such as traction, strength training, stretching, massage, or manipulation therapies. If symptoms persist or worsen, then additional treatment including biofeedback or cognitive therapies may be added along with interventional procedures such as epidural steroid injections, facet joint radiofrequency denervation, or trigger point injections.

These treatments are not panaceas for this disease process, with over $80 billion dollars a year spent on the pain and symptoms related to the non-surgical management of spinal disorders (Brook 2008). This can be contrasted to the $570 million that CMS paid in professional fees in 2007 for the entire field of neurosurgery (cranial and spinal), which represents less that ¾ of 1% of what has been spent on non-surgical treatment. Non-surgical treatments have resulted in an increase in expenditures of 65% (adjusted for inflation) from 1997 to 2005. (add reference) Unfortunately despite these treatments, patients continue to experience physical function limitation and decrease in the activities of daily living with persistent issues related to their mental health, physical functioning, work, school and social limitations.

This debilitating degeneration disease was first noted by Bailey and Casamajor in 1911 when they first described osteo-arthritis of the cervical spine. Clarke and Robinson in 1956 noted that this was not a static problem, but rather that disease and symptom progression was common, albeit gradual. However, improvement was rare and prognosis was generally poor. Cervical spondylosis and associated myelopathy remains the most common cause of nontraumatic spastic paraparesis and quadriparesis, and represents 23.6% of these severely disabled and medically needy patients (add reference).

This unacceptable natural history of this disease has lead to the development of surgical treatments and techniques. Typically, surgical patients have failed 2-6 months of conservative therapy and are unable to perform their activities of daily living due to pain or neurological symptoms. In these patients, surgery, most commonly anterior cervical diskectomy and fusion (ACDF) with or without plate fixation has resulted in the resolution of symptoms in over 80% of those treated (Xie 2007, Yue 2005). The excellent results have resulted in increased use of surgery for cervical spondylosis, especially as more surgeons are trained in this technique. The frequency of cervical surgeries performed has grown from 26,000 per year in 1988-90 to 124,000 procedures in 1999 (add reference).

Although surgery has improved on the patient's health as compared to their natural history of their disease, it is not without its own drawbacks. Chief amongst these are concerns regarding adjacent segment spondylosis, which has been reported to occur at a rate of 2.9% per year with an overall incidence of 25.6% based on survivorship analysis. This has been felt to be related to variables related to the patient's underlying clinical disease along with iatrogenic and lifestyle choices, but also related to the fusion construct itself as related to the biomechanical alterations of a functioning joint.

This plus a desire to speed recovery and maintain normal neck motion has lead to the advent of artificial intervertebral disc arthroplasty as an alternative to anterior cervical fusions in patients with cervical spondylosis and degenerative disc disease (Acosta 2005, Anderson 2007, Smucker 2006, Phillips 2005, Anderson 2004, Pracyk 2005, Bertagnoli 2005). Additional studies have shown that cervical arthroplasty is safe and at least as effective as cervical fusions in those patients who had similar surgical indications to ACDF such as radiculopathy and myelopathy (Brown 2006; McAfee 2004). There are

reports that the patients with cervical arthroplasty have an improved post-operative course possibly due to the absence of an anterior plate or the need for an orthoses, and also have a shorter recovery period due to not using bone grafts (Traynelis 2007, Goffin 2006). As well, cervical disc arthroplasty has been associated with maintaining cervical disc height, along with lordosis and motion at the index and at the adjacent cervical spine levels (Sears 2006). This has been postulated to reduce the risk of adjacent level degeneration (Traynelis 2007) and improve the force/load transfer to the adjacent cervical levels (Phillips & Garfin 2005).

Biomechanical models show that there is altered adjacent segment kinematics in patients or spines with a fusion, but as these are biomechanical studies, they do not portend to establish clinical relevance (Anderson 2007, Phillips 2005, Wigfield 2002). It is only in the recent past that further development of available tools to study cervical spine kinematics in a clinical setting has been developed and this shows that there is preserved adjacent segment kinetics in patients with an arthroplasty (Cheng 2007).

Cervical disc arthroplasty is a technology that has final approval from the appropriate governmental regulatory bodies, with the Prestige ST Cervical Disc receiving FDA marketing approval on July 16, 2007 and the ProDisc™-C Total Disc receiving a premarketing application (PMA) approval on December 17, 2007 and further FDA marketing approval on December 22, 2007. In addition, the Bryan Cervical Disc received an approvable decision by an FDA advisory panel on July 17, 2007 but has not received a final marketing approval.

These devices have similar indications for use in skeletally mature patients with cervical spine disease at C3-C7 necessitating a single-level decompression. The devices are implanted via an open anterior approach, similar to that of an ACDF, and used for symptoms similar to an ACDF for patients with intractable pain, radiculopathy, and/or myelopathy associated with radiographic studies showing a herniated cervical disc or cervical spondylosis and osteophytes.

Three large multicenter prospective randomized IDE studies have been completed comparing cervical disc arthroplasty with anterior cervical diskectomy and fusion (add references). They have concluded that disc arthroplasty is a safe and reasonable alternative to anterior cervical fusion.

Mummaneni[14] in 2007 reported statistical noninferiority for disc arthroplasty versus ACDF in all three primary outcome variables (Neck Disability Index (NDI), neurological status, and functional spinal unit height (FSU)) and for the overall success composite outcome. The neurological status was the only primary outcome variable for which statistical superiority was achieved. The arthroplasty patients showed preservation of motion with retention of sagittal angular motion of over 7 degrees and also a 2-point greater improvement in the Neck Disability Index (NDI).

They were unable to show that variables such as functional spinal unit (FSU) height reached predetermined levels, but it should be noted that they had difficulty due to

anatomical interference and that alternate determinations were made without the FSU height included. Although it was not statistically significant, there was an overall success with better SF-36 at 12 and 24 months associated with a greater relief of neck pain and earlier return to work in the arthroplasty group. There were no serious associated adverse events and no cases of implant failure or migration, along with a lower rate of revision surgeries ($p = 0.0277$) including a lower rate of supplemental fixation ($p = 0.0031$) and of re-operations at the adjacent segment ($p = 0.0492$).

Murrey[16] reported a prospective, randomized, controlled trial of 209 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive PRODISC-C® or ACDF with plate and allograft with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that Prodisc-C® is "not inferior" to ACDF 2 years after surgery in Overall Success, the study's primary endpoint.

Heller[15] reported a prospective, randomized, controlled trial of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or Atlantis ® Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that the BRYAN® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with improved NDI Success (superiority), improved clinical outcomes, and 13 days faster return to work compared to ACDF patients. Statistical superiority in Overall Success (study's primary endpoint) was demonstrated at 24 months.

Criticism has been raised regarding the non-inferiority design of these trials, and how such a study design does not provide sufficient evidence insufficient to justify coverage. While the studies do not prove superiority, they consistently demonstrate improvement in pain and function that is equivalent to fusion. Additionally the studies have been criticized (BC/BS TEC Assessment (http://www.bcbs.com/blueresources/tec/tec-assessments.html) due to their non-blinded nature. However, this is confusing the science behind device studies with those from other non-surgical disciplines. It would be physically impossible to double blind a surgeon regarding an implant that is to be surgically placed.

Cervical disc arthroplasty is not frequently used in Medicare age patients, with the average study population being young with patients in their mid-40s. Prior IDE studies included patients only between the ages of 18-60, and along with their exclusion criteria which excluded patients with severe disabilities and comorbidities, do not capture patients within the Medicare population. The study by Mummaneni did include patients with cervical arthroplasty up to age 72, and had fusion control patients up to age 73, this was a very small number of patients and data on this subgroup will not be able to show any statistical significance.

It remains unknown if cervical disc arthroplasty will decrease the incidence of adjacent level disc degeneration. There is some evidence that the early re-operation rate is less for disc arthroplasty than the fusion group, but this is due to psedoarthrosis at the index level in the fusion group and not adjacent level degeneration. Reasonable long term wear

characteristics are suggested by biomechanical studies, but clinical data are not available at this time.

Recommendations- Cervical disc arthroplasty

1. For cervical spondylosis and disc herniation in non-Mediciare population- Recommend coverage

2. For cervical spondylosis and disc herniation in the Medicare population- Literature is insufficient to make recommendation. Further study should be encouraged.

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14. Mummaneni, et al. Journal of Neurosurgery Spine. 2007 Mar; 6(3):198-209. Clinical and Radiographic Analysis of Cervical Disc Arthroplasty Compared with Allograft Fusion: A Randomized Controlled Clinical Trial. [Medtronic Funded, PRESTIGE® Cervical Disc* (Medtronic)]

    This was a prospective, randomized, controlled trial of 541 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive PRESTIGE® Cervical Disc or ATLANTIS® Cervical Plate with allograft (ACDF) and followed up at 3 and 6 weeks, 3, 6, 12 and 24 months. The results noted that the PRESTIGE® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with improved neurological status (superiority), improved clinical outcomes, and a reduced rate of secondary surgeries compared to ACDF. Superiority in overall success (study endpoint) was demonstrated at 24 months in the PRESTIGE® Cervical Disc cohort.

15. Heller, et. Al. Abstract, 2007 North American Spine Society Annual Meeting. Comparison of BRYAN® Cervical Disc Arthroplasty with Anterior Cervical Decompression and Fusion: Clinical and Radiographic Results of a Randomized Controlled Clinical Trial. [Medtronic Funded, BRYAN® Cervical Disc (Medtronic)]

    This was a prospective, randomized, controlled trial of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or Atlantis ® Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that the BRYAN® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with improved NDI Success (superiority), improved clinical outcomes, and 13 days faster return to work compared to ACDF patients. Statistical superiority in Overall Success (study's primary endpoint) was demonstrated at 24 months in the BRYAN® Cervical Disc cohort.

16. Murrey, et. Al. Abstract, 2007 Cervical Spine Research Society Annual Meeting. Twenty-four month results from the prospective, randomized, multi-center IDE Trial of PRODISC-C® vs. ACDF. [PRODISC-C®, Synthes Spine]

    This was a prospective, randomized, controlled trial of 209 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive PRODISC-C® or ACDF with plate and allograft with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results showed that Prodisc-C® is "not inferior" to ACDF 2 years after surgery in Overall Success, the study's primary endpoint.

17. Sasso, et. Al. J Spinal Disord Tech. Vol. 20, Number 7, Oct. 2007. Clinical Outcomes of BRYAN® Cervical Disc Arthroplasty: a Prospective, Randomized, Controlled, Multi-Center Trial With 24-month Follow-up. [BRYAN® Cervical Disc, Medtronic]

This was a prospective, randomized, controlled trial of 115 patients from 3 U.S. IDE study sites for the BRYAN® Cervical Disc IDE Study Subset of 463 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft (ACDF) with follow-up of 3 and 6 weeks, 3, 6, 12, 24 months. The results noted that the BRYAN® Cervical Disc maintained segmental motion at 24 months after implantation and was associated with statistically superior scores in Neck Disability Index, Neck Pain, and SF-36 PCS 24 months after surgery.

18. Porchet, etl al. Neurosurg Focus 2004 Sept; 17:36-43. Clinical Outcomes with the PRESTIGE® II Cervical Disc: Preliminary Results from a Prospective Randomized Clinical Trial. [Medtronic Funded, PRESTIGE® Cervical Disc*, Medtronic]

    This was a prospective, randomized, controlled trial of 55 patients consisting of 27 PRESTIGE® II Cervical Disc with 28 iliac crest autograft fusion and with 2-year follow up with most of the outcome measures tending to favor the PRESTIGE® II Cervical Disc, and with the PRESTIGE® II Cervical Disc maintaining motion at treated level without adjacent segment compromise.

19. Hacker, et al. Journal of Neurosurgery Spine 2005 Dec; 3:424-28. Cervical Disc Arthroplasty: A Controlled Randomized Prospective Study With Intermediate Follow Up Results. [Medtronic Funded, BRYAN® Cervical Disc, Medtronic]

    This was a prospective, randomized, controlled trial of 46 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft with follow up of 3 and 6 weeks, 3,6,12 and 24 months. The results show that all patients reported in this study had reached a minimum of 1-year follow up with no device related complications and with equivalent results in releif of arm and neck pain seen in both study groups. The treatment parameters other than OR time were similar with no serious neurological or systemic complications observed and preserved motion was revealed in all BRYAN® Cervical Disc-treated patients.

20. Coric, et al. Journal of Neurosurgery Spine, 2006 Jan, Vol 4:31-35. Prospective Rrandomized Controlled Study of the BRYAN® Cervical Disc: Early Clinical Results from a Single Investigational Site. [Medtronic Funded, BRYAN® Cervical Disc, Medtronic]

    This was a prospective, randomized, controlled trial of 33 patients with 1-level DDD with concordant radiculopathy and/or myelopathy randomized 1:1 to receive BRYAN® Cervical Disc or ATLANTIS® Cervical Plate with allograft and follow up of 3 and 6 weeks, 3, 6, 12, 24 months. The results noted that at mean follow up at time of report of 19 months, there was no device related complications and had similar improvements seen in both study groups. The BRYAN® Cervical Disc patients demonstrated maintenance of motion at treated level.

21. Nabhan, et al. Eur Spine J, 2007 Mar; 16(3):423-30. Disc Replacement Using PRODISC-C® versus Fusion: A Prospective Randomized and Controlled Radiographic and Clinical Study. [PRODISC-C®, Synthes Spine]

    This was a prospective, randomized, controlled trial of 25 patients with cervical disc herniation who were randomized to receive either a PRODISC-C® or ACDF. Radiostereometric analysis was used to quantify intervertebral motion immediately and at 3, 6, 12 and 24 weeks. Clinical results were judged using VAS and neuro examination. Motion decreased in both groups over time; however, the loss of segmental motion was significantly higher in the ACDF group. Significant pain reduction was observed in both groups ($p>0.05$). The cervical spine disc prosthesis preserves cervical spine segmental motion within the first 6 months after surgery. Clinical results were the same as early results of ACDF.

22. Anderson, et al. Journal of Neurosurgery, 2004. Comparison of Simulator-Tested and Retrieved Cervical Disc Prostheses. [BRYAN® Cervical Disc, Medtronic].

    This sudy compared wear/debris of human explanted BRYAN® Cervical Discs and PRESTIGE® Cervical Discs to wear/debris from discs tested on a spine simulator. Simulator predicted adequate wear for prostheses out to 40 years and human explants exhibited less wear than predicted by simulators (5 to 10 fold).

23. Anderson, et al. The Spine Journal, 2004. The BRYAN® Cervical Disc: Wear Properties and Early Clinical Results. [BRYAN® Cervical Disc, Medtronic]

    This was an in vitro study to assess the BRYAN® Cervical Disc's wear properties and clinical results with an in vitro mechanical testing in a caprine animal model and in a prospective European human trial. In vitro wear averaged approximately 1.76% by weight at 10M cycles and 18% by weight at 40 million cycles. Wear debris were present in periprosthetic tissues without inflammatory response in animals. 90% of European trial patients had satisfactory results.

24. Bertagnoli, et al. Journal of Neurosurgery, 2005. Early Results After PRODISC-C® Cervical Disc Replacement [PRODISC-C®, Synthes Spine]

    This was a case series with follow up at 3, 6, and 12 months and looking at radiographic examination (ROM), ODI, and VAS. At 12 months 63.6% patients completely satisfied, 36.4% satisfied, and 0% unsatisfied.

25. Bertagnoli, et al. Ortho. Clin N. Am., 2005. Cervical Disc Replacement:Part II Clinical Results. [PRODISC-C®, Synthes]

    This was a case series of 27 patients with follow up at 3 and 6 wks, 3, 6, 12 months looking at NDI, VAS, ROM, and other clinical parameters. At 12 months it was noted that 52% completely satisfied, 36% satisfied, 12% unsatisfied.

26. Cummins, et al. Journal of Neurosurgery, 1998. Surgical Experience with an Implanted Artificial Cervical Joint. [BRISTOL-CUMMINS DISC]

    This is a retrospective cohort study looking at the surgical experience with the implantation of movable stainless-steel joints in 20 patients. Joint motion was determined by measuring the distance between cervical spine segments during flexion/extension. Follow up 3-65 months. No patients required additional motion segment surgery. Radiography did not demonstrate fusion at the treated level in any patient. Adjacent segment joint degeneration was absent. 16 of 20 patients reported improvement in pain relief. Three patients were considered failures because pain persisted or worsened. Complications were attributed to poor screw placement, incompatible screws, one-size-fits-all implants, and manufacturing errors. Stainless steel appears too suitable for this joint replacement design. With appropriate modification of sizes, this joint is shown to be capable of stability and motion and deserves further clinical evaluation.

27. Datta, et al. J Spinal Disord Tech, Vol. 20, Number 1, Feb. 2007. Sagittal Split Fractures in Multilevel Cervical Arthroplasty Using a Keeled Prosthesis [PRODISC-C®, Synthes Spine]

    This is a case report of a 34-year old male with a 2-level cervical spondylosis unresponsive to nonoperative care for 24 months. FDA compassionate use granted for treatment with Prodisc -C® at C5-6 and C6-7 levels The PRODISC-C® was inserted successfully at the C6-7 level. Following that, during use of a keeled osteotome at the C5-6 level, a loss of resistance was felt and radiographic imaging revealed a sagittal split fracture of the C6 vertebral body with no instability or loose fragments observed. Insertion of the PRODISC-C® at C5-6 was performed as planned. Postoperative radiographic evaluation revealed a fracture of the C5 vertebral body that was not detected during surgery. The patient had immediate relief of his preoperative symptoms and eventual relief of neck pain related to the fracture. The author concludes that this adverse event may be attributed to the keeled design of the prosthesis, as well as the need for chisel cutting before and during insertion of the prosthesis.

28. Dmitriev, et al. SPINE, 2005. Adjacent Level Intradiscal Pressure and Segmental Kinematics Following Cervical Arthroplasty. [PCM®, Cervitech, Inc.]

    This is a laboratory study looking at intradiscal pressure at levels adjacent to an arthroplasty. In 10 cadavers, similar adjacent level IDP's were recorded between TDR and intact spine in all loading conditions ($p<.05$). Segment above both arthrodesis groups had higher intradiscal pressure at adjacent level above ($p<.05$).

The North American Spine Society and (insert any supporting organizations) appreciates the opportunity to offer these comments to CMS regarding potential NCD topics. We look forward to our continued relationship to further improve patient access to quality spine care.

Sincerely,

Tom Faciszewski, MD
President

cc: Eric Muehlbauer, Executive Director, NASS

Washington State Health Care Authority

Health Technology Assessment

Artificial Disc Replacement

Peer Review and Public Comments and Responses

September 18, 2008

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SPECTRUM RESEARCH RESPONSE TO PEER REVIEW COMMENTS

Note: Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included. However, comments related to program decisions, process, or other matters not pertaining to the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness.

1. Michael J. Lee, M.D., Assistant Professor, University of Washington, Spine Service

Dr. Lee's comment 1 response: Methods section, cervical – Peng Fei et al and Nabhan et al were removed from the level of evidence summary table. See L&I Comment 23 response on page 13 below.

Dr. Lee's comment 2 response: Results section, Key question #3 – Added a comment that no studies were found evaluation L-ADR in workers compensation populations.

2. Sean D. Sullivan, RPh, PhD, Professor of Pharmacy and Health Services, Director of the Pharmaceutical Outcomes Research and Policy Program, University of Washington

Dr. Sullivan's comment 1 response: Superiority can be concluded from an inferiority study, but not the other way around. I added the following text on page 49 of the report. "A non-inferiority clinical trial design is often used in FDA trials to show that a new treatment is no worse than a reference treatment. In order to accomplish this, a pre-stated margin of non-inferiority is defined for the treatment effect of a primary outcome. The new treatment will be recommended if it is similar to or better than the existing one, but not if it is worse by more than the pre-stated margin. It is acceptable to assess whether the new treatment is superior to the reference treatment using the appropriate statistical test.[124,152,168]"

Dr. Sullivan's comment 2 response: The following text was added to the report: There were no reports of death relating to the device or surgical procedure with either ADR or fusion in either study.

Dr. Sullivan's comment 3 response: The short term complications (up to 2 years) are similar with L-ADR and fusion, and fewer with C-ADR compared with ACDF. The real effect on cost will be determined when longer term data are available.

Dr. Sullivan's comment 4 response: The rate of device failure up to 2 years is low with most of the failures reported at one and two years. We plotted the information and concluded that a figure would not be particularly helpful. However, we agree that time to

device failure and reoperation are valuable pieces of information, especially as longer term data become available.

Dr. Sullivan's comment 5 response: Appraisal was changed to Assessment.

Dr. Sullivan's comment 6 response: The following statement was added to the summary:

- One study suggests that surgeons and institutions with a high volume of L-ADR cases have shorter operating time and hospital stay, and lower complication rates which may have an economic effect. No effect on clinical outcomes was reported between high and low volume surgeons or institutions.

Dr. Sullivan's comment 7 response: We added information from three local payers.

Dr. Sullivan's comment 8 response: We accessed the literature references from the manufacturers of the devices undergoing FDA IDE clinical trials.

Dr. Sullivan's comment 10 response: Registry studies are considered observational studies and depending on the quality of the registry and the design of the study, would be evaluated as a cohort or case series. No large registry study was found for this report.

Dr. Sullivan's comment 11 response: Meta analysis is performed to estimate the size of the pooled association between treatment and outcome, to seek evidence that the association varies according to the level of some other factor, and to estimate a variance so that the precision of the pooled estimate may be determined using a confidence interval.[1] This can be done with two or more studies that are similar or homogeneous both clinically and statistically. See comment to Washington State L&I on page 12 below for our rationale for conducting a meta analysis.

[1]Cummings P. Meta-analysis based on standardized effects is unreliable. Arch Pediatr Adolesc Med; 158, 2004, 595-6

3. Ann M. Derleth, PhD, Health Services Research Postdoctoral Fellow, VA HSR&D, Seattle, Wa

Dr. Derleth's comment 1 response: Background – we made corrections throughout the report to reflect that one indication for surgery was failed conservative care for six months for the lumbar spine and six weeks for the cervical spine.

Dr. Derleth's comment 2 response: Methods – we used the FDA data when there was an unresolved conflict between the FDA reports and the published articles because the FDA data were often more completely reported. We added a text in the report to state this reasoning.

Dr. Derleth's comment 3 response: Results – The summary scores from the SF-36 physical and mental (PCS, MCS) were used and reported as such within the results section.

Dr. Derleth's comment 4 response: Results - Text added to clarify that ASD rates were among patients receiving L-ADR.

Dr. Derleth's comment 5 response: The footnote was corrected to point out that the risk difference in the Prodisc trial favored ADR with respect to major complications.

Dr. Derleth's comment 6 response: We added the MAUDE database into the methods section.

4. Jens R. Chapman, M.D., Professor; University of Washington, Director, Spine Service

Dr. Chapman's comment 1 response: The phrasing of the key questions comes from the Washington State HCA to Spectrum Research, the independent vendor.

Dr. Chapman's comment 2 response: We interpreted ADR as mechanical total disc arthroplasty and added a sentence to reflect this under the key questions listed in the executive summary.

Dr. Chapman's comment 3 response: We defined safety profile as complications, adverse events, device failure and reoperation. This is included in Key question 2.

Dr. Chapman's comment 4 response: Background – we added a phrase to emphasize that this frequently stated comment was anecdotal.

Dr. Chapman's comment 5 response: See response 2 above.

Dr. Chapman's comment 6 response: We added a short paragraph on the success of peripheral total joints as a motivation for spinal ADR.

Dr. Chapman's comment 7 response: We added some information about the Bristol disc, a precursor to the Prestige.

Dr. Chapman's comment 8 response: See response to Clinician's/Professional Organization Comment 4 Response on page 10 below.

Dr. Chapman's comment 9 response: The definition of the composite score is listed under section 2.5, Description of study outcomes, just preceding the results section.

Dr. Chapman's comment 10 response: We used the FDA recommended 15 point cut off, and we added that to the figures for ODI to help clarify this point.

5. Brian M. Drew, M.D., Assistant Clinical Professor, McMaster University, Medical Director, Hamilton General Hospitals Spine Unit

Dr. Drew's comment 1 response: We added a bullet in the summary to emphasize the issue of high volumes and its possible effect on outcomes/safety.

SPECTRUM RESEARCH RESPONSE TO PUBLIC COMMENTS

Responses to Industry Association Comments

DePuy Spine Comment 1 Response:
There are many systems available to evaluate the Level-of-Evidence in an Evidence Based Medicine environment. Spectrum Research has chosen a system adapted from the orthopedic surgery field and used by the *Journal of Bone and Joint Surgery*.[1] Its current system for articles pertaining to therapeutic intervention is reproduced below and can be accessed from the Journal's website, http://www2.ejbjs.org/misc/instrux.dtl.

Levels of Evidence for Primary Research Question[1]	
	Therapeutic Studies—Investigating the Results of Treatment
Level I	• High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review[2] of Level-I randomized controlled trials (and study results were homogeneous[3])
Level II	• Lesser-quality randomized controlled trial (e.g., <80% follow-up, no blinding, or improper randomization) • Prospective[4] comparative study[5] • Systematic review[2] of Level-II studies or Level-I studies with inconsistent results
Level III	• Case-control study[7] • Retrospective[6] comparative study[5] • Systematic review[2] of Level-III studies
Level IV	Case series[8]
Level V	Expert opinion

1. A complete assessment of the quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (e.g., with cemented hip arthroplasty) compared with patients treated another way (e.g., with cementless hip arthroplasty) at the same institution.
6. Study was started after the first patient enrolled.
7. Patients identified for the study on the basis of their outcome (e.g., failed total hip arthroplasty), called "cases," are compared with those who did not have the outcome (e.g., had a successful total hip arthroplasty), called "controls."
8. Patients treated one way with no comparison group of patients treated another way.

This chart was adapted from material published by the Centre for Evidence-Based Medicine, Oxford, UK. For more information, please see www.cebm.net.

This system is designed to distinguish between high- and lesser-quality randomized controlled trials. Of course, the hallmark feature of a properly conducted randomized controlled trial is that the random assignment of trial participants tends to minimize differences between study populations in factors that may influence outcome. In other words, it minimizes the effect of selection bias. As much as a randomized controlled trial is desired, it must be remembered that there are other places within a clinical trial where other forms of bias may enter. A potentially significant bias can result when the patient or the evaluator is not blinded to treatment. Blinding the patient is difficult for many surgical procedures, especially when compared with non-surgical care. Nevertheless, whether a study did not or could not blind the patient, the result is that bias is possible. In the current study, it is likely that many patients sought to be enrolled hoping they would receive ADR (a "newer" treatment). To the extent that was the case, those who were randomized to the ADR group would likely be more satisfied and report better outcomes than the fusion group. With respect to evaluator blinding, we expect any evaluation reported for the clinical study to be done with knowledge of the intervention when possible. When not possible, we expect the evaluator to be independent of the investigating team.

DePuy Spine Comment 2 Response:
Surgical intervention for lumbar DDD in these trials is offered to patients who continue to have symptoms after receiving at least six months of nonoperative care. We acknowledge that within this population, operative and nonoperative options may not be "competitive/interchangeable" in the sense that these patients are more likely to seek the surgical option and have greater expectation for improvement compared with continued nonoperative care. The SPORT study cited is a good example to illustrate this point (albeit in a different patient population) in that half of those randomized to nonoperative care for degenerative spondylolisthesis after at least 12 weeks of failed conservative care opted for surgery. However, after 2 years of follow-up, only 64% of those randomized to surgery underwent surgery. What happened to the 36% who didn't undergo surgery is not completely known; nonetheless, it is reasonable to assume that some improved without surgery. The optimum nonoperative care for lumbar DDD continues to be debated. What is needed is a better mechanism to identify which subgroups of patients that will positively respond to different treatment strategies.

Reference:
1. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. *J Bone Joint Surg Am.* 2003;85-A(1):1-3.

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Medtronic Comment 1 Response: Background - We added a section that better discusses the historical perspective of ACDF.

Medtronic Comment 2 Response: See DePuy Spine Comment 1 Response on page 6 above.

Medtronic Comment 3 Response: Summary Table 26 was edited to state that motion at the index segment for L-ADR is maintained or improved compared with preoperative levels.

Medtronic Comment 4 Response: Omission of studies – Anderson et al (2008), Sasso et al (August 2008), Riina et al (2008), and Yang et al (2008) were added to Pubmed after our search date but will be evaluated in future updates. The purposes of Sasso et al (Feb 2008) and Kim et al (2008) were to evaluate motion or sagittal balance primarily, not complications.

Medtronic Comment 5 Response: In addition to the national coverage plans, we added some state coverage policies from Washington State to include Premara Blue Cross, Regence, and Group Health Cooperative.

Medtronic Comment 6 Response: This report did not include data from presentations or abstracts. The two presentations listed will be reviewed when they are published in the peer-reviewed literature.

Medtronic Comment 7 Response: The references are organized in alphabetical order to facilitate citation identification.

Medtronic Comment 8 Response: We made corrections throughout the report to reflect that one indication for surgery was failed conservative care for six months for the lumbar spine and six weeks for the cervical spine.

Medtronic Comment 8 Response: Wear debris citation corrected.

Medtronic Comment 9 Response: The longitudinal study citation was separated from the case series so that it reads clearer.

Medtronic Comment 10 Response: Changed the sentence to reflect that many technology assessments were performed prior to any RCTs.

Medtronic Comment 11 Response: Reference to Tables 4 and 6 were added which contain the nine HTAs.

Medtronic Comment 12 Response: We did not detail the identification of the case series based on the report's inclusion/exclusion criteria found on Table 7 of the report.

Medtronic Comment 13 Response: The citation was corrected.

Medtronic Comment 14 Response: Non-inferiority studies can be evaluated for superiority. See L&I Comment 32 Response on page 14 below for more discussion on superiority in non-inferiority studies.

Medtronic Comment 15 Response: Statistical significance is not important in comparing baseline differences since P-values depend on sample size, variance and effect size. The effect size (the magnitude of the difference between the two groups) is what is important. Remember, the P-value is the probability that the difference is due to chance. In a randomized controlled trial, this makes no sense since the probability that any difference is from chance is 100% (given that random allocation was done correctly).

Medtronic Comment 16 Response: See Clinician's/Professional Organization Comment 4 Response on page 10 below.

Medtronic Comment 17 Response: Though VAS pain was not the primary outcome for this study, Nabhan et al reported that there was no statistical difference between groups for this outcome. Our comment is meant to reflect that for this outcome, this no statistical difference may be a result of a small sample.

Medtronic Comment 18 Response: We made the following corrections: % was changed to points, and the changes in the SF-36 scores were rectified.

Medtronic Comment 19 Response: Goffin et al (reference #124) reports one evacuation of a paravertebral hematoma.

Responses to Clinician's/Professional Comments

Clinician's/Professional Organization Comment 1 Response:
With respect to the level-of-evidence rating for surgical trials, please see the discussion on page 5 above, *Depuy Comment 1 response.*

Clinician's/Professional Organization Comment 2 Response:
We acknowledge that lumbar and cervical ADR are indicated for different spinal conditions; one essentially treats the symptoms of pain thought to arise from the degenerative disc (lumbar) while the other treats signs associated with neurological compromise (cervical). The report attempted to make this clear in all major sections to include the results and summary sections. Spectrum is an independent vendor, and the decision to include lumbar and cervical in one report belongs to the Washington State Health Care Authority (HCA).

Clinician's/Professional Organization Comment 3 Response:
The Washington State HCA asked us to see if there was evidence available to compare ADR with nonoperative therapy. We concluded that there was not.

Clinician's/Professional Organization Comment 4 Response:
The comment was meant to point out that the two populations being compared had some potentially important differences at baseline. With a big enough sample, we expect that these will even themselves out from random assignment. However, they don't always do so and therefore, studies should list robust baseline characteristics so that the reader can see if potentially important differences occur. When they do, we believe they should be adjusted for in the analysis or at least evaluated to see if they are potential confounders. One mistake that authors often make is to compare the differences in characteristics between groups using a statistical test, and concluding if the P-value is not statistically significant, then the difference is not big enough to be important (see CONSORT statement)[1]. An example is the smoking proportions in the Prodisc study. The effect size (11% difference in the proportion of patients who smoked between the two treatment groups) is relatively large even though the P-value is "non significant". As to whether the smoking could have confounded the results due to the unequal distribution of smokers, the point made by the clinician's comment is well taken with respect to its effect on fusion. Since it had no apparent effect on the fusion rates, we removed this discussion point.

With respect to the number of patients who were "enrolled" versus "treated", the issue for analyses is how many patients received random assignment. From the Prodisc study using the published journal article or the SSED, we were unable to determine for certain if those who were enrolled were randomized even if they did not receive treatment. The fact that there were 21 of these in the ADR group and 13 in the fusion group implies that they were randomly assigned and therefore should count in the follow-up even though they did not receive treatment. This type of analysis process helps to ensure the integrity of the random allocation process.[1]

[1]Altman DG, Schulz KF, Moher D, et al. The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration. *Ann Intern Med.* 2001;134:663-694. See especially page 677.

Clinician's/Professional Organization Comment 5 Response:
The comparison we were looking for was between ADR and ***continued*** nonoperative care in cohort or RCT study design. Therefore, the sentence was changed to state that there were no studies found comparing lumbar ADR with continued nonoperative care.

Clinician's/Professional Organization Comment 6 Response:
Spectrum Research is an independent vendor, and as such received no such mandate from the Washington State HCA. It is curious that the readers perceived that the analyses were structured in a way to emphasize the negative aspects and to downplay the positive aspects when the bullet points on efficacy/effectiveness state:

- that there is moderate evidence that the efficacy/effectiveness of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery
- There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index, and pain up to two years following surgery.

Spectrum Research Response To Washington State L&I Comments

L&I Comment 1 response. This statement is not meant to convey that the fusion is the standard of care; rather, that fusion is the SURGICAL standard. That is, when surgery has been decided, fusion is the current surgery of choice. We ensured that this statement and all others similar have the words "surgical standard" included.

L&I Comment 2 response. This statement is not meant to imply that this has been proven. It simply meant to state that this is one of the aims of ADR.

L&I Comments 3&4 response. We acknowledge that there is debate on which studies should be pooled for a meta analysis. In general, variation across studies (heterogeneity) should be considered in two main areas: clinical and statistical heterogeneity. Clinical heterogeneity has a subjective component that should take into account the similarity of the patient populations, the treatments and the outcomes among studies. Though we recognize that there are some differences between the studies for this technology assessment (the case for all meta analyses), we judged that there was sufficient clinical homogeneity to pool. Consider the following: With respect to the patients in the two lumbar FDA trials, their demographics (age, gender, race, BMI, prior spine surgeries) were similar. With respect to ADR treatment, one ADR was semiconstrained, one unconstrained. At this point, there are no data to suggest outcomes from one are different than another. One control group received ALIF, one circumferential fusion. 91% of the ALIF patients fused compared with 97% of the circumferential fusion patients. A 2005 Systematic Review[1] was unable to draw conclusions about the relative effectiveness of anterior, posterior, or circumferential fusion due to lack of evidence. With respect to outcomes, both lumbar studies relied on the ODI by itself as a functional outcome and as the core to a composite score of "overall clinical success". And though the sponsors had different cutoffs for minimal clinically important differences (MCID) in ODI improvement, each provided data for the FDA for the 15 point MCID cut point which we were able to use. In that regard, the outcomes were homogeneous. It is noted that the Prodisc study had the addition of any improvement in the SF-36 score and radiological success in their composite score for clinical success compared with the Charite study. However, we agree with The Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, who state, "It was thought that the addition of these 2 variables to the composite definition of clinical success would make it harder to achieve clinical success and therefore not bias the result in favour of clinical success. Because of this, synthesizing the data from these slightly different definitions was thought to be acceptable." (MSAC HTA, page 40). With respect to the statistical heterogeneity, we did not pool when heterogeneity was present.

[1]Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001352. Review.

L&I Comment 5&6 response. We agree with these comments. We also believe that our statement that the connection between motion and ASD is unclear, and the connection between ASD and patient symptoms is not established articulates this point.

L&I Comment 7 response. See response 3 & 4 above.

L&I Comment 8 response. We removed the section in question.

L&I Comment 9, 10 response. See response 1 above

L&I Comment 11-14 response. The information in this section is for context purposes primarily and includes a wide range of estimates based on marketing data. We added some text to emphasize that the potential impact of these devices on cost of medical care is dependent on the extent that certain predictions are correct. We omitted a press release and added a statement on post approval studies.

L&I Comment 15 response. Additional text was added in the background.

L&I Comment 16 response. We added a comment about the technical demands of L-ADR vs. fusion. It should be noted that some surgeons believe that the learning curve for ADR may be the same as fusion, and is probably a function of surgeons being more comfortable with fusion surgery due to the long history of the procedure.

L&I Comment 19 response. Both are expected to last for 40-50 years.

L&I Comment 20 response. We included a comment to reflect this.

L&I Comment 21 response. The FDA statistical review noted that there was no *a priori* statistical plan initially submitted. The peer reviewed Blumenthal article states, "The sample size was computed using the Blackwelder methodology, 13 assuming that 70% of the patients in both the investigational and control groups would have a successful result and that a clinically insignificant difference in success rates between groups (delta) was 15%. Choosing a type I error of 5% (one-sided) and 80% power, the sample size in the investigational group was 174 patients, and the sample size in the control group was 87 patients, for a total of 261. Allowing for a potential dropout rate of 10% resulted in approximately 194 patients in the treatment group and 97 patients in the control group, for a total of 291 patients."

L&I Comment 22 response. The data presented were interim data on the Bryan FDA panel summary.

L&I Comment 23 response. We added a sentence that there was not enough information in the methods section of the Peng-Fei or the Nabhan articles to warrant a level of evidence rating.

L&I Comment 24 response. The current trend when fusing for back pain associated with lumbar DDD is to do a 360 degree or circumferential procedure which was done by Zigler et al. Blumenthal et al appeared to do a stand alone ALIF. See response 3 & 4 for the rationale for pooling the data from these two studies.

L&I Comment 25 response. We included an intent to treat and sensitivity analysis on the pooled data providing information on the various scenarios for imputing missing or discontinued data.

L&I Comment 26 response. See response 3 & 4.

L&I Comment 27 response. Yes, and text is added to reflect that.

L&I Comment 28 response. Putzier et al values were included and text added to highlight the heterotopic ossification/spontaneous fusion rates in two studies with 10 plus years of follow-up, and a possible explanation as to the difference in rates.

L&I Comment 29 response. Noted. We attempted to summarize adverse events and listed each from the FDA trials in the appendix.

L&I Comment 30 response. Mehren et al was not initially included in the table because their rates were based on the number of spinal segments, not the number of people in the denominator. We have subsequently added this study to the table and text

L&I Comment 31 response. The figure may be helpful for some.

L&I Comment 32 response. Superiority can be concluded from an inferiority study, but not the other way around. I added the following text on page 49 of the report. "A non-inferiority clinical trial design is often used in FDA trials to show that a new treatment is no worse than a reference treatment. In order to accomplish this, a pre-stated margin of non-inferiority is defined for the treatment effect of a primary outcome. The new treatment will be recommended if it is similar to or better than the existing one, but not if it is worse by more than the pre-stated margin. It is acceptable to assess whether the new treatment is superior to the reference treatment using the appropriate statistical test.[124,152,168],,

L&I Comment 33 response. Since we don't have all the data available, we omitted this sentence.

L&I Comment 34 response. Longer term results from case series still report a wide variance in the number of failures and spontaneous fusions. In the two lumbar studies with over 10 years of follow-up (Putzier and David), the results were very different (60% HO/fusion vs. 3%). One difference between the two studies is the postoperative motion. They both had their patients initially immobile for several weeks following surgery. David changed his postoperative follow-up after he noted some HO forming, and allowed the rest of his patients early mobilization. He noted a significant reduction in HO in those later patients. We need longer term data from the RCTs and we need prospective safety data from case series.

L&I Comment 35 response. See response 3 & 4.

PEER REVIEW COMMENTS

1. Michael J. Lee, M.D., Assistant Professor, University of Washington, Spine Service

INTRODUCTION Comments

Lumbar: The overview is well defined. Specific questions and goals of the paper are well defined and exhaustively researched. The topic is important to address and the public policy and clinical relevance are well delineated in the introduction. The introduction/executive summary provides a concise overview of the paper.

Cervical: Overview of topic is adequate. The introduction adequately describes the clinical scenario relevant to cervical artificial disc replacement. Because the technology is newer than lumbar disc replacement, the report also adequately contrasts the indications for lumbar and cervical disc replacement. In addition, a nice historical background is provided leading up to the advent of ACDF. The incidence of adjacent segment disease is well described on page 25 of 224. It should be noted that while adjacent segment degeneration is widely discussed and supported by biomechanical and clinical studies, some surgeons feel that "adjacent segment degeneration" may only be a progression of the "natural history of cervical spondylosis" and "probably unaffected by the operative management" (Hilibrand et al JBJS 1999). These opinions originate from the original study that is oft quoted for its 2.9% rate of adjacent segment degeneration.

BACKGROUND Comments

Lumbar: The literature review and background are sufficient. On page 16, line 11, prior to stating "in 2001 122,469 lumbar fusion surgeries were performed…", I believe there should be statement as to what the cause of pain is. There seems to be a disconnect between lower back pain, and then fusion. I would recommend a statement to the effect that the degenerated disc is believed to be the pain generator, and traditionally, fusion has been used to eliminate motion at the pain generator site and subsequently the patient's pain. Then I would continue with the fusion statistics. I believe this allows the reader to make the connection of why fusion is being used to treat DDD.

Cervical: Literature review and background are sufficient. Biomechanical studies (Eck et al Spine 2002) would further support increase stresses at segments adjacent to a fusion. Adjacent segment degeneration is well described, and the authors do a good job of differentiating radiographic adjacent segment degeneration, clinically symptomatic ASD, and clinically symptomatic ASD requiring surgery.

REPORT OBJECTIVES & KEY QUESTIONS Comments

Lumbar: If the formal report begins on page 16, then I do not see the report objectives in this report. They are clearly defined in the Appraisal section of the report (pg 10-15). It seems it may allow for more linear thought process to restate the objectives and questions on page 36 prior to introducing Section 2 the evidence. Otherwise, the objectives and key questions are clearly defined in the Appraisal and Executive Summary.

Cervical: The objectives and key questions are well delineated in the Summary, however it may be nice to revisit them prior to addressing the methods section, so the reader may follow what questions are being answered while assessing the literature.

In regard to key Question #1, I believe it is inappropriate to compare C-ADR to non-operative treatment. The most valid comparison would be to operative treatment, the ACDF, which is the gold standard with a well-documented history of success.

METHODS Comments
Lumbar: The method for identifying relevant studies is well defined on page 39.
The method for selecting appropriate studies is adequate. Exclusion and Inclusion criteria are well defined. Level of Evidence rating is appropriate. It should be noted that no study evaluated in the report held a Level I rating. It should be further noted that blinded assessment is not possible (from a reviewer) and not ethical (from a patient). Therefore, no study examining lumbar ADR can qualify as a Level 1 study using these criteria.

Cervical: This was a little confusing. The 3 FDA studies are well described. Initially it was not clear to me which studies were the FDA studies. After reviewing the Pang Fei and Nabhan summary, I initially was confused why certain studies were excluded (Sasso et al Dec 2007 Spine). For me, the summary of the Pang Fei and Nabhan studies added confusion. While certainly important to note, the meat of the analysis really lies in the FDA study comparisons (which is well done). It may be less confusing to address the other studies afterwards the FDA comparison.

RESULTS Comments
Lumbar: The detail in the results section is exhaustive and appropriate.
The key questions are answered appropriately. Key question #1 is well answered in detail. Regarding "patient satisfaction", I would note that pre-operative impressions of L-ADR vs fusion are important data not reported. Anecdotally, many patients sought to be enrolled in these studies because they wished for a L-ADR. Everything else being relatively equal, the ones randomized to L-ADR would likely be "more satisfied" than those with fusion because these patients (anecdotally) were seeking ADR.

Key question #2 is well answered.

Key question #3 reports the available data examining the question. There are limited reports at this time looking at "special populations." This will likely be investigated in future studies. Of note, the Key Question #3 mentions workers compensation populations, but does not address them in the text.
Key question #4 is addressed as best can be by the available literature. The authors provide a detailed evaluation of available reports examining cost effectiveness.

Cervical: The results were easy to follow. The charts were easy to follow. The analysis was appropriately done with and without the Bryan data for completeness. The Key questions are answered as best can be in this early stage of analysis. As stated in the text,

C-ADR is newer than L-ADR and studies with longer follow-up are required to fully investigate the safety issues and the incidence of adjacent segment disease.

CONCLUSIONS Comments
Lumbar: The conclusions essentially state that at this time, the current literature suggests that L-ADR appears to be comparable to lumbar fusion in regards to clinical improvement and safety and efficacy. As the authors clearly state, long term data are still required to better assess the incidence of adjacent segment disease. In addition, the authors appropriately point out that different lumbar disc replacement designs and fusion strategies may affect future comparisons.

Cervical: The conclusions are valid. As stated in the conclusion, studies with longer follow-up are required to further investigate safety and sequelae of these procedures. At this time, the clinical improvement appears to be comparable between ACDF and C-ADR, however longer follow-up is required.

OVERALL PRESENTATION and RELEVANCY Comments
This review is very well structured and organized. The main points are very clearly presented. The executive summary does an outstanding job of summing up the major points. The depth of reporting data in the text can be challenging to follow, however does accurately report the current literature. As stated in the background, DDD is a major source of disability and is quite relevant to clinical medicine and public policy and health.

2. Sean D. Sullivan, RPh, PhD, Professor of Pharmacy and Health Services, Director of the Pharmaceutical Outcomes Research and Policy Program, University of Washington

(1) Executive Summary. You indicate there is moderate evidence that C-ADR is superior to ACDF? You then cite 2 non-inferiority studies. Were the trials powered for superiority, even though non-inferiority was the main design feature? Can you really say the evidence suggests superiority?

(2) Are surgical mortality rates in patients undergoing the ADR procedures versus non-ADR surgical procedures comparable? It seems that these data would be available somewhere, even if they did not come from a clinical trial.

(3) I note that the economic data and previously conducted HTA report suggest that complications rates (and therefore costs) may be higher in ADR? Should this be reflected more prominently in the risk section of your report?

(4) One of the main economic drivers for the cost-effectiveness of ADR is device failure and re-operation. It would be interesting to see a chart with time on the x-axis and failure rate on the y-axis so that decision-makers can visualize the failure rates for the ADR technology and the non-ADR comparators – even if you only have 24 months of data

from the published reports.

(5) On page 10, you use the term Appraisal. Are you required to use this term by Washington state? If not, you might consider changing this to Assessment. You will note that the UK NHS process defines Assessment as the systematic evaluation of the evidence (what you are doing) and Appraisal as the process that the decision makers use to review the assessment and make a recommendation to the NHS. The HTAi and EUnetHTA organizations make the same distinction.

(6) It would seem to me that one of the findings to highlight in the executive summary is that higher surgical volume is associated with better outcome in lumbar procedures. This is important, because if Washington state issue a positive coverage determination, they may decide to make coverage conditional upon use of a high-volume surgeon.

(7) In table 5 and 6 you describe payer policies for the ADRs. The policies would be more useful to the Washington state HTA program if you included local payers like GHC, Regence and Premera.

(8) Did you query the manufacturers for studies? Did you submit the list of studies to the manufacturers and ask them if you may have missed any recent reports?

(9) I like that you used the QHES.

(10) From Table 9, it is not clear how you would rate a high quality registry study? Would you place registries alongside a cohort study? In any event, were there large registries available for ADRs?

(11) You know I am not an expert on meta-analysis. However, I question the need to perform a meta-analysis on 2 or 3 studies, unless the study designs, research questions and treatments were exactly the same. Can you assure a reader that this is the case?

(12) You did a nice job with the economic section.

Ann M. Derleth, PhD, Health Services Research Postdoctoral Fellow, VA HSR&D, Seattle, Wa

Introduction:
Overview of topic is adequate and important to address. With new technology it is important to assess whether it provides an improvement on the current standard of care.

Page 10 - lines 7-13 Important to be clear that increased incidence of procedures performed is not necessarily increase in underlying condition it is seeking to correct. It can be either increase in incidence of the condition or change in surgical practice where the procedure is used more frequently or a combination of the two.

Background:
The literature review is thorough and sufficient.
Page 23 Line 30: clarify whether this is six weeks or six months.

Report objectives and key questions:
The aims clearly address relevant policy and clinical issues. The key questions are clearly defined and adequate to achieve the aims.

Methods:
The search methods for identifying the relevant studies is thorough and well presented, including specification of inclusion and exclusion criteria. The Level of Evidence (LoE) clearly explained and provides an excellent way to characterize the rigorous standards used to evaluate the reports reviewed. Methods of data abstraction and analysis are very good.
Page 41 Line 5: Explain why the FDA data were used vs those in peer reviewed reports when there was a conflict - are the FDA standards more restrictive?

Page 43 First paragraph: QHES is well presented and evaluated.

Results: the results section is very well presented in terms of organization, level of detail and clarity of tables and figures. Limitations are well stated.
Page 54 - State which score of the SF-36 is used - whether it is one or more scale scores (there are 8) or a summary score (PCS or MCS). This matters because it is reported as >15 point difference and that is easier to achieve on a scale score than on a summary score.

Page 65: paragraph on ASD, line 2 - it is not stated whether the patients are fusion, ADR or both.

Page 79: Table 20 footnote: risk difference in Bryan trial is reported to be in favor of ADR but the CI is (-.06-0.01)

Page 80, bottom of page: I was pleased to see mention that the MAUDE database was searched. But I didn't see this mentioned in the methods section - suggest it should be.

Conclusions: The conclusions reached are valid and well stated.

Overall Presentation and Relevancy
This is a well organized and thorough review of the literature and available information on the current state of knowledge for lumbar and cervical artificial disk replacement technology. It is very relevant to clinical medicine and important for public policy and public health. It is appealing to use new technology when it appears it might lead to improved patient outcomes, but often can be implemented before long terms results are known. This kind of assessment provides an objective guide to policy makers and clinicians for their decision making.

4. Jens R. Chapman, M.D., Professor; University of Washington, Director, Spine Service

INTRODUCTION Comments

Lumbar: This report fundamentally suffers from lack of scientifically sound " four key questions" as basis for its analysis, which clearly hampered the attempts of this research group to try to answer the questions posed. Each of these "key questions" by themselves reflects lack of familiarity with the subject matter or poor scientific background by those who were asking them and introduces a potential for considerable bias introduced by their phrasing. If it is the goal of the HCA to obtain a fair and unbiased review of a current or emerging health technology these 4 key questions do not provide the basis for such an analysis. I am afraid that a great opportunity has been squandered and Washington state tax-payer dollars have been wasted by not asking questions which may actually benefit interested or affected citizens of the State of Washington to gain insight into emerging health care technologies such as disc replacement technology. Pertinent and highly interesting questions were either not posed or addressed in a roundabout fashion.

Aspects of the limitations of this analysis lie in the phrasings of its key questions 1-4:
Key question 1
What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

The term lumbar disc arthroplasty is not defined anywhere in this text. There are many variants of mechanical total disc arthroplasties, which are listed in some detail (page 18, paragraph 2). What about nucleus replacements, anular reconstruction techniques and other forms of intradiscal spacers, which are all variants of lumbar disc arthroplasty? What about disc transplants, disc regeneration techniques? The wide area of disc replacement surgery has not been defined from the onset. It seems that this analysis is concentrated on the assumption that lumbar artificial disc replacement is synonymous with mechanical total disc arthroplasties, a hypothetical premise which should have been defined from the onset.

The premise of comparison of disc arthroplasty to nonoperative care is flawed from the start as all the US trials mandate a failure of all supervised nonoperative management as premise for exclusion. To assume parity of fusion results to nonoperative care based on some European PRCT study populations is a highly problematic assumption based on highly divergent study populations between the US and the European cohorts at hand.

Key question 2
What is the evidence related to the ADR safety profile (including device failure, reoperation)?

What is a ' safety profile', how is it defined? Again, the use of a non-defined term does not provide a basis for a scientific analysis.

Key Question 3

What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

Convoluted and conditional question writing does not provide a sound basis for any exploration, especially not for a complex subject matter, such as the one at hand. What, please are 'special populations', do they bear any similarities with contestants at 'Special Olympics'? What is an elderly population? I am still waiting for general comparative workers compensation population studies comparing 'differential efficacy' of workers compensation systems of various states in the U.S. and other countries compared to those in the State of Washington.

Key Question 3

What are the cost implications and cost effectiveness for L-ADR?

Yet again, definitions, please. What are cost implications? I have never heard this term used in any analysis before. Did the question writers wish to compare disc arthroplasty patients to any specific other cohort?

Cervical: The study at hand suffers from poorly phrased key questions, which serve as determinants for the project at hand. Each of the key questions fails in providing defined terms for its questions and posing answerable questions. Since the key questions posed by the HCA of Washington were left unchanged the same criticisms applied to the lumbar disc assessment apply here as well and will not be reiterated. The fundamental differences in human anatomy, biomechanics, clinical indications and expected long term outcomes that present as differences between lumbar and cervical disc pathology were not at all reflected in these questions. I am not sure how the citizens of the state of Washington were helped with this project in the context of these undifferentiated questions.

BACKGROUND Comments
Lumbar: Page 17, paragraph 2, line 4. No reference for Fernstrom failure rates given, stated argument of 'After a short period of symptom relief, the prosthesis ultimately failed secondary to subsidence of the implant within the spine vertebra leading

to abandonment of the technique' is hearsay and should be eliminated unless details quoted. Long-term data on Fernstrom cages suggests differently.

Page 117-18. All explanations for disc arthroplasties pertain to mechanical total disc replacements and do not address 'disc arthroplasty' as term posed in question.

Page 26. The references to other health technology reviews having taken place was illustrative and helpful.

I would expect a reference to other forms of arthroplasties in this part, such as hip and knee replacements, which are considered some of the most successful heath related quality of life procedures known in medicine. We derive much of our knowledge and concerns for spinal mechanical arthroplasties from the 50 year history of utilizing these devices in major extremity joints.

Cervical: Page 13, paragraph 1, line 5. No mention of electrodiagnostics as supplement to physical examination is given. Page 20, C-ADR and onward. No mention of the Bristol disc and its lengthy track record is made in this paragraph. The Bristol disc is relevant as the minimally modified precursor to the Prestige disc. There is some 20 year data available for this model of disc replacements.

REPORT OBJECTIVES & KEY QUESTIONS Comments

Lumbar: See above comments regarding key questions.
I remain confused as to the objectives. Were these objectives formulated by the HCA or by the research organization? How are the objectives and key questions supposed to interface? Is the objective of this undertaking to formulate health care policy, advance medical knowledge, improve informed decision making of affected Washington State patients or produce a summary statement on the state of research of clinical studies pertaining to lumbar disc arthroplasties? The purposes of this undertaking are not articulated and spelled out, which adversely affects its relevance.

Cervical: As with the L-ADR I am missing a clear objectives statement in conjunction with the key questions. The flaws of the key questions have been outlined above and in my comments on L-ADR and are not repeated herein, but remain in full effect.

METHODS Comments

Lumbar: A thorough and comprehensive attempt at compiling articles pertaining to total mechanical disc arthroplasties was made. In- and exclusion criteria for review of studies were reasonable and meet scientific and fairness and relevancy standards.
Level of evidence determination deserves further commentary. The Oxford Centre for Evidence-based Medicine, precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[4] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ) are widely accepted, no doubt. These standards were developed with pharmacologic trials in mind and are incompatible with current surgical practices and the realities of performing research in most countries of the Western civilized world. The downgrading of the 2

main PRCT's (Blumenthal and Zigler) to moderate or poor quality RCT's is harsh and as stand-alone statement can induce a bias against the undeniable and unprecedented quality of either of these trials. It would improve the fairness of this presentation to provide a more balanced and detailed discussion of why the downgrading to IIb) occurred. In this context the realities of FDA study regulations and time periods to insurance approval for some elective surgeries may explain differences in enrollment numbers and treated numbers. These are factors clearly are outside of the control of any US investigator and usually will not introduce a methodological bias, thus should not be used as a reason for downgrading. The same goes for completers versus ITT population. The data acceptable to the FDA has to be obtained in specified time sections, data outside of that specified window is not of interest to the FDA, and will thus usually not be published.
A downgrading of LoE for differences in smoking status appears not appropriate since the data analyses in these 2 study populations don't support different complication rates for fusion patients. Extrapolation from previous publications in this regard doesn't meet scientific standards if the data presented specifically contradicts this variable having a confounding influence.

Cervical: Assignment of Level of Evidence status to category II: The reviewers have pointed out the incompatibility of the GRADE system with surgical trials under FDA premises (which, for instance, explicitly governs timing of device disclosures to patients).
Page 67. Please define 'success' as a composite 'all-or-nothing' term introduced by the FDA and list its subcomponents. This definition of success has never been validated statistically and should be used with some caution.

RESULTS Comments
Lumbar: Page 56. The issue of "success" of disc arthroplasty is discussed prominently in the opening paragraphs of the result section in reference to the 2 'index studies' by Blumenthal and Zigler. Nowhere is it made clear that the definitions of success are "all-or nothing " composite scores created by the FDA without scientific validation based on a number of outcomes scores, radiographic observations and absence of complications, which were different for the 2 trials. It would seem reasonable to point these circumstances out and cut and paste these FDA derived definitions into the text for a clearer understanding of the definition of 'Success' for the benefit of the readership at large.

Page 59: does the ODI data presented, for instance in Figure 8, assume a > 15 point difference throughout, or are there different standards applied by either study?

Cervical: The available results are presented in a fair and clear fashion.

CONCLUSIONS Comments
Lumbar: The evidence tables provided reach valid conclusions within the diffuse parameters set by the study sponsor.

Cervical: A fair representation of the data available to date has been made

OVERALL PRESENTATION and RELEVANCY Comments
Spectrum has done a fair and reasonable job with the foundations it was provided trying to answer the questions it was given. The main issues concerning disc arthroplasty unfortunately have not been adequately addressed. These include identifying patients with especially good results and differentiating these from those with poor results. What are failure mechanisms of disc arthroplasty – are there any predictors for poor outcomes based on indications, surgical technique and postoperative care? What are the biomechanical and clinical foundations for development of - and prevention of adjacent disc degeneration? Are there differences in efficacy and effectiveness, and if so what factors play a role? How did complications affect HrQoL outcomes? Did maintenance of motion lead to better or worse outcomes? Does quality of surgery with disc replacements influence outcomes and complication rates?

5. Brian M. Drew, M.D., Assistant Clinical Professor, McMaster University, Medical Director, Hamilton General Hospitals Spine Unit

INTRODUCTION Comments
I thought the introduction was accurate in terms of the scope and overview of DDD and the general surgical indications for DDD, specifically when ADR is an option.

In the summary and implications section (page 7, last paragraph) I thought the 6 week period of conservative treatment is too short and should be 3 months. I did not feel 6 weeks is wrong but just a bit on the aggressive side unless there was progression of neurological signs. Otherwise this section was clinically relevant, particularly with respect to a) special subpopulations and b) the last paragraph on page 9 regarding the different biomechanical designs

Page 10, 3rd paragraph—very important to highlight the fact that adjacent segment disease is a controversial issue and not well understood. This is addressed here well and at several other points in this document.

Page 12-15 - The primary and secondary outcomes and complications are clinically relevant measures and issues.

The comment at page 13 regarding new indications and off-label use is clinically very relevant. There is a long history of new products coming to market with strict indications that then widen overtime creating new complications and issues not previously known.

On page 15, the last paragraph is important as it highlights the issue of high-volumes. Most of the studies referenced would be performed by surgeons with significant experience in this procedure. The complications would be expected to increase with lower volume surgeons performing the procedure. The extent of the increase is difficult to quantify.

BACKGROUND Comments
Page 16. 1.1-- The epidemiology is accurate. The anatomy and pathophysiology is basic but gives an accurate and sufficient basis for the understanding of the rationale for the use of an ADR in DDD.

Page 17-25. 1.2-- A good description of the history of L-ADR is given as well as the various types of products are well described. The biomechanical principles, classifications and material components are accurate. The clinical symptoms and unique design differences in C-ADR are highlighted and are accurate. The surgical description and potential complications of C-ADR are accurate.

The indications and contraindications are sufficient.

Page 19 paragraph 3 highlights the importance of the lack of long term data to help clinicians understand what possible adverse outcomes may lay ahead. Surgeons currently lack a good understanding of how they may need to deal with implant failures over the long term.

The summary of the indications and contraindications of L-ADR are reasonable

Page 23-25. The alternative non-operative and operative treatment options to L&C-ADR are described sufficiently and accurately.

Section 1.4 summarizes all relevant technology assessments in a comprehensive and well organized fashion. This includes both lumbar and cervical ADRs. The tables are particularly helpful (tables 3 & 4)

Finally in section 1.6 it reveals a comprehensive and very current review of the latest evidence despite it being incomplete. Caution is required in interpreting this data until full enrollment and follow-up is achieved. But it is important to note this clinically important work is currently being undertaken.

REPORT OBJECTIVES & KEY QUESTIONS Comments
I believe this was done well. Certainly the aims and objectives were clearly addressed. They represent relevant policy and the important current clinical issues.

The key question were clearly described and thoroughly addressed and discussed throughout the document. Limitations in what the literature had to offer were well described as it pertained to the key questions.

METHODS Comments
Page 36-38. Table 7 summarizes the inclusion and exclusion criteria well. The population, intervention, study design and outcomes are appropriate.

Page 38-50. The search strategy & the algorithm for article selection are described well and are appropriate. Figures 2 & 3 help explain the rationale for selection and the relationship to the key questions in an organized fashion.

In reviewing the document I believe the relevant studies were reviewed or at least considered based on the studies methodological merits and its relationship to answer the key questions. The studies selected from the current literature were of high quality. Tables 10 through 13 help to summarize this well.

The definitions used to differentiate the levels of evidence for articles on therapy fit standard definitions and are quite appropriate. This use of these definitions was instrumental in helping to rate the LoE. The use of meta-analysis to interpret primary outcomes is well described and then a good flow sheet is available in Appendix D.

The Quality of the studies used to evaluate both the lumbar and cervical ADR are well described on pages 45 to 51. I felt this was quite comprehensive.

Page 51-55. The description of the study populations and study outcomes for both the lumbar and cervical are summarized well and are more than adequate.

RESULTS Comments

My comments in this section do not include page numbers as my comments are more general in nature and are aimed helping to answer the questions above.

The detail in the section is very comprehensive. It includes all clinically relevant outcome measures needed to determine clinical success and evaluate the safety of the various ADRs. The figures and tables were quite helpful in summarizing the large quantity of date and they highlighted the major findings well.

The key questions were answered thoroughly. The strongest available data was sought out and I believe interpreted appropriately to assist in answering these four questions well. The data regarding possible adverse outcomes was summarized very well and this is critical when evaluating new technologies.

The limitation of the literature was highlighted well with respect to adverse events and complications. The document recognizes and highlights the gap present here. The document acknowledges these devices are designed for long term implantation yet the available studies lack the long term follow-up necessary to objectively analyze this.

The implications of the major findings were described well. Perhaps the clinical significance or nature of some of the complications (for example DVT or vessel laceration) could have been described in a little more detail to give a better general understanding of the m and their significance. This may help in the understanding that these complication could in some circumstances be life threatening. A lay person reading

this document may not understand the significance of some of the complications. However the breadths of complications were well covered.

Key Question 3 is important but details in the literature are sparse. This explains the lack of clinical data to review on this area. This is a significant gap in the literature that is highlighted well in this document and is clinically important. The populations listed here (smokers, athletes and the elderly) are not insignificant in society and they will experience DDD of the lumbar and cervical spine. There will be no doubt that they will request these forms of treatment from surgeons as these devices come to market. There will be pressure on surgeons to use these treatment modalities but the lack of data on this population exists and hence the importance of this question. Despite the sparse data here it is the best information available to date.

I do not have any experience or much knowledge regarding the cost implications and economic analyses and therefore can not comment on the details in Key Question 4. However it is clearly an important issue and it is extensively addressed in this document.

CONCLUSIONS Comments

The Summary and Implications section summarizes the clinically important issues succinctly. The conclusions reached are an accurate interpretation of the current literature. They reflect the important clinical issues and address the lack of data on other clinically important issues.

I believe the conclusions were reached in a valid manner. The methods section was well described and appropriate search strategies were used to identify and eliminate appropriate evidence.

OVERALL PRESENTATION and RELEVANCY Comments

The review was certainly well organized and easy to follow. The order in which the information was described helped achieve this goal. The use of tables, charts and figures was helpful to clarify and summarize the results.

The main points were clearly presented. The written descriptions were easy to follow and the again the use or tables, charts and figures helped with this. The main points were often repeated to various degrees in multiple sections including the conclusion to help with clarity and importance.

The details of this document cover all important clinical material with respect to ADR. Especially the complications and adverse event components, indications and contraindications and the clinical difficulties surgeons encounter to reach certain treatment decisions. This was particularly well described when noting the difficulties in selecting patients for lumbar fusion or L-ADR. These issues are controversial. The issue of ASD is well addressed and is controversial as well. ASD is a key argument in the use of L & C-ADR but it is not well understood. This important point was addressed sufficiently.

It is important to note the significant differences in clinical indications and patient selection between the 2 devices(L & C-ADR). This was addressed but I think could have been stressed a little more.

Although I stated my knowledge on the specific economics of these devices is limited it is clearly an important public policy issue given the expense of these devices and relative lack of long term data when compared to current treatment.

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September 9, 2008

Ms. Leah Hole-Curry
Program Coordinator
Washington State Health Care Authority
Health Technology Assessment
Health Care Authority 676 Woodland Square Loop SE P.O. Box 42712 Olympia, WA 98504-2712

Re: Health Technology Assessment Draft Report – Artificial Discs Replacement (ADR)

Dear Ms. Hole-Curry:

Thank you for the opp ortunity to comment on the Artificial Discs Replacem ent Draft report from Aug 26, 2008, for the Washington State Health Care Authority.

DePuy Spine, Inc. is an operating com pany of DePuy, Inc. one of the world's leading designers, manufacturers and suppliers of orthopedic devices and supplies. We are known throughout the m edical world for the developm ent of innovative solutions for a wide range of spinal pathologies.

The two issues discussed in this letter re late to: 1) the m ethodology utilized by Spectrum Research Inc. (SRI) to assess the qu ality of the evidence; an d 2) c linical comparisons of ADR to continued conservative nonoperative care.

1. Methodology to Assess the Quality of the Evidence.

SRI's methodology to assess the quality of the evidence uses a 4-Level grading system , defined on page 44 of the draft HTA. Leve l I evidence is defined as a "Good Quality RCT" and requires all of the following crit eria: concealm ent; blind or independent assessment for im portant outcom es; co-interve ntions applied equally; follow-up rates of 85%+, adequate sample size and intent-to-treat. Evidence from studies that vio late any of these methodological criteria is graded Level II ("m oderate or poor quality RCT"), Le vel III (moderate or poor quality cohort or case-control) or Level IV (case-series).

SRI's evidence assessment system may be appropriate for pharmaceutical studies. However, there are unique considerations related to surgical device trials. For example, "blind or independent assessment for important outcomes" may not be feasible in surgical device trials[1], and as such, no trial can possibly be designed to qualify for Level I. As listed in Appendix G, none of the studies reviewed in this report was graded Level 1. This grading system may therefore not be appropriate for reviewing surgical evidence for spinal devices.

2. Clinical comparisons of ADR with continued conservative nonoperative care.

The Summary and Implications section page 92-94 reports the lack of studies comparing ADR to continued conservative nonoperative care. The use of nonoperative control arms was previously discussed in great details at the Washington State Health Technology Assessment on Fusion, on November 16, 2007. Whether a nonoperative control arm is compared to a fusion or an ADR group, similar considerations apply. Specifically:

1) The assumption that surgery (whether fusion or ADR) and nonoperative care are competitive/interchangeable treatments utilized under similar circumstances is incorrect, as was stated by Dr. McCormick during the Washington State Health Technology Assessment on Fusion on November 16, 2007. In fact, patients are only considered surgical candidates after failing nonoperative care. The same applies to arthroplasty: in the CHARITÉ IDE study, patients in the ADR group were on non-operative care for an average of 32.4 months (median: 23.0 months) while patients in the fusion group were on nonoperative care for an average of 26.7 months (median 19.0 months) [non-published data – on file at DePuy Spine].
2) The fact that surgery is a treatment offered when nonoperative care fails has been made apparent in the SPORT trial. In this study, out of 145 patients assigned to nonoperative treatment for lumbar degenerative spondylolisthesis, 49% (71) underwent surgery. The magnitude of this cross-over rate illustrates the fact that as patients worsen, surgery becomes the main treatment option[2]. It also points out to the inherent difficulty in generating statistically meaningful data that can conclusively address the issue of nonoperative care vs. surgery.
3) No standardized nonoperative treatment exists for patients with degenerative disc disease. While pilot studies have discussed the potential effectiveness of specific rehabilitation programs, these programs have not been validated. The clinical effectiveness of nonoperative treatments still need to be established, prior to being used as controls to ADR in randomized controlled trials[3,4].

As the comments included herein may potentially impact the overall interpretation of available evidence for ADR, we would like to respectfully suggest that these points be considered in the final version of the ADR HTA.

Sincerely,

Chantal E. Holy, PhD
Director of Scientific Affairs
DePuy Spine

Reference List

1. Lilford,R., Braunholtz,D., Harris,J., & Gill,T. Trials in surgery. [Review] [66 refs]. *British Journal of Surgery* **91**, 6-16 (2004).

2. Weinstein,J.N. *et al.* Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. *N. Engl. J Med.* **356**, 2257-2270 (2007).

3. Fairbank,J. *et al.* Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *BMJ* **330**, 1233 (2005).

4. Brox,J.I. *et al.* Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine* **28**, 1913-1921 (2003).

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September 9, 2008

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RE: HTA Artificial Disc Replacement Draft Report Comments

Dear Ms. Hole-Curry:

We appreciate the opportunity to comment on the Artificial Disc Replacement Draft Report. As you are probably aware, Medtronic Spinal and Biologics Division manufactures products that treat a variety of disorders of the spine. These products are utilized by spinal and orthopedic surgeons to treat patients and restore their quality of life. As the manufacturer of the first cervical disc to market, we are very interested in this review and want to ensure that patients in Washington retain access to the latest and most effective technologies.

We have reviewed the Draft Report prepared by Spectrum Research, Inc. (Spectrum) and found it to be thorough. However, we do have several comments pertaining to the findings and analysis regarding cervical disc arthroplasty.

Summary of Findings Does Not Reflect the Review/Analysis

As stated in the report, there is moderate evidence in support of the safety and effectiveness of C-ADR compared to ACDF (see questions 1 and 2). However, in the Summary of Findings on page 9, the report diminishes the strength of the data with the statement that there is "insufficient evidence to draw extensive efficacy/effective conclusions comparing ADR with a broad range of treatment options." In this regard, statements are made that there is no direct comparison to conservative operative care or other forms of surgical intervention. We believe these statements are misleading for two reasons. First, patients who are candidates for disc arthroplasty would have already exhausted an appropriate period of conservative care. And second, ACDF is historically the standard of care. See further discussion below.

Additionally, the methods, grading, rating, and application of the evidence are unclear, particularly in regard to reference numbers 76, 77, and 78; further explanation would be useful and helpful to ensure consistent evidence evaluation.

Non-operative Care and Other Surgical Procedures

Patients who are indicated for C-ADR have undergone at least six weeks (note the report has a couple of erroneous references to six *months*) of non-operative care without success. As noted on page 24, non-operative care does not reverse or stop the disease progression or resolve pain in 50-70% of myelopathy patients and 25% of radiculopathy patients. Further weakening and worsening pain often occurs in patients with cervical disc herniation or spondylosis causing radiculopathy or myelopathy. To relieve these symptoms, decompression is required, and as noted on page 26, the current definitive standard of care for these patients is ACDF.

The background of surgical options for these patients is a necessary component of the report in laying out the history of treatment options for these patients (see pages 11,17, 18,25 and 26) and ultimately reaching the conclusion that ACDF is the relevant comparison to C-ADR. However, we find that further explanation of the historical perspective and reference to broader literature (i.e. beyond two articles on myelopathy, and one on Blue Cross Blue Shield's disc arthroplasty technology assessment in references 5, 6 and 7) would improve the quality of the report. In general, beginning in the early 1900s and for many years, posterior decompressions were the standard of care. However, with limited access and exposure to midline disc fragments and calcified spurs, anterior approaches were introduced in the 1950s. Instrument reconstruction and fusion was necessary to promote fusion, allow for earlier return to activities of daily living, and avoid kyphosis. Posterior decompression continues to be a treatment option for soft accessible disc fragments and foraminal osteophytes in radiculopathy. However, anterior decompression and fusion have become the standard of care for central and paracentral disc herniation, radial osteophytes and uncovertebral joint spurs in radiculopathy and myelopathy.

It is important to clarify that not all patients who currently undergo cervical spine surgery would be candidates for C-ADR. Auerbach (2008) conducted a retrospective study of 167 patients who underwent cervical spine surgery. Based on assessment of the patients' history in terms of the indications and contraindications for C-ADR, 43% would have been candidates.

Level of Evidence: Questions 1 and 2

The Spectrum report cites several sources on rating the evidence; it is not clear from the report how the rating methods were selected or utilized to rate the studies. The AHRQ report (#78) notes that there are numerous methods for rating clinical evidence, and that "[u]sers wishing to adopt a system for rating the quality of RCTs will need to consider the topic under study, whether they prefer a scale or checklist, and ease of use of the system." Two other reports were cited by Spectrum to support their rating of the

evidence, the Phillips/Oxford Centre's guidance for rating evidence (#76) and the Atkins' criteria (#77). Because the AHRQ report conclusions on rating evidence suggest a system related to the topic studied, the Phillips/Oxford Centre's rating system is fairly complex to interpret and Atkins' is relatively general, we suggest that more details are necessary and should have been included in order to accurately support the bases of the ratings.

In other methodologies, it is more typical to rate a randomized control study, such as the studies cited in the report, as Level I studies with several subgroups (SIGN 2008 and van Tulder 2003). Due to the inherent difficulties of conducting a randomized, blinded medical device surgical trial, compared to a drug trial, it is not logistically or ethically feasible to meet 100% of the criteria for the highest rated RCT. Nevertheless, the quality of the referenced studies warrants a higher rating than moderate, level II.

Ms. Leah Hole-Curry, Program Director
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Page Three

Based on the analysis of three level II RCTs (see pages 66-81), the evidence meets the criteria for quality, quantity and consistency evidence showing that C-ADR is superior to ACDF for overall study success and neurologic success, and comparable for NDI, pain, and safety. The report acknowledges this with its statement on page 97, third column, that "this result is based on FDA criteria for overall success and pooled estimates from two completed trials and interim FDA analysis of a 3rd trial." To reflect this, "quantity" in the evidence strength table (see pages 97 and 98) should be changed from "-" to "+". In addition, for these listed outcomes, the comment regarding further research in column two should be removed.

With regard to motion, as noted on pages 9 and 93, there is evidence that motion is maintained or improved up to four years. For text on pages 74 and 97, "improved" should be included with "maintained."

For adjacent segment disease, Mummaneni (2007, #98) and Robertson (2005, #124) report lower risk of ASD requiring surgery for C-ADR vs. ACDF (see page 76). While longer term data are necessary, these two year results are worthy of acknowledgement on pages 9, 93 and 97.

Omission of Studies: Question 2

There are several studies addressing key question 2 that we recommend Spectrum include in its analysis. In addition to the 22 studies cited in the technology assessment contributing to the evidence on the safety of cervical disc arthroplasty, the following six studies also provide information on safety outcomes.

- Anderson et al. (2008) compared the adverse events associated with the Bryan artificial disc to anterior cervical athrodesis in a randomized controlled trial (n=463). This study found that both procedures had a low incidence of significant adverse events related to the procedure. Statistically, more serious adverse events and reoperations occurred in the fusion group while a significantly greater number of less serious surgically related events occurred in the investigational group.

- Sasso et al. (August 2008) found no evidence of migration, no subsidence at 24 months, and no evidence of bridging bone across the implant disc spaces in cases implanted with the Bryan disc in the same randomized controlled trial reported on by Anderson et al (2008). The radiologists did find a 2.5 % incidence of anterior osteophytes in the investigational patients.

- Rates of adverse events between fusion and artificial cervical disc (Prestige ST) arms of a single center randomized controlled trial (n=19) were similar in Riina et al. (2008) after 24 months follow-up.

- In Sasso et al. (February 2008), flexion/extension range of motion was not determined to be significantly different between populations (randomized clinical trial comparing fusion to Bryan cervical disc replacement, n=22) at adjacent segments. There was a significant difference in translation at the level above the fusion after the surgery. To accomplish similar flexion/extension range of motion at the level above the fusion, increased translation was found in the fusion group. This increased translation at the adjacent level may place excessive loads on the annulus and the facet joints above a cervical fusion.

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- Yang et al. (2008) identified no cases of prosthesis subsidence or excursion in a case series of 19 patients implanted with the Bryan artificial disc after an average of 24 months follow-up.

- In a 47 patient case series of patients who received the Bryan artificial disc, Kim et al. (2008) reported that the overall sagittal balance of the cervical spine was usually preserved. The study also reported that no definite clinical deterioration due to kyphogenesis of the functional spine unit or overall cervical alignment was observed.

We believe these studies provide additional evidence to support the safety profile question reviewed by Spectrum Research; and furthermore, that the report would not be complete without them.

Treatment Guideline/Coverage Policy Omissions

The Spectrum report provides an overview of pa yer assessments and policies for cervical disc arthroplasty. However, m any key payer policies and state workers' com pensation treatment guidelines were not included. In order to provide a com plete and comprehensive analysis, these policies should be included.

Currently, several state workers' compensation policies and/or treatment guidelines allow coverage of the cerv ical artificial disc and others allow coverage and paym ent on a c ase-by-case basis. Colorado's workers' com pensation guideline was created by a physician advisory p anel th at reviewed the clinical ev idence and determ ined that the cerv ical disc should be covered. Montana established a coverage policy in the workers' com pensation program for FDA approved devices used in a single level af ter a period of conservative care. W yoming also has a positive workers' co mpensation guideline f or cervic al discs which was estab lished by a physician comm ittee. Finally, m any states have propo sed guidelines that establish coverage f or cervi cal discs, including New York and Oregon. These guide lines/policies are cur rently in th e regulatory process a nd have not yet been finalized.

In addition, there are various pos itive co mmercial payer policie s in cluding Aetna's national coverage decision a nd certain Blue Cross Blue Shield p lans. The Fe deral Employee Health Benefit Plan also provides positive coverage that allows reimbursement for any FDA approved device. W e would encour age review of those plans and inclusion in Table 6 on page 34 of the report.

Economic Data Omitted

There are two recent econom ic presentations that we would encourage Spectru m to include in the disc arthroplasty review:

- Anderson, Paul, Traynelis, Vincent. Econom ic Analysis of Artificial Cervical Disc Replacement versus Anterior Cerv ical Fusion Surgery in th e Non-Elderly: Im pact on Hospital and Societal Costs. Presente d at the North Am erican Spine Society Meeting, Seattle, Washington, September 27-30, 2006.

- Menzin, Joseph, Zhang, Bin. The Econom ic Impact of The Prestige Cervical Disc System: Results From A Random ized Clin ical Trial. Presented a t Am erican Association of Neurological Surgeons M eeting. Chicago, Illinois, April 27-May 1, 2007.

The Anderson study is an economic analysis of three prospective, multi-center, randomized clinical trials and 2 single arm trials assessing arthroplasty and anterior cervical fusion. The study included 649 disc and 580 fusion patients with single level radiculopathy or myelopathy with a mean age of 44 years. The results show that disc surgery saves $200 per patient, on average, relative to fusion. From a societal perspective, the savings were $5273 per patient favoring disc and the finding was based on a 35-day faster return to work.

The Menzin study is a randomized clinical trial of 541 patients with single-level disease; 276 of the patients received cervical disc arthroplasty and 265 received fusion surgery. Clinical data were collected preoperatively and postoperatively for a maximum time period of two years and the study measured direct medical costs and work productivity. The results showed that compared to fusion, disc arthroplasty resulted in higher neurological success rate and better functional outcomes, fewer secondary procedures and an earlier return-to-work. The net economic benefit, defined as the difference between value of work productivity and direct medical costs, was $5988 for the cervical disc arthroplasty patient.

Although these economic studies have not yet been published, they have been presented at two leading physician specialty society meetings and represent valid information that should be considered in a review of cervical disc arthroplasty. We would encourage Spectrum to include this information in the final report.

Errors to Be Corrected

Prior to release of this report in a final form, we recommend a final quality check of the document, including consistency of the narrative and accuracy of the references. Examples follow.

Page	Description
General	In various tables, author/year only citations are provided. As the bibliography is not ordered alphabetically, it is not easily possible to find these citations. If an author/year reference is included, the citation number should also be provided.
21	6 weeks vs. 6 months of conservative care
23	Discussion of wear debris evaluation; reference to Singh (#9), which is a paper on C-ADR impact on physician practices Reference to the Prestige and ProDisc indications is incorrectly listed as #40, which is for the Bryan disc.
24	6 weeks vs. 6 months of conservative care
26	Sentence including “”the most methodologically rigorous longitudinal study” includes references 62-67; #62 only is correct
29	Statement made that all assessments performed prior to any RCTs. This is not accurate as the Hayes and NICE study reference RCTs.

40	"Nine" HTAs are referenced. It's not clear which studies comprise the nine.
42	The flow chart focus es solely o n the RCTs. It's not clear how the search/exclusion/selection of the additional 22 articles was completed.

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47	In reference to the 2007 Bryan panel overview, two references (101 and 102) are provided relative to the Bryan Disc. One is incorrect (N abhan 102), as it includes the ProDisc.
50	The Mummaneni study included a s econdary hypothesis for superiority, which is not cited.
50, 54	The baseline differences in patient characteristics were not statistically significant; this should be stated.
51	References to the "high percen t of lost to f ollow-up" f or the Mumm aneni study are in accurate. A priori, th e analysis in tended to loo k at th e first 250 completers in each grou p and the lost to follo w-up are reported for these patients. The other cases were not yet due for follow-up.
52	Nabhan's study was not designed to assess VAS pain; therefore the statement regarding the small sample size is inappropriate.
73	SF-36: all references to "%" should be points. The Mummaneni changes in SF-36 scores should be verified; rather than 11 and 9, and 7 and 8, it appears that 13.1 and 11.8 and 7.4 and 7.5 are correct.
81	In addition to the total num ber of pa tients with c omplications, addition of a column with the to tal nu mber of patien ts in the "x" specified articles would be helpful to put in perspective the range of complications. Double check references. As an exam ple, #124 m ay not report on hematomas.
91	With exception of the 2007 cases, all pr ior years would represent patients in IDE trials.

Thank you again for th e opportunity to comm ent on the Artificial Disc Replacem ent Draft Report and to pa rticipate in the HTA process. W e stand ready to answer any questions o n these co mments and will gladly respond to non-proprietary inform ation requests from Spectrum. Such requests for in formation, however, should be directed to my attention rather than our customer service or sales staff.

Sincerely,

Dena Scearce, JD

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Additional References

Auerbach J, Jones K, Fras, C, et al. The pr evalence of i ndications and contraindications to cervical disc replacement, Spine Journal. 8(5): 711-6, 2008.

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Kim SW. Shin JH. Arbatin JJ. Park MS. C hung YK. McAfee PC. E ffects of a cervical disc prosthesis on maintaining sagittal alignment of the functional spinal unit and overall sagittal balance of the cervical spine. European Spine Journal. 17(1):20-9, 2008 Jan.

Riina J. Patel A. Dietz JW . Hoskins JS. Trammell TR. Schwartz DD. Com parison of single-level cerv ical f usion and a m etal-on-metal cerv ical d isc replacem ent device. American Journal of Orthopedics. 37(4):E71-7, 2008 Apr.

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Sasso RC. Best NM. Metcalf NH. Anderson PA. Motion analysis of Bryan cervical disc arthroplasty versus anterior discectom y and fusion: results from a prospective, randomized, m ulticenter, clinical trial. J ournal of Spinal Disorders & Techniqu es. 21(6):393-399, 2008 Aug.

Yang S. Wu X. Hu Y. L i J. Liu G. Xu W . Yang C. Ye S. Early and in termediate follow-up results after treatm ent of degenerative disc disease with th e Bryan cervical disc prosthesis: single- and multiple-level. Spine. 33(12):E371-7, 2008 May 20.

September 9, 2008

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VIA E-MAIL

RE: HTA Draft Evidence Report on Artificial Disc Replacement (ADR)

Dear Ms. Hole-Curry:

We would like to thank the Washington State Health Care Authority Health Technology Assessment Program (HTA) for the opportunity to provide comment on the draft health technology assessment to systematically review the evidence available on the safety, efficacy and cost-effectiveness of artificial disc replacement (ADR). We fully endorse and applaud the HTA's ultimate goal of improving patient care through application of scientifically grounded therapies, including newer health technologies. As medical specialty societies representing the primary providers of ADR, we have some concern about the content of the evidence report, but more about the process by which it was achieved. The comments provided herein are submitted with the intent of assisting in providing the residents of Washington State with the best, most cost-efficient healthcare possible.

HTA Draft Report: Artificial Disc Replacement (ADR) 8.26.08
General Comments on the Lumbar Arthroplasty Section of the Assessment. This draft evidence report summarizes the preclinical and clinical literature available on lumbar arthroplasty, and defines the levels of evidence presented in the articles based on a 4-point scale (page 44). Level-1 data requires studies with blinding of treatment and analyses, follow-up rates of 85%, adequate sample size and intent-to-treat analyses. Violation of any of these conditions down classifies trial results to lower levels of evidence.

This methodology is particularly challenging in the realm of spinal device trials. Surgeons are obviously not blinded to treatment arms, and patients are aware of the nature of their implants immediately post-surgery. Blinding of imaging results for analyses purposes is also not achievable, as various devices are clearly identifiable on x-rays.

As a result, and not surprisingly, all RCTs reviewed in this report are described as Level-II studies or "Moderate or Poor Quality RCT," despite the fact that these studies were mandated, reviewed and accepted by FDA using strict clinical and statistical methodologies. In fact, it is unclear whether any RCT conducted to date for spinal surgery could possibly qualify as a Level I study. It is therefore questionable whether this 4-point scale is adequate to qualify RCTs for spinal surgery and lumbar arthroplasty. This specific issue was raised and discussed

recently by Lilford *et al.*, who similarly confronted the issue of blinding and overall quality of resulting evidence, from surgical trials.[1]

In November 2004, the National Institute for Clinical Excellence (NICE – UK) issued a Guidance on Prosthetic Intervertebral Disc Replacement, indicating that "current evidence on the safety and efficacy of prosthetic intervertebral disc replacement appears adequate to support the use of this procedure." This report was based on data available before January 2004. Since that time, both the Blumenthal *et al.* and Zigler *et al.* studies were published, further describing the safety and efficacy of lumbar arthroplasty.

A common consideration among technology assessments is the lack of data to determine the longer term safety and efficacy of lumbar arthroplasty compared to fusion (e.g., page 93 of the WA HTA draft report). The five-year CHARITE Artificial Disc IDE study, recently completed and presented at CNS/AANS Joint Section and EuroSpine 2008, addresses this shortfall (see attached abstract). This data was accepted for publication by *The Spine Journal* on August 5, 2008, and is currently in press.[2] This study represents the largest and longest RCT performed on arthroplasty to date, and addresses the need for long-term safety and efficacy data, as indicated in the WA HTA draft report.

Combined Review of Lumbar and Cervical ADR. One overall concern is that, despite disclaimers, the results from lumbar and cervical ADR appear to have been blended. These two treatments are very different—lumbar ADR is an alternative to fusion for the primary treatment of mechanical disabling low back pain, while cervical ADR is a motion alternative to the segmental reconstruction that is required after decompression for a primary extrinsic neurologic problem. Blending the two types of ADR is like comparing a car to a building because they are both made of steel. Their functions are very different. Assessment of these entities needs to be made separately.

Executive Summary. Efficacy/Effectiveness of Artificial Disc Replacement (ADR) (p. 8). The report indicates that "neither the type of conservative treatment nor the level of patient compliance with pre-study conservative treatment was detailed in the published studies used in this technology assessment and therefore, unknown." We would refer you to the comments below regarding the section *Results 3.1.* However, it is also arguable that if the type and compliance with conservative treatment are unknown, the comparison between ADR and nonoperative treatment cannot be effectively made in this technology assessment.

Critical Appraisal of Study Methods, ProDisc-L (p.49). The report refers to "a number of methodologic flaws..." that dropped the study to a Level of Evidence II. However, only two "flaws" are mentioned:

1. The report indicates that there were 32% smokers in the fusion group and only 21% smokers in the ADR group, and states "smoking has been shown to increase the risk of nonunion in patients undergoing lumbar fusion." However, the fusion rate in this study, verified by independent third party radiologists on digital radiographs, was 97%. The independent radiologists felt that only 1 of the 75 fusion patients did not meet strict radiographic criteria for fusion (and that patient

was clinically asymptomatic). What is the methodologic "flaw," when smoking did not have any significant deleterious effect on fusion?

2. The report points out that although 183 ADR patients and 93 fusion patients were enrolled, only 162 ADR and 80 control patients were treated. This occurred because once the threshold for treated patients was reached, the study stopped. There were 21 + 13 patients in the "pipeline" awaiting insurance authorization, medical clearance, surgical scheduling, etc. who were enrolled, but not treated. Once the study numbers had been reached and the study closed, these patients were not subsequently treated within the study. They had to choose between more conservative care, either accepting conventional surgical treatment (fusion) or wait for another FDA clinical study. They were no longer considered part of the ProDisc-L study population. Continuing to include these patients in the overall follow-up rates, as the report suggests, is not logical. The FDA had no interest in including these non-treated patients, since they had no treatment data points.

Results 3.1 (p. 57). The report states that, "There were no studies found comparing lumbar ADR with nonoperative care." This is untrue. Minimum requirements for patient enrollment in the ProDisc-L IDE study were six months of failed conservative nonoperative treatment. In fact, the average patient in the ProDisc-L IDE study had nine months of conservative nonoperative treatment.

The baseline Pain Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores for patients in this study represent the best each patient could achieve with nine months of conservative care. Within the first six weeks after surgery, this patient population demonstrated an immediate and significant improvement in both pain VAS and ODI, which was maintained to the two year study window (and has now been shown to be maintained out to five years on subsequent reporting). The only variable introduced between the preoperative baseline score and the six week postoperative score was the surgical intervention. Nine months of static, failed nonoperative therapy with an immediate and significant change postoperatively is a fair comparator.

In response to the criticism that the nonoperative care was not standardized, we would point out that the nonoperative care used in the study was the conservative care patients receive in communities across the US. The value of a multicenter, multisurgeon study is exactly that: it normalizes the variations one might see in a single facility or single surgeon's practice. Since there is so little agreement on what constitutes adequate conservative care, this actually represents a better nonoperative control than one designed as part of a study, since consensus would never allow all readers to agree that this structured treatment was adequate. This was a real-life, same-patient conservative care control model that could easily be considered a third study arm.

Summary and Implications (p. 92-93). Remarks on all five points and subpoints are negatively biased to the degree that it gives the perception that this study group was given a mandate to show negative results. The analysis appears structured to emphasize the negative aspects of this new technology, and to downplay positive aspects.

Disclaimer (p. 2). The disclaimer on the report is appropriately included and should be considered. "…Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider

this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability."

The HTA Process

The work group would like to provide comments based upon its experience with the process in an effort to continue to improve upon it.

Dedicated Review Time for Draft Evidence Report. One of the primary goals of the health technology assessment program is … to make the "coverage decision process more open and inclusive by sharing information, holding public meetings, and publishing decision criteria and outcomes." (www.hta.hca.wa.gov). At least for this topic, inadequate review time was allowed for the public comment period on the draft evidence review. The 200+ page draft evidence report took months to write. A two week review period (including a holiday weekend) was not enough time to generate substantive public comments. At least one month needs to be made available to potential reviewers to allow truly inclusive and substantive comment.

Technology Selection. Given that three of the first ten topics selected for assessment by HTA are directly related to spine (lumbar fusion, discography, ADR), the work group is concerned that there is an inordinate focus on spine. This raises concern about bias in the selection process.

Although topics under consideration for selection are eventually ranked according to a specified process, the initial selection of topics for briefing and ranking is done in such a manner that there is a concern about bias. The initial topic suggestions are made by agency medical directors alone (at least until a public process is implemented) which allows political bias and budget conflicts to potentially enter the process and bias which topics are put in the pipeline for consideration before briefing and ranking in a more transparent manner occurs. The fact that technologies not selected still remain on the list for future consideration is also concerning. Each technology should be individually vetted at the time of consideration, not wait-listed if initially rejected.

Clinical Committee and Panel Hearing. We would also encourage the participation of experts in the process for each topic area considered. In addition, scheduling of the panel meeting in conflict with a professional medical meeting of major stakeholders discourages input from key stakeholders.

The HTA should also consider the concept that there is variability of opinion in the selection of any treatment. A mature process brings in individuals who represent the spectrum of variation. This inclusion of diversity of opinion at the start of the process allows the best critical analysis, weighing the advantages and disadvantages of new or existing interventions. It also has to weigh the evidence for benefit of the alternative treatment. In this process of technology assessment, cost is not supposed to be a consideration. It is recognized that the follow-on step is allocation of scarce resources. In order to apply that step appropriately, cost-effectiveness analysis is then required. Unfortunately, in most surgical interventions, robust cost-effectiveness data is limited and cost minimization is substituted for cost-effectiveness analysis which does not optimize patient care.

Lumbar disc arthroplasty is a potentially valuable technology that may ultimately play a significant role in the treatment of patients with axial back pain. Currently, there are significant knowledge gaps regarding the true benefit of lumbar disc arthroplasty in patients previously considered candidates for fusion. It is apparent that the indications for arthroplasty may not be the same as the indications for fusion and that patients who are candidates for one procedure may not always be candidates for the other. Prospective series and randomized trials have demonstrated that these devices do provide substantial pain relief and functional benefits for some patients. We encourage the Washington State HTA to consider the potential benefits of both lumbar and cervical devices on a case-by-case basis and not categorically restrict covered patients access to evolving technologies.

Once again, we would like to congratulate the State on its initial steps towards using a logical, evidence-based process to evaluate technologies for coverage. Thank you for this opportunity to comment and we look forward to participating in the October panel meeting.

James R. Bean, MD
American Association of Neurological Surgeons

Thomas A. Zdeblick, MD
Cervical Spine Research Society

Anthony L. Asher, MD
Congress of Neurological Surgeons

Tom Faciszewski, MD
North American Spine Society

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Spine Arthroplasty Society

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1. Lilford R, Braunholtz D, Harris J, Gill T. Trials in surgery. [Review] [66 refs]. *British Journal of Surgery.* 2004; 91:6-16.

2. Guyer RD, et al. Prospective, randomized multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the Charité™ artificial disc versus lumbar fusion—5 year follow-up. *The Spine Journal.* In press. 2008.

Attachment: 5-Year Charité Abstract—EuroSpine 2008

MONDAY, MAY 26

EUROSPINE - MOTION PRESERVATION

SP1

PROSPECTIVE, RANDOMIZED, MULTICENTER FOOD AND DRUG ADMINISTRATION INVESTIGATIONAL DEVICE EXEMPTION STUDY OF LUMBAR TOTAL DISC REPLACEMENT WITH THE CHARITÉ ARTIFICIAL DISC VERSUS LUMBAR FUSION,
5 YEAR FOLLOW-UP.

RD Guyer, PC McAfee, RJ Banco, F Bitan, A Cappuccino, FH Geisler, H Hochschuler, LG Jenis, JJ Regan, SL Blumenthal
Texas Back Institute, Texas, USA

BACKGROUND CONTEXT AND PURPOSE: The purpose of this study was to compare the safety and effectiveness at the 5-year follow-up time point of the CHARITÉ Artificial Disc with that of anterior lumbar interbody fusion (ALIF) with BAK cages and iliac crest autograft.
STUDY DESIGN/SETTING: Randomized controlled trial, 5-year follow-up, 90 arthroplasty patients and 43 fusion patients.
METHOD: Of the 277 CHARITÉ IDE eligible for the 5-year study, 160 patients completed the 5-year follow-up (133 randomized and 27 non-randomized - only randomized cases presented). Clinical evaluations included the following validated outcome scales: ODI, VAS, and SF-36, as well as patient satisfaction and work status. In addition, individual patient success/failure status as per the non-validated FDA binary criteria was defined as improvement greater than or equal to 15 pts in ODI vs. baseline, no device failure, absence of major complications and maintenance or improvement of neurological status.
RESULTS: Mean changes for ODI (CHARITÉ: -24.0 points vs. BAK: -27.5 points), VAS pain scores (CHARITÉ: -38.7 vs. BAK: -40.0) and SF-36 questionnaires (SF-36 PCS: CHARITÉ: 12.6 points vs. BAK: 12.3 points) were similar across groups. In patient satisfaction surveys, 78% CHARITÉ patients were satisfied vs. 72% BAK patients. Sixty-six percent patients in the CHARITÉ vs. 46.5% patients in the BAK group were employed full-time. This difference was statistically significant (p=0.0403). Long-term disability was recorded for 8.0% CHARITÉ patients and 20.9% BAK patients, a difference that was also statistically significant (p=0.0441). Additional index-level surgery was performed in 7.7% in the CHARITÉ group and 13.9% in the BAK group. Overall success was 57.8% in the CHARITÉ group vs. 51.2% in the BAK group (Blackwelders test: p=0.0359, D=0.10).
CONCLUSIONS: The results of this 5-year, prospective, randomized multi-center study are consistent with the 2-year reports of non-inferiority of CHARITÉ Artificial Disc vs. ALIF with BAK and iliac crest autograft. No statistical differences were found in clinical outcomes between groups.

Note: Personally identifiable health information redacted.

To whom it concerns:

This letter is to express my frustration and disgust with the insurance industry and their stranglehold on good, practical medical treatments that are available. The particular treatment to which I am referring is Artificial Disc Replacement (ADR) for pain and disability due to injury and/or degenerative disc disease.

I am a 54-year-old firefighter. I have been a career firefighter [redacted] Washington, since March 20, 1978 (30+ years now). The job is demanding, both physically and mentally, and I love it. I have had back pain for a fair portion of my life. Off and on at first, and constantly for the last several years, with some days being severe. I saw Dr. [redacted] a neurosurgeon [redacted] several years ago after he had performed a single level ADR surgery on one of my coworkers. The insurance carrier for the [redacted] paid for his surgery, which was part of a clinical trial, after they had initially denied coverage for it. That surgery was performed in [redacted], Washington.

I had a knee injury at work in 2007. While recovering from that, I was seen by my orthopedic doctor because I was having pain and numbness in my right hand and arm. He offered me a choice of injections in my neck or physical therapy. For anything other than that he said he would have to send me elsewhere as he would not do surgery on my neck. The physical therapy did little or nothing for the problems in my neck, nor for the pain and numbness in my arm and hand.

In October of 2007, after finally being pronounced fit for duty following the knee injury and its surgical repair, I woke up in the morning with worse than my normal back pain. My back got progressively worse over the next couple of days and left me hardly able to walk. My wife finally got me in to see an orthopedic surgeon who is a back specialist. He took x-rays and viewed an MRI of my lumbar spine. His recommended treatment was to have the lumbar spine fused and, at the same time, to perform decompression surgery (surgical removal of parts of the bones and ligaments around the nerve beds so they are not constantly inflamed or impinged upon). He felt I would be on pain medication for the rest of my life. I would not be able to return to work as a firefighter. I would most likely never be pain free, but he was sure I would be in "less pain than you are right now." This was not an acceptable solution to my wife or me.

While researching ADR on the Internet my wife found [redacted] Hospital in Germany. We e-mailed and talked to several people who had gone there to have ADR surgery. Everyone we talked to was positive [redacted] Hospital was the best place to have this type of surgery. All of them were thrilled with the outcome of their surgeries. We sent the doctors at [redacted] the x-rays and MRI films of my back to see if I was a candidate for ADR surgery. I was; so we made plans to go to have the surgery, hoping it would allow me to continue working or at least to be pain free and not dependant on pain medication for the rest of my life. We went back to [redacted] to see Dr. [redacted] before going to Germany. He was happy we had found out about [redacted] Hospital and had decided to go to there for the ADR surgery. He reviewed the films for my back and also looked at the neck films. He told us I would likely need ADR surgery on my neck as well. We were

shocked at this, but felt if the doctors in Germany felt the same, we would have it done at the same time, as we would likely never be able to afford to go back there again for a second surgery. When I contacted my employer's HR insurance person to see if I had to have the surgery pre-approved, I was told I did not need pre-approval, but that they may not cover it. The reason for this is that multi-level ADR surgery is considered "experimental" in the US. Mind you, the cost to have the surgery in Germany would be less than $60,000 and the cost for the spine surgeon's recommendation was around $250,000, and carried with it the likelihood of leaving me partially disabled. In our opinion ADR surgery is hardly "experimental." It has been being done successfully for over 20 years in Germany. On November 29th I had two cervical ADR done in my neck and two lumbar ADR done in my low back.

My recovery has been phenomenally successful. I have been released to return to work, as a firefighter, [redacted] (I could have likely gone back sooner but the doctors in Germany recommended I stay off for a full 6 months, if I could do so.) This would not be the case had I not had the means to go to Germany and have this surgery. I would have had to involuntarily retire from firefighting, would likely be partially disabled and would always have pain.

For my wife and I, this was only possible with a huge sacrifice. We were very fortunate to have found a way to afford to have the surgery. Our RV, which we had purchased after selling our home, would have to be used as collateral on a new loan. We are therefore "re-buying" it with money we thought we would have for our living expenses and our retirement. Due to the expense of the loan, our RV is up for sale and we will not have it for our future retirement; and that is because the insurance company has refused to cover any of the bills from the surgery. While I recognize that I used a "non-participating provider" for my surgery, I still feel the insurance should have covered the bills at the standard 60% they pay on non-participating provider's bills for other medical treatments. It seems ludicrous to me that the insurance company that gets it premium money from me has the right to tell me I can have the US treatment **at FOUR times the cost** with **no chance of a full recovery** rather than getting treated in the manner that is most likely the best hope I have for a full recovery at a hospital that specializes in this type of surgery **at ONE-FOURTH of the cost of the "standard" treatment in the US**, which is actually substandard treatment, in our opinion.

There are many people in this State suffering with back pain that can benefit from this surgery. Please make it possible for patients to get the surgery they need and require the insurance companies to cover their bills for this. Insurance companies should not be allowed to side step good treatments simply because they do not want to recognize how well they work. I have talked to several people since my surgery who have debilitating back pain. Some of these people have doctors that tell them **not to get fusion surgery done**, as it will not cure the problem, it only helps for a while and causes more problems at the adjacent disc levels in the back to where the fusion was done. These people live with pain and often have to be on drugs because ADR surgery is not available to them. ADR surgery is being done in the US in a few places. The FDA has approved ADR surgery. Please force the insurance companies to cover this type of surgery, even if it

means patients have to go overseas to have it done, so others do not have to wait needlessly in pain and continue to suffer.

Please feel free to contact me if you have any questions about what I had done, and why.

Thank you.

[redacted]

[redacted]

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Health Technology Assessment
Subject: Artificial disc

This document is intended to provide information and criteria for consideration by the Washington state Health Assessment (HTA) team in their evaluation process of artificial disc arthroplasty as a preferred standard of care in the treatment of Degenerative Disc Disease (DDD). As I considered artificial disc as an option for myself, I did extensive study and research. After denial for coverage from my private insurance carrier I reviewed many more reports along with the policies and "supporting" data assessments for those policies from the insurance carriers. My discovery is that those policies were taken from limited data reports, used interpretive methods inconsistent with good scientific principals, drawing conclusions with little or no bases. The resulting policies use statements out of context of the clinic study data. While the results and recommendation of the HTA team will not be binding on the Insurance companies those findings and recommendations will most certainly influence their future policies. It is imperative that the HTA team consider all data weighing poor outcomes carefully to avoid such situations as patient selection, patient compliance, and non device related complications, i.e. Infections.

While certainly not a scientific method or statistical evaluation method consideration by the HTA an evaluation of artificial Discs must incorporate the important factor "quality of life". As with all medical treatment options for major conditions that affect quality of life pain is one of the most difficult to assess. Beyond the loss of strength, function, and numbness, pain is the motivation to seek a remedy. Yet pain is also is one of the most debilitating, affecting both physical and emotional wellbeing. Frustrated and almost unable to work or walk even a short distance I refinanced my house and had the surgery in Germany. My personal testimony is echoed by many who have found the hope offered by ADR to be a reality, restoring movement with NO pain related to my back except the joy of regained motion and few sore muscles. Evident to all that know me is my restored joy of life and purpose that goes far beyond expectations. It cannot be expressed in words the promise fulfilled by this miracle. I implore the HTA team to carefully evaluate this technology as their findings will significantly affect the lives of many.

The opening paragraph of the HTA Draft key questions and background states that important clinical questions have not been answered. I as laymen to the medical community found ample evidence to convince me that ADR was a good choice. The data included in the PMA for several of Fusion methods considered the "gold standard" and the AD clinical trials along with many other peer reviewed studies clearly established ADR as better in most cases. Further I consulted five prominent experienced surgeons (University of Washington, Cedars- Sinai, and UCLA medical center); each one articulated the same caution against fusion, with one stating, in writing, that fusion would be "disastrous". Then there are many studies and reports that analyze ADR and fusion outcomes including 10 plus years follow-up of ADR patients. The more appropriate question might be are the current evaluation methods susceptible to misinterpretation or bias?

Recognizing the HTA team to be highly qualified doctors and surgeons with many years of education and experience I am confident that each member recognizes the importance of comprehensive studies and subsequent reports. As with all research and development there will be results or situations that were not expected or desired. However a comprehensive medical study or report will present all the data collected in the expectation that by its inclusion a surgeon can better evaluate a particular treatment and avoid situations that caused undesirable results. With this in

mind the HTA team must use care to evaluate poor outcomes relative to the situation that caused them, and relative to the severity or recoverability.

One significant consideration is to acknowledge nothing is perfect there will always be unfortunate situations yet these should not unduly influence the promise Artificial Discs provides to patient and the health and well being.

There is no expectation that ADR will replace fusion in all cases, as many factors enter into the decisions made by surgeons as to treatment plan. But in most cases ADR will prove a better option than fusion. Thus the HTA team should evaluate ADR and set forth guidelines rather than limitations allowing the doctors and the patients to select the most appropriate technique that values the quality-of-life of the patient.

Sources of data

There are many sources of data on artificial discs and spinal fusion and outcomes of both. It seems inadequate to attempt to provide all the actual data. Along with the various sources available through peer reviewed journals, clinical studies and the FDA trials etc. I have included a link to the clinical report for the Maverick Lumbar Disc. I offer this for two reasons; this was the device that was successful for me and this device while still awaiting final FDA approval has a significant history in Europe. Further I will offer criteria and guidelines to be considered by the HTA team during the evaluation process.

Link to Maverick Disc report http://www.getadr.com/ADR%20Study.asp

- Because the recommendations of the HTA team will be used by the State of Washington in purchasing Health related services the HTA should carefully evaluate the sources of data to assure compliance with Washington Administrative Code (WAC). Definitions listed in WAC 388-501-0165 of "credible evidence" and "Hierarchy of evidence..."may affect how the HTA team should accept and evaluate data. As provided in WAC 388-531-0050 the definitions of "Peer reviewed medical literature" seem to restrict the use of data publications from many sources including insurance carriers. Thus, as addressed later in this document, evaluations, conclusions or recommendations from insurance companies and the affiliate organizations should not be included. Members of the HTA team will then be free to determine the efficacy of ADR based on peer reviewed documents and other sources not driven exclusively by financial gain.

- Numerous data sources are available: Use only data generated from the clinical environment at major medical or spine centers both in the US and in Europe. Use reports and studies published in peer reviewed journals submitted by credentialed board certified or recognized investigators and/or practitioners. Include data from medical centers that have participated in the long term success of ADR both in US and Europe. This may seem to bias the data however data from centers that have long term use history will mitigate the factors of training and low experience allowing device related factors to be evaluated effectively.

- Disallow data from policies or evaluations provided directly or indirectly from Insurance companies or the technology evaluation centers, affiliated with or controlled by the insurance companies. A review of one such evaluation on artificial discs provided no new data; it appeared as though the authors selected studies that supported the pre-determined conclusion sighting data, and statements taken out context of reports with otherwise complete and positive studies. As noted above, this source of data may not meet the

definition of peer reviewed document for the purposes of compliance with Washington code.

NOTE: as a reference source only, one Insurance company has compiled a comprehensive list of references to acceptable studies. See Aetna corporate policy on ADR.

- It is assumed the HTA team will use the recent HTA findings for Lumbar fusion as one comparative source for that method.

Evaluation

The following is intended to provide some general guidelines in the evaluation process of artificial disc.

- The HTA team must evaluate all artificial Discs available to patients regardless of FDA approval status. Failure to be inclusive will reduce the credibility of the HTAs findings and may limit a superior treatment from consideration and use after approval has been obtained.

- Evaluate each type of Disc separately: Examine the data for each type of artificial disc evaluating the results of Charite, ProDisc, and Maverick as used for Lumbar each separately. It may be discovered that a particular device has somewhat lower success than another. Comparison of all devices in the same "pool" may mislead and falsely lower the effectiveness of a device(s) that has superior performance. I.e. the Charite has some initial concerns that may be contributed to poor patient selection, lack of surgical instrumentation developed later for alignment of the device, un-constrained core and other factors.

- Evaluate cervical discs separately: Again these discs have various designs each with feature and limitations. Evaluate all discs both those that have FDA approval and those that are pending FDA approval. This may require the HTA team to review data from European clinics that use these devices and along with studies pending completion in the US clinical trials. Acquiring clinical trial data is restricted due to Federal laws during the approval process. The HTA panel may have the authority to request and receive that information the result of the effort will be a more comprehensive evaluation.

- Success worldwide: Artificial Disc Replacement (ADR) has been used in Europe for 15- 20 years with significant success. Data and associated reports from clinics where Artificial Disc replacement are the standard of care for DDD should be given maximum consideration. It may fall to the HTA to request and collect data that has not been specifically published in the United States.

- Evaluation should consider numbers of actual patients treated at hospitals where ADR technology has been used to treat a high number of patients along with comparative results of fusion as treatment option. This should focus on surgeons that have used fusion and ADR as treatment of DDD for many years. Limiting evaluation data to only the outcomes as presented in clinical trial reports may bias the data due to factors such as improper patient selection due to inexperience, inadequate training of surgeons, and limited numbers of actual cases at a particular location or performed by a particular surgeon. Particularly important is experience based improvement in both technique and instrumentation development.

Comment: Maverick has highly successful record in Europe and is pending US FDA approval. Do not disregard the Maverick or other devices solely because the FDA process is pending. I have the Maverick disc and I am 100% pain free!!!!! Able to do almost anything with significantly regained flexibility. Please see attached letter from a firefighter that had significant disability and very successful ADR surgery (2 lumbar 2 Cervical).

- Evaluation should consider the general success of the surgeon /medical center: Data that can be identified from a surgeon, clinic or hospital with a limited number of successes should be evaluated carefully to avoid non device related morbidity. It may be that the HTA panel should recommend ADR be performed at centers specializing in ADR, even if those treatment centers are outside the State. Not all surgeons have the experience to perform ADR without significant training. Example: the most effective cancer assessment and treatment is performed at only a few regional centers that specialize in new treatment regiments along with proven methods.

- Consider the factors related to bone graft donor site, dural damage, as presented in the HTA evaluation for fusion 11-07. The higher incidence to these complications added to the higher re- surgery for non fusion issues along with longer healing time the additional known limitation of loss of flexibility, and potential adjacent disc damage certainly raised questions of efficacy in my consideration process.

- Avoid comparing device data for non artificial disc such as the Dynesis system. This type of device can provide benefit in the proper application but should not be compared to ADR.

- Seek and use data that was generated from patient s that have had surgery many years ago. It may be necessary for the HTA team to request data from larger clinics and Spine centers to evaluate the long term viability of fusion as well as ADR.

- Consider return to work rates and quality of life. Since the well-being of the citizen of Washington should be the goal of this review. The patients overall benefit should consider quality of life along with financial interests of the patient. This is very significant since return to work rates can be important factors on the individual. Evaluation of the financial impact on the state, insurance companies, or L&I should only be a secondary consideration. However: Return to work and long term wellbeing of a patient may result in reducing the drain of L&I and welfare subsidies.

- Consider multiple levels ADR: While the FDA clinic trial limited the study to a single level as appropriate for good comparative data results, many patients primarily in Europe and at major spine treatment centers in the US have benefited from two and even three level replacement. One of the letters provided with this document is from a fire fighter that had two lumbar and two cervical disc ADR surgery performed at the same time. He is back to full time work as a fire fighter in Richland WA just six months after surgery (his doctor and the City insisted he wait that long). My roommate in Germany is a fellow that had twenty plus years of pain he received three discs. He is playing golf and riding horses etc.

- Review carefully the requirements of the manufacturers and the FDA PMA report for both methods. Whereas the FDA did not approve multi level ADR the prerogative of the surgeon allows them to provide multilevel ADR as an off label benefit. However in its findings the PMA on some of the fusion options strictly forbid the multi level option for fusion.

- Compare the results of ADR with the failure and re-surgery rate of fusion. Failure of the HTA review on fusion did not report the long term results of lumbar fusion nor did not appear to address the, failure of adjacent discs. Return to work or other factors

  Comment: While Washington State L&I Medical Treatment Guidelines do not meet the proposed requirements, noted below, for data acceptability, the guideline document on spinal fusion does provide an overall outline of the probability of failure of the fusion option. Follow link to Washington L&I web site.
  http://www.lni.wa.gov/ClaimsIns/Files/OMD/MedTreat/LumbarFusion.pdf

In reviewing the Draft Key Question and Background document the last paragraph identified a significant point, that of long term serviceability of ADR.

- When evaluating the long term efficacy of ADR Consider the longer term affects of fusion where patients experienced additional pain as a result of disc damage and failure of adjacent discs to the fusion site. Because disc height is restored by ADR pain producing impingement is this also corrected along with the pain associated directly with the degenerated disc and vertebrae.

- Consider return to work rates for each type of artificial disc and fusion methods.

- Consider the re-surgery rates for all devices.

- Consider non work related activity levels for patients from both treatment options. Consider pain short and long term pain. Consider pain management requirements for both ADR and fusion.

- Consider hospital stay: perhaps this factor should be given lower consideration however the benefit to the patient and the payee can be significant. Even one day less in the hospital can offset any differences in device costs.

- Since results of this assessment will certainly be scrutinized by the insurance industry consideration and conclusions should provide clear recommendations or guidelines in the areas of patient selection, individual device success, and medical center success.

Relative to Proposed Key Questions

Question 3

- This question suggests that efficacy or the safety of ADR is dependent upon factors other than the physical or physiological condition for Degenerative Disc Disease and the treatment option for it. The draft question identifies one special population as those seeking treatment under workers compensation. The assessment team must be especially diligent to separate the attributes and success of ADR without biasing conclusion of efficacy on those individuals that misuse a system. Data on pain return to work, or any other factors dependant on the "subjective nature" of those patients intent on benefiting from the system should be scrutinized to eliminate unreliable reporting. Further the history and credibility of the L&I system may not provide suitable source of data for any treatment method for back conditions like DDD and therefore it may advisable to exclude any data from that source from consideration.

- Another special population named under this question is the elderly. During the clinical trial process for approval of Artificial Discs this population was specifically and appropriately

excluded thus data from clinical trials is not available. However there may be patients that could benefit from ADR and that evaluation should be left to the experience of a qualified surgeon.

Comment: Certainly those that are advanced in age may not realize the greater flexibility benefit of ADR However: for those patients where some surgical intervention is required, I would submit that even a limited benefit of ADR might well be better than the slow process of bone fusion. In other words since the Artificial disc allows movement the patient is not limited during the healing process and since bone healing is slower they may well recover quicker with less risk of non-fusion.

Question 4

- Several factors should be considered in evaluation of the cost implications and cost effectiveness of ADR. Yet cost should not be the driving factor, if the goal of the HTA is the most effective benefit to the patient as is the intent of health care cost must not enter in to the evaluation until all other factors have been evaluated and then only after the options are found to be equal.

- Costs of new methods are often higher due to many factors and reduce significant after acceptance of both hospital and the medical professional.

- Consider the return to work rates. Fusions reported frequency for re-surgery alone should be a financial deterrent. Consider also patient risk and pain for second surgery. Add then quality of life, and return to work potential these costs may be indirect but must be part of the HTA's comprehensive assessment.

- Use cost analysis data from clinical institutions that perform both ADR and fusion methods and do so in sufficient numbers to establish usual and customary fee structure. These same institutions may also provide costs associated with re-surgery.

- Avoid cost data provided by Insurers: Data reported by insurance companies are likely to be skewed because insurers have not generally included ADR as a necessary treatment option thus any data will be limited. Further once ADR is an accepted option insurers can use their negation power to establish cost effective payment schedules. A few health insurers do accept ADR as medically necessary Aetna for one. A few self insured companies like Microsoft allow ADR Premera Blue Cross is the administrator of their plan. But those covered under Blue Cross's private plans are denied this treatment.

- Carefully review cost data from hospitals or medical centers that have established contracts for fusion etc. as it may bias the cost.

- One noteworthy article on patient return to work is provided in the link below.

http://www.washingtonpost.com/wp-dyn/content/article/2008/04/28/AR2008042802162.html

Comment: I received a quote from a prominent surgeon at UCLA medical center that would have performed surgery for me. (Had the insurance covered the recommended treatment) The hospital and surgeon provided surgeons fee, hospital and device costs for both fusion and ADR. Cost for ADR was slightly less due directly to anticipated shorter hospital stay.

Comments from the Washington State Agencies

Page 7: Comment [m1]
Fusion is not the standard of care for DDD in the absence of other findings.

Page 7: Comment [m2]
Theoretically intended to preserve motion...

Page 8: Comment [m3]
How is it decided to that 2 devices are similar enough to warrant pooling of outcomes data?
What is the effect of pooling data when the studies are not completely reported (database closed early, or not all randomized subjects reported at 24 months)?
It seems the treatments are not the same, the patients (at least for lumbar studies) are different enough at baseline to require some discussion of when it is or is not ok to combine populations.

Page 9: Comment [m4]
In the Charite RCT the comparator treatment was a technique no longer used.

Page 9: Comment [m5]
But there is not evidence showing mobility correlates with improved outcome or reduced ASD

Page 9: Comment [m6]
CMS assessment states “The theoretical mobility provided by the artificial disc has yet to directly correlate to a proven benefit in how the patient feels or functions, making the clinical significance of post treatment range of motion unclear. Therefore, CMS does not consider post treatment range of motion an important clinical outcome of interest in this memorandum."

Page 10: Comment [m7]
Why?

Page 12: Comment [m8]
Questions about the quality of these references.

Page 12: Comment [m9]
Do not agree and recommend deleting “standard of care” with regard to fusion.

Page 14: Comment [m10]
We do not agree with this statement. Some fusion trials have shown fusion surgery to be no better than non-operative treatments. The jury remains out on the question of ADR superiority to non-op treatment.

Page 15: Comment [m11]
This seems highly speculative. Does the investment marketing material take into account the available evidence on efficacy? What is the quality and value of this information?

Page 16: Comment [m12]
Seems highly speculative and not evidence based.

Page 16: Comment [m13]
What is the quality of the unpublished cost-effectiveness study that resulted in this statement and estimate? Why include it unless it is supportable?

Page 16: Comment [m14]
Post approval studies are required for the Prodisc-L and the cervical discs. Data from these post approval studies may help us understand the longer-term outcomes and costs.

Page 16: Comment [m15]
Perhaps more discussion of the uncertainty surrounding the diagnosis of disc pain and DDD.

Page 22: Comment [m16]
The procedure is technically more demanding, has a steeper learning curve, and requires greater precision than fusion surgery.
Especially if reoperation becomes necessary.

Page 24: Comment [m19]
Is the life span expected to differ between lumbar and cervical?

Page 32: Comment [m20]
CMS completed interal HTAs. Iniital report addressed Charite, second consideration addressed Prodisc when it was approved. Available here:
http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=170 and
here: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=197

Page 48: Comment [m21]
The BCBS TEC report on Charite and the FDA statistical review note the lack of an a priori statistical plan for charite. Did they address sample size/power in the paper and SSED?

Page 49: Comment [m22]
Is there data that is not interim?

Page 51: Comment [m23]
There does not appear to be enough information in the methods section of this paper to warrant inclusion with rating as LOE II.
The discussion section is good.

Page 58: Comment [m24]
Half of the control group in this pooled analysis received an outdated form of fusion.

Page 59: Comment [m25]
The BCBS Tec assessment had this to say (in part) about the Charite trial:

The second concern is that the lack of a prespecified analysis plan, unexplained closure of the database before all patients reached completion, and lack of intent-to-treat analysis may cast some doubt on the analysis. Although the sponsor provided TEC with additional analysis that included patients that were excluded from the analysis presented to the FDA, it was unclear how many additional patients actually provided 24-month outcome data and what imputation was performed for missing or discontinued data.

Page 61: Comment [m26]
The Prodisc FDA summary shows the fusion group with and ODI of 39.8 at 24 months and the ADR group at 34.5. The entry ODI was 40. Though both groups improve the resultings disability score is not very good. The Charite study has and ODI entry of at least 30 and the baseline for these patients was about 10-12 points lower than the Prodisc. It doesn't seem reasonable to combine the results from these studies for meta-analysis given the differences in device, characteristics on key entry/outcome criteria and control
treatment. CMS included the whole ODI table from the SSED in their HTA.

Page 67: Comment [m27]
These are patients who received ADR and have ASD?

Page 80: Comment [m28]
What about the Putzier paper (ref 114), 2005- 60% of a subset that did not have disc removed for fusion had HO? Hetertropic ossification in majority reported on. Paper included in CMS analysis.

Page 80: Comment [m29]
Please see the CMS report. The section on adverse events is thorough and includes excerpts from key longterm follow-up studies.

Page 82: Comment [m30]
Mehren study not included here? Rate of ossificiation almost 70% at 1 year.

Page 86: Comment [m31]
Is this chart necessary?

Page 93: Comment [m32]
If the study is designed to be a non-inferirority trial, how is it possible to reach a conclusion of superiority?

Page 93: Comment [m33]
"If the results following completion of the trial are similar to the interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase." This comment is speculative.

Page 94: Comment [m34]
But long-term follow-up studies seem to show the potential for a high number of failures leading to fusion or spontaneous fusion. How doe s that fit with the 2 year, interim study outcome data?

Addtionally the FDA is requiring Post Approval studies for all patients in these trials. Do interim reports continue to support the original 2 year findings? When will we know the true outcomes for all people treated in these IDE studies?

Page 94: Comment [m38]
It was deemed reasonable by spectrum: Why?

Washington State Health Care Authority, HTA Program
Artificial Disc Replacement (ADR)
Key Questions and Background

Health Technology Assessment Report

HTA has selected Artificial Disc Replacement (ADR) to undergo a health technology assessment where an independent vendor will systematically review the evidence available on the safety, efficacy, and cost-effectiveness of ADR. Back and neck pain are the most common cause of disability, yet diagnosis and management of chronic pain remain subject to controversy. ADR is not a new treatment, with modern procedures dating back nearly 20 years, however important clinical questions have not been answered about the safety and effectiveness of the intervention and its widely variable use.

Key Questions

1. **Key Question 1:** What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including non-operative therapy; spinal fusion; other surgery)?
2. **Key Question 2:** What is the evidence related to the ADR safety profile? (including device failure, reoperation)
3. **Key Question 3:** What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?
4. **Key Question 4:** What are the cost implications and cost effectiveness for ADR?

ADR Background

Back and neck pain are common conditions, with sixty to eighty percent of U.S. adults afflicted at some time during their life. Back pain, and then neck pain, are the most common causes of disability and loss of productivity. Approximately 90% of low back pain is of the nonspecific type, and a similar majority of neck pain is non-specific. Most patients' symptoms resolve satisfactorily within a relatively short time span (within six weeks). Non-surgical treatments for include cognitive behavioral therapy, medications, and rehabilitation (including psychological care, exercise, education, interdisciplinary rehabilitation, and spinal manipulation).

In 5 – 10% of patients, pain does not satisfactorily resolve and the symptoms can be disabling and the social and economic impact of chronic pain is enormous. Discovering the cause for nonspecific low back and neck pain symptoms remains challenging. Some psychosocial risk factors for the progression to chronicity have been identified, but the origin and neurophysiologic pain sensations are poorly understood. Frequently, persistent pain is attributed to a damaged intervertebral disc. Disc damage, or degeneration, can occur as an ongoing process where ultimately the disc's reparative

capacity is overwhelmed. Degenerative disc disease is common in middle age and a universal condition in old age, though not all individuals experience pain.

For these patients with unresolved pain, surgical treatment is considered. Fusing discs has been the predominant surgical treatment. Spinal fusion is used to reduce pain by permanently immobilizing the spinal column vertebrae surrounding the disc(s) that is (are) thought to cause pain. Indications for spinal fusion are variable and not clearly defined. These different opinions concerning the indications for surgery are reflected in the significant regional variation of rates of surgery, surgical techniques used, technical success and rate of fusion. Short term relief of pain may occur with the various types of fusion procedures, but long-term results remain controversial, particularly accelerated adjacent degeneration.

In response to these concerns, ADR was developed and is the complete removal of the damaged disc and implantation of an artificial disc. The intent is to treat the pain and disability believed to be caused by the degenerative disc disease by removing the diseased disc, with the primary potential benefits of preserving normal range of motion and restoring disc height.

The potential harms include surgical risks; mechanical failure of the implant, re-operations, and spontaneous fusion. Additionally, concerns remain due to the controversial diagnosis and management of back pain and the uncertainty over the extent of benefit of surgery. Further, unlike fusion where recent trials suggest intensive physical and behavioral therapy produce equivalent outcomes, ADR has not been directly compared to these interventions. Finally, given that the target population requiring discs are aged 30 to 50 years, disc implants need to last up to 40 years to avoid the need for repeat procedures and the intervention itself needs to be assessed for long term health improvement.

Washington State Health Care Authority

Health Technology Assessment

HTA Final Report
Artificial Discs Replacement (ADR)

Date: September 19, 2008

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August 26, 2008

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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EXECUTIVE SUMMARY

Introduction

Low back pain is a major health problem throughout the world and is the leading cause of pain and disability in adults in the United States. As much as 40% of chronic low back pain is thought by some to originate in the intervertebral disc. Chronic low back pain with degenerative disc disease (DDD) is typically managed conservatively for at least six months before surgery is considered.

Cervical radiculopathy and myelopathy are neurologic conditions characterized by dysfunction of the spinal nerve or spinal cord often as a result of degenerative disc disease or spondylosis. The average annual age-adjusted incidence of radiculopathy has been reported as 83 per 100,000, and the prevalence as high as 350 per 100,000 people. While the overall prevalence of cervical spondylotic myelopathy (CSM) is unknown, it is the most prevalent spinal cord dysfunction in people 55 years or older. It is not uncommon for both conditions to be present. It is estimated that nearly one fourth of surgical patients being treated for cervical DDD have a combination of radiculopathy and myelopathy.

Surgery is generally indicated when nonoperative conservative treatments fail to relieve symptoms attributed to lumbar DDD or relieve signs of neurological compression or prevent progression of nerve damage in the case of cervical DDD. The current surgical standard of care for lumbar DDD is lumbar fusion. The goal of this surgery is to remove the disc and fuse the vertebrae, thereby limiting the motion at the painful segment. For cervical DDD resulting in radiculopathy or myelopathy, the current surgical standard is anterior cervical discectomy and spinal fusion. The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. Spinal fusion is thought by some to promote the degeneration of the vertebrae above or below the fusion site (adjacent segment disease); however, many uncertainties remain regarding the extent to which this occurs.

Lumbar artificial disc replacement (L-ADR) is a potential alternative to spinal fusion in patients with disabling mechanical low back pain. Cervical artificial disc replacement (C-ADR) offers a possible surgical alternative to spinal fusion for patients with radiculopathy and/or myelopathy secondary to DDD. Both L-ADR and C-ADR are intended to preserve motion at the involved spinal level and therefore decrease stresses on adjacent segment structures and the risk of adjacent segment disease.

In light of the possible benefits of ADR, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short and long term, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of ADR. Thus, the objective of this technology assessment is to critically appraise and analyze research evidence on the efficacy/effectiveness and safety of ADR in the lumbar and cervical spine in patients with degenerative disc disease and to the extent possible, consider the potential financial impact. To that end, the following key questions developed by the Washington State Health Technology Assessment Program will be addressed:

- **Key Question 1:**

  What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

- **Key Question 2:**

  What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?

- **Key Question 3:**

  What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

- **Key Question 4:**

  What are the cost implications and cost effectiveness for ADR?

Note: In this technology assessment, artificial disc replacement will refer to mechanical total disc arthroplasties and not nucleus replacements, annular reconstruction techniques or other forms of intradiscal spacers.

Methods for evaluating comparative effectiveness

Spectrum Research, Inc.'s (SRI) method for technology assessment involves formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Each included study is critically appraised using SRI's Level of Evidence (LoE) system which evaluates the methodological quality based on study design as well as factor which may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Meta-analysis was conducted on the primary outcomes using a random effects model to determine risk difference (RD) when data from two or more RCTs were available and when there was no clinical or statistical heterogeneity among studies. Two analytic perspectives on the meta-analysis for effectiveness are presented: intent-to-treat (ITT) analysis and completer-only analysis.

Throughout the process, SRI sought clinical review to assure that the clinical components are accurately represented and relevant. In addition, peer-review by clinical experts, health services researchers and those with expertise in economic and outcomes evaluation provide an assessment of the systematic review methodology, analyses and report conclusions.

Summary and Implications

1. Efficacy/effectiveness of artificial disc replacement (ADR)

- Findings contained in this technology assessment reflect the use of lumbar or cervical ADR in patients who have failed conservative treatment. For the lumbar spine, conservative treatment for at least six months was required prior to study enrollment. For the cervical spine, six weeks of conservative treatment or a progression of neurological signs was an indication for ADR. Neither the type of conservative treatment nor the level of patient compliance with pre-study conservative treatment was detailed in the published studies used in this technology assessment and therefore, unknown.
- There is insufficient evidence to draw extensive efficacy/effectiveness conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the efficacy/effectiveness of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion. One study is underway that includes three surgical treatment arms for cervical radiculopathy: C-ADR versus anterior cervical discectomy without fusion versus anterior cervical discectomy with fusion (ACDF).
- With respect to the comparison of L-ADR and fusion, there is moderate evidence that the efficacy/effectiveness of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery. This evidence is based on two moderate quality randomized controlled trials conducted as FDA Investigational Device Exemption non-inferiority trials. Overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving L-ADR and 48% receiving lumbar fusion. Though the results suggest that 24 month outcomes for L-ADR are similar to lumbar fusion, it should be noted that a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question.
- There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index, and pain up to two years following surgery. The evidence is based on two moderate quality randomized controlled FDA Investigational Device Exemption non-inferiority trials. An interim analysis of approximately 65% of a third RCT was reported in an FDA Panel Executive Summary. If the results following completion of the trial are similar to the

interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase.

- There is evidence that segmental motion is maintained or improved up to three years in the L-ADR patients and up to four years in C-ADR patients compared with preoperative motion. It is unclear the true extent to which preserving segmental motion by using ADR instead of fusion influences rates of adjacent segment disease (ASD). Whether ASD is a continuation of a disease process necessitating fusion or a result of fusion continues to be disputed. Furthermore, there continues to be debate on whether the presence of ASD is clinically important given that patients with marked radiographic ASD often have no symptoms.

2. Safety of artificial disc replacement (ADR)

- There is insufficient evidence to draw extensive safety conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the safety of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion.

- There is moderate evidence that L-ADR is as safe as lumbar anterior or circumferential fusion, and that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery.
- There is insufficient data at this time to determine the longer term safety of both L-ADR and C-ADR.

3. Special or subpopulations

- There is insufficient evidence to draw conclusions regarding the safety and efficacy of L-ADR in the few special populations studied (elderly, smokers, athletes). No studies or sub-analyses were found on the use of C-ADR in special or subpopulations.

4. Economic implications

- There are inadequate data from partial economic studies reflecting short time horizons for L-ADR and no economic studies for C-ADR to truly assess the potential cost-effectiveness of ADR technology. One report and one previously done HTA suggest that the type of fusion may influence complication rates and therefore costs.

5. Additional implications

- The studies primarily reflect outcomes measured up to 24 months and therefore questions remain regarding the longer term safety and efficacy of L-ADR or C-ADR compared with fusion. This is an important matter, particularly in those receiving C-ADR where the average age is near 45 years. Since these are mechanical devices, future failure is a possibility and may influence complication rates and costs in the longer-term.

- Findings contained in this report primarily reflect use of ADR at a single level and it may not be appropriate to extrapolate the results to patients with ADR at multiple levels or for indications other than those evaluated during the FDA trials. As diffusion of these devices increases and they are used for additional indications, the safety and efficacy profiles may change.
- Studies which met the inclusion criteria for this report encompassed only two biomechanical types, an unconstrained device and a semiconstrained device. While it was deemed reasonable to pool information from trials despite difference in device design, it is probably appropriate to consider that such differences may influence longer term outcomes. There are a variety of different biomechanical designs for ADR. There is limited data which directly compare outcomes and complications for different devices in the short-term or longer term and thus, the influence of different designs is unknown.
- One study suggests that surgeons and institutions with a high volume of L-ADR cases have shorter operating time and hospital stay, and lower complication rates which may have an economic effect. No effect on clinical outcomes was reported between high and low volume surgeons or institutions.

ASSESSMENT
ARTIFICIAL DISC REPLACEMENT

Final Scope

Rationale for the Assessment

Low back pain is a major health problem throughout the world and leading cause of pain and disability in adults in the United States.[60] As much as 40% of chronic low back pain may originate in the intervertebral disc.[143] Chronic low back pain with degenerative disc disease (DDD) is typically managed conservatively for at least six months before surgery is considered. For those patients who do not experience pain relief during that time, the natural history of the disease is not well documented.

Cervical spondylotic myelopathy (CSM) is the most prevalent spinal cord dysfunction in people 55 years or older.[167] A study of 450 surgical patients being treated for DDD reported that 61% presented with radiculopathy, 16% with myelopathy, and the other 23% had a combination of the two[133]. A study of Nationwide Inpatient Sample (NIS) data collected between 1993 through 2003 shows that the number of cervical spinal fusion procedures conducted in the U.S. increased from 26 to 50 per 100,000, with symptomatic DDD representing more than four out of every five cases of cervical DDD cases in 2003.[26,167]

Surgery is generally indicated when nonoperative conservative treatments fail to relieve symptoms attributed to lumbar DDD or relieve signs of neurological compression or prevent progression of nerve damage in the case of cervical DDD. The current surgical standard for lumbar DDD is lumbar fusion. The goal of this surgery is to remove the disc and fuse the vertebrae, thereby limiting the motion at the painful segment. For cervical DDD resulting in radiculopathy or myelopathy, the current surgical standard is anterior cervical discectomy and spinal fusion. The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. Spinal fusion is thought by some to promote the degeneration of the vertebrae above or below the fusion site (adjacent segment disease); however, many uncertainties remain regarding the extent to which this occurs.

Lumbar artificial disc replacement (L-ADR) is a potential alternative to spinal fusion in patients with disabling mechanical low back pain. Cervical artificial disc replacement (C-ADR) offers a possible surgical alternative to spinal fusion for patients with radiculopathy and/or myelopathy secondary to DDD. Both L-ADR and C-ADR are intended to preserve motion at the involved spinal level and therefore decrease stresses on adjacent segment structures and the risk of adjacent segment disease.

Although such devices have been used outside of the U.S. for many years and a number of research reports have described positive outcomes, questions remain regarding a number of important issues:

1. How does the effectiveness of ADR compare with conventional surgical treatment (and if appropriate, nonsurgical treatment) with respect to patient functional outcomes and pain relief as well as other outcomes including those related to quality of life?
2. How does the safety of ADR compare with conventional surgical treatment both over the short-term and over the long-term (eg, ASD, heterotopic ossification, spontaneous fusion), given that implants are intended to remain intact for the life-time of the patient?
3. Might specific patient populations in particular benefit from ADR or have increased risks for complications from its use?
4. Do different biomechanical designs influence comparative safety and efficacy?
5. How might the substitution of ADR for fusion in a proportion of patients with the appropriate indications impact health care systems and costs?

In light of the possible benefits of ADR, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short term and longer time horizons, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of ADR.

Objective

To critically appraise and analyze research evidence on the effectiveness of and complications related to the use of ADR in the lumbar and cervical spine. If available, formal economic analyses of ADR will also be critically appraised.

Key questions

Key questions were developed by the Washington State Health Technology Assessment Program. A conference call with Spectrum Research and representatives of the HTA program provided clarification of the questions and outcomes.

- **Key Question 1:**

  What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

- **Key Question 2:**

  What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?

- **Key Question 3:**

  What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

- **Key Question 4:**

  What are the cost implications and cost effectiveness for ADR?

Note: In this technology assessment, artificial disc replacement will refer to mechanical total disc arthroplasties and not nucleus replacements, annular reconstruction techniques or other forms of intradiscal spacers.

Outcomes
The following outcomes were sought:

- Efficacy and effectiveness measures
  Primary outcomes
  - Overall clinical success
  - Disability indices (Oswestry Disability Index for lumbar, Neck Disability Index for cervical)
  - Neurological success defined as maintenance or improvement in neurological status
  - Pain or pain reduction

  Secondary outcomes
  - Quality of life (SF-36)
  - Return to previous activity or work status
  - Rate of adjacent segment disease (ASD)
  - Range of motion at the instrumented segment
- Complications and adverse events
  - Device failure (reoperation due to revision, reoperation, or removal)
  - Complications or adverse events reported in included studies and based on regulatory/FDA surveillance
- Economic measures
  - Costing data

Key considerations highlighted by clinical experts:

1) **Interventions**
   Lumbar - Indications for L-ADR include, among other factors, primary lumbar and/or leg pain in the absence of nerve root compression. This group of patients is different than those undergoing cervical ADR and results from one group should not be inferred to the other. Cervical ADR is performed in patients with radiculopathy (cervical nerve root compression) causing arm pain and possibly motor weakness, or even myelopathy (compression of the spinal cord that could affect upper extremities, lower extremities, bowel, and bladder function). Consolidating cervical and lumbar disc replacements into one assessment will defeat the purpose of an evidence-based review by too broadly defining the topic area.

   Currently L-ADR is indicated for patients who have failed conservative care for a minimum of six months. Often patients have suffered for much longer without relief from nonoperative care. As a result, some believe that comparison of arthroplasty surgery to conservative management is not appropriate in that failure of conservative care is a prerequisite for surgical intervention. For many patients enrolling in a clinical trial, nonsurgical options are not acceptable at the time of enrollment. L-ADR is a surgical procedure to help remedy a degenerative disc disease that has not responded to conservative care.

In addition to currently available devices, over 40 industry competitors are involved in the development of devices for disc replacement, annular repair and nuclear repair/replacement technologies.[9] Differences in biomechanical design and materials for future devices may influence the overall picture of safety and efficacy for these devices in both the short-term and the long-term. In addition to the use of such devices for indications listed for the devices, as is the case with many technologies, diffusion of L-ADR for new indications as well as off-label use may have a potential impact on the overall safety and efficacy as well as the costs and longer-term trends in device use.[151]

Cervical - Surgery results in mechanical alteration of specific anatomic structures. The surgeon decides to operate when three conditions are met[34]:

- Knowing that the specific anatomic structure is diseased
- Believing that the diseased structure is responsible for the clinical problem
- Judging that the condition is suitable to treatment

For patients with cervical radiculopathy or myelopathy, the anatomical structures can often be identified through physical exam and imaging studies. Tying the diseased structures to the cause of the clinical problem can often be done in these conditions. However, the evidence for the efficacy/effectiveness of various treatments for these conditions remains unclear.

For patients with neck pain without neurological compromise, the cause of pain is frequently unknown. Often physical exam and imaging studies do not uncover any specific pathology. And in those patients in whom imaging studies do reveal common degenerative disease, it is not certain that these changes are the cause of the disease. In fact, the prevalence of many degenerative changes on imaging studies has been found to be similar among those without cervical disease symptoms compared with those with symptoms.

By contrast, the symptoms are less discrete in those presenting for lumbar artificial disc replacement (L-ADR) since such patients most frequently present with back pain without neurological deficit, which may or may not be associated with a specific disc problem. There are greater diagnostic challenges in determining the cause of low back pain compared with cervical radiculopathy or myelopathy and intervention options differ. The loading characteristics of the cervical spine and lumbar spine are also different. Thus, although similar types of ADR technology may be used for both cervical and lumbar sites, there are potential differences with regard to outcomes for treating cervical DDD compared with lumbar DDD. For these reasons, consideration of C-ADR and L-ADR should be separate.

FDA approval of C-ADR devices is fairly recent (2007) and there are a number of devices with various designs that are still under development and/or currently undergoing clinical trials. It is not yet clear what biomechanical designs, if any, may provide the best outcomes over the long term.

2) **Costs:**
Citing data from a 2003 JP Morgan marketing analysis, Singh, et al report that by 2010, 70% of spine procedures may involve some sort of disc replacement technology.[151] The report estimates that by that time, the worldwide spine arthroplasty market may range from $1.4 to more than $3 billion and that at least 47.9% of the fusion market may be converted to motion-sparing devices. More recent market assessments suggest that the U.S. market for artificial disc replacement will grow from $55 million in 2007 to $440 million by 2013.[9] To the extent that these predictions are correct, the potential impact of these devices on the costs of medical care is likely to be significant.[151] However, evaluation of long term costs or savings is difficult given the lack of high quality evidence from which to determine patient outcomes beyond 24 months.

Evaluation of long term costs or savings is difficult given the lack of high quality evidence currently available in the peer-reviewed literature from which to determine patient outcomes, particularly beyond 24 months. While it is postulated that ADR may reduce the likelihood of adjacent segment disease, it unclear how this and other potential longer-term complications, possible need for revision and other factors may ultimately influence costs as well as patient quality of life. Post approval studies are required for some lumbar and cervical ADRs, and data from these may help us understand the longer-term outcomes and costs.

3) **Patient considerations**
Lumbar - Identifying the right patient with spine disease who will respond to any specific treatment remains important yet often illusive. In many clinical trials, some patients clearly benefit from a specific treatment while others do not. The key to applying any new technology to patient care is to properly recognize those patients who have the greatest probability of success. In the area of spine treatment, this concept is most important due to the complex etiology of spine disability which includes physical and psychosocial factors. This problem of identifying those likely to respond to treatment is of concern for L-ADR in that the surgical procedure is designed to treat degenerative disc disease that is thought to be the origin of the patient's pain. Certainty around the diagnosis as the cause of low back symptoms varies. If the pain arises from non-disc structures, replacing the disc is unlikely to be successful. The surgeon must be convinced that a patient's symptoms are coming from the disc before proceeding with this procedure.

Though L-ADR for degenerative disc disease has been compared with lumbar fusion, not all patients who have an indication for fusion are candidates for L-ADR. Those include patients with nerve root compression, spondylolisthesis, stenosis and osteoporosis. In fact, some estimate that the proportion of patients who have an indication for L-ADR make up only about 5% of those who have an indication for lumbar fusion.[81]

Cervical - The current indications for currently approved C-ADR devices are for patients with intractable symptomatic single-level cervical DDD who have failure of at least six weeks non-operative treatment presenting with neck or arm pain and

functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, X-ray):

- Herniated nucleus pulposus
- Spondylosis (defined by the presence of osteophytes)
- Loss of disc height

For some contraindications, such as osteoporosis, there may be some subjectivity on the part of the surgeon regarding the degree to which it is present and therefore a problem to C-ADR placement. Expansion of C-ADR use for new indications combined with off-label use may have a potential impact on the overall safety and efficacy as well as the costs and longer-term trends in device use.[151]

4) **Professional considerations:**

Lumbar - High-surgical volume is associated with better clinical outcomes across a wide range of procedures and conditions to include orthopedic procedures such as total joints.[88] It is reasonable to expect similar findings with L-ADR. In fact, one study was recently published that made 3 comparison of patients receiving L-ADR: nonrandomized cases (n = 71) versus randomized cases (n = 205); randomized cases performed by high-enrolling surgeons versus low-enrolling surgeons; and randomized cases at high-volume institutions versus low-volume institutions.[135] The investigators found that surgeons and institutions with a high volume of L-ADR cases have reduced key perioperative and postoperative negative outcomes that provide a clinical and/or economic benefit. There needs to be more work done to determine the optimum surgeon and institutional volume of L-ADR cases to achieve the best possible results.

Cervical – None identified.

1. Background

1.1 The Condition

Back pain caused by degenerative disc disease (DDD) is a major health problem throughout the world. Over 90% of spinal procedures are performed because of disc degeneration and a reported 15%-20% of patients do not recover from back pain after lumbar surgery.[13,41] DDD is the leading cause of pain and disability in adults in the United States.[60] Data indicate that at least 80% of Americans have at least one significant episode of low back pain in their lifetime, and 5% have chronic low back pain.[15,169] Approximately 2.4 million Americans are disabled by lower back pain at any given time, and half of those are chronically disabled.[120] The annual incidence rate of lower back pain is estimated to be 5%, and upwards of 13 million physician visits are for chronic lower back pain, according to the National Center for Health Statistics.[120] Lower back pain due to DDD peaks at 40 years of age and affects both men and women equally.[120] In 2001, 122,469 lumbar fusion surgeries were performed for DDD at an estimated cost of $4.8 billion.[47] In Australia, according to data from the 1995 National Health Survey[105], the incidence of back problems was estimated to be 65,938 per 100,000. A Swiss study reported that approximately 14% of the population had chronic back pain.[112] Using information from the 1990 Ontario Health Survey database[17], the overall prevalence of back and neck disorders in residents of Ontario was determined to be around 11%.

Cervical radiculopathy and myelopathy are neurologic conditions characterized by dysfunction of the spinal nerve or spinal cord often as a result of degenerative disc disease or spondylosis. Cervical spondylotic myelopathy (CSM) is the most prevalent spinal cord dysfunction in people 55 years or older.[167] The major risk factor for cervical spondylosis is aging; although trauma may contribute, there is usually no history of significant trauma. An estimated 60% of individuals older than 40 years of age have radiographic evidence of cervical DDD secondary to spondylosis.[26,155] By age 59, 70% of women and 85% of men have radiographic evidence of these changes, and by age 70, the number increases to 93% and 97%, respectively.[64] One study found that 11% of patients between 70-102 years of age experienced neck pain in a month's time.[73] Another study of 450 surgical patients being treated for DDD found that 61% presented with radiculopathy, 16% with myelopathy, and the other 23% had a combination of the two.[133]

Because aging is the primary risk factor, as the US population ages, the incidence of DDD is expected to increase. A study of Nationwide Inpatient Sample (NIS) data collected between 1993 through 2003 shows that the number of cervical spinal fusion procedures conducted in the U.S. increased from 26 to 50 per 100,000, with symptomatic DDD representing more than four out of every five cases of cervical DDD cases in 2003.[26,167]

Intervertebral discs are soft, spongy pads of tissue that separate and provide stability to the individual vertebrae of the spine, and function by absorbing shock and facilitating motion of the spine. They are composed of water, collagen, and proteoglycans. Intervertebral discs consist of an annulus fibrosus, located in the outer region of the disc that surrounds the nucleus pulposus. The annulus fibrosus consists primarily of collagen and functions to resist tensile loads; the nucleus pulposus has a higher water and proteoglycan content that makes it jelly-like in substance, and functions to prevent compression of the spine.[112,139] Cervical spondylosis has been associated with the aging process, during which discs lose moisture content and elasticity, leading to a loss of disc height. These changes put increased stress on the articular cartilage of

the vertebrae and their endplates, and osteophytic spurs may form at the endplates.[26,64,112,139,167] In addition, annular degeneration may lead to disc herniation or protrusion.[139] Narrowing of the spinal canal by osteophytic spurs, ossification of the posterior longitudinal ligament, or bulging of a large central disc can compress the cervical spinal cord resulting in myelopathy, and impinge the spinal nerve roots, causing radiculopathy. As a result of this disc deterioration, patients may experience neck, shoulder, and arm pain as well as various degrees of neurological symptoms and impairment, including unsteady gait and clumsiness.[64,167] In severe cases, stenosis of the cervical spine can result in myelopathy affecting the lower extremity and radiculopathy affecting the upper extremity.[159]

1.2 The Technology and its Comparator(s)

Lumbar artificial disc replacement (L-ADR)

The success of total joint arthroplasty of the hip and knee for patients with osteoarthritis gives some hope that a similar remedy can be developed for the spine patients. The improvements in patients undergoing total hip and knee arthroplasty are large by any measures of responsiveness commonly used in orthopedic research.[7,8,33,71,72,85,94] In a 1979 publication of the Mayo Clinic Proceedings, total hip arthroplasty was declared one of the most successful orthopedic procedures of the century as it provided relief of pain and improved function in a wide variety of hip conditions[33]. It was recognized at that time as early long term follow-up studies were being evaluated, that some problems were being observed especially with the femoral prosthesis which led to improvements that continue to this day. Similar publications have followed, ultimately leading to consensus statements by the NIH decades after initial development that hip and knee replacement surgeries are strongly supported by more than 20 years of follow-up data concluding that there is rapid and substantial improvement in patient's pain, functional status, and overall health related quality of life in about 90% of patients with 85% being satisfied with the results of surgery.[7,8]

The success of total hip and knee replacement has helped to motivate the development of spinal artificial discs. Like these procedures, ultimate success will be based on a continuous monitoring of outcomes and complications with concurrent improvements in the technology. Similarly, these previous procedures had few alternate treatment remedies apart from continued pain management through conservative care or fusion of the joint, neither of which have been a solution to these problems, leading to decades of treatment and technology improvement in total joint replacement.

Disc replacements have a relatively long history as far as spinal implants are concerned. Ulf Fernstrom is widely believed to have inserted 191 simple Swedish Ball Bearing spheres into the lumbar and cervical spine of approximately 125 patients in the early 1960's.[54] Anecdotal information suggests that after a short period of symptom relief, the prosthesis ultimately failed secondary to subsidence of the implant within the spine vertebra leading to abandonment of the technique. However, failure rates have not been found in the published literature. Since that first prototype, more complex designed prostheses have been developed to maintain height, replicate the range of motion of a healthy spinal disc, and provide stability.[101]

Around the world the market penetration and regulatory status of artificial discs has remained varied. In the United States, only the SB Charité (DePuy Spine, Inc., Raynham, MA) and the Prodisc-L (Synthes, Inc., West Chester, PA) are currently approved for clinical use. In Canada, there are four types of lumbar artificial discs available for clinical use: the SB Charité, the Prodisc-L, the Maverick (Medtronics, Memphis, TN), and the Active L (Aesculap Implant Systems, Center Valley, PA). In Europe, the SB Charité, the Prodisc-L, the Activ-L, and the Maverick have European CE (Conformité Européne) mark certification. In Australia, the SB Charité and the Prodisc-L are available for use. Other discs currently being used or tested include the MobiDisc (LDR Medical, Cedex 9, France), the Flexicore (Stryker, Allendale, NJ), the Kineflex Lumbar Disc (SpinalMotion, Inc., Mountain View, CA), the Lumbar Motion Preservation (LMP; Vertebron, Stratford, CT), the eDisc (Theken Disc, Akron, OH), the CAdisc (Ranier Technology, Cambridge, United Kingdom), Freedom Lumbar Disc (AxioMed, Garfield Heights, OH), the Percutaneous Disc Reconstruction (PDR; TranS1, Wilmington, NC), the SaluDisc (SpineMedica, Marietta, GA), the Rescue Total Disc Replacement (Biomet/EBI, Warsaw, IN), the Min T Total Disc Replacement (Biomet/EBI, Warsaw, IN), the Altia Spine Disc (Amedica, Salt Like City, UT), the Physio-L (Nexgen Spine, Inc., Whippany, NJ), the Spartacus (US Spine, Boca Raton, FL), the Dynardi Artificial Lumbar Disc (Zimmer, Inc., Warsaw, IN), and the Total Spine Motion Segment System (TSMS; Disc Motion Technologies, Boca Raton, FL).

Each artificial disc is comprised of two or three components including two endplates and an articulating mechanism with either a metal-on-metal (eg, the Maverick and Flexicore) or metal-on-polymer surface (eg, the SB Charité and the Prodisc). To secure the disc in place and provide stability within the host vertebral body, devices feature a number of designs, such as teeth-like components called spikes or fins that are driven into the vertebral bone, a porous coated surface on the endplates which promotes bony in-growth around these structures, or are secured into the recipient vertebral body with screws.[106]

Each intervertebral disc is sandwiched between two adjacent vertebrae, and is anterior to paired facet joints that link the adjacent vertebrae. The facet joints and disc make up a single motion segment which is referred to as the "tri-joint complex".[139] This motion unit in its healthy state allows for six potential motion directions: compression, distraction, flexion, extension, lateral bending, and axial rotation.[111] The ability of artificial disc prostheses to mimic these ranges of motion provides the basis for a biomechanical classification system.[51] "Unconstrained" refers to a device that provides no mechanical assistance and allows for hypermobility beyond the normal physiological range for a given motion excursion. A "semiconstrained" device allows unrestricted motion within the normal physiological range but is blocked (ie, mechanically restrained) beyond that range. "Constrained" devices provide a fixed center of rotation that does not change and prohibit natural motion by imposing mechanical restrictions within the normal range of segment motion.[51] The constrained design concept is thought to minimize anteroposterior movement at the treated facet level, potentially reducing stresses on these structures. Table 1 below provides an overview of biomechanical classification of the most frequently studied devices.

Table 1. Biomechanical classification of select lumbar total disc arthroplasty prostheses [14,56,101]

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
SB Charité III	unconstrained	mobile	CoCrMo UHMWPE	metal on polymer	2 sm	all fins/ bone ingrowth
Prodisc-L (also called Prodisc II in European literature)	semiconstrained fi	xed	CoCrMo UHMWPE	metal on polymer	1 keel	
Maverick sem	iconstrained	fixed	CoCrMo	metal on metal	1 keel	
FlexiCore	fully constrained	fixed	CoCrMo	metal on metal	1 sm	all fins/bone ingrowth
Mobidisc unc	onstrained	mobile	CoCrMo UHMWPE	metal on polymer	2 keel	

COR = center of rotation.
CoCrMo = cobalt-chromium-molybdenum alloy.
UHMWPE = ultra-high molecular weight polyethylene.

Another important aspect of disc design that relates to restoration and preservation of natural motion and stability is the center of rotation (COR). In both the cervical and lumbar spine, the center of rotation is not a fixed point but rather a locus of points that tend to be posterior to the midline and caudal to the inferior endplate.[14] Some artificial discs are designed with the center of rotation fixed, either in the center of the disc or in the posterior aspect of the disc space. Alternatively, other devices create a mobile center of rotation so that the locus of points that define the normal centers of rotation can be replicated.[14]

Metals and polymers are the primary material components of disc prostheses used in total disc replacement. Polymers provide low friction surfaces for articulating bearings and shock absorption. Metals supply the necessary material properties such as high strength, ductility, hardness, corrosion resistance, formability, and biocompatibility needed for use in load-bearing. The three main metal alloys used are titanium based, cobalt based, and stainless steal based alloys.[69]

The material components may influence the wear of the ADR. Wear is the physical process caused by motion across a bearing surface, and in prostheses it can be associated with loss of joint height and subsequent failure. Typically, the softer of the two material components bearing against each other will generate the most debris, so in a metal-on-polymer disc, the polymer generates nearly all the wear debris.[69] The local and systemic response to particulate wear debris is a potential clinical concern, as wear debris may cause an inflammatory response or infection leading to pain, osteolysis, pannus formation, and prosthetic loosening.[14] Metal debris of implants has been shown to be associated with upregulation of cytokines, however, analysis of both animal studies and human explants of various disc prostheses have not demonstrated any significant inflammatory response or osteolysis.[14] These results only describe short term effects, however, and future studies evaluating long term outcomes are needed.

Artificial discs are intended for the full life span of the patient. Inclusion criteria for the FDA clinical trials for the Prodisc-L and Charité lumbar ADR were patients 18-60 years of age, and the studies were conducted in patients with a mean age of 39 (Prodisc-L) and 40 (Charité) years.[28,171] Artificial disc prostheses should be designed to last at least 40-50 years, which are conservative approximations for the average time a 35-year old patient will need a functioning disc prosthesis.[69,111]

Indications for FDA-approved use of the Charité and Prodisc-L artificial lumbar discs can be summarized as follows:

- Skeletally mature patients
- Single-level DDD from L3-S1 (Prodisc-L) or L4-S1 (Charité)
    - DDD confirmed by patient history and radiographic studies
- If spondylolisthesis (vertebral displacement towards an adjacent vertebrae) is present at the involved level, it cannot be more than grade 1 (Prodisc-L) or 3 mm (Charité)
- Failure of at least six months of nonoperative treatment

Contraindications for FDA-approved Charité and Prodisc-L artificial lumbar discs can be summarized as follows:

- Active systemic infection or infection localized to site of implantation
- Osteopenia or osteoporosis
- Bony lumbar spinal stenosis
- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Isolated radicular compression syndromes, especially due to disc herniation
- Pars defect (spondylosis)
- Involved vertebral endplate that is dimensionally smaller than 34.5 mm in the medial-lateral and/or 27mm in the anterior-posterior directions (Prodisc-L only)
- Clinically compromised vertebral bodies at the affected level due to current or past trauma (Prodisc-L only)
- Lytic spondylolisthesis or degenerative spondylolisthesis of more than grade 1 (Prodisc-L only)

A 2004 retrospective review on the prevalence of contraindications for L-ADR in 100 patients who underwent lumbar surgery found that 10% of patients had osteoporosis, 70% had lumbar stenosis, 35% had a herniated nucleus pulposis with radicular compression, 7% had spondylosis, and 44% had spondylolisthesis.[81]

Lumbar artificial disc replacement (L-ADR) is designed to preserve motion at the target spinal level. As well as possibly providing greater pain relief, this motion preservation may potentially decrease stress on and mobility of the adjacent segment structures, factors that are thought to contribute to adjacent segment disease (ASD). L-ADR can also restore pre-degenerative disc height and spinal alignment and does not require a bone graft. Other theoretical advantages include maintenance of mechanical characteristics, decreased perioperative morbidity compared with fusion, and early return to function.[14] Insertion of the prosthesis involves an anterior approach and is usually performed by a vascular or general surgeon and a spine surgeon (with orthopaedic or neurologic surgery background) working in tandem to facilitate exposure. The

procedure is technically more demanding, has a steeper learning curve, and requires greater precision than fusion surgery. Potential problems associated with L-ADR may include injury to other structures (vascular, neurologic, intestinal, or urogenital), infection, loosening/dislodgment, polyethylene or metal wear, loss of motion over time, impact/pressure on adjacent discs and facet joints, subsidence, implant failure, heterotopic ossification, and device related endplate fracture.[122,155]

Cervical artificial disc replacement (C-ADR)

Given the reported success of lumbar artificial disc devices, The Department of Medical Engineering at Frenchay Hospital, Bristol, United Kingdom, began the initial design process for a cervical device in the late 1980's. Referred to as the Bristol-Cummins artificial joint, this disc was comprised of a two-piece, stainless steel, metal-on-metal, ball-in-socket construct with anchoring screws placed anteriorly. The results of a clinical study comprised of 20 patients implanted with this disc were promising, with most patients reporting symptomatic improvement as well as showing radiographic evidence of preserved intervertebral motion. However, several complications, mainly screw breakage and pullout, occurred attributed to poor screw placement and the fact that the joint was uniform in size.[146] Later, a second generation design, the Frenchay (now called the Prestige), was developed. This disc was less bulky, had a redesigned screw locking mechanism, and allowed for more physiological motion preservation, theoretically having less effect on adjacent vertebral segments as well. Following the reported success of the Bristol discs, other artificial cervical discs began to emerge, some using a new metal-on-plastic design (ie, Bryan).[80]

Artificial discs are functional prostheses that were developed to mimic the decompressive and supportive properties of intervertebral discs. ADR is designed to preserve motion at the target spinal level by restoring the natural distance between the vertebrae. In addition to reducing pain, this preservation of motion is hypothesized to decrease stress on and increase mobility of adjacent segments, which is theorized to reduce the incidence of adjacent segment degeneration (ASD), thought to accompany spinal fusion.[26,112]

The cervical artificial discs evaluated in this report are comprised of two or three components including two endplates and an articulating mechanism with either a metal-on-metal (e.g., the Prestige) or metal-on-polymer surface (e.g., the Bryan). To secure the disc in place and provide stability within the host vertebral body, devices feature a number of designs, such as a porous coated surface on the endplates to promote bony in-growth around the structure, or can be secured into the recipient vertebral body with screws.[155] Artificial discs are composed of the same materials used in other well-established prostheses, such as those used to replace hips or knees.[112]

The C-ADR surgical procedure involves a standard anterior cervical discectomy followed by C-ADR implantation, and is performed on an in-patient basis by an orthopedic surgeon or neurosurgeon specializing in cervical spinal conditions. Following disc and osteophyte removal, the nerves are carefully decompressed, and the artificial disc is then inserted.[112] Potential problems associated with ADR may include injury to other structures (vascular, neurologic, esophageal), temporary paralysis or loss of voice, infection, loosening/dislodgment, subsidence, polyethylene or metal wear, loss of motion over time, new or worsening pain, impact/pressure on

adjacent discs and facet joints, implant failure, heterotopic ossification, subsequent revision surgery, and device-related endplate fracture.[14,112,155]

The motion of a healthy cervical spine allows for six potential motion directions: compression, distraction, flexion, extension, lateral bending, and axial rotation.[111] The ability of the artificial disc prostheses to mimic these ranges of motion provides the basis for a biomechanical classification system. There are currently two types of cervical artificial discs available: "unconstrained" and "semiconstrained." "Unconstrained" refers to a device that provides no mechanical assistance and allows for hypermobility beyond the normal physiological range for a given motion excursion. A "semiconstrained" device allows unrestricted motion within the normal physiological range but is blocked (i.e. mechanically restrained) beyond that range.[51] Table 2 provides an overview of biomechanical classifications for the most frequently studied devices.[14,26,90]

Table 2. Biomechanical classification of select cervical total disc arthroplasty prostheses

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
Prestige (Frenchay)	semiconstrained m	obile	stainless steel	metal on metal	1 d	ual rails/ bone ingrowth
Prodisc-C sem	iconstrained	fixed	CoCrMo UHMWPE	metal on polymer	1 keel	/ bone ingrowth
Bryan u	nconstrained	mobile	titanium alloy polyurethane	metal on polymer	2 m	illed cavities/ boneingrowth
CerviCore u	nconstrained	NR	CoCrMo	metal on metal	NR d	ual rails/ bone ingrowth
Kineflex C	unconstrained	NR	CoCrMo	metal on metal	NR keel	/ bone ingrowth
Mobi-C u	nconstrained	mobile	titanium UHMWPE	metal on polymer	NR NR	
PCM sem	iconstrained	fixed	CoCrMo UHMWPE	metal on polymer	2 d	ual rails/ bone ingrowth

COR = center of rotation.
CoCrMo = cobalt-chromium-molybdenum alloy.
UHMWPE = ultra-high molecular weight polyethylene.

Another important aspect of disc design related to restoration and preservation of natural motion and stability is the center of rotation (COR). In the cervical spine, the center of rotation is not a fixed point, but instead a locus of points that tend to be posterior to the midline and caudal to the inferior endplate. Artificial discs are designed either with the center of rotation fixed in the center or in the posterior aspect of the disc, or with a mobile center of rotation so that the locus points that define normal centers of rotation can be replicated.[14]

Artificial discs should have a life expectancy of at least 50 years to accommodate the younger patient, and the materials that constitute the disc directly affect its long-term wear.[69] Disc prostheses are primarily composed of polymers and metals. Polymers provide shock absorption and low friction surfaces on articulating bearings, while metals supply the necessary material

properties such as high strength, ductility, hardness, corrosion resistance, formability, and biocompatibility needed for use in load-bearing. The primary metal alloys used are titanium based, cobalt based, and stainless steel based alloys.[69] Wear is caused by motion across a bearing surface, and in prostheses it can be associated with the formation of debris, loss of joint height, and disc failure.[14] Metal debris of implants has been shown to be associated with upregulation of cytokines, however, analysis of both animal studies and human explants of various disc prostheses have not demonstrated any significant inflammatory response or osteolysis[9]. These results only describe short term effects, however, and future studies evaluating long term outcomes are needed.

While artificial intervertebral discs have been used for almost two decades in Europe and some Asian countries, only two of the artificial discs described in Table 1 are marketed in the United States and there are no high quality long-term studies yet available. The Prestige (Frenchay) artificial disc received FDA marketing approval on July 16, 2007. The second FDA approved ADR, the Prodisc-C, was approved on December 17, 2007. Indications and contraindications for these devices are summarized below. A third product, the Bryan Cervical ADR, received an approvable decision by an FDA advisory panel on July 17, 2007, but at this time has not received final marketing approval from FDA.[6] Other discs currently being used or tested include the PCM (Porous Coated Motion) Cervical Disc System (Cervitech, Inc., Rockaway, NJ), the Mobi-C (LDR Spine, Austin, TX), the Kineflex/C Cervical Disc (SpinalMotion, Mountain View, CA), the CerviCore Artificial Cervical Disc (Stryker Spine, Kalamazoo, MI), the Secure-C Cervical Artificial Disc (Globus Medical, Audubon, PA), the Discocerv (Scient'x, Maitland, FL), the NeoDisc (NuVasive, San Diego, CA), the Discover Artificial Cervical Disc (DePuy Spine, Raynham, MA), the Cervical Motion Preservation Device (CMP; Vertebron, Stratford, CT), and the Advent Cervical Disc (Blackstone Medical, Springfield, MA).

Indications for FDA-approved Prestige and Prodisc-C artificial cervical discs can be summarized as follows[4,5]:

- Skeletally mature patients
- C3-C7
- Patients with intractable symptomatic single-level cervical DDD
  - Neck or arm pain
  - Functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, X-ray):
    - Herniated nucleus pulposus
    - Spondylosis (defined by the presence of osteophytes)
    - Loss of disc height
- Failure of at least six weeks of nonoperative treatment
- Implanted via an open anterior approach

Contraindications for FDA-approved Prestige and Prodisc-C artificial cervical discs can be summarized as follows[4,5]:

- Active systemic infection or infection localized to site of implantation
- Osteoporosis
- Cervical instability

- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Severe spondylosis characterized by bridging osteophytes or a loss of disc height >50% or an absence of motion (< 2°), as this can result in limited range of motion and may promote bone formation

Nonoperative treatment, lumbar

In general, treatment of symptomatic DDD initially consists of non surgical approaches such as physical therapy, acupuncture, facet joint injections, epidural steroids, anti-inflammatory drugs, analgesic medication, ultrasound, and cognitive behavioral interventions.[27,108,138] Percutaneous laser discectomy and intradiscal electrothermal therapy are two examples of minimally invasive methods used to relieve pain. It is estimated that 10% to 20% of people with lumbar DDD and up to 30% with cervical DDD will be unresponsive to nonsurgical treatment.[46] Patients who do not respond to conservative treatment are then potentially referred for fusion.

Nonoperative treatment, cervical

Initially, patients with mild DDD are typically treated with conservative, noninvasive therapies in order to relieve pain and prevent permanent injury to the spinal cord and nerves. These nonoperative treatments may include the use of a cervical collar, temporary bed rest, application of heat or ice, physical therapy (muscle-strengthening exercises, aerobic training), weight control, electrical therapy, and the administration of analgesics, including anti-inflammatory medications and epidural injections.[26,112,133] However, nonoperative management typically does not reverse or permanently stop the progression of the disease.[133]

If no improvement is seen after six weeks of nonoperative treatment or if symptoms significantly worsen, patients become candidates for surgical treatment.[26]
Many patients with symptomatic DDD become eligible for surgery; the pain of 50 to 70% of patients with cervical myelopathy and 25% with cervical radiculopathy fails to resolve with nonoperative treatment.[155] Furthermore, surgical treatment is frequently a consideration for patients with cervical DDD due to the risk of neurological deterioration.[133]

Operative treatment (lumbar fusion)

Spinal fusion is currently the surgical standard for patients with symptomatic DDD of the lumbar spine who do not respond to conservative treatment. However, there are many disadvantages to the procedure as well as concerns about its long-term consequences and benefits that have prompted research on alternative surgical methods. Complications include the potential for adjacent segment degeneration (development of disc degeneration, hypertrophic facets, dynamic instability, and/or spinal stenosis in adjacent levels), pseudoarthrosis, bone graft donor site pain and infection, instrumentation prominence or failure, neural injuries, and simple failure to relieve pain. [27,57,157] Four RCTs comparing lumbar fusion to nonsurgical treatments found that nearly 15% (58/399) of patients receiving lumbar fusion experienced complications.[30,31,53,59]. The most frequent complications reported included reoperation (with rates ranging from 0%-46.1%), infection (0%-9%), device-related complications (0%-17.8%), neurologic complications (0.7%-25.8%), thrombosis (0%-4%), bleeding/vascular complications (0%-12.8%), and dural injury (0.5%-29%).[30,31,53,59] In another study, a 12% two-year incidence rate of major complications following lumbar spinal fusion was reported, with a reoperation rate of 14.6% for that

population.[58]

Because surgical fusion results in loss of movement in the spine, adjacent vertebrae experience increased mobility and stress due to motion transfer from the immobile fused vertebrae. Spinal fusion is believed by some to promote the degeneration of the vertebrae above or below the fusion site. Evidence from one study suggests that approximately 26% of patients receiving lumbar fusion may develop new lumbar adjacent segment disease (L-ASD) within the first 10 years following fusion.[62] Annualized incidence rates of symptomatic ASD from case-series ranged from 0%[38] to 3.9%[52]. Length of follow-up varied from 32 months to 215 months across studies. It is unclear whether there is a greater risk for radiographic L-ASD in fusion patients compared with nonfusion patients. L-ASD rates among fusion patients ranged from 14.2% to 44.3% compared with 7.4% to 26.0% among patients who didn't receive fusion based on four comparative studies.[70,86,92,144] From case-series, radiographic ASD rates ranged from 1%[37] to 100%[114] following lumbar fusion and again, varied based on definition. The poor quality of these studies, divergent definitions of ASD, and the lack of correlation between radiographic L-ASD and symptomatic clinical disease make definitive conclusions regarding the extent to which L-ASD occurs following fusion difficult.

Operative treatment (anterior cervical fusion)

Surgery is generally indicated when nonoperative conservative treatments fail to prevent neurologic progression. A variety of surgical approaches and procedures are available, and the optimal choice of treatment remains controversial. Surgical procedures designed to decompress the spinal cord and, in some cases, stabilize the spine have been shown to be successful, but there is a persistent percentage of patients who do not improve with surgical intervention.[134] Additionally, the potential complications of surgery for cervical DDD may depend on the various methods of surgical management.

For many years, the posterior approach to decompress the cervical spine was used. In general this procedure resulted in favorable results for soft, accessible disc fragments. However, in order to better access midline fragments and calcified spurs, the anterior approach was developed.[48] Anterior approaches include anterior cervical discectomy alone (ACD) and anterior cervical discectomy with fusion (ACDF, using autograft, allograft, bone graft substitutes).[126] ACD has usually been associated with postoperative neck pain, low fusion rates and higher rates of cervical deformity.[11,104,116] As a result, for ACDF has become the treatment of choice for many surgeons for the treatment of radiculopathy or myelopathy as a result of central or paracentral disc herniations, or osteoarthritis of the facet or uncovertebral joint.

A range of factors must be considered when deciding which surgical technique to use, and surgeons are often challenged with determining the most appropriate technique because there is limited information about whether there is a difference between surgical procedures in terms of clinical and radiographic outcomes or in postoperative complication rates. Among surgically managed patients, an anterior or posterior approach may be employed.[133] Among those managed posteriorly, laminoplasty or laminectomy with fusion are common surgical techniques. With several standards of care available for this population, a better understanding of the corresponding positive and negative outcomes with respect to clinical and patient-centered outcomes is warranted.

The current definitive standard of care is anterior cervical discectomy and spinal fusion (ACDF). The goal of this procedure is nerve decompression and restoration of spinal alignment and stability. The spinal fusion procedure begins with a partial or complete discectomy and decompression. The remaining intervertebral space is then filled with bone graft. The graft may be an autograft taken from patient's hip bone, an allograft taken from a donor, or synthetic and composed of bone morphogenic proteins. The bone graft stabilizes the spine by filling the intervertebral space and also promotes fusion of the vertebral endplates.[112,133,139,155]

There is a general trend for patients to see continued improvement for a few years after spinal fusion, but this improvement is often followed by functional deterioration. When the anterior surgical approach is used, this deterioration is thought to be caused by adjacent segment degeneration (ASD).[133] Because surgical fusion results in loss of movement in the spine, adjacent vertebrae experience increased mobility and stress due to motion transfer from the immobile fused vertebrae. Spinal fusion is believed to promote the degeneration of the vertebrae above or below the fusion site. The incidence of ASD following cervical fusion is difficult to estimate due to the lack of comparative studies and poor quality of the few existing studies. In addition, varying definitions of ASD make definitive diagnosis difficult. For symptomatic C-ASD, the most methodologically rigorous longitudinal study found reported a 2.9% annual incidence rate of C-ASD[79], and case-series report rates of ASD between 6%-17%.[65,87,103,154,168] Radiographic evidence of ASD has been reported to occur in 41%-92% of patients following spinal fusion based on varying definitions.[65,75,87,91,154,168] Importantly, there is a lack of correlation between radiographic ASD and clinical symptoms. Studies which were able to effectively evaluate the separate effects of degeneration due to aging and degeneration which may be exacerbated following fusion were not identified. The development of symptomatic ASD can increase the need for subsequent surgery if it causes pain or disability.[155] Data from two studies suggest that while the majority of patients (74%–84%) appeared to remain free of symptomatic C-ASD at 10 years after surgical fusion, survival analysis suggests that 16%–26% of patients have new disease within the first 10 years.[79,83] By 17 years, the rate of C-ASD increased to 33% in one study.[83]

Spinal fusion surgery is also associated with complications such as pseudoarthrosis, graft or implant failure, instrument failure, continued growth of osteocytes, and neural injuries, as well as reoperation.[133,155] There is also the risk of prolonged pain, deep infection, adjacent nerve and artery damage, and increased risk of stress fracture at the bone donor site in the hip; immunological reactions to allografts may also occur.[112]

1.3 Clinical Guidelines

National Guideline Clearinghouse

No clinical guidelines related to the use of artificial discs were found when the AHRQ, NGC database was searched. Personal contact with professional organizations confirmed that evidence-based, transparently-developed clinical guidelines have not yet been formulated.

National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE), (which provides guidance on health technologies and clinical practice for the National Health Service in England and Wales) concluded in 2004 that "current evidence on the safety and efficacy of prosthetic intervertebral

disc replacement appears adequate to support the use of this procedure." NICE acknowledges that longer term data are required to compare results with spinal fusion, and further recommended that physicians should ensure patients understand the long-term uncertainties of the ADR procedure; and that clinical outcomes be audited. Since this guidance was issued, additional studies have been reported.

1.4 Previous Systematic Reviews/Technology Assessments

Lumbar

Previously conducted reviews/assessments have reached somewhat differing conclusions regarding the safety and efficacy of lumbar ADR. Table 3 provides an overview of previous assessments.

Table 3. Overview of previous technology assessments of lumbar ADR

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Ontario Medical Advisory Secretariat Health Technology Policy Assessment (2006)	2003 through 9/2005	SB Charité, Prodisc-L, Maverick	• 2 RCTs (90% f/u, 24 months); N =540; monolevel arthroplasty only • 6 case series (98% f/u, 15–136 months); N = 285	Yes- Cochrane Musculoskeletal Injuries Group Quality Assessment Tool Overall study quality was considered moderate for effectiveness and short-term complications and very low for ASD based on GRADE analysis.	One RCT was unpublished and conducted by the device manufacturer. More recent literature now available.	**Efficacy:** Based on 2 RCTs, lumbar ADR is 79% superior to spinal fusion, although data for long-term (>2 year) outcomes are not available. **Safety:** The rates of major complications were less than 13% per L-ADR implanted, although data for long-term (>2 year) outcomes are not available. **Economic:** Lumbar ADR is more costly than fusion.
Commonwealth of Australia Medical Services Advisory Committee (MSAC) Assessment Report (2006)	1966 through 2/2005	Charité, Prodisc-L, Acroflex	• 3 RCTs (69% for 1/3 reports, 6–24 months); N = 398; monolevel and/or bilevel arthroplasty • 14 case series (% f/u NR, 12–51 months); N = 579	Yes- Level of evidence as defined by the National Health and Medical Research Council; NHS Centre for Reviews and Dissemination validity criteria Overall quality of studies was moderate and presented several limitations, case series reviewed for safety considerations only.	More recent literature now available. No overall formal level of evidence scores presented.	**Efficacy:** Recommends interim funding for L-ADR in eligible patients with monolevel DDD. **Safety:** No significant differences in complication rates were found in L-ADR versus fusion. The long-term (>5 years) safety is unknown; adverse events occurred in less than 14% of patients in all case series evaluated. **Economic:** Lumbar ADR is less costly than fusion.
Federaal Kenniscentrum voor de Gezondheidszorg KCE reports vol.39A (2006)	through 2/2006	SB Charité	• 1 RCT (% f/u NR, 24 months); N =304; monolevel arthroplasty	Yes- Dutch Cochrane Center checklist used Overall study quality was rated as fair, although overall quality of evidence available is poor.		**Efficacy:** Based on only 1 available RCT, L-ADR should be considered an experimental procedure. **Safety:** Concerns remain due to based on unavailable information on rate of ASD and long-term complications. **Economic:** Considers information to be lacking.
NHS National Institute for Clinical Excellence Interventional Procedure	through 10/2002	SB Charité III	• 1 RCT (% f/u NR, 24 months); N = 304; monolevel arthroplasty only • 1 nonrandomized CT	Not reported Literature lacks good-quality long-term evidence.	More recent literature now available. No formal grading of	**Efficacy:** Current evidence is adequate to support ARD, although long-term efficacy is uncertain. **Safety:** Current evidence is

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
Guidance 100 (2004)			(% f/u NR, time of f/u NR); N = 20 • 4 case reports (97% f/u for 1/4 studies, 12–52 months); N = 294		evidence quality.	adequate to support ARD, although long-term data is needed. **Economic:** not addressed
ECRI Institute (2007)	through 9/2006	Charité, Prodisc-L, Activ-L, Maverick, FlexiCore, Kineflex	• 2 RCTs (61% f/u for 1/2 reports, 6–24 months); N = 460	Yes- State of Evidence Base grading system The available quality of evidence was rated as low.	More recent literature now available.	**Efficacy:** Limited data suggests that L-ADR may offer advantages over fusion. **Safety:** The long-term (>2 years) safety of L-ADR is uncertain. **Economic:** The cost of L-ADR is comparable to that of fusion.
Institute for Clinical Systems Improvement Technology Assessment Report (1995)	1995 through 2005	Charité, Prodisc-L, Maverick	• 3 RCTs (90% f/u for 1/3 reports, 18–24 months); N = 526; monolevel arthroplasty only (in 2/3 reports) • 6 case series (75% for 3/6 reports, 12–120 months); N = 494	Yes- Evidence Grading System as described The overall study quality has many inconsistencies.	More recent literature now available.	**Efficacy:** The long-term efficacy of L-ADR is not known, and its use not supported. **Safety:** The long-term safety of L-ADR is not known. **Economic:** ARD is more expensive than fusion ($10,000–$12,000 for ARD, $4,000–$5,000 for fusion).
Hayes brief (2007)	2002 through 8/2007	Charité, Prodisc-L, Maverick, FlexiCore, LIDR	• 2 RCTs (87% f/u for 1/2 reports, 24 months); N = 540 (plus an additional 348 nonrandomized patients); monolevel arthroplasty only • 7 case series (87% for 4/7 reports, 18–158 months); N = 714	Yes- Hayes Ratings System The overall study quality prevents clear interpretation of the data.		**Efficacy: L-ADR** for DDD using Charité or Prodisc may lead to improved outcomes versus fusion for at least 2 years after surgery, only recommended as a last resort. **Safety:** The long-term safety of L-ADR remains uncertain. **Economic:** not addressed
California Technology Assessment Forum (2007)	1966 through 1/2007	Charité, Prodisc-L	• 2 RCTs (94% f/u, 24 months); N = 540; monolevel arthroplasty only (in 1/2 reports) • 11 case series (86% f/u for 3/11 reports, 12–208 months); N = 644; some case series were reported in multiple papers with overlapping patient populations	Yes- Studies graded for level of evidence (system not described) Overall quality of available evidence was moderate, noting that case series provide weak evidence.		**Efficacy: L-ADR** using Charity or Prodisc discs does not meet TA criteria for effectiveness or outcome and is not recommended. **Safety: L-ADR** using Charity or Prodisc discs does not meet TA criteria for safety and is not recommended. **Economic:** not addressed
Washington State Department of Labor and Industries HTA (2004)	through 7/2004	Charité III, Prodisc II, PDN	• 2 RCTs (100% f/u for 1/4 reports), 6–24 months); N = 393; monolevel and bilevel arthroplasty • 9 case series (78% f/u for 5/9 reports, 3–48 months); N = 403	Not reported The overall quality of the literature is poor and limited	No formal grading of the overall quality of evidence.	**Efficacy:** Data insufficient to draw conclusions, L-ADR should be considered experimental only. **Safety:** No conclusions were drawn. **Economic:** not addressed
Workers' Compensation Board of BC Review (2005)	through 10/2004	Charité III, Prodisc-L, PDN	• 1 RCT (% f/u NR, 24 months); N = 366; monolevel arthroplasty only	Yes- WCB of BC grading system. The overall quality of	RCT conducted by manufacturer of Charité III disc. More recent	**Efficacy:** Efficacy cannot be determined at this time and L-ADR should be considered experimental. **Safety:** Safety cannot be

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal‡	Comments	Primary conclusions
				the literature is poor (?) and limited.	literature now available.	determined at this time. **Economic:** not addressed

ADR: artificial disc replacement.
ASD: adjacent segment degeneration.
GRADE: Grading of Recommendations Assessment, Development and Evaluation.
NR = not reported.
PDN = Prosthetic Disc Nucleus.
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Percent follow-ups were not given for all RCTs or case studies. Mean time of follow-up is reported here.
† N reflects numbers before loss to follow-up.
‡ Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

Cervical

Many previously conducted reviews/assessments have primarily been formulated prior to the publication of randomized trials related to cervical ADR. Consequently, they have used case-series and concluded that there is a lack of evidence for the use of C-ADR. Table 4 provides an overview of previous assessments.

Table 4. Overview of previous technology assessments of cervical ADR

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal?‡	Comments	Primary conclusions
Ontario Medical Advisory Secretariat Health Technology Policy Assessment (2006)	2003 through 9/2005	Bryan	▪ 4 case-series (59% f/u, 12–24 months) N = 229	Yes- Cochrane Musculo-skeletal Injuries Group Quality Assessment Tool Overall study quality was considered to be very poor based on GRADE analysis.	No RCT data available. RCT data became available after publication (in 2007). Complication rates were not assessed beyond a 2-year follow-up, ASD rate not reported.	**Efficacy:** Without data from RCTs, the effectiveness of C-ADR versus spinal fusion could not be determined. **Safety:** The rates of major complications ranged from 0-8.1% per C-ADR implanted, the rate of ASD is not reported. **Economic:** none.
Commonwealth of Australia Medical Services Advisory Committee (MSAC) Assessment Report (2006)	1966 through 2/2005	Prestige I/II, Bryan, Bristol/ Cummins, porous coated motion disc	▪ 1 RCT (preliminary report, 44% f/u, 24 months) N = 55 Monolevel arthroplasty ▪ 11 case-series (% f/u NR, 12–65 months) N = 578	Yes- Level of evidence as defined by the National Health and Medical Research Council; NHS Centre for Reviews and Dissemination validity criteria Quality of RCT was inadequate and presented several limitations, case-series reviewed for safety considerations only.	RCT data became available after publication (in 2007). Formal level of evidence scores not presented.	**Efficacy:** Does not recommend public funding for C-ADR in the cervical spine due to inadequate evidence of effectiveness. **Safety:** No significant differences in complication rates were found between patients treated with C-ADR versus fusion, although the long-term (>5 years) safety is unknown; adverse events occurred in less than 14% of patients in all case-series evaluated. **Economic:** Cervical ADR is more costly than fusion.
Institute for Clinical Effectiveness and Health Policy-Argentina (abstract) 2007	NR Prestige,	Bryan, Prodisc	▪ 5 RCTs (65% f/u for 1/5 reports, 6–24 months) N = 1117 The 5 RCTs include	Not reported There are few RCTs, some with few patients and methodological defects.	No formal grading of evidence quality described.	**Efficacy:** There are no significant differences in C-ADR versus fusion, in studies with up to 2 year follow-up. Longer follow-up periods are necessary.

Assessment (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Critical Appraisal?‡	Comments	Primary conclusions
			FDA IDE studies, one preliminary report and two small RCTs independent of FDA trials			**Safety:** not addressed **Economic:** not addressed
NHS National Institute for Clinical Excellence Interventional Procedure Guidance 143 (2005)	through 2/2005	Bryan, Prestige I/II	▪ 2 RCTs (16% f/u for 1/2 studies, 6–24 months) N = 68 Monolevel arthroplasty only (reported for 1/2 RCTs) ▪ 3 case-series (% f/u NR, 6–24 months) N = 168	Not reported	More recent literature now available. No formal grading of evidence quality described.	**Efficacy:** Current evidence supports the short-term efficacy of C-ADR, although can't compare C-ADR to fusion without long-term data. **Safety:** There are no major safety concerns for C-ADR, although long-term outcomes are unknown. **Economic:** not addressed
Hayes brief (2007)	1/2000 through 9/2007	Prestige	▪ 1 full RCT (78% f/u, 24 months) N = 541 Monolevel arthroplasty ▪ one preliminary RCT report (44% f/u, 24 months) N = 55 ▪ 2 case-series reports (27% f/u, 24–48 months) N = 70	Not reported The RCT was sponsored by the manufacturer and is subject to bias.	No formal grading of the overall quality of evidence described.	**Efficacy:** Results from one RCT suggest that C-ADR is at least equivalent to fusion for at least two years after surgery. **Safety:** Long-term safety has not been demonstrated, and there are no significant differences between C-ADR and fusion in results from one RCT. **Economic:** The cost of cervical ADR is similar to that of fusion.
Workers' Compensation Board (WCB) of BC Review (2005)	through 10/2004	Bryans, Prestige ST, Prodisc-C, CerviCore (FlexCore), PCM	▪ 2 RCTs (73% f/u, 12–24 months) one is an initial report, the other a meeting abstract N = 115 Monolevel arthroplasty only ▪ 13 case-series (59% f/u for 5/13 reports, 6–60 months) N = 500 (NR for 1 study)	Yes- WCB of BC grading system. The overall quality of the literature is limited.	More recent literature now available.	**Efficacy:** Efficacy cannot be determined at this time and C-ADR should be considered experimental. **Safety:** Safety cannot be determined at this time. **Economic:** not addressed

ADR: artificial disc replacement
ASD: adjacent segment degeneration
GRADE: Grading of Recommendations Assessment, Development and Evaluation
NR: not reported
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Percent follow-ups were not given for all RCTs or case studies. Mean time of follow-up is reported here.
† N reflects numbers before loss to follow-up.
‡Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.

1.5 Medicare and Representative Private Insurer Coverage Policies

Variations exist in coverage policies for L-ADR for CMS and selected bell-weather payers. Table 5 provides an overview of policy decisions. There is currently no Centers for Medicare and Medicaid Services (CMS) National Coverage Determination specific to cervical spine disc replacement. It is slated as potential topic for the third quarter of 2008. Overview of payer assessments and policies for C-ADR are found in Table 6 below.

- **Medicare**
  The Centers for Medicare and Medicaid Services (CMS) will not cover lumbar ADR for patients older than 60 years of age and decisions regarding coverage of patients younger than 60 years of age are at the discretion of local CMS contractors. CMS's assessments include information from the BCBS TEC reports. An internal assessment used data from the two primary IDE randomized controlled trials for the Charite and ProDisc L as well as case series and one non-randomized study. Information on long-term outcomes was derived from case-series. A critical appraisal scheme for assessing study quality was described. The assessment deals only with lumbar ADR.

- **Aetna**
  Aetna considers FDA-approved prosthetic intervertebral discs medically necessary for spinal arthroplasty in skeletally mature person with lumbosacral degenerative disc disease at one level from L3 so S1, and who have failed at least 6 months of conservative management.

- **Blue Cross/Blue Shield**
  Coverage was not recommended.

- **Cigna**
  Cigna covers the implantation of a SB Charité or Prodisc-L lumbar intervertebral disc prosthesis for chronic, unremitting, discogenic low back pain and disability secondary to single-level degenerative disc disease (DDD) as medically necessary in a skeletally mature patient when ALL of the following criteria are met:
  - The unremitting low back pain and disability described has been refractory to at least six consecutive months of standard medical and surgical management (eg, exercise, analgesics, physical therapy, spinal education).
  - Single-level disc degeneration has been confirmed on complex imaging studies (ie, computerized tomography [CT] scan, magnetic resonance imaging [MRI]).
  - The planned implant will be used in the L4-S1 region if Charité or the L3-S1 region if Prodisc-L.

- **Harvard Pilgrim**
  Harvard Pilgrim does not cover artificial disc replacement for DDD as an alternative to spinal fusion.

Table 5. Overview of payer technology assessments* and policies for L-ADR

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services (2007)	2002- 2007	Prodisc-L	▪ 2 RCTs (86% f/u, 24 months); N = 596; monolevel arthroplasty only ▪ 1 nonrandomized CT (% f/u NR, 24 months); N = 24 ▪ 19 case series (87% f/u for 5/19 reports, 1–204 months); N = 1082 ▪	▪ The Centers for Medicare and Medicaid Services (CMS) will not cover lumbar ADR for patients older than 60 years of age and decisions regarding coverage of patients younger than 60 years of age are at the discretion of local CMS contractors.	▪ No clear conclusion can be drawn as to whether L-ADR is beneficial in patients younger than 60 years old. ▪ There is not enough evidence of benefit of L-ADR for patients over 60 years old.
Aetna Clinical Policy Bulletin (2007)	2000-2007	SB Charité Prodisc-L	▪ 1 RCT (87% f/u, 24 months); N = 304; monolevel arthroplasty only ▪ 1 nonrandomized CT (% f/u NR, 24 months); N = 24 ▪ 11 case series (91% f/u for 4/11 case reports), 24–91 months); N = 588 (not reported for all case series)	▪ FDA-approved prosthetic discs are considered medically necessary for adults with monolevel DDD (L3-S1) and who have failed at least six months of conservative treatment. ▪ Considered investigational for all other indications.	▪ No rationale for policy stated ▪ Policy is in accordance with FDA recommendations ▪ CPT codes if selection criteria are met: 0090T, +0092T, 0093T, +0095T, 0096T, +0098T, +0163T, +0164T, +0165T, 22857, 22862, 22865 ▪ Other CPT codes related to the CPB: 22533, 22558, 22612, 22630
BlueCross BlueShield Techonology Evaluation Center Assessment (2007)	through 5/2007	SB Charité Prodisc-L	▪ 2 RCTs (86% f/u, 24 months); N = 546; monolevel arthroplasty only (noted for 1/2 RCTs) ▪ 1 nonrandomized CT (100% f/u, 12 months); N = 24 ▪ 6 case series (94% f/u, 24–104 months); N = 334	▪ Not recommended	▪ There is insufficient evidence from RCTs to establish effectiveness
Cigna HealthCare Coverage Position (2007) **Cigna HealthCare**	1994 through 2007	Charité Prodisc-L Maverick	▪ 2 RCTs (75% f/u for 1/2 reports, 24 months); N = 596; monolevel arthroplasty only ▪ 19 case series (95% f/u for 1/19 reports, 3–120 months, NR for 5 studies); N = 1873	▪ Single-level L-ADR using Charity or Prodisc discs is considered superior to fusion and will be covered in patients who have failed six months of conservative treatment. ▪ Charité disc can be used in the L4-S1 region. ▪ Prodisc can be used	▪ Evidence has shown that the use of Charité and Prodisc disc proteheses are safe and effective. ▪ Results from short-term studies show that L-ADR improves range of motion within the lumbar spine and stabilizes the invertebral disc space.

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
Coverage Position (2007) (continued)				in the L3-S1 region.	▪ ADR is regarded as safe, although more data is needed regarding the long-term safety and rate of complications. ▪ CPT codes covered when medically necessary: 22857 ▪ CPT codes considered experimental, investigational, unproven, not covered: 0090T, 0092T, 0163T ▪ No specific HCPCS codes
Harvard Pilgrim HealthCare TA Policy (2006)	1994 through 3/2006	Charité	▪ 1 RCT (% f/u NR, 24 months); N = 304 ▪ 2 case series (% f/u NR, 120–204 months); N = 153	▪ Not covered	▪ Long-term data on safety, efficacy, and durability of the discs are needed. ▪ ADR is a more technically difficult surgery than spinal fusion.
Nordian Medicare B 2006	Through 8/2006	Charité		▪ Lumbar ADR will not be covered for patients older than 60 years of age. For patients under 60 years of age, there is no national coverage policy, and local contractors will determine coverage.	▪ No clear conclusion can be drawn as to whether L-ADR is beneficial in patients younger than 60 years old. ▪ There is not enough evidence of benefit of L-ADR for patients over 60 years old. ▪ CPT codes covered for patients over 60 years of age if procedure performed under an approved IDE/clinical trial and/or approved by the contractor: 00091T, 00092T
Washington State Payers					
Premera Blue Cross (2008)	2000-2008	Charité Prodisc-L	▪ 2 RCTs (88% f/u reported for 1/2 reports, 24 months); N = 546 ▪ 3 case series (39% f/u reported for 1/3 reports, 12-104 months); N = 216	▪ Lumbar ADR is considered investigational.	▪ ADR is appropriate for some patients in which lumbar fusion is indicated, but not in patients who need additional procedures such as laminectomy or decompression. ▪ CPT category I codes for single-level ADR: 22857, 22862,

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available†‡	Policy	Rationale/Comments
					22865 ▪ CPT category III codes for multi-level ADR: 0163T, 0164T, 0165T
Regence (2008)	through 2008	Charité Prodisc-L	▪ 2 RCTs (% f/u NR, length of follow-up NR); N = NR	▪ Lumbar ADR is considered investigational	▪ No clear conclusions can be drawn from RCTs about long-term health outcomes, safety, and durability
Group Health Cooperative (2007)	through 2007	Charité	▪ 1 RCT (88% f/u, 24 months); N = 304 ▪ 1 cohort analysis (% f/u NR, 24 months or longer); N = 688	▪ Not covered	▪ There is insufficient evidence to demonstrate the safety or efficacy of lumbar ADR in comparison to current standard treatments ▪ Other plans, including Medicare, do not cover cervical ADR at this time ▪ Noted that the Group Health Permanente chief of neurosurgery recommended to wait until ADR has been shown to yield better results than spinal fusion before covering this procedure

ADR: artificial disc replacement.
DDD: degenerative disc disease.
NR: not reported.
*Formal critical appraisals were not reported in any of the payer HTAs. The CMS report does provide description as does the BCBS report.
†Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Mean time of follow-up is reported here.
‡N reflects numbers as reported in the assessment before loss to follow-up.

Table 6. Overview of payer assessments and policies for C-ADR

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Policy	Rationale/Comments
Centers for Medicare and Medicaid Services (CMS) (2007)	N/A N/A		▪ N/A	There is currently no National Coverage Determination.	
Aetna Clinical Policy Bulletin (2007)	2000-2007	Prestige SP	▪ 1 RCT (78% f/u, 24 months) ▪ N = 541 ▪ Monolevel arthroplasty only ▪ 1 RCT compared postoperative imaging quality before and after arthroplasty at the operated and adjacent levels and between implant types in 20 patients.	▪ FDA-approved prosthetic discs are considered medically necessary for adults with monolevel DDD (C3-C7) and who have failed at least six weeks of conservative treatment. ▪ Considered investigational for all other indications.	▪ No rationale for policy stated ▪ Policy is in accordance with FDA recommendations ▪ CPT codes if selection criteria are met: 0090T, +0092, 0093, +0095, 0096, +0098, +0163, +0164, +0165, 22857, 22862, 22865 ▪ Other CPT codes related to the CPB: 22533, 22558, 22612, 22630
BlueCross BlueShield Technology Evaluation Center Assessment (2007)	Through 8/2007	Prestige ST	▪ 1 RCT (46% f/u, 24 months) ▪ N = 541 ▪ Monolevel arthroplasty only	▪ Not recommended	▪ Cervical discs considered experimental ▪ Insufficient evidence from RCTs ▪ The 24-month follow-up period is insufficient to prove long-term safety and efficacy.
Cigna HealthCare Coverage Position (2007)	2002 through 2007	Prestige, Frenchay, Bryan	▪ 2 RCTs (71% f/u, 24 months) ▪ N =596 ▪ Monolevel arthroplasty only ▪ 6 case-series (48% f/u for 2/6 reports, 12–48 months) ▪ N = 617 ▪	▪ Not covered	▪ Insufficient evidence from RCTs ▪ There is a lack of long-term data to prove safety and efficacy.
Nordian –CMS Medicare B 2006	Through 8/2006	NR		▪ Cervical ADR is non-covered per the LCD for Artificial Disc ▪	

Payer (year)	Lit search dates	Disc(s) evaluated	Evidence Base Available*†	Policy	Rationale/Comments
Washington State Payers					
Premera Blue Cross (2008)	2007-2008	Prestige ST Bryan ProDisc-C	▪ 1 RCT (52% f/u, 24 months) ▪ N = 541	▪ Cervical ADR is considered investigational	▪ 24 months f/u is not adequate to evaluate long-term results, especially ASD, durability, safety, and revisability ▪ RCT was not blinded leading to potential bias ▪ CPT category III codes: 0090T, 0092T, 0093T, 0095T, 0096T, 0098T
Regence (2008)	through 2008	Prestige	▪ 2 RCTs (% f/u NR, 24 months) ▪ N = 55 for 1/2 studies	▪ Cervical ADR is considered investigational	▪ No clear conclusions can be drawn from RCTs about long-term health outcomes, safety, and durability ▪ There are significant design and analysis flaws in one RCT
Group Health Cooperative (2007)	through 2007	Prestige	▪ 1 RCT (83% f/u, 24 months) ▪ N = 541	▪ Not covered	▪ There is insufficient evidence to demonstrate the safety or efficacy of cervical ADR in comparison to current standard treatments ▪ Other plans, including Medicare, do not cover cervical ADR at this time ▪ Noted that the Group Health Permanente chief of neurosurgery recommended to wait until ADR has been shown to yield better results than spinal fusion before covering this procedure

ADR: artificial disc replacement.
DDD: degenerative disc disease.
NR: not reported.
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Mean time of follow-up is reported here.
† N reflects numbers as reported in the assessment before loss to follow-up.
Formal critical appraisals were not reported in any of the payer HTAs.

1.6 Other Significant Evidence

Lumbar

Two other L-ADRs are currently undergoing clinical trials: the Flexicore and the Activ-L.

The FlexiCore L-ADR is currently undergoing a prospective, randomized, controlled, multicenter investigational device exemption (IDE) study to compare its effectiveness versus standard circumferential fusion for the treatment of discogenic pain due to single-level degenerative disc disease (DDD). The cohort is made up of 401 patients randomized to FlexiCore group or fusion group with a 2:1 ratio. Inclusion criteria consist of skeletally mature patients between 18 and 60 years of age with DDD at a single level between L1 and S1. Confirmation of the diagnosis of DDD is made by MRI, CT myelography, or lateral flexion/extension films demonstrating either translational instability, angular instability, or disc height decreased by greater than 2 mm compared to adjacent disc height. Outcomes to be measured are the Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) to determine preoperative and postoperative function and pain level. To be included in the study, patients have to score at least 40 on a 0 to 100 point scale on both the ODI and VAS.

The Activ-L Artificial Disc is being investigated for the treatment of single-level degenerative disc disease of the lumbar spine that has been unresponsive to prior conservative treatment of at least six months duration. The design incorporates a center core intended to allow both translation and rotation and to more closely approximate physiological motion. The study is being conducted under an investigational device exemption (IDE) and is a prospective, randomized, single-masked, controlled, multicenter clinical trial consisting of an estimated 387 subjects. In the study, the Activ-L ADR is being compared with the Prodisc-L ADR and the Charité Artificial Disc. Between 15 and 20 investigational sites will participate in the investigation.

Cervical

The Bryan artificial disc is currently undergoing clinical trials both in the US as part of an FDA IDE, and in the Netherlands as part of the PROCON trial (referring to the pros and cons associated with each treatment). Initial results from an international trial of the Prestige II C-ADR were published in 2004, but no further peer-reviewed publications on this trial were found.[129]

The FDA Bryan C-ADR trial

A randomized controlled trial to evaluate the safety and effectiveness of the Bryan disc was initiated in May 2002.[6] Patients recruited for the trial were those with radiculopathy or myelopathy attributable to single-level cervical disc disease refractory to nonoperative interventions. Patients were randomized in a 1:1 ratio to single-level anterior cervical discectomy and fusion (ACDF) using bone graft and plate stabilization or single-level cervical arthroplasty with the Bryan cervical disc prosthesis. A total of 463 patients participated, 242 receiving the Bryan ADR and 221 receiving ACDF. The study was designed to demonstrate non-inferiority of the Bryan ADR compared with ACDF. The primary endpoint for the clinical investigation was "overall success", a composite variable that included the following:

1. An improvement of at least 15 points from the baseline Neck Disability Index (NDI) score;

2. Maintenance or improvement in neurological status;
3. No serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
4. No additional surgical procedure classified as "Failure."

Treatment success was based on the 24-month overall success rate being statistically non-infererior to the control group rate.
The secondary endpoints included:

Operative time	Blood loss	Hospital stay
Treatment levels	External orthosis	Overall neuro status
NDI score	Neck pain score	Arm pain score
SF-36 Health Survey	FSU height/implant subsidence	AP implant migration
Change in angular motion	Translation	Gait
Bending at target level	Fusion status Patien	t satisfaction
Angular motion at adjacent levels – below	Summary of radiographic success	Angular motion at adjacent levels – above

Two preliminary reports have reported on subsets of patients from this FDA trial. The first report published in 2006 included 33 patients (17 receiving Bryan ADR and 16 receiving ACDF) from one site.[43] Follow-up ranged from 13 to 25 months. The authors concluded that the Bryan disc treatment group showed similar improvements in clinical parameters compared with those in the fusion group.

The second report published in 2007 included the results from 115 patients enrolled at three centers.[142] At the 2-year follow-up, the investigators report reduced arm pain (14 versus 28, P = .014), reduced neck pain (16 versus 32, P = .005), better SF-36 physical component scores (51 versus 46, P = .009), and more motion retained at the index level (P = .006) for the Bryan ADR compared with ACDF. There were six additional operations in this report, two in the C-ADR group and four in the ACDF group. There were no intraoperative complications, no vascular or neurologic complications, no spontaneous fusions, and no device failures or explantations in the Bryan group. The authors concluded that the Bryan ADR compares favorably to anterior cervical discectomy and fusion for the treatment of patients with 1-level cervical disc disease.

The initial study protocol called for an interim analysis which has been done on the first 300 patients to complete 24 month follow-up (about 65% of the entire study population) and reported in an FDA Executive Summary from a July 12, 2007 Panel Meeting.[6] This Technology Assessment presents some results with and without data from the interim analysis.

The PROCON Bryan C-ADR trial
The PROCON multicenter trial is designed to accomplish three aims[18]:

- To conduct a multicenter, randomized controlled trial comparing the clinical outcome of three different surgical options: cervical anterior discectomy without fusion, cervical anterior discectomy and fusion using a cage and, finally, C-ADR using the Bryan's disc prosthesis
- To define differences in disc degeneration of the adjacent discs between the three surgical options

- To estimate the cost-effectiveness of the three surgical options
  The study population will include 18 to 55 year old patients with radiculopathy from single-level cervical disc disease. Patients with myelopathy will be excluded. Primary outcomes will include SF-36, McGill Pain score, the NDI, and the Work Limitations Questionnaire. Follow-up will last 60 months.

The Prestige II C-ADR trial
A multicenter RCT was published in 2004 involving four centers in the United Kingdom, Australia, Belgium and Switzerland.[129] The investigators enrolled 55 patients experiencing intractable radiculopathy or myelopathy caused by herniated disc or osteophyte formation; 27 were randomized to receive the Prestige II C-ADR and 28 to receive ACDF with iliac crest autograft. Only patients with single-level disease in C4-5, C5-6 or C6-7 were included. At the time the time of publication, only 67% and 16% of the patients had reached the one and two year follow-up, respectively. During the available follow-up, the C-ADR group experienced 17 adverse events. One patient had persistent pain and a subsequent fusion. One WHO Grade 3 adverse event was recorded which was considered unrelated to the surgery (pancreatitis). Two other permanent events (Grade 2) included continuous neck pain and continuous shoulder pain without evidence of neurocompression. The ACDF group had 19 adverse events, three directly related to the surgical procedure. Two WHO Grade 3 events were recorded; both involving secondary myelopathy requiring additional adjacent segment surgery. Three additional patients with continuous neck pain were considered permanently affected and required symptomatic treatment.

2. The Evidence

2.1 Systematic Literature Review

Objectives
The primary objective of the systematic literature review was to compare physical function/disability, pain, economic measures, complications, and adverse events in patients receiving artificial disc replacement versus other forms of treatment for lumbar degenerative disc disease without neurological compromise or cervical degenerative disc disease resulting in radiculopathy or myelopathy.

Secondary outcomes assessed include quality of life, return to previous activity or work, the rate of adjacent segment disease (ASD), and range of motion at the instrumented segment. Evidence of differential efficacy or safety issues among special populations was sought within the literature on test characteristics, supplemented with evidence obtained from review articles and expert guidance.

2.2 Methods

Inclusion/exclusion
- *Population.* Studies of adults who underwent primary L-ADR for DDD without neurological compromise and primary C-ADR for DDD resulting in cervical

radiculopathy or myelopathy and who had not had prior spine surgery at the instrumented level were included.

- *Intervention.* Included studies evaluated L-ADR and C-ADR using commercially available devices: FDA approved or unapproved devices in Phase III trials with ≥ 1 year of follow-up data in a peer-reviewed journal. Studies reporting on disc nucleus replacement were excluded.
- *Study design.* Eligible studies compared L-ADR and C-ADR with other treatments for lumbar and cervical DDD utilizing a randomized or cohort study design. In order to provide additional context regarding key questions 2 and 3, studies with historical/nonconcurrent controls and/or summaries of case series of greater than 10 patients were included. Formal economic analyses published in peer-reviewed journals were eligible for inclusion to help answer key question 4 as were cost data reported in other systematic reviews or technology assessments.
- *Outcomes*. Eligible studies reported on at least one of the following outcomes: physical function/disability (overall clinical success, ODI [L-ADR] or NDI [C-ADR]), pain, device failure (revision, reoperation, or removal), or complications.

Table 7 below summarizes the inclusion/exclusion criteria.

Table 7. Summary of inclusion and exclusion criteria for both L-ADR and C-ADR

Study Component	Inclusion	Exclusion
Population	• Patients undergoing primary L-ADR for DDD without neurological compromise and who have not had prior spine surgery at the instrumented level • Patients undergoing primary C-ADR for DDD resulting in radiculopathy or myelopathy and who have not had prior surgery at the instrumented level	• Patients with contraindications to receive L-ADR or C-ADR • ADR in the thoracic spine
Intervention	• L-ADR or C-ADR with commercially available device: FDA approved or unapproved devices in Phase III trials with ≥ 1 year of follow-up data in a peer-reviewed journal	• Disc nucleus replacement
Comparator	• Nonoperative treatment • Spinal fusion • Other spine surgery	
Outcomes	Studies must report on at least one of the following • Physical function/disability (overall clinical success, ODI [L-ADR] or NDI [C-ADR]) • Pain/pain reduction • Device failure (revision, reoperation or removal) • Complications (eg, migration, subsidence, neurologic injury as well as infection, vascular damage, others) The following secondary outcomes are reported if presented with studies meeting the above criteria: • Quality of life (SF-36) • Preservation of motion • Incidence of adjacent segment disease	

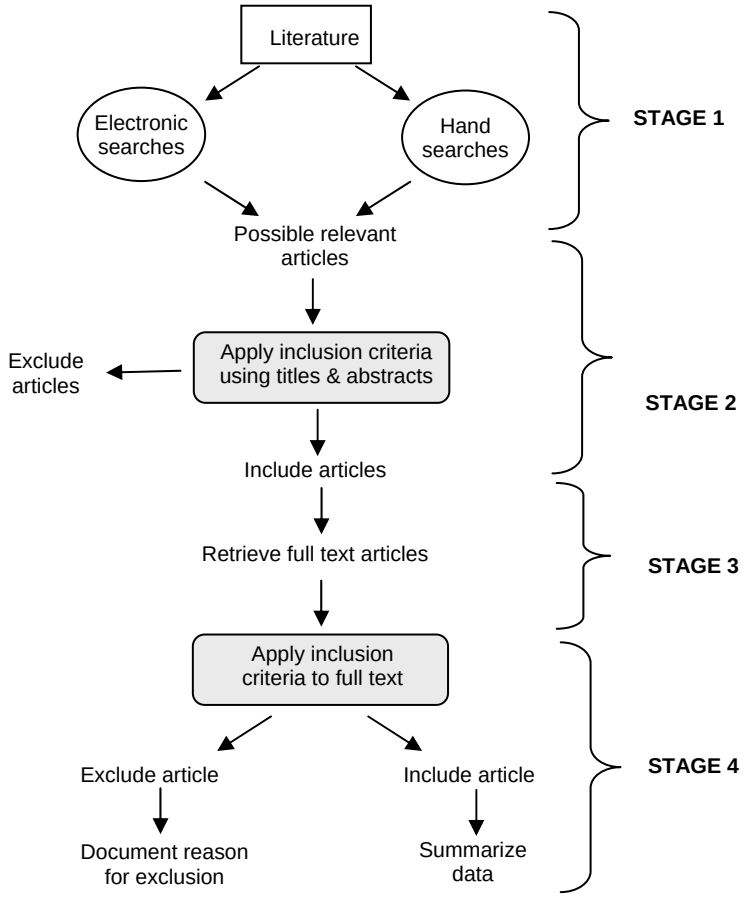
Study Component	Inclusion	Exclusion
Study Design	• Only randomized controlled trials (RCTs) and comparative studies with concurrent controls were considered for question 1. • RCTs and comparative studies with concurrent controls were sought initially for questions 2 and 3. • In order to provide additional context regarding questions 2 and 3, studies with historical/non-concurrent controls and/or summaries of case-series were obtained and very briefly summarized. • For question 4, formal economic analyses (eg, cost-utility study) were sought. • In the absence of formal economic analyses, cost data reported in other systematic reviews or technology assessments were briefly summarized.	• For question 1, studies other than RCTs or comparative studies with concurrent controls were excluded • Case reports • Case-series with fewer than 10 patients

Publication	• Studies published in English in peer reviewed journals
	• FDA reports
	  • L-ADR: Summary of Safety and Effectiveness Data (SSED), In-depth Statistical Review, In-depth Clinical Review
	  • C-ADR: Summary of Safety and Effectiveness Data (SSED), Executive Summary of FDA panel meeting
		• Abstracts, editorials, letters
		• Duplicate publications of the same study which do not report on different outcomes
		• Single site reports from multicenter trials
		• White papers
		• Narrative reviews
		• Articles identified as preliminary reports when results are published in later versions

Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Figure 1 below. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Figure 1. Algorithm for article selection



Electronic databases searched included PubMed, EMBASE, CINAHL, ClinicalTrials.gov, CRISP, HSTAT, *The Cochrane Library*, EconLIT, PsychINFO, MAUDE, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. Reference lists of all eligible studies were also searched. The search strategies used for PubMed and EMBASE, are shown in Appendix A. Figures 2 and 3 on the next two pages show a flow chart of the results of all searches for included primary studies for L-ADR and C-ADR, respectively. The searches went through May 9, 2008.

For L-ADR, in addition to two primary studies, searches identified one Cochrane systematic review[63] and 16 HTAs, six of which were done by insurance carriers. Two FDA Summary of Safety and Effectiveness Data (SSED) reports were obtained, one for the Charité and one for the Prodisc-L ADR. An additional FDA In-depth Statistical Review and an In-depth Clinical Review were also included for the Charité ADR. Two partial economic analyses were found in the peer-reviewed literature and included.

Searches for C-ADR identified three randomized controlled trials and nine HTAs. The technology assessments are listed in Tables 4 and 6. No systematic reviews were found. Two FDA Summary of Safety and Effectiveness Data (SSED) reports were obtained, one for the

Prestige ST and one for the Prodisc-C ADR. An additional FDA Panel Meeting Executive Summary was found for the Bryan C-ADR that included a pre-specified interim analysis of approximately two-thirds of the enrolled patients with 24 month follow-up. No economic analyses were found in the peer-reviewed literature.

Figure 2. Flow chart showing results of literature search for L-ADR

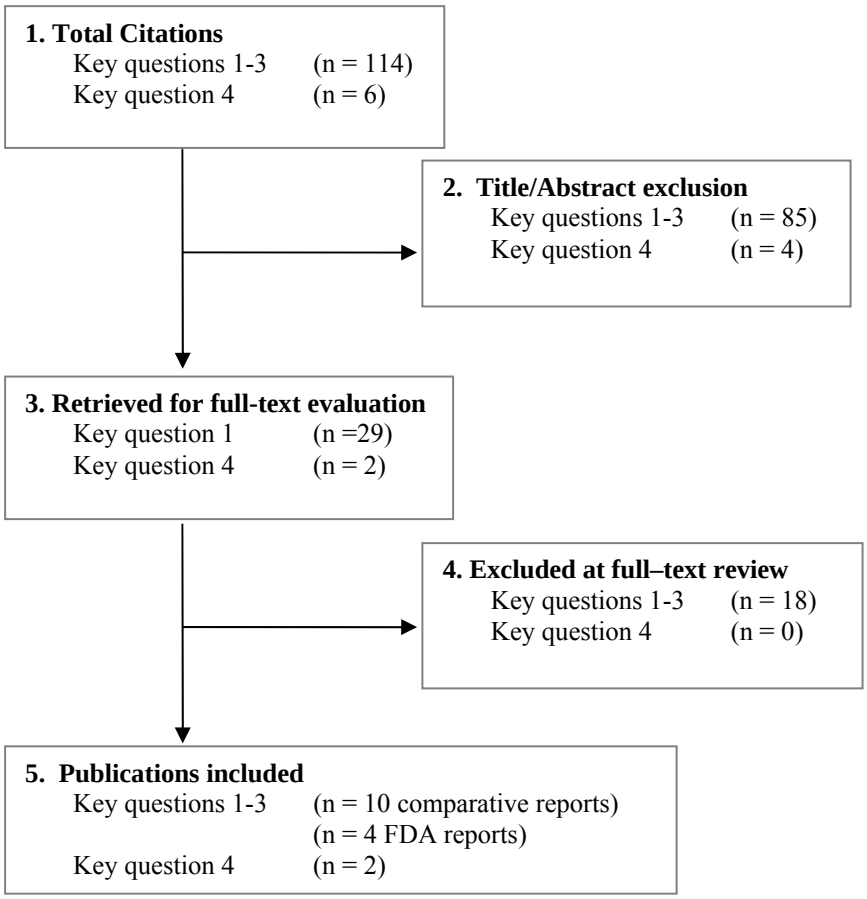
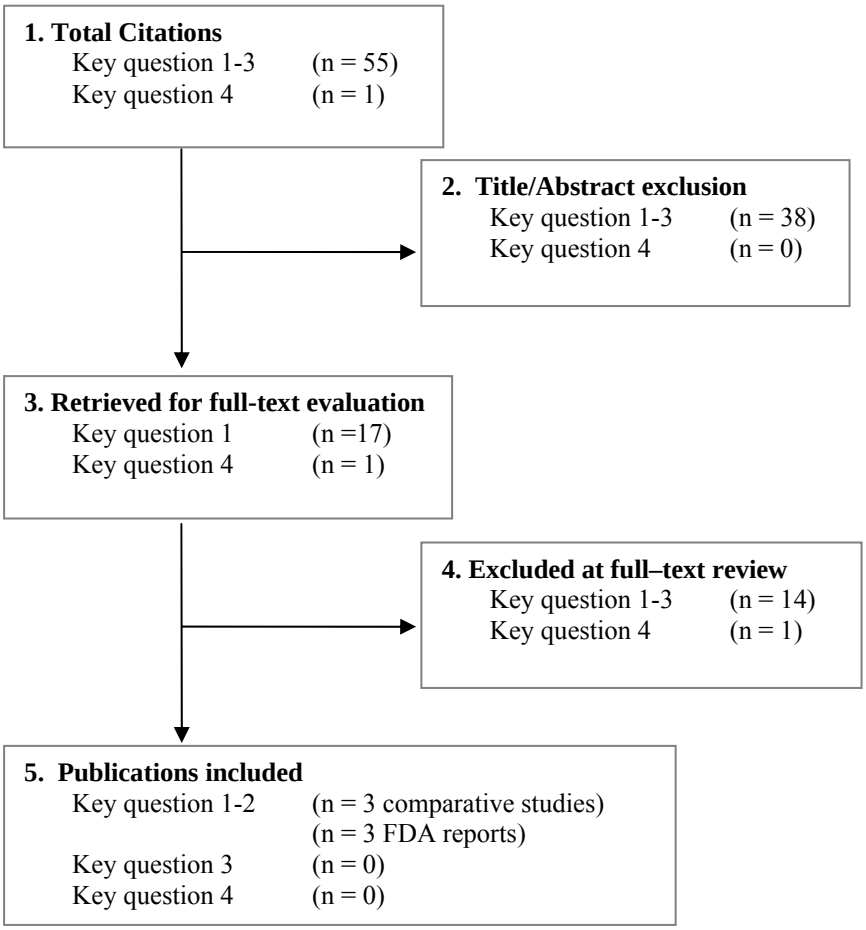


Figure 3. Flow chart showing results of literature search for C-ADR



Data extraction

Reviewers extracted the following data from the included clinical studies: study population characteristics, study type, study eligibility/exclusion criteria, study interventions, study outcomes, follow-up time, complications, and adverse events. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. When this occurred between the FDA reports and the published peer-reviewed reports, the FDA data were used since patient accounting tended to be more complete.. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

Data were abstracted from the July, 2007 FDA Panel Meeting Executive Summary regarding the Bryan cervical disc (P060023). An approval order had not been posted as of May 20, 2008 for this device. The Executive Summary provides an overview of the indications, safety and efficacy data provided by Medtronic Sofamor Danek regarding the PMA for this device. This report describes a 24 month, multicenter, prospective randomized controlled trial sponsored by Medtronic to compare the Bryan cervical disc with standard anterior fusion using a non-inferiority study design. A total of 242 patients with cervical degenerative disc disease received C-ADR and 221 received fusion between May 28, 2002 and October 8, 2008. The summary and data are based on interim data

available at the time of the report and do not represent all enrolled patients through the end of the study. The results and conclusions in the PMA are based on a pre-specified interim analysis of 300 patients with 24 month follow-up. In particular, it appears that 82 C-ADR patients and 81 ACDF controls had not yet reached 24 month follow-up. Thus, approximately 2/3 of patients receiving treatment were represented in the interim analysis. Information on loss to follow-up is not explicitly stated.

Since any given individual patient's procedure may be deemed an "overall success" at 12 months, but a failure at 24 months or alternatively a failure at 12 months but a success a 24 months, the Spectrum Research team chose to report only the outcomes at 24 months. Abstracted data are based on the presentation of the "primary analysis dataset". According to the Bryan Panel Executive Summary, intention to treat (ITT) analyses were not presented initially but were provided in a PMA amendment (not available) and considered to be "qualitatively similar" to the results obtained based on analysis of the primary dataset as presented in their Executive Summary, table 16. The data on "overall success" below are based on this table and on data in tables 14 and 15 of the Bryan Panel Executive Summary.

Table 8. Data from FDA Panel Meeting[6] on Bryan C-ADR used for Spectrum Research analysis

	ADR	ACDF
n at 24 month based on interim report	160	140
n with "overall success" at 24 months based on interim report	129 (80.6%)	99 (70.7%)
Neurological improvement – number of successes	150 (93.7%)	128 (91.4%)
Neurological improvement – number of failures	10 (6.3%)	12 (8.6%)
NDI score success – number of successes	134 (83.7%)	106 (75.7%)
n not yet observed at 24 months	82 (33.9%)	81 (36.7%)
Total N receiving treatment	242	221

Study quality assessment: Level of evidence (LoE) evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine[123], precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[16], recommendations made by the Agency for Healthcare Research and Quality (AHRQ)[160], and the system used by the *Journal of Bone and Joint Surgery*.[163]

Details of the level of evidence (LoE) methodology are found in Appendix B. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Table 9 below for therapeutic studies. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.

Table 9. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Cointerventions applied equally • F/U rate of 85% + • Adequate sample size • Intent-to-treat
II	Moderate or poor quality RCT	• Violation of one or more of the criteria for a good quality RCT
	Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Cointerventions applied equal • F/U rate of 85% + • Adequate sample size • Controlling for possible confounding†
III	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	
IV	Case-series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those potential prognostic variables that are unequally distributed between treatment groups.

There is no universally accepted, standardized approach to critical appraisal of economic evaluation studies. The criteria described in the Quality of Health Economic Studies (QHES) tool[119] provided a basis for the critical appraisal of included economic studies and was augmented with the application of epidemiologic appraisal precepts (see Appendix B). The QHES employs widely accepted criteria for appraisal, such as choice and quality of cost and outcomes measures, transparency of model and presentation, use of incremental analysis, uncertainty analysis, and discussion of limitations and funding source and was primarily used to facilitate description of primary strengths and limitations of the studies. A weighted global score can be obtained based on these measures with a possible range of scores from 0 (worst) to 100 (best), theoretically providing a common metric to compare study quality. This tool and the weighted score have not yet undergone extensive evaluation for broad use but provide a valuable starting point for critique.

Two individuals critically appraised each study independently using the QHES. Discrepancies were resolved by discussion to arrive at a final appraisal. In addition, elements of critical appraisal consistent with epidemiologic principles and evaluation of bias (e.g., selection bias) were applied.

Data analysis

Meta-analysis was conducted on the primary outcomes when data from two or more RCTs were available and when there were no clinical or statistical heterogeneity. A random effects model was used following the DerSimonian and Laird method for pooling which accounts for

heterogeneity among studies, if it is present. Dichotomous data were reported using risk difference (RD). Associated 95% confidence intervals are reported for all estimates unless otherwise noted. The data analysis was performed using the procedure "metan", within the software STATA 10. The procedure also generates the Cochran's Q statistic to test heterogeneity of the studies, from which the I^2 statistics was derived.[77,78]

Two analytic perspectives on the meta-analysis for effectiveness are presented: intent-to-treat (ITT) analysis and completer-only analysis. ITT analysis includes all randomized patients in the groups to which they were randomized without regard to the actual treatment received or to whether they withdrew from treatment. The completer-only analysis considers only those patients who completed the study up until the last follow-up. The ITT is conservative for a superiority study. However, in a non-inferiority trial, ITT tends to make the treatments appear more similar in effect than they are, when subjects receive the unintended treatment or are otherwise noncompliant. This could result in a truly inferior treatment appearing to be non-inferior.

In contrast, a completer-only analysis excludes data from patients who violate protocol or fail to follow-up. Excluding these data can bias the results in either direction. Therefore, non-inferiority studies are often analyzed using both ITT and completer-only analyses, and an intervention is considered non-inferior only if both approaches support non-inferiority. Therefore, both types of analyses were done.[152]

A non-inferiority clinical trial design is often used in FDA trials to show that a new treatment is no worse than a reference treatment. In order to accomplish this, a pre-stated margin of non-inferiority is defined for the treatment effect of a primary outcome. The new treatment will be recommended if it is similar to or better than the existing one, but not if it is worse by more than the pre-stated margin. It is acceptable to assess whether the new treatment is superior to the reference treatment using the appropriate statistical test.[124,152,168] Therefore, results of the meta-analysis for the primary outcome of clinical success were interpreted using the following steps (see Appendix D for flow sheet):

1. The results were evaluated for superiority; was the ADR superior to the comparator treatment in both the ITT and completer-only analyses?
2. If so, what effect do the missing data have on the results (sensitivity analysis)?
3. If not, check for non-inferiority; was the L-ADR non-inferior to comparator treatment in both the ITT and completer-only analyses using a-10% non-inferiority boundary as per the FDA analyses of the Blumenthal et al[28] study? Was the C-ADR non-inferior to the cervical fusion in both the ITT and completer-only analyses using a -10% non-inferiority boundary as per the FDA request for the Prestige ST and Prodisc-C studies?
4. If non-inferiority is supported, what effect does missing data have on the results (sensitivity analysis)? Does sensitivity analysis support non-inferiority using -12.5%* non-inferiority boundary?

* Blumenthal et al and Zigler et al set non-inferiority boundaries at -15% and -12.5%, respectively. The FDA required a -10% non-inferiority boundary for their analysis. The FDA -10% was used in this technology assessment based on the ITT and completer-only analysis. However, the FDA's lead was followed when it came to assessing the effect of missing data by using the non-inferiority boundary of the sponsor. In the In-depth Statistical Review of the Blumenthal et al paper, the FDA used -15%. For this review, the more conservative -12.5% established by Zigler et al was used.

The remaining outcome measures were interpreted for superiority. Ranges of means or proportions are given to summarize secondary outcomes.

2.3 Quality of literature available

Quality of studies retained, lumbar

The literature search resulted in 114 citations using the search strategy in Appendix A. There were 10 comparative reports (7 RCT reports, 3 cohort studies) and one systematic review.[63] From among these, two index RCTs were identified: one evaluating the Charité L-ADR[28] and one the Prodisc-L ADR.[171] One preliminary study was found that reported on partial data from two sites of a multicenter RCT assessing the FlexiCore L-ADR.[141] Four FDA reports were located in the grey literature: three reporting on the Charité L-ADR (one Summary of Safety and Effectiveness Data (SSED)[3], one In-depth Statistical Review[2], one Clinical Review[1]) and one SSED reporting on the Prodisc-L. All compared L-ADR with lumbar fusion. No studies were found comparing L-ADR with any other treatment. Studies retained for analysis are listed in Table 10 below.

For the Charité ADR, the index study and six companion reports[44,61,67,109,110,156] along with the three FDA reports were retained and are included. Three of the six companion studies reported on complications[61,110,156] and two on secondary outcomes.[44,109] These five studies are graded as level of evidence (LoE) II. One companion study on a subset of patients collected in the index study was a prognostic study evaluating the outcome of L-ADR in different age groups.[67] This study was graded as LoE III.

For the Prodisc-LADR, one FDA SSED and four published reports are included: the index study (LoE II), two cohort studies,[21,22,150] and a costing study.[68] The cohort studies evaluated outcome of L-ADR on subpopulations and all graded as LoE III.

For the FlexiCore L-ADR, the only publication found reported limited data from two sites of a multicenter study with only 27% of patients available for the 24 month follow-up.[141] This study was excluded from analysis in this technology assessment. Description of this ongoing study can be found in section 1.6 above.

In addition, 25 case series (LoE IV) were included to help address short and long term complication rates and secondary outcomes.

Two economic analyses, one related to Charité ADR[68] and another related to the Prodisc-L[99] were identified in the peer-reviewed literature and critically appraised. The Levin report is based on data from one of 19 centers participating in the randomized FDA study of Prodisc-L. It is unclear whether the Guyer study is linked to the FDA trial of the Charité device.

Table 10. Comparative clinical studies retained to answer key questions for L-ADR

Disc	Author	Study Type	Key Questions Addressed	Level of Evidence
Charité	**Blumenthal (2005)**	**RCT (index study)**	1 and 2	II
	FDA (2004)	SSED	1 and 2	--
	FDA (2004)	In-depth Statistical Review	1 and 2	--
	FDA (2004)	Clinical Review	1 and 2	--
	Geisler (2004)	RCT (companion study to Blumenthal)	2	II
	McAfee (2005)	RCT (companion study to Blumenthal)	1	II
	McAfee (2006)	RCT (companion study to Blumenthal)	2	II
	Tortalani (2007)	RCT (companion study to Blumenthal)	2	II
	Cunningham (2008)	RCT (companion study to Blumenthal)	1	II
	Guyer (2008)	Cohort* (companion study to Blumenthal)	3	III
	Guyer (2007)	Costing study	4	n/a†
Prodisc-L	**Zigler (2007)**	**RCT (index study)**	1 and 2	II
FDA	(2006)	SSED		--
	Bertognoli (2006)	Cohort*	3	III
Seipe	(2007)	Cohort	3	III
	Levin (2007)	Costing study	4	n/a†

SSED = Summary of Safety and Effectiveness Data.
*Study design is determined relative to the exposure being compared. For example, Bertognoli et al compared outcomes between smokers and non-smokers in those who received L-ADR only. In this case, the exposure is smoking status. As a result, the study, while part of the index RCT comparing L-ADR with fusion, is considered a cohort study for the purposes of comparing the effect of smoking status on outcomes in the L-ADR group only.
†Criteria for economic analysis critical appraisal do not provide a level of evidence rating.

Study quality assessment, lumbar

The two index trials (Blumenthal for the Charité and Zigler for the Prodisc-L) were each conducted as a randomized, multicenter, FDA regulated Investigational Device Exemption, non-inferiority clinical trial. A summary of the methodological quality for these two studies are reported in Table 12.

Table 11. Methodological quality of RCTs comparing L-ADR with lumbar fusion

Methodological principle	Blumenthal	Zigler
Study design Randomized controlled trial Cohort study Case-series	✓	✓
Statement of concealed allocation	✓	
Intention to treat		✓
Independent or blind assessment		
Cointerventions applied equally	✓	✓
Complete follow-up of ≥ 85%		✓
Adequate sample size	✓	✓
Controlling for possible confounding		✓
Evidence class	**II**	**II**

Critical appraisal of study methods, Charité ADR

The essential data from the 14-site multicenter FDA trial on the Charité L-ADR was published in 2005.[28] A number of methodological flaws in this study led to its classification as a moderate randomized clinical trial (LoE II). Baseline characteristics between the L-ADR and control groups were different with respect to a few potentially important variables. Compared with the L-ADR group, the control group tended to weigh more (82 kg versus 78 kg) and have lower activity level at enrollment (6% versus 17% moderate or active) suggesting that the control group may have been slightly worse than the L-ADR group prior to treatment.

The accounting of patients through the completion of the study was reported differently among the three FDA reports and the Blumenthal publication. Using the Blumenthal publication, the two-year follow-up rate was reported at 91.5% (161/176) for the L-ADR group and 89.2% (66/74) for the control group. However, the denominators for these proportions did not include deaths, failures, or early discontinuation. When all patients randomized to a treatment are considered, follow-up rates are lower, 161/205 (78.5%) for the L-ADR group and 66/99 (66.7%) for the control group. In order to determine the effect of those not available for follow-up, an intent-to-treat (ITT) analysis was reported. However, the investigators excluded from the analysis those who had not yet reached or were overdue for their 24-month visit. Excluding such randomized patients from the analysis could lead to strong bias in either direction (either in favor of or against the technology). The ITT population should consist of all patients who were randomly allocated to receive treatment.

Blinding of treatment providers and study subjects can be difficult in surgical interventions. The investigators acknowledged that blinding was not carried out in this trial for providers, patients, or assessors. Bias arising from the lack of blinding is possible.

Critical appraisal of study methods, Prodisc-L

The essential data from the17-site multicenter FDA trial on the Prodisc-L ADR were published in 2007.[171] In this study, like many surgery studies, the patient was not blinded to the treatment. Radiographic assessments were completed by an independent evaluator. There was no mention as to who completed the physical and neurological exams at follow-up or whether these evaluators were blinded to the treatment received. Investigators compared demographic characteristics between groups by way of statistical testing and found no significant differences.

The accounting of patients through the completion of the study was reported differently between the FDA report and the Zigler et al publication. The FDA report identifies 183 L-ADR and 93 control patients “enrolled”, but only 162 L-ADR and 80 control patients treated. It is not clear if all enrolled patients received random assignment or not. The two-year follow-up rate was reported at 91.0% (142/156) for the L-ADR group and 89% (69/78) for the control group. Using all enrolled and treated patients, the more accurate follow-up rates for L-ADR and control groups are 88% (142/161) and 86% (69/80), respectively.

Quality of studies retained, cervical

Data from randomized controlled trials (RCTs) published in peer review journals and those available from publicly available FDA reports were used to answer questions 1 and 2. No studies addressing questions 3 and 4 were found.

The literature search resulted in 55 citations using the search strategy in Appendix A. A total of three RCT reports and three FDA reports were used in this technology assessment. For the Prestige ST C-ADR, there was one full report of the FDA randomized controlled trial published in the peer-reviewed literature[115] and its associated FDA Summary and Safety of Efficacy Data (SSED) report (P060018).[4] For the Prodisc-C, no full published reports of an RCT were found other than the FDA SSED report (P070001).[5] A summary of the July, 2007 FDA Panel Meeting Executive Summary regarding the Bryan cervical disc (P060023)[6] was located, as was one RCT evaluating the Bryan C-ADR that was not associated with the Bryan FDA trial.[121] It should be noted that the Bryan summary and data are based on interim data available at the time of the report and do not represent all enrolled patients through the end of the study. The results and conclusions in the PMA report presented in the executive summary are based on a pre-specified interim analysis of 300 patients with 24 month follow-up. In particular, it appears that 82 C-ADR patients and 81 ACDF controls had not yet reached 24 month follow-up. Thus, approximately 2/3 of patients receiving treatment were represented in the interim analysis. Information on loss to follow-up is not explicitly stated. Additional study information from this report is found in Appendix G.

In addition, 22 case-series (LoE IV) were included to help address short and long term complication rates and secondary outcomes.

Table 12. Comparative studies retained to answer key questions for C-ADR

Disc	Author	Study Type	Key Questions Addressed	Level of Evidence
Prestige ST	Mummaneni (2007)	RCT (index study)	1 and 2	II
	FDA (2007)	SSED	1 and 2	II
Prodisc-C	FDA (2007)	SSED	1 and 2	II
	Nabhan (2007)	RCT	1 and 2	*
Bryan	FDA (2007)	FDA panel summary	1 and 2	II
	Feng-Pei (2008)	RCT	1 and 2	*

SSED = Summary of Safety and Effectiveness Data
*There is not enough information in the methods section of this paper to warrant an evidence rating

Study quality assessment, cervical

The three primary clinical trials were conducted as a randomized, multicenter, FDA regulated Investigational Device Exemption (IDE), non-inferiority clinical trials. Full data from one of the trials reporting on the Prestige ST ADR has been published in the peer review literature.[115] Since only partial methods are given in the FDA SSED, no critical appraisal of those reports is undertaken. The level of evidence for randomized controlled trials in general may be level of evidence I or II depending on how well the investigators limited bias on key principles. Given that the SSEDs report on randomized controlled trials, a LoE of I or II would be considered, however since information on such methodological principles is not completely available in these reports, the more conservative level of evidence for the SSEDs is used without formal critical appraisal. Two additional studies not associated with the FDA trial were found. One

was conducted by Peng-Fei et al[121] on a small sample size using the Bryan C-ADR and the second by Nabhan used the Prodisc-C also in a small number of patients.[118] There was not enough information in the methods section of the Peng-Fei or the Nabhan articles to warrant a level of evidence rating. A summary of the methodological quality for the one published FDA trial is reported in Table 13.

Table 13. Methodological quality of studies comparing single-level C-ADR with anterior cervical discectomy and fusion

Methodological principle	Mummaneni
Study design Randomized controlled trial Cohort study Case-series	✓
Statement of concealed allocation	✓
Intention to treat	✓
Independent or blind assessment	*
Complete follow-up of ≥ 85%	†
Adequate sample size	✓
Controlling for possible confounding	✓
Evidence Level	**II**

Blank space indicates criterion is either not present or not reported by authors
*Independent radiologist used for radiographic assessment. However, no blinding for other outcomes
†Criteria met for twelve month follow-up but not 24 month.

Critical appraisal of study methods, Mummaneni et al (Prestige ST)

Data from a 32-site FDA trial conducted within the US on the Prestige ST ADR was published in 2007.[115] This trial compared the Prestige ST C-ADR (n = 276) with interbody fusion (n = 265) via cortical ring allograft spacers and an Atlantis Cervical Plate System (Medtronic Sofamor Danek) using a non-inferiority design with a non-inferiority margin of 10%. Efficacy/effectiveness was determined by the primary endpoint of overall success, defined as achieving all the following criteria: NDI increase from pre- to postoperative score of ≥15 points, maintenance or improvement in neurological status, no serious implant-associated or implantation procedure-associated adverse event or have undergone a second surgery classified as a failure. Safety was determined by assessing adverse events, complications and secondary surgeries defined as revisions, hardware removals, supplemental fixations, or reoperations. An interim analysis was performed on the first 250 patients in whom there were overall success data 24 months postoperatively.

Random assignment was described as occurring after informed consent by giving a sequential computer generated clinical trial number to the patient. What is not clear in the description of the study is whether any patient after receiving the treatment assignment withdrew from the study. It appears that allocation concealment from the surgeon prior to enrollment was sufficient. Patient characteristics between groups were similar, though the fusion group tended to be slightly less educated, to use alcohol more and to have a slightly less proportion of patients who worked preoperatively. A multivariate analysis that included these small baseline differences had no effect on the results.

One significant shortcoming of this study with respect to methodology is the low follow-up, 80% in the C-ADR group and 75% in the fusion group. This follow-up rate is due in part to the fact that not all patients enrolled had reached their 24-month follow-up at the time the analysis was performed. The authors attempt to assess the impact of the missing data by doing a sensitivity analysis; however, they perform this analysis on 12-month follow-up rather than the 24-month follow-up.

Blinding in a surgical study remains difficult to carry out. In most instances, patients cannot or should not be blinded to the surgical intervention they receive. Whenever possible, those who assess outcomes should be blinded. In this study, neurological exam was conducted as part of the overall success and safety of the intervention, and the examiner could and should have been blinded to the treatment. There is no recording of who performed the exam and whether that person was blind to the treatment. Radiographic evaluation was done by independent radiologists; a good alternative since radiographs reveals the treatment given.

Given the high rate of missing values and the lack of blinding in the evaluation of the patients, this study was determined to be level of evidence II.

Critical appraisal of study methods, Peng-Fei et al (Bryan C-ADR)
Twenty four patients with disc herniation at C5-6 were randomly assigned to receive the Bryan C-ADR or interbody fusion. The average follow-up time was 17 months (range, 10 to 35 months). Percent follow-up was not given. Outcome was assessed using the Japanese Orthopaedic Association (JOA) cervical scale, adjacent segment motion and complications.

This small study has many methodological flaws which makes it difficult to interpret. First, the main effectiveness outcome used by the investigators is the JOA. The JOA is primarily a clinician-based assessment of neurological status in four areas: (1) the ability to feed oneself using utensils (motor function of the arm); (2) the ability to walk (motor function of the legs); (3) sensation of arms, trunk and legs; (4) bladder function. Potentially important outcomes for patients were not assessed with this instrument such as pain, disability, leisure activity and sleeping. The trial is portrayed as a randomized controlled trial, but the method of allocation is unclear. The authors describe the patients as being "divided into two groups", but do not explain how. The length of follow-up was not fixed; the patients' results were recorded from as early as 10 months postoperatively and as late as 35 months postoperatively. Since outcomes are, in part, time-dependent, comparisons may be confounded by length of follow-up.

Critical appraisal of study methods, Nabhan, et al (Prodisc-C)
Forty-nine patients were randomly assigned to receive either C-ADR using the Prodisc C (Synthes) or ACDF using a Solis cage (Stryker Howmedica GmbH) with titan anchoring spikes. The authors report that 25 received C-ADR and 24 had ACDF. Measures for 3, 6, 12, 24 and 52 weeks post-surgery were recorded. The focus was on roentgen stereometric analysis (RSA) of segmental motion in the medial-lateral (x) axis, proximal-distal (distraction-compression, y) axis and the anterior-posterior (sagittal, z) axis. With the exception of the three week y –axis measure, mean values for segmental motion were

significantly better for C-ADR compared with ACDF (P = .0083). The only clinical outcomes reported were arm and neck pain assessed using a VAS. Although both treatment groups experienced reduction in pain, there was no statistically significant difference in pain reduction between groups. It is possible that the sample size was too small to detect a difference between groups on this outcome.

Methodological details related to study execution; follow-up, analysis and other factors which may lead to potential bias are not well-reported. Some of these areas are described below.

Although the authors report that randomization was carried out by drawing cards in sealed envelopes, there is potential for bias if these were not opaque. While randomization generally results in even distribution of confounding factors (e.g. age, smoking status), no information on the distribution of such factors was given for the treatment groups. The authors do not state that an intention-to-treat analysis was performed or whether any cross-over between treatments occurred, although they do state that 25 patients received C-ADR and 24 had ADCF.

It is not clear whether the RSA examination/positioning and interpretation, or determination of VAS for pain, were done by persons who were blinded with regard to treatment status. Because of the report's focus on RSA, eight patients were excluded from the analysis since RSA measurements were compromised by implants and bony structures. These exclusions combined with one death, lowered the follow-up rate to 82% by 12 months.

2.4 Description of study population

Lumbar

Both studies included patients with single-level symptomatic degenerative lumbar disc disease without neurological compromise who failed conservative treatment of at least six months duration. The inclusion and exclusion criteria are listed for each study in Appendix C. Operative and demographic data are presented in Table 14 below.

Study population, Charité ADR

The average age of study participants in the Blumenthal et al study[28] was 40 years, range 19 to 60 years. Fifty two percent were males. One third of the participants had previous spinal surgery, and 87% reported their pre-enrollment activity level as minimal to light. Thirty percent of the procedures were carried out at L4-L5 disc space and 70% at L5-S1 disc space. The control and L-ADR groups were similar in most baseline characteristics. The control group compared to the L-ADR group tended to have fewer males (44% versus 55%), to be slightly heavier (82 kg versus 78 kg), and to be less active at time of enrollment (6% versus 17% reporting moderate to active activity level).

Study population, Prodisc-L

In the Zigler et al study[171], the average age of study participants was 40 ± 8 years, and included equal proportion of males and females. One third of the participants had

previous spinal surgery, and 94% reported their pre-enrollment activity level as none to light. Three percent of the procedures were carried out at L3-L4 disc space, 33% at L4-L5 disc space and 64% at L5-S1 disc space. The control and L-ADR groups were similar in most baseline characteristics. The control group compared to the L-ADR group tended to have fewer males (46% versus 51%), to have slightly fewer prior spinal surgeries (31% versus 35%), and to have more current smokers (30% versus 21%).

Table 14. Operative and demographic data for the two index randomized controlled trials for L-ADR

Variable Ch	Blumenthal et al		Zigler et al	
	arité (n = 205)	Fusion (n = 99)	Prodisc -L (n = 161)	Fusion (n =75)
Implant level				
No. L3–L4 (%)	0	0	3 (2)	3 (4)
No. L4–L5 (%)	61 (30)	32 (32)	254 (34)	22 (29)
No. L5–S1 (%)	144 (70)	67 (68)	104 (65)	50 (67)
Operative time, min; mean (SD)	110.8 (47.7)	114 (67.9)	121 (59.2)	229 (75.9)
Blood loss, ml; mean (SD)	205 (211.7)	208.9 (283.9)	204 (231.3)	465 (440.0)
Length of hospital stay, day	3.7 (1.2)	4.2 (2.0)	3.5 (1.3)	4.4 (1.5)
Patient demographics				
Gender				
No. males (%)	113 (55.1)	44 (44.4)	82 (51)	34 (45)
No. females (%)	92 (44.9)	55 (55.6)	79 (49)	41 (55)
Age, years mean (SD)	39.6 (8.16) 39	.6 (9.07)	38.7 (8.0)	40.4 (8)
Race				
No. Caucasians (%)	188 (91.7)	87 (87.9)	133 (82.6)	59 (78.7)
No. African-Americans (%)	8 (3.9)	5 (5)	5 (3.1)	5 (6.7)
No. others (%)	9 (4.4)	7 (7.1)	13 (14.3)	11 (14.6)
Body mass index, kg/m2; mean (SD)	26 (4.23)	27 (4.76)	26.7 (4.2)	27.3 (4.3)
Smoking status				
No. never (%)	not recorded	not recorded	87 (54)	34 (45)
No. former (%)	not recorded	not recorded	40 (25)	17 (23)
No. current (%)	not recorded	not recorded	34 (21)	24 (32)
Prior surgical treatment				
Yes	70 (34)	33 (33)	57 (35)	23 (31)
No	135 (66)	66 (67)	104 (65)	52 (69)
Preoperative activity level				
Minimal to none	116 (56.6)	66 (66.7)	94 (58.0)	38 (50.0)
Light	54 (26.3)	27 (27.3)	59 (36.4)	33 (43.8)
Moderate, active, or sport	35 (17.1)	6 (6.0)	9 (5.6)	5 (6.2)

Cervical

The three studies included patients with single-level symptomatic degenerative lumbar disc disease without neurological compromise who failed conservative treatment of at least six weeks duration. The inclusion and exclusion criteria are listed for each study in Appendix C. Operative and demographic data are presented in Table 15 below.

Study population, Prestige ST

The average age of study participants in the Mummaneni et al study was 43 ± 8 years. Forty-six percent were males. Less than 1% had previous neck spinal surgery. Fifty-four percent of the procedures were carried out at C5-C6 disc space and 38% at C6-C7 disc space. The control and C-ADR groups had similar baseline characteristics.

Study population, Prodisc-C

In the Prodisc-C FDA report, the average age of study participants was 43 ± 8 years and included 45% males. Patients with prior neck surgery at the treatment level were excluded from the study. Fifty-seven percent of the procedures were carried out at C5-C6 disc space and 33% at C6-C7 disc space. The two groups were similar in most baseline characteristics. The control group compared to the C-ADR group was slightly heavier (180 lbs versus 171 lbs).

Study population, Bryan

The Bryan Panel study reported an average age of 44 years for study participants, range 25 to 78 years. Forty-eight percent of the patients were male. Fifty-four percent of the procedures were carried out at C5-C6 disc space and 39% at C6-C7 disc space. Baseline characteristics showed a few minor differences between the study groups. The control group had more males (51%) than the C-ADR group (45%). The mean weight of the control group was heavier than the C-ADR group (180 lbs versus 173 lbs).

Table 15. Operative and demographic data for the three FDA randomized controlled trials for C-ADR

	Mummaneni		Prodisc-C FDA SSED		Bryan FDA interim analysis*	
Variable	Prestige ST (n = 276)	Fusion (n = 265)	Prodisc-C (n = 103)	Fusion (n = 106)	Bryan (n = 242)	Fusion (n = 221)
Implant level						
No. C3–C4 (%)	7 (2.5)	10 (3.8)	3 (2.9)	1 (0.9)	3 (1.2)	0 (0)
No. C4–C5 (%)	14 (5.1)	15 (5.7)	10 (9.7)	6 (5.7)	12 (5.0)	17 (7.7)
No. C5–C6 (%)	142 (51.4)	149 (56.2)	58 (56.3)	61 (57.5)	140 (57.9)	110 (49.8)
No. C6-C7 (%)	113 (40.9)	91 (34.3)	32 (31.1)	38 (35.8)	87 (36.0)	94 (42.5)
Operative time; mean	1.6 hrs	1.4 hrs	107.2 min	98.7 min	2.2 hrs	1.4 hrs
Blood loss, ml; mean	60.1	57.5	83.5	63.5	91.5	59.6
Length of hospital stay, day	1.1	1.0	1.4	1.3	1.1	1.0
Patient demographics						
Gender						
No. males (%)	(46.4)	(46.0)	46 (44.7)	49 (46.2)	110 (45.4)	113 (51.1)
No. females (%)	(53.6)	(54.0)	57 (55.3)	57 (53.8)	132 (54.5)	108 (48.9)
Age, years; mean (SD)	43.3 (7.6)	43.9 (8.8)	42.1 (8.42)	43.5 (7.15)	44.4 (25.0-78.0)	44.7 (27.0-68.0)
Race						
No. Caucasians (%)	260 (94.2)	243 (91.7)	88 (85.4)	97 (91.5)	NR	NR
No. African-Americans (%)	6 (2.2)	13 (4.9)	4 (3.9)	1 (0.9)	NR	NR
No. others (%)	10 (3.6)	9 (3.4)	11 (10.7)	8 (7.5)	NR	NR
Body mass index, kg/m2; mean (SD)	NR	NR	26.4 (5.3)	27.3 (5.5)	NR	NR
Weight, lbs; mean (SD or range)	181.7 (39.7)	184.7 (41.5)	171 (42)	180 (47)	173 (108-312)	180 (100-285)
Smoking status						
No. never (%)	NR	NR	51 (50)	49 (46)	NR	NR
No. former (%)	NR	NR	18 (18)	20 (19)	NR	NR
No. current (%)	(34.4)†	(34.7)†	34 (33)	37 (35)	61 (25.5)†	53 (24.0)†
Prior surgical treatment						
Yes	1 (0.4)	2 (0.8)	NR	NR	NR	NR
No	275 (99.6)	263 (99.2)	NR	NR	NR	NR
Worker's compensation (%)	(11.6)	(13.2)	NR	NR	15 (6.2)	11 (5.0)
Involved in litigation (%)	(10.9)	(12.1)	NR	NR	NR	NR

*Demographic and patient characteristic data listed in the FDA Panel summary are for all those who received treatment. Data for primary outcomes in this report are based on the 300 (160 ADR and 140 ACDF) participants available for interim analyses

†Described as "tobacco user" (Bryan) or "tobacco use" (Prestige)

2.5 Description of study outcomes

Lumbar efficacy and effectiveness measures
The primary efficacy/effectiveness outcome measure is a composite clinical measure referred to as overall clinical success measured 24 months following surgery. This clinical success measure was defined using similar but not identical criteria between the two index studies. Both index studies contained the following core criteria:

- ≥ 25% improvement in the Oswestry Disability Index (ODI) at 24 months compared with preoperative score (≥ 15 point improvement from baseline ODI was also reported at the request of the FDA)
- No device failure requiring revision, reoperation or removal
- No neurological deterioration compared with preoperative status

Blumenthal et al added the criteria of no major complications, defined as major vessel injury, neurological damage, or nerve root injury. Zigler et al added one quality of life criteria and five radiographic criteria:

- Improvement in the SF-36 physical and mental component scores at 24 months compared with preoperative score
- No radiographic evidence of device subsidence > 3 mm
- No radiographic evidence of device migration > 3 mm
- No extensive radiolucency along the implant/bone interface (< 25% of the interface's length for each endplate defined as a success)
- Range of motion at the implanted level maintained or improved from the preoperative baseline for L-ADR; no motion on flexion/extension films (defined as < 3 mm translation and < 5° angulation)
- No loss of disc height > 3 mm
- No evidence of bony fusion for L-ADR; strong evidence of fusion, including > 50% trabecular bridging bone or bone mass maturation and increased or maintained bone density at the site for the control group

Success for this outcome in each study occurred when all the criteria in the respective study were met.

Other outcomes used as primary outcomes to answer the efficacy/effectiveness question for this technology assessment are the ODI, neurological success (defined as the maintenance or improvement of neurological status), and pain reduction. Secondary outcomes include satisfaction, quality of life (SF-36), and range of motion.

Safety outcomes
Primary outcomes assessed for safety include:

- Device failure (defined as reoperation due to revision, reoperation, or removal)
- Other adverse events/complications reported in the included studies

Economic outcomes
Two partial economic studies described costs using different costing methods and compared costs for arthroplasty with those for fusion.[68,100]

Cervical efficacy and effectiveness measures
There were sufficient data on the following outcomes to perform meta-analysis:

- Overall clinical success composite measure as defined by the FDA for PMA approval studies
- Individual components of the overall clinical success composite measure including
  - Functional success based on a 15 or greater point improvement in Neck Disability Index (NDI). The NDI is a patient-reported measure consisting of 10 categories (pain intensity, self-care, lifting, reading, headaches, concentration, work, driving, sleeping and recreation), each of which is scored from 0-5 for a maximum of 50 points. The higher the score, the greater the disability[76]
  - Neurological success (defined below)
  - Device success (defined below)
- Data for other outcomes (pain or pain relief, quality of life, adjacent segment disease and return to work) were not consistently reported by all trials or different trials used varying definitions or measures to assess these. Thus, summary data are given where possible and individual study data reported as appropriate.

Overall Clinical Success-Definitions and Meta-analysis
As defined by the FDA, "overall success" was a composite of measures as described below. Definitions were sufficiently similar such that pooling of data was considered appropriate for the overall composite as well as individual components where data were available. "Success" for this outcome in each study occurred when all the criteria in the respective study were met.
A summary of what was included in the composite scores is as follows:

Mummaneni (Prestige ST C-ADR):

- NDI ≥ 15 point improvement
- Neurological success: Maintenance/improvement in neurological status
- No serious implant associated or implantation procedure adverse event
- Device Success: No second surgery classified as a failure

Prodisc FDA report (Prodisc-C ADR):

- NDI ≥ 15 point improvement
- Neurological success: motor, sensory and reflexes are maintained or improved
- Device Success: No revisions, removals, reoperations, or supplemental fixation at the index level
- No adverse events related to the implant or implantation

Bryan FDA report: (Bryan C-ADR, based on interim PMA analysis):

- NDI ≥15 point improvement from baseline
- Neurological Success: Maintenance or improvement in neurological status
- No serious adverse event classified as implant-associated or implant/surgical procedure-associated
- Device Success: No additional surgical procedure classified as "failure"

Published reports by Nabhan and Peng-Fei did not report on these criteria, nor did they use other definitions of "success". Therefore, they could not be included in the meta-analysis.

Assessment of pain reduction when reported was also considered as a primary outcome to help answer the efficacy/effectiveness question. Secondary outcomes used include satisfaction, quality of life (SF-36), adjacent segment disease and range of motion.

3. Results

3.1 Key question 1 - What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?

Lumbar

There were no studies found comparing lumbar ADR with continued nonoperative care. The only comparison of L-ADR with surgical procedures was with spinal fusion. Therefore, the results presented refer to the efficacy and effectiveness of L-ADR compared with lumbar spinal fusion.

Overall Clinical Success

The FDA criterion of at least a 15-point improvement from baseline ODI scores was used for both RCTs to minimize heterogeneity in the meta-analysis. The definition of overall clinical success was similar in the two studies, but not identical. In the Prodisc-L study, success was defined more conservatively than the Charité study in that it required improvement in the SF-36 and radiological success as additional criteria. The addition of these parameters would make success more difficult to achieve resulting in a lower proportion of patients attaining overall clinical success, but not likely biasing the results between study groups. Therefore, these two studies were pooled.

Using the baseline sample size as reference (ITT analysis), 52% of patients receiving the Charité L-ADR compared with 44% of those receiving lumbar fusion achieved success 24 months following surgery. In those receiving the Prodisc-L ADR, 49% were clinically successful compared with 39% receiving fusion. The meta-analysis of clinical success resulted in 51% (186/366) of patients receiving L-ADR compared with 42% (73/174) of those receiving fusion obtaining clinical success at 24 months, risk difference of 9% (95% CI, 0, 18%, $P = .05$), Figure 4. Using data from only those who completed the study, the risk difference was 8% (95% CI, 2%, 17%, $P = .11$), Figure 5. Since superiority of L-ADR was demonstrated in the ITT analysis but not the completer-only analysis, superiority was rejected. Non-inferiority at -10% inferiority margin was then assessed and non-inferiority was found to be supported by evaluating the lower bounds of the confidence intervals of the pooled results (0% ITT and -2% for completer-only analysis).

Sensitivity analyses to assess the effect of missing data supported non-inferiority at the -12.5% non-inferiority margin of lumbar ADR compared with spinal fusion, Table 16 and Figure 6.

Figure 4. Clinical Success (using ≥ 15 point difference over baseline for ODI) 24 months following L-ADR (intention-to-treat analysis)

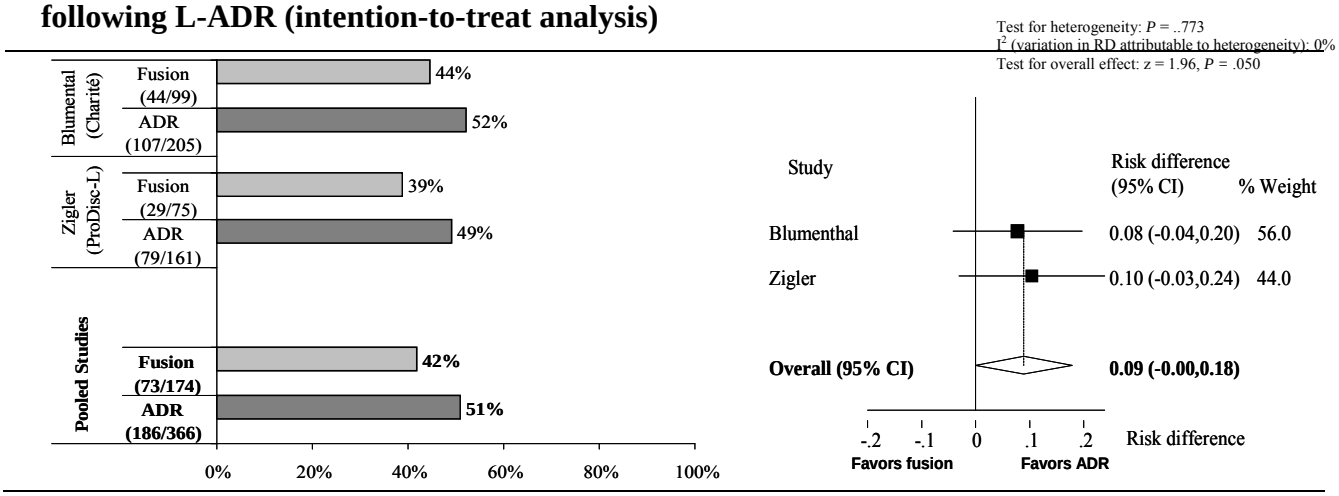


Figure 5. Clinical Success (using ≥ 15 point difference over baseline for ODI) 24 months following L-ADR (completer-only analysis)

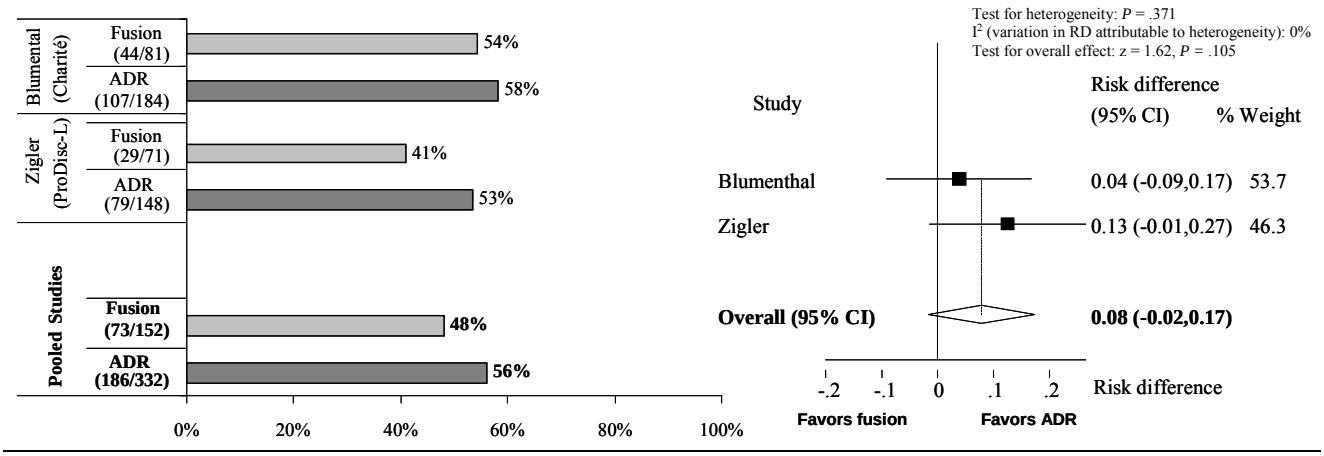
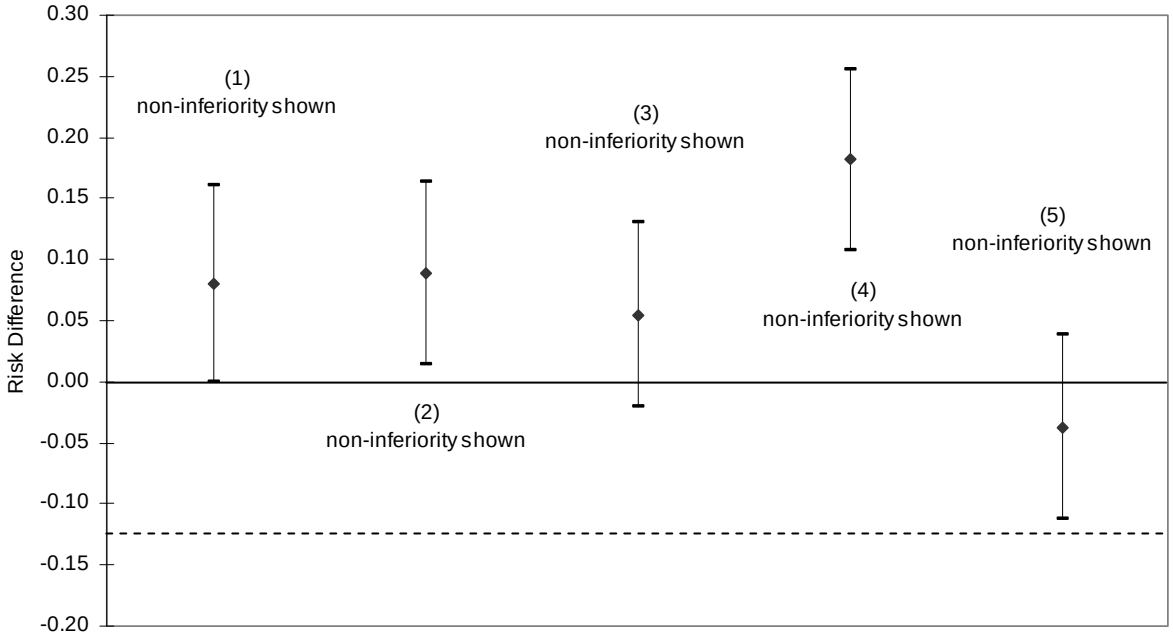


Table 16. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for the pooled results of the Blumenthal (Charité) and Zigler (Prodisc-L) studies

	L-ADR (n = 366)	Fusion (n = 174)	
Overall clinical success			
Yes 186		73	
No 146		79	
Unknown 34		22	
Rate of clinical success	n/N (%)	n/N (%)	Absolute difference (90% CI)*
Completer-only	186/332 (56.0)	73/152 (48.0)	.080 (-.016, .176)
Assuming poor outcome	186/366 (50.8)	73/174 (42.0)	.089 (-.001, .178)
Assuming good outcome	220/366 (60.1)	95/174 (54.6)	.055 (.-034, .144)
Extreme case favoring ADR	220/366(60.1)	73/174 (42.0)	.182 (.093, .270)
Extreme case favoring fusion	186/366 (50.8)	95/174 (54.6)	-.038 (-.128, .052)

*Two-sided 90% CI are shown for display purposes. The analysis was based on 1-sided 95% lower bound CI which is used in non-inferiority studies and corresponds to the 2-sided lower 90% CI shown in the figure (ie, the lower error bar on each plot can be read as either a 1-sided 95% CI or a 2-sided 90% CI).

Figure 6. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for L-ADR



(1): Completer-only
(2): ITT assuming failure for all missing data
(3): ITT assuming success for all missing data
(4): Missing data in ADR group = success, fusion group = failure
(5): Missing data in ADR group = failure, fusion group = success

ODI

Patients treated with L-ADR more often experienced substantial improvement (≥ 15 points over baseline) in ODI than those treated with fusion, 60% versus 49% for ITT analysis (*P* = .027) and 66% versus 57% for completer-only analysis (*P* = .062) 24 months following surgery, Figures 7 and 8. The completer-only analysis did not reach statistical significance. In both studies, mean percent improvement in ODI was greater for L-ADR patients than fusion patients at six weeks, three months, and six months, Figure 9. The differences between treatment groups diminished at 12 and 24 months.

Figure 7. ODI (≥ 15 point difference over baseline) 24 months following L-ADR (intention-to-treat analysis)

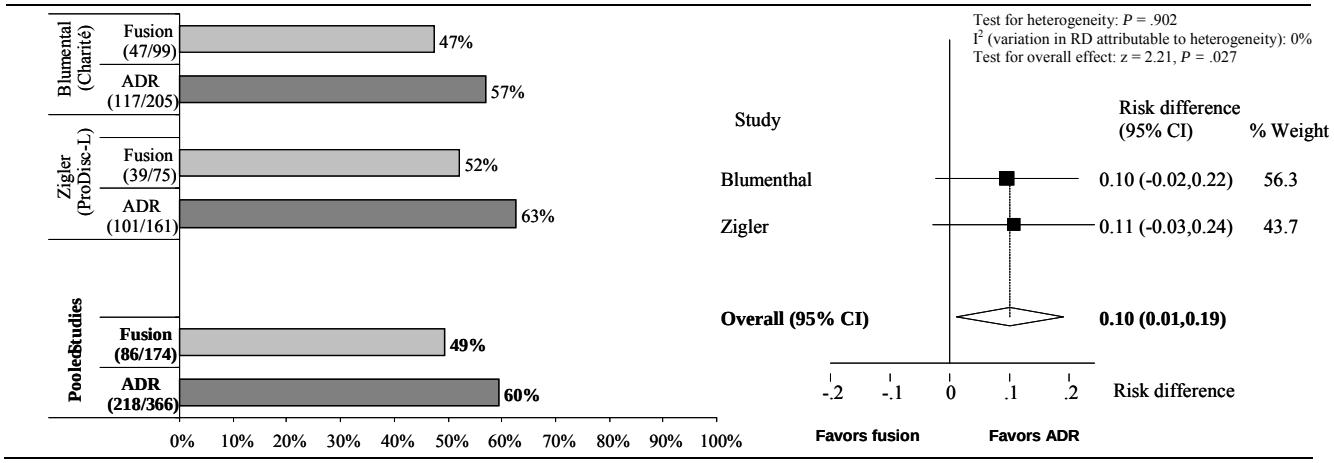


Figure 8. ODI (≥ 15 point difference over baseline) 24 months following L-ADR (completer-only analysis)

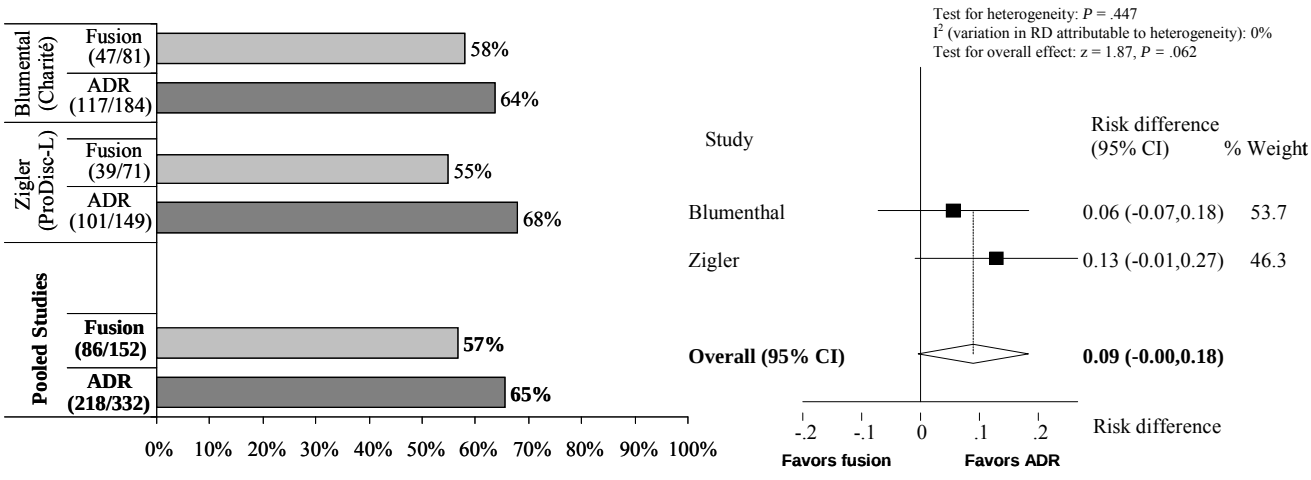
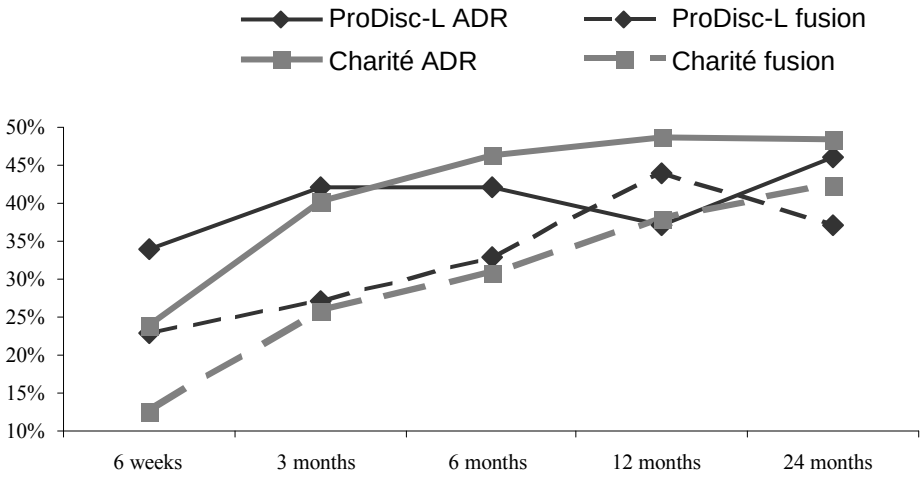


Figure 9. ODI (≥ 15 point difference over baseline) results over time following L-ADR*



*The differences were statistically better for the L-ADR group compared with fusion group at 6 weeks, 3 months, 6 months, and 12 months in the Blumenthal et al study, and at 6 weeks, 3 months, and 6 months in the Zigler et al study.

One nonrandomized trial[149] examined differences in ODI according to spinal segment treated. That study reported that patients treated by the Charité L-ADR only at L4-L5 experienced a greater mean reduction in ODI (63.4%), compared with those treated only at L5-S1 (53.9%) or those treated at both of these segments (43.2%). These differences were not statistically significant, perhaps due to the small size of the study (N = 99).

Neurological Success

Neurological success was defined as the maintenance or improvement of neurological status 24 months following surgery. Generally, neurological success was achieved by approximately 80% of all patients in the ITT analysis, and 90% of all patients in the completers-only analysis, Figures 10 and 11. There was no statistical difference between L-ADR and fusion with respect to neurological status. Data from completer-only analysis were not pooled due to heterogeneity between studies.

Figure 10. Neurological success 24 months following L-ADR (intention-to-treat analysis)

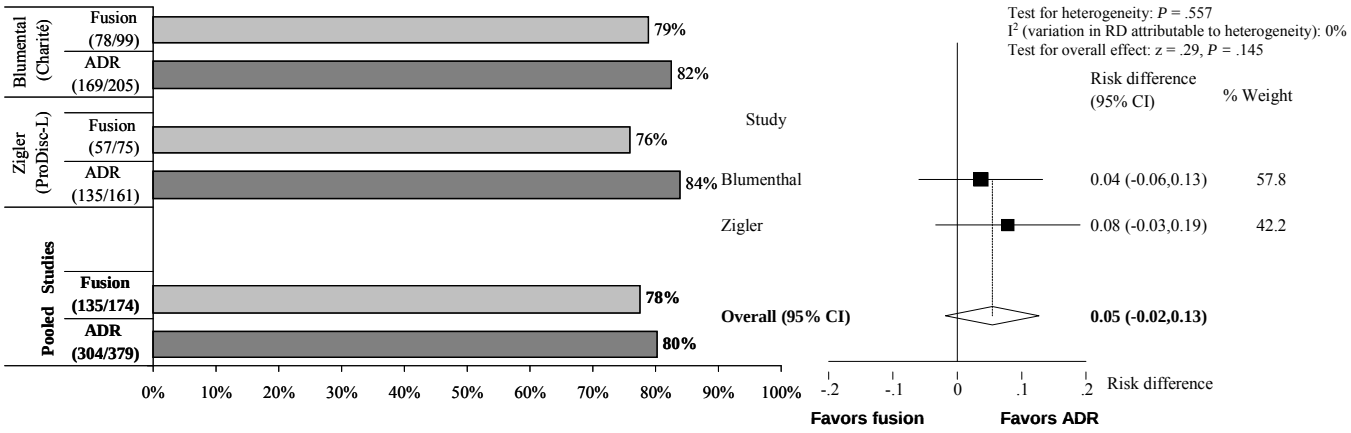
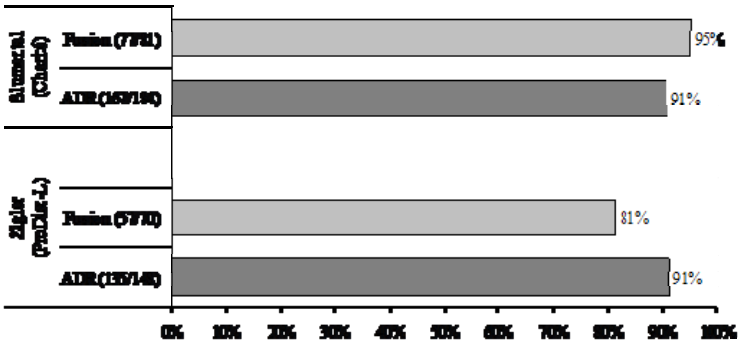


Figure 11. Neurological success 24 months following L-ADR (completer-only analysis)



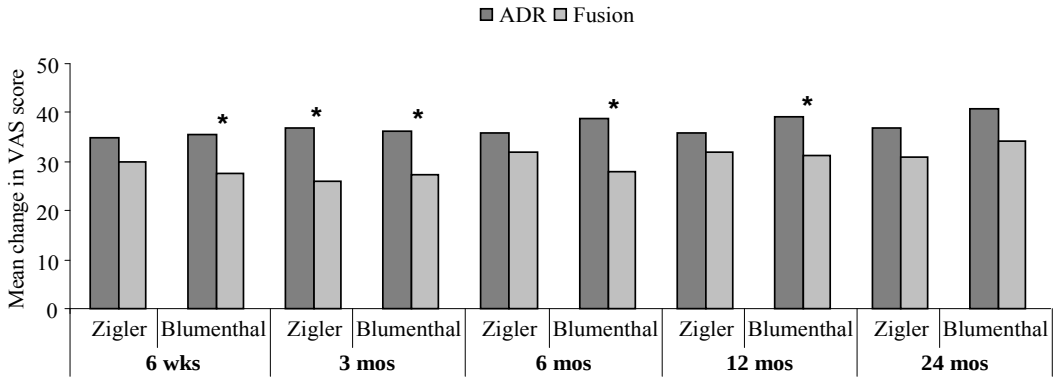
Pain reduction

L-ADR appears to provide as good or greater relief from pain than fusion procedures for those with single-level degenerative disc disease. There is no evidence that this effect varies with the type of artificial disc used, and some evidence that the effect is more pronounced in those with disease treated at L4-L5 than those with disease treated at L5-S1. Results are less clear for the use of narcotics, perhaps because of differences between studies in how this outcome was measured or due to the fact that use of narcotics is influenced by factors other than pain, such as patient preference, comorbidities, dependency, or practice style.

- *VAS Pain*

  Patients in both index studies receiving either treatment reported statistically significant pain reduction compared with preoperative pain levels. This occurred at every time point up to 2 years following surgery. Patients receiving L-ADR had a slightly greater mean improvement in VAS pain scores than patients receiving fusion in both index studies. However, this comparison reached statistical significance only once in the Zigler et al study (3 months) and in all the time periods except at 2 years in the Blumental et al study, Figure 12.

Figure 12. Mean change in pain (VAS) from preoperative pain scores at various time periods following L-ADR



* denotes statistically significant difference between L-ADR and fusion.

A single nonrandomized study compared improvements in VAS for pain among those with degenerative disc disease treated with a Charité artificial disc at L4-L5 with those treated at L5-S1 and those treated at both levels.[149] VAS improvements were statistically better comparing monolevel L4-L5 patients to bisegmental patients (74% versus 41%, *P* = .02) and better than monolevel L5-S1 patients (74% versus 58%, *P* > .05). The latter difference was not statistically significant, but this may be due to the modest size of the groups being compared (n = 22 for L4-L5 and n = 57 for L5-S1).

- *Use of narcotics*
  Blumenthal et al reported that among those using narcotics at baseline, 64% of patients treated with the Charité L-ADR were still using narcotics at 24 month follow-up, compared with 80% among those treated with fusion (*P* = .04).[28]

  Zigler et al, which did not report continued use of narcotics explicitly, suggests a lower proportion of continued narcotic users. Eight-four and 76% of the Prodisc-L and fusion patients were using narcotics at baseline, and 48% and 46% in each group were using at 24 months, implying a maximum of approximately 57% and 61% of each group continued to use narcotics. (No tests of significance were reported for this outcome). [171]

SF-36

Blumenthal et al reported on the proportion of patients experiencing substantial improvement, defined as ≥ 15% improvement from baseline on the SF-36 questionnaire. Those receiving the Charité L-ADR more often experienced a ≥ 15% improvement from baseline in the physical component score of the SF-36 questionnaire compared with those receiving fusion (72% versus 63%, test of significance not reported). Fifty percent of the L-ADR group and 51% of the control group had a ≥ 15% improvement from baseline in the mental component score section of the SF-36 questionnaire (test of significance not reported).

Zigler et al reported on the proportion of patients reporting any improvement compared with their preoperative SF-36 score. A slightly greater proportion of those receiving L-ADR experienced some improvement in SF-36 at 24 months than those receiving fusion, although this difference was not statistically significant (79% versus 70%, *P* = .09). Those receiving L-ADR more often experienced some improvement in SF-36 than those receiving fusion at six weeks (72% versus 56%, *P* = .02), three months (87% versus 70%, *P* = .004), six months (80% versus 75%, *P* = .2), and twelve months (81% versus 77%, *P* = .3) following surgery.

Patient satisfaction

- *Satisfaction.* When asked if they were "satisfied", "slightly satisfied", "slightly dissatisfied", or "dissatisfied" with their treatment, patients receiving the Charité L-ADR were statistically more likely to report they were "satisfied" (74%) than patients treated by fusion (53%, *P* = .001).[28] Zigler et al reported greater patient satisfaction with the Prodisc-L compared with fusion using a visual analog scale, mean 76.7 ± 29.2 mm versus 67.3 ± 31.5 mm, *P* = .015.[171]

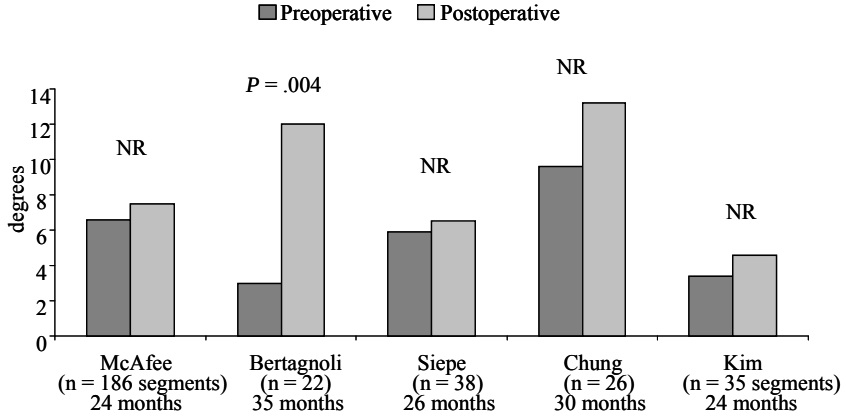
- *Willingness to choose again.* Both index studies asked patients if they would choose their treatment again. In each, a significantly higher proportion of patients receiving L-ADR responded affirmatively compared with patients treated by fusion (70% versus 50% in Blumenthal et al, *P* = .006 and 81% versus 69% in Zigler et al, *P* = .0004).

Preservation of motion

- *Preoperative versus postoperative flexion-extension (Figure 13)*
  McAfee et al[109] in a companion study to the Blumenthal et al RCT reported on maintenance of motion following L-ADR. They reported a slight increase in flexion-extension 24 months following surgery (7.5°) compared with preoperative measurements (6.6°) at the instrumented segment. When the investigators divided the surgical technical accuracy of the L-ADR into three groups (ideal, suboptimal, and poor), they found that flexion-extension improved with the surgical technical accuracy (*P* = .003).

  Four nonrandomized trials also reported pre- and postoperative flexion-extension and found increased movement 24 to 35 months following surgery compared with preoperative measurements at the instrumented segment.[22,40,89,150] This increase was statistically significant in one study (n = 22), which found on average patients increased from 3° preoperative flexion-extension to 12° post-operation (*P* = .004).[150] It should be noted that this population consisted of high level athletes only.

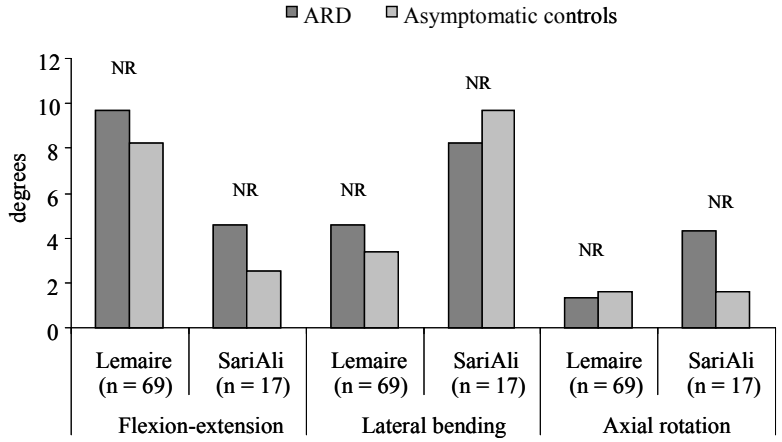
Figure 13. Mean flexion-extension before surgery and at follow-up for L-ADR



NR = *P* value not reported.

- *Postoperative range of motion versus asymptomatic controls (Figure 14)*
  Two small cohort studies[97,140] evaluated the long term motion at L4-L5 in people receiving a Charité L-ADR compared with asymptomatic controls after > 10 years follow-up. Segmental motion was generally slightly greater or similar to asymptomatic controls in flexion-extension, lateral bending, and axial rotation.

Figure 14. Long term motion at L4-L5 in patients receiving Charité L-ADR compared with asymptomatic controls after > 10 year follow-up

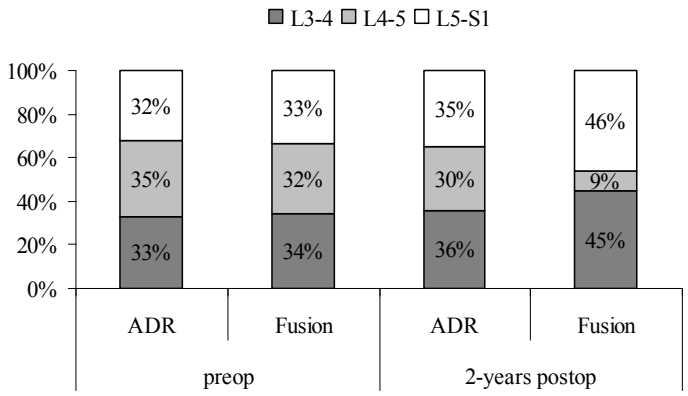


NR = *P* value not reported.

- *Postoperative range of motion versus normative data*
  One small study (N = 41) compared flexion-extension of the instrumented (Prodisc-L) and adjacent (untreated) segments with normative values 24 months following L-ADR.[96] The investigators found that the L-ADR failed to restore segmental sagittal rotation compared with the normative values. It should be noted that the normative values were obtained in a population different in demographics from the study population with respect to sex and age (74% males ranging in age from 19-57 years in the normative group versus 46% males ranging in age from 31-60 years in the study group). Also, worth noting is that nearly half of the 61 normative subjects performed the motion passively and half actively. Furthermore, imaging was unobtainable in 20% and 40% of the L4-L5 and L5-S1 segments, respectively.

- *Motion profile of the lowest three motion segments comparing L-ADR with fusion*
  One study[44] evaluated the motion profile (flexion-extension) at three motion segments (L3-4, L4-5, L5-S1) in 93 patients who received implants at L4-5 as part of the Charité index study. Comparison was made between L-ADR (n = 61) and fusion patients (n = 32). The proportion of motion following L-ADR more closely resembled preoperative motion compared with fusion, Figure 15. The authors concluded that one-level arthroplasty may replicate the normal distribution of motion of the intact spine at the implanted and adjacent levels.

Figure 15. Motion profile of L3-4, L4-5, and L5-S1 comparing L-ADR with lumbar fusion in patients who received implants at L4-5.



Adjacent segment disease (ASD)

Among non-randomized studies reporting radiologic lumbar ASD rates among patients receiving L-ADR, two studies with ≤ 10 years of follow-up reported 0% and 24% of patients had lumbar ASD,[82,158] and one study with > 10 years of follow-up found 17.0% of patients had lumbar ASD.[131] In the later study, ASD was only seen in patients with loss of motion at the instrumented segment. When patients were divided into those with motion of 5º or greater versus less than 5º, the rate of ASD was 0% (0/13) in the high motion group and (10/29) 34% in the low motion group (odds ratio = 13.5, *P* = .021). There were no differences in preoperative age, weight, or gender between patients with or without L-ASD.

Cervical

No studies were found comparing C-ADR with nonoperative care. The only comparison of C-ADR with surgical procedures was with spinal fusion. Therefore, the results presented refer to the efficacy and effectiveness of C-ADR compared with cervical spinal fusion.

Overall Clinical Success

Using the baseline sample size as reference (ITT analysis), 64% of patients receiving the Prestige ST C-ADR compared with 51% of those receiving anterior cervical fusion achieved success 24 months following surgery. In those receiving the Prodisc-C ADR, 71% were clinically successful compared with 65% receiving fusion. The pooled estimate from meta-analysis of clinical success resulted in 66% (250/379) of patients receiving C-ADR compared with 55% (203/371) of those receiving anterior cervical fusion obtaining clinical success at 24 months, risk difference of 11% (95% CI, 4, 18%, *P* = .002), Figure 16. Using data from only those who completed the study, the risk difference was 9% (95% CI, 2%, 16%, *P* = .009), Figure 17. The risk difference of 9%

equates to a number-needed-to-treat (NNT) of 11; that is, for every 11 patients who receive C-ADR instead of anterior fusion among patients with the same cervical disease as those in the studies, 1 additional patient will achieve overall success 24 months following surgery. Adding the interim analysis from the FDA Bryan report did not influence the pooled results or conclusions drawn, Figure 18.

Figure 16. Clinical success 24 months following C-ADR (intention-to-treat analysis)

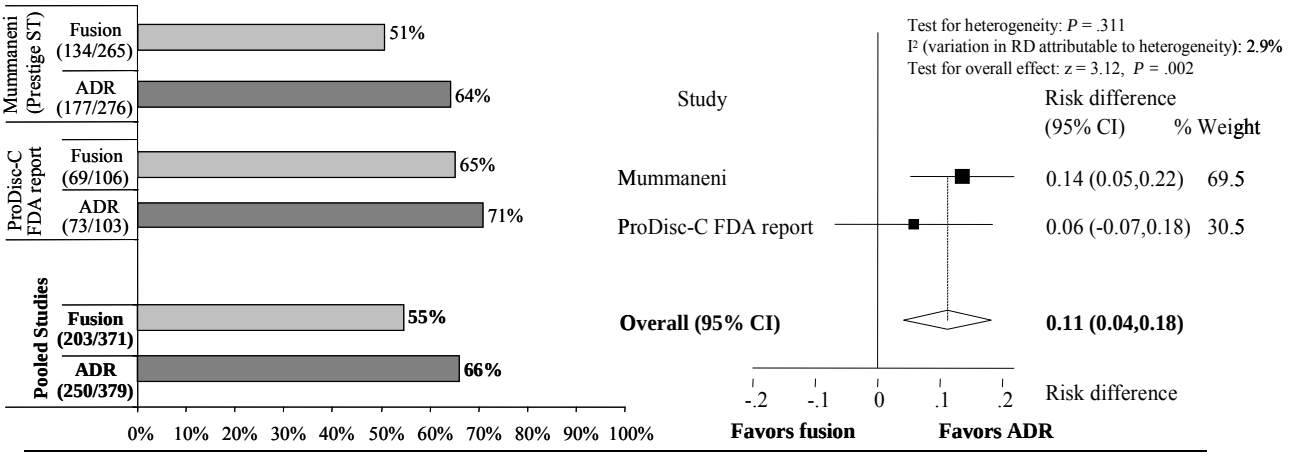


Figure 17. Clinical success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA interim report)

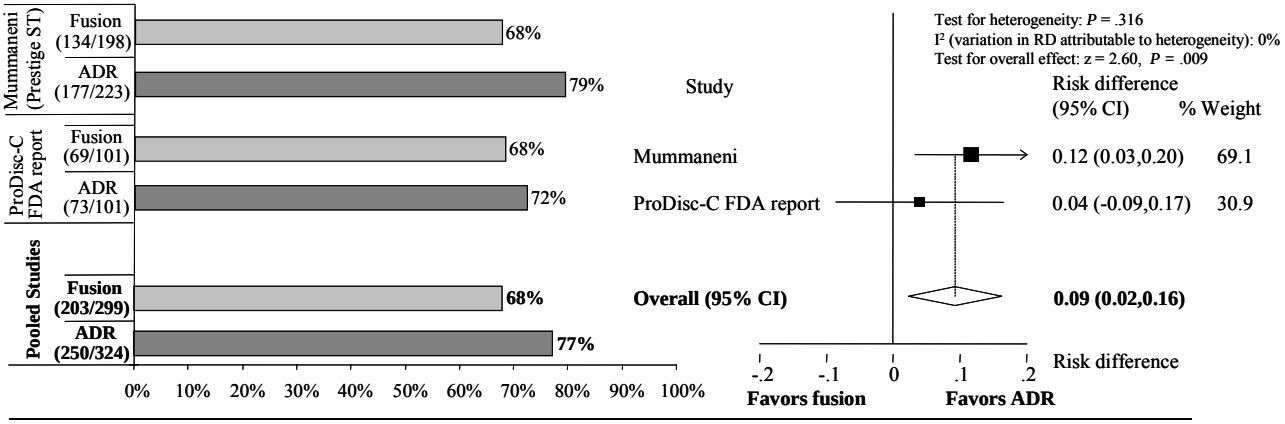
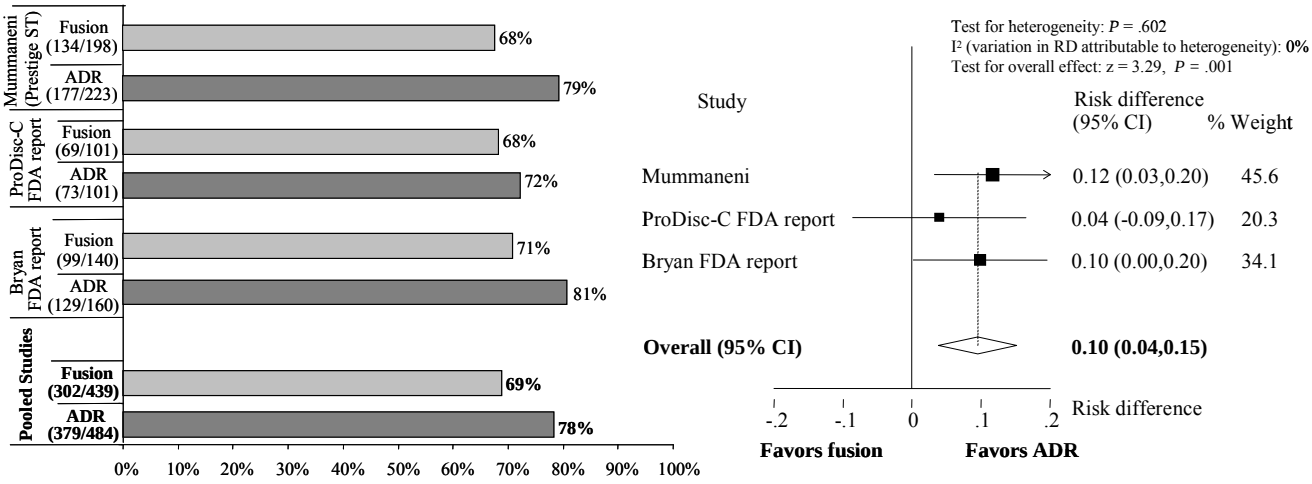


Figure 18. Clinical success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



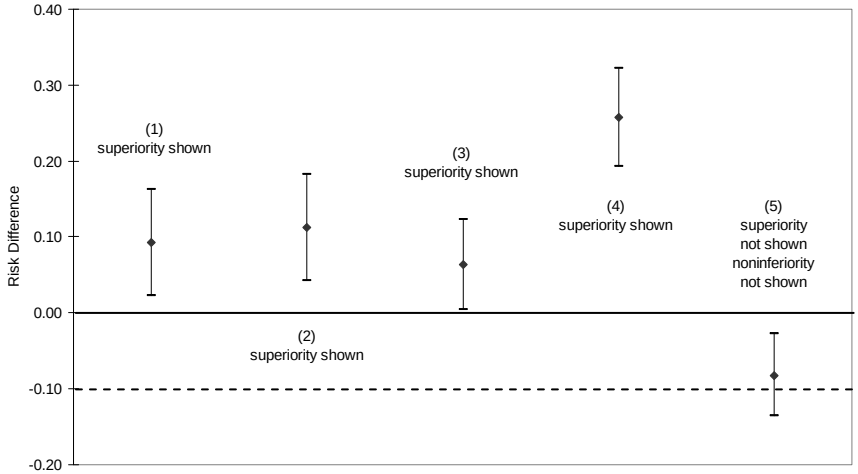
Sensitivity analysis was done to assess the effect of missing data on the pooled estimate for overall success for the Prestige ST (Mummaneni) and Prodisc-C FDA studies. Superiority was shown in four of the five scenarios, Table 17 and Figure 19. A description of each scenario appears with Figure 6. In the extreme case where all missing data in C-ADR group were assigned as "failure" and all missing data in the fusion group were assigned as "success", superiority of C-ADR was not shown. In fact in this extreme case, non-inferiority was not demonstrated at the 10% inferiority margin. Though this outcome is unlikely, the results of the sensitivity analysis leave open the remote possibility that missing data can have an important effect on the results of these studies.

Table 17. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for the pooled results of the Mummaneni (Prestige ST) and Prodisc-C FDA studies

	C-ADR (n = 379)	Fusion (n = 371)	
Overall clinical success			
Yes 25	0	203	
No 74		96	
Unknown 55		72	
Rate of clinical success	n/N (%)	n/N (%)	Absolute difference (95% CI)
Completer-only	250/324 (77.2)	203/299 (67.9)	.093 (.023, .163)
Assuming poor outcome	250/379 (66.0)	203/371 (54.7)	.112 (.043, .182)
Assuming good outcome	305/379 (80.5)	275/371 (74.1)	.064 (.004, .123)
Extreme case favoring ADR	305/379 (80.5)	203/371 (54.7)	.258 (.193, .322)
Extreme case favoring fusion	250/379 (66.0)	275/371 (74.1)	-.082 (-.136, -.027)*

*Two-sided 90% CI is shown for display purposes. The analysis was based on 1-sided 95% lower bound CI which is used in non-inferiority studies and corresponds to the 2-sided lower 90% CI shown in the figure (i.e., the lower error bar on each plot can be read as either a 1-sided 95% CI or a 2-sided 90% CI).

Figure 19. Sensitivity analyses assessing the effect of missing data on the results of overall clinical success for C-ADR



(1): Completer-only
(2): ITT assuming failure for all missing data
(3): ITT assuming success for all missing data
(4): Missing data in ADR group = success, fusion group = failure
(5): Missing data in ADR group = failure, fusion group = success

NDI

Patients treated with C-ADR more often experienced substantial improvement (≥ 15 points over baseline) in NDI than those treated with fusion, 70% versus 62% for ITT analysis (P = .027) and 82% versus 80% for completer-only analysis 24 months following surgery, Figures 20 and 21. The completer-only analysis did not reach statistical significance, risk difference of 2% (95% CI -4%, 9%; P = .465). Adding the

interim analysis from the FDA Bryan report did not change the statistical conclusions, Figure 22.

Figure 20. NDI success 24 months following C-ADR (intention-to-treat analysis)

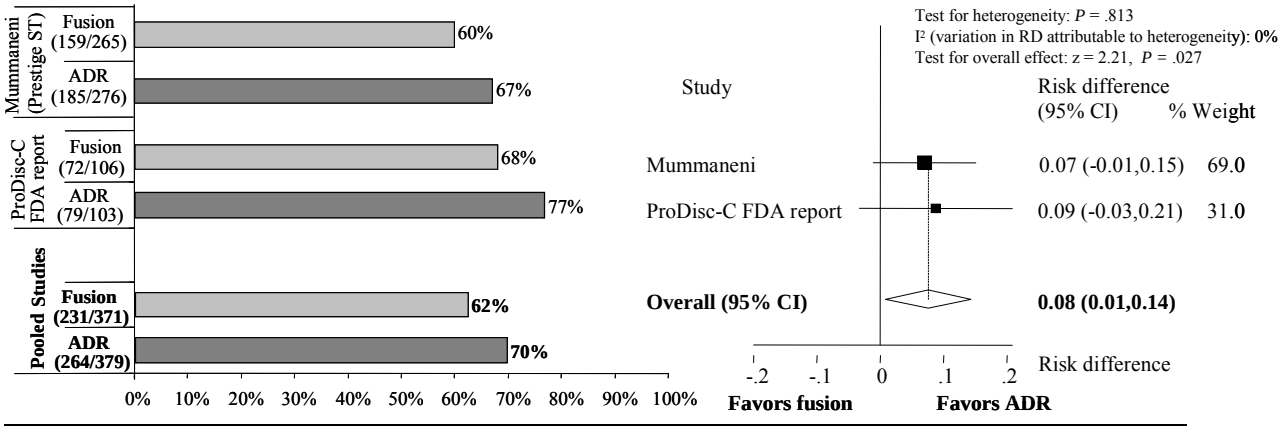


Figure 21. NDI success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA report)

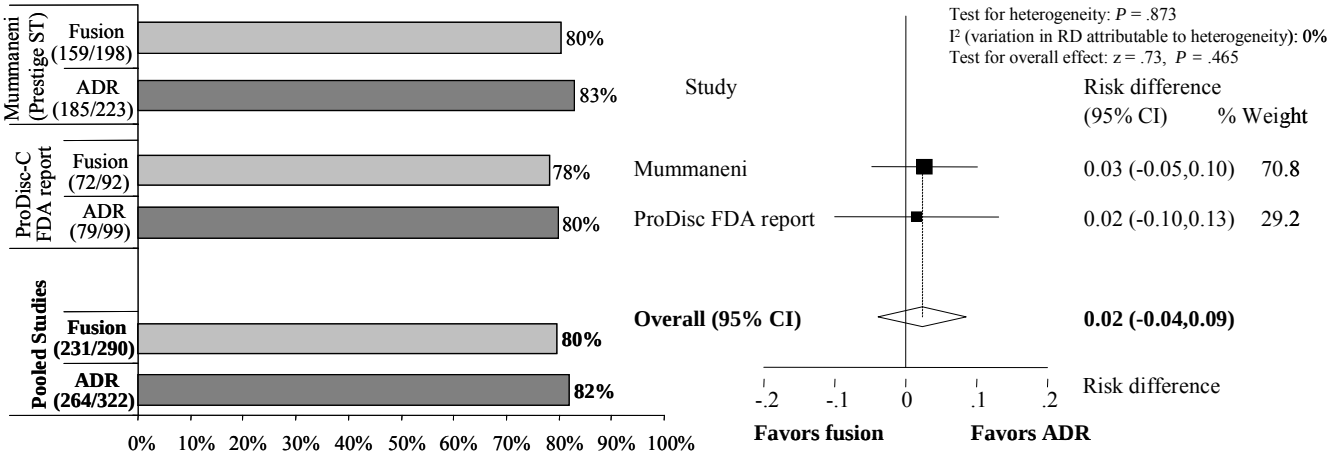
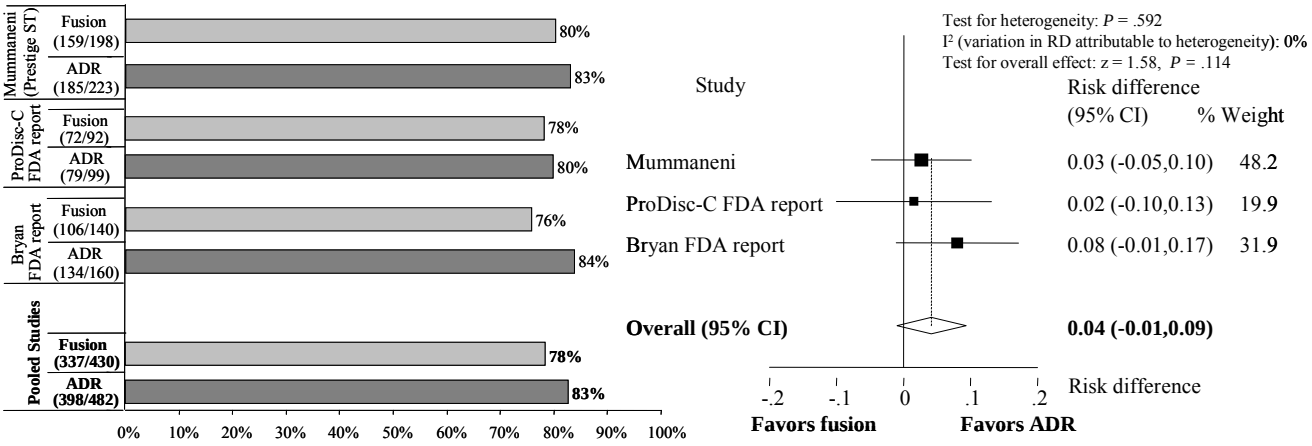


Figure 22. NDI success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



Neurological Success

Neurological success was defined as the maintenance or improvement of neurological status 24 months following surgery. Using the baseline sample size as reference (ITT analysis), neurological success was achieved by 78% of patients receiving C-ADR compared with 67% of those receiving fusion 24 months following surgery, risk difference of 12% (95% CI 5%, 18%, $P < .0001$), Figure 23. Using data from only those who completed the study, the risk difference was 7% (95% CI, 1%, 12%, $P = .022$), Figure 24. Adding the interim analysis from the FDA Bryan report lowered the risk difference to 5%, but did not influence the conclusions drawn, Figure 25.

Figure 23. Neurological success 24 months following C-ADR (intention-to-treat analysis)

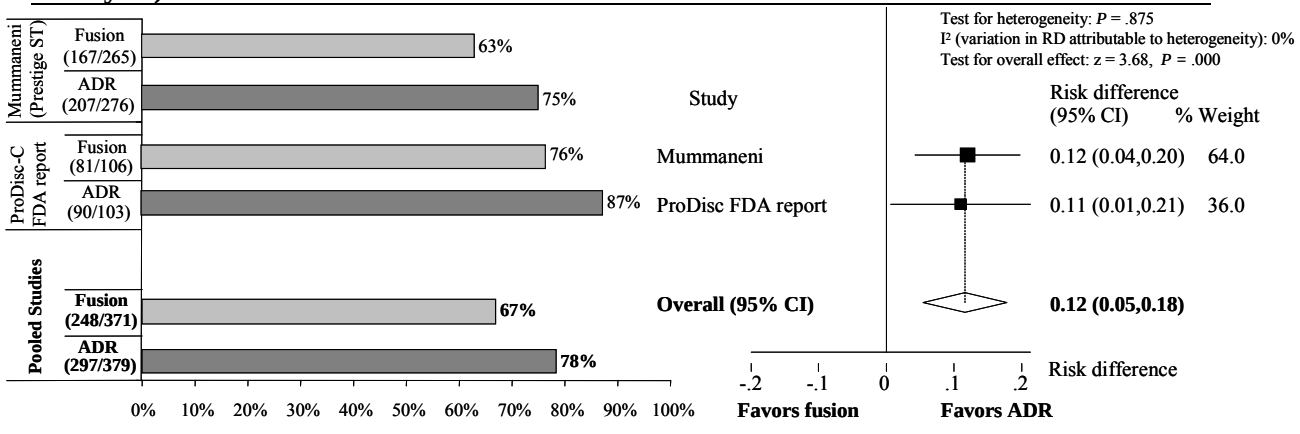


Figure 24. Neurological success 24 months following C-ADR (completer-only analysis excluding the Bryan FDA report)

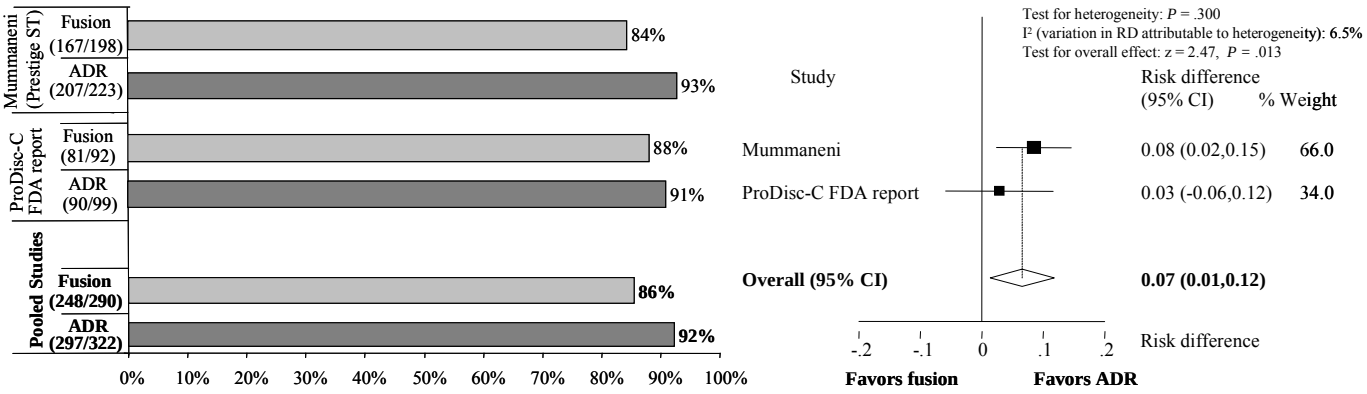
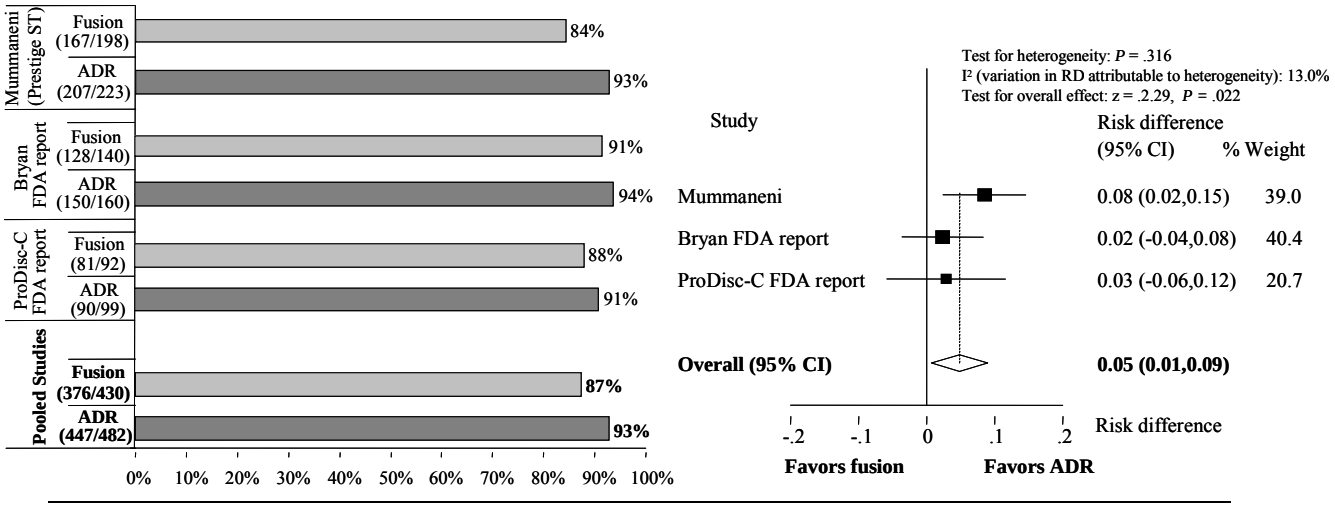


Figure 25. Neurological success 24 months following C-ADR (completer-only analysis including the Bryan FDA report)



Pain

Pain was assessed differently among the RCTs. Two studies measured the intensity of pain only, one on a 10 point scale[118] and one on a 100 point scale.[6] One study measured pain on a 100 point scale as the product of intensity (0-10) and frequency (0-10), [115] and another measured pain intensity and frequency separately.[5] Lastly, Peng-Fei et al[121] did not specify how pain was assessed.

Comparison of scores between baseline and follow-up: Patients undergoing either C-ADR or ACDF for cervical degenerative disc disease experienced significant relief of

neck and arm pain, as measured by the various methods described above, at 24 month follow-up compared with baseline.[5,6,115]

Comparison between treatment groups at 24 months: There were no statistical differences in the change of the intensity of neck or arm pain comparing the C-ADR group with the fusion group at follow-up. In the Bryan study[6], arm pain score changed by 50.1 in the C-ADR group compared with 50.0 in the fusion group 24 months following surgery. Neck pain and arm pain were reduced to equal degrees comparing C-ADR and fusion after 12 months in another RCT, 4.2 versus 4.2 for neck pain and 6.3 versus 6.0 for arm pain.[118] The proportion of patients who reported at least a 20 mm improvement in pain intensity comparing preoperative pain with pain at 24 months was similar in the Prodisc-C study,[5] 78.6% versus 75.6% for neck pain and 71.4% versus 76.7% for arm pain. Similar proportions were reported for at least 20 mm improvement in pain frequency in the same population for neck and arm pain. A composite score representing the product of pain intensity and duration was used in one study,[115] again with similar results between groups; a change composite score of 53 versus 53 for the C-ADR and fusion groups for neck pain, and 46 versus 49 for arm pain.

SF-36

The Prodisc-C SSED reported on the proportion of patients experiencing substantial improvement, defined as $\geq$ 15 point improvement from baseline on the SF-36 questionnaire. Those receiving the Prodisc-C ADR more often experienced a $\geq$ 15point improvement from baseline in the physical component score (PCS) of the SF-36 questionnaire compared with those receiving fusion (52% versus 34 %, test of significance not reported). Thirty six percent of the C-ADR group and 42% of the fusion group had a $\geq$ 15point improvement from baseline in the mental component score (MCS) section of the SF-36 questionnaire (test of significance not reported).

Mummaneni et al reported on the improvement in mean postoperative SF-36 scores compared with mean preoperative scores. A change in the scores for the C-ADR and fusion groups were 13.1 and 11.8, respectively, for the PCS, and 7.4 and 7.5 for the MCS 24 months after surgery (test of significant not reported).

The Bryan FDA executive summary reported a mean improvement from baseline for the PCS (C-ADR = 14.4, ACDF = 14.5) and the MCS (C-ADR = 8.1, ACDF = 7.3). Twenty four months following surgery, the C-ADR group compared with the fusion group had a 85.5% versus 90.6% success rate in the PCS and a 69.8 versus 72.5% in the MCS. Success for the SF-36 was not defined, however.

JOA score

In one small RCT, the functional outcome assessed was the Japanese Orthopaedic Association cervical myelopathy measure (JOA score). This study found no difference in the JOA score after a short follow-up ranging from 10 to 35 months. The JOA score of the group with C-ADR increased from an average of 8.6 to 15.8 (the higher the score, the better the function) compared with the ACDF group which increased from an average of 9.0 to 16.2.

Patient satisfaction

One study, the Prodisc-C FDA trial, reported on this important outcome. Using a VAS, the investigators asked the patient how satisfied they were with the surgery they received on a 100 mm scale with 100 representing the maximum satisfaction. Seventy one percent of those receiving C-ADR reported an 80 mm or higher for satisfaction compared with 68% in the ACDF group (test of significance not reported). When asked whether they would have the same surgery again, 86% of the C-ADR patients and 81% of the ACDF patients responded affirmatively.

Preservation of motion

The five RCTs and nine nonrandomized studies evaluated cervical C-ADR by comparing postoperative motion with preoperative motion, or by comparing postoperative motion between a C-ADR group and a fusion or an asymptomatic control group. Five studies had follow-up of two years or more.

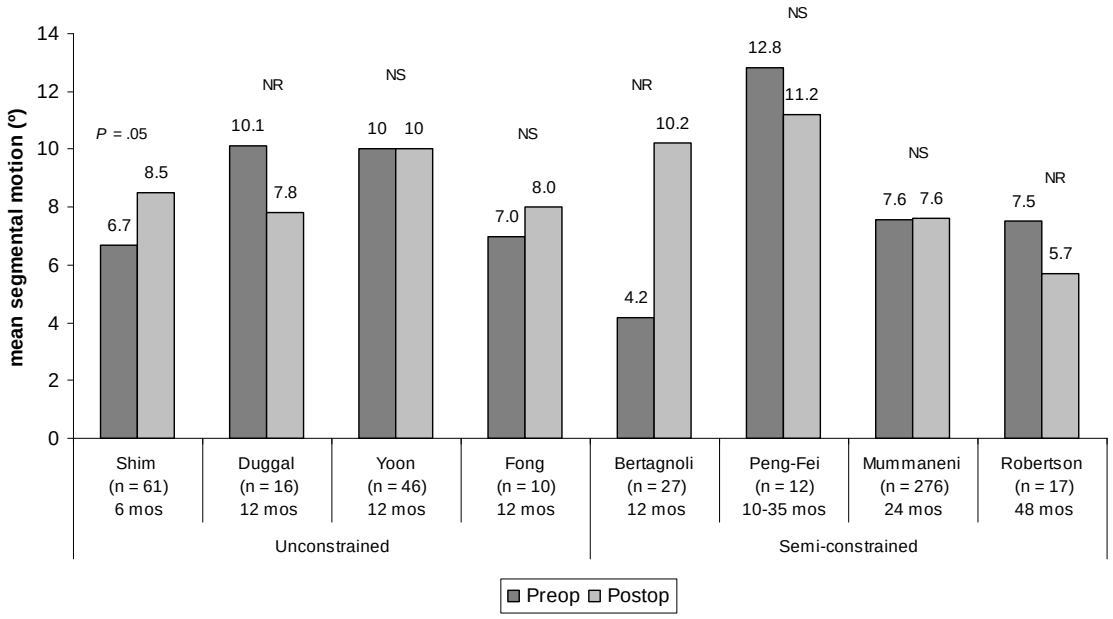
Preoperative versus postoperative flexion-extension (Figure 26)

Segmental flexion-extension at the level of instrumentation was generally maintained after C-ADR comparing preoperative motion with postoperative motion from 6–48 months following surgery. In some cases, motion was slightly increased postoperatively,[24,55,147] in some cases the motion was slightly decreased,[50,121,136] and in some cases the motion was the same compared with preoperative motion.[115,166] This pattern occurred with both the unconstrained and semiconstrained devices.

Postoperative range of motion in C-ADR versus fusion

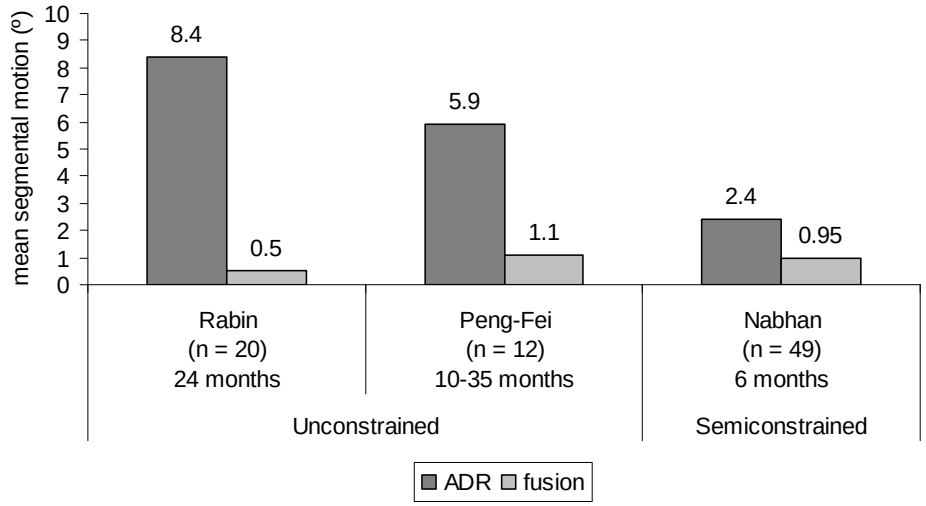
Three studies evaluated segmental motion comparing C-ADR with fusion at various follow-up periods.[118,121,132] Mean flexion-extension at the instrumented level was consistently and substantially higher in the C-ADR groups, for both an unconstrained and semiconstrained model at final follow-up, Figure 27. In one study, mean motion in the frontal and horizontal planes also was greater in the C-ADR group compared with ACDF group at the instrumented level.[117]

Figure 26. Average segmental flexion-extension at the C-ADR instrumented level comparing preoperative with postoperative motion at final follow-up



NR = not reported
NS = not statistically significant

Figure 27. Average segmental flexion-extension at the instrumented level comparing C-ADR with ACDF

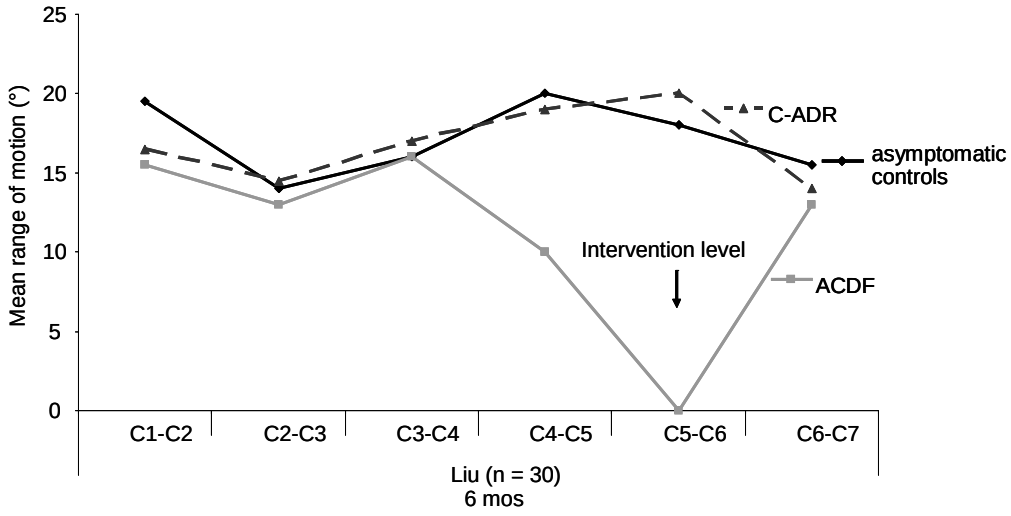


Postoperative range of motion in C-ADR versus asymptomatic controls
One small study evaluated motion in C-ADR (n = 10) and age- and sex-matched asymptomatic control (n = 10) groups. Segmental motion was similar in the ADR group (20°) compared with the controls (18°). [102]

Postoperative range of motion in adjacent segments for ADR, fusion, and control groups (Figure 28)

One small study evaluated segmental motion in ADR (n = 10), fusion (n = 10), and asymptomatic control (n = 10) groups. The motion patterns in the adjacent segments for ADR were similar to the motion of asymptomatic controls in terms of percent of total motion. The relative contribution of motion in the adjacent segment one level cephalad in the fusion group was decreased compared with ADR or asymptomatic controls.[102]

Figure 28. Average proportion adjacent segment motion (flexion-extension) at follow-up for C-ADR, ACDF, and asymptomatic controls



Adjacent segment disease (ASD)

Mummaneni et al reported a rate of symptomatic cervical ASD requiring surgical intervention of 1.1% in C-ADR patients and 3.4% in anterior cervical fusion patients after 2 years of follow-up [115], a relative risk decrease of 67% (absolute risk difference of 2.3%), *P* = .049. One retrospective cohort study reported a lower risk of cervical ASD requiring surgery following C-ADR compared with fusion (0% versus 7.0%).[137] In this study's analysis of symptomatic C-ASD patients only, (i.e., those with symptoms who received conservative or operative care), there was a marked difference between the ADR group (1.3%) compared with the fusion group (33%). The interpretation of these results should be tempered given that the groups were treated at two different time periods, there were no detailed comparisons of population characteristics at baseline, and there was no attempt to control for potential confounding that often affects cohort studies.

Two case-series report 1%[66] and 7%[161] symptomatic cervical ASD 24 months following a Bryan and Prestige C-ADR, respectively.

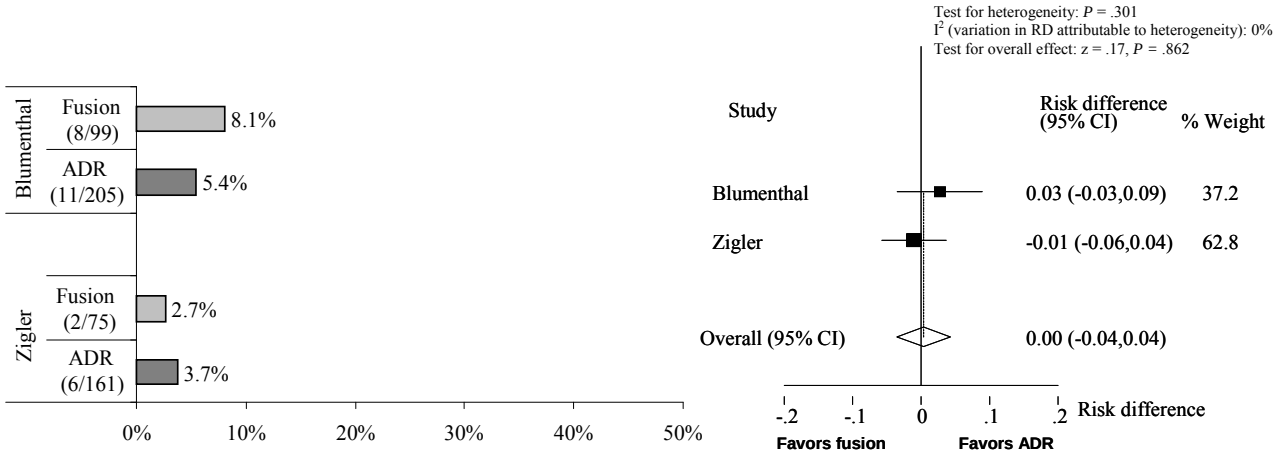
Few studies report on radiographic (asymptomatic) cervical ASD following C-ADR. One small RCT found no cases of radiographic C-ASD in either group after one year follow-up.[117] Robertson et al reported a high rate of radiographic cervical ASD after two years follow-up, 17.5% among C-ADR patients and 34.2% among fusion patients.[137] Again, caution interpreting the results from Robertson should be exercised based on the methodological issues above. Two small case-series report no cases of radiographic C-ASD 12 months following a Bryan or Prodisc C-ADR.[19,84] In general, radiographic evidence of changes to adjacent segments do not highly correlate with patient symptoms.

3.2 Key question 2 - What is the evidence related to the ADR safety profile (including device failure, reoperation)?

Device failure

The frequency of device failure (defined as reoperation, revision, or removal of the implant) was 5.4% and 3.7% in patients receiving L-ADR, and 8.1% and 2.7% in those receiving fusion in the Blumenthal et al and Zigler et al studies, respectively. There was no statistical difference in device failure between L-ADR and fusion, Figure 29.

Figure 29. Device failure for L-ADR (reoperation, revision, or removal of the implant)



Complications or adverse events

Blumenthal et al reported three major complications (defined as major vessel injury, neurological damage, nerve root injury, or death), two in the L-ADR group and one in the fusion group. One in the L-ADR group led to death (associated with narcotic use). Approach related complications (venous injury, retrograde ejaculation, ileus, perioperative vein thrombosis, clinically significant blood loss [> 1500 cc], incisional hernia, epidural hematoma, dural tear, deep vein thrombosis, arterial thrombosis) occurred in 20 L-ADR patients (9.8%) and 10 fusion patients (10.1%). Infections (superficial wound with incision site pain, other nonwound related, UTI, wound swelling, pulmonary, peritonitis, graft site) were reported in 26 patients (12.7%) and eight patients (8.1%) in the L-ADR and lumbar fusion groups, respectively. Device collapse, subsidence, or displacement was reported in eight L-ADR patients (3.9%) and one fusion patient (1.0%). Additional surgery at the index level was necessary in eleven patients (5.4%) in the L-

ADR group and nine patients (9.1%) in the fusion group. Neither group reported any catastrophic device failure.

Zigler et al reported no major complications in either group of the Prodisc-L study. However, two patients (2.7%) in the fusion group and none in the L-ADR group experienced clinically significant blood loss of > 1500 cc. Retrograde ejaculation occurred in two L-ADR patients (1.2%) and in no fusion patient. Deep vein thrombosis was reported in two patients (1.2%) in the L-ADR group and in one patient (1.3%) in the fusion group. No infection occurred in those receiving L-ADR, but did occur in two patients (2.7%) who underwent fusion. Device migration or subsidence was reported in four L-ADR patients (2.5%) and in one fusion patient (1.3%). Loss of disc height or radiolucency was not seen in the L-ADR group but occurred in six patients (8.0%) in the fusion group. In the fusion group, there were two cases (2.7%) of nonunion. No cases of spontaneous fusion were seen in the L-ADR group.

There were no statistical differences in the risk of all, device related, or major adverse events/complications between patients receiving L-ADR compared with fusion in the two index randomized controlled trials, Table 18. There were no reports of death relating to the device or surgical procedure with either ADR or fusion in either study. A list of all recorded adverse events from each study is found in Appendix F.

Table 18. Risk of all, device related and major adverse events/complications for the two index randomized controlled trials comparing L-ADR with fusion

Blum	enthal			Zigler		
Adverse events/complications	ADR (n = 205) no. (%)	Fusion (n = 99) no. (%)	Risk difference* (95% CI)	ADR (n = 162) no. (%)	Fusion (n = 80) no. (%)	Risk difference* (95% CI)
All irrespective of relationship to treatment	156 (76.1)	77 (77.8)	-0.02 (-0.12, 0.08)	136 (84.0)	70 (87.5)	-0.04 (-0.13, 0.06)
Device related	15 (7.3)	4 (4.0)	0.03 (-0.02, 0.09)	29 (17.9)	16 (20.0)	-0.02 (-0.13, 0.08)
Major complications	2 (1.0)	1 (1.0)	-0.00 (-0.02, 0.02)	0 (0.0)	0 (0.0)	0

*A negative risk difference signifies a benefit for L-ADR. There is no statistical difference between L-ADR and fusion groups in either study.

Other complications reported in case-series

Complications following L-ADR were reported for 1319 patients from 22 case-series. Risks of complication were calculated using the number of patients at follow-up when available. When follow-up data were not available, risks were calculated using the number of patients at the start of the study, which may underestimate the actual rate of complications for some studies. Mean follow-up ranged from 6 months to 17 years. In general, complication risks varied widely between studies, Table 19. Different length of follow-up, different patient populations and varying definitions of complications could partially explain the wide range in risks.

Two case-series with a minimum follow-up of at least 10 years have been reported evaluating the rate of heterotopic ossification or spontaneous fusion.[45,131] David et al[45] reported a heterotopic ossification or spontaneous fusion frequency of 2.8% for Charité ADR while Putzier et al[131]

reported a frequency of 60%. The former study changed the postoperative regimen to active physiotherapy beginning on the sixth postoperative day while Putzier et al kept patients in a brace with no active motion for 8 weeks following surgery. The postoperative motion protocol may explain the large difference in the incidence of heterotopic ossification or spontaneous fusion between these two studies.

Table 19. Complications following L-ADR reported from case-series

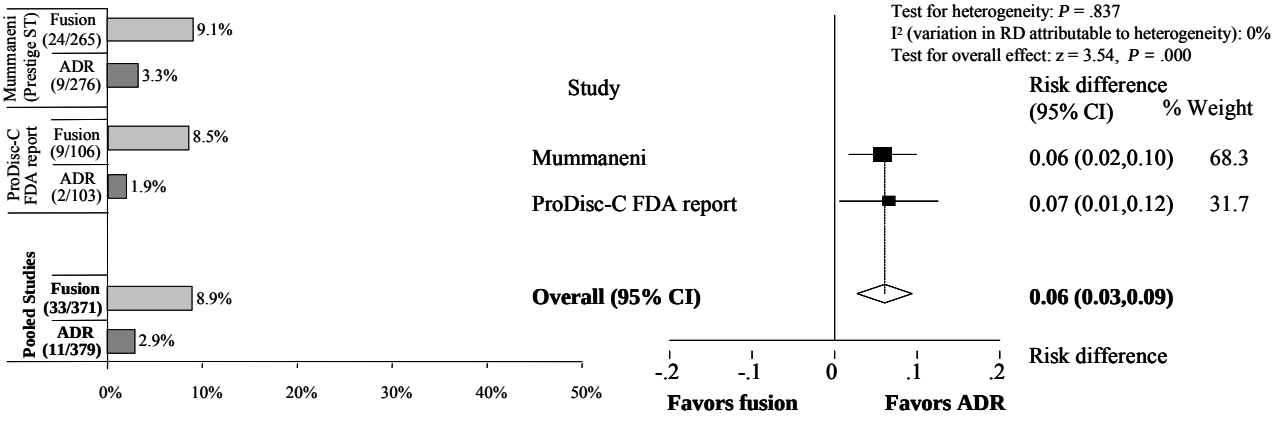
Complication	No. of studies	No. of patients with complication	Range of rates reported
New or residual pain	13 [20,25,39,42,45,56,95,107,131,157,158,170]	67 1.	0%-36.9%
Vein or vessel laceration	7 [39,95,97,148,157,164,170]	10	1.6%-5.6%
Hematoma	3 [25,149,170]	17	1.0%-28.3%
Retrograde ejaculation	5 [24,25,56,97,157,170]	5	1.0%-4.0%
Heterotopic ossification	8 [35,42,45,56,95,97,131,149]	28	1.0%-60.0%
Prosthesis migration	3 [35,95,130]	15	7.8%-10.7%
Subsidence	8 [24,45,95,97,130,131,148,157]	54	1.6%-52%
Prosthesis malposition	4 [42,149,158,170]	8	1.0%-7.0%
Secondary fusion	4 [35,42,45,131]	37	5%-23%
Disc replacement surgery	1 [45]	6	5.7%

Cervical

Device failure

Using the baseline sample size as reference (ITT analysis), the frequency of device failure (defined as reoperation, revision, or removal of the implant) was 2.9% in the C-ADR group compared with 8.9% in the ACDF group, risk difference of 6.0% (95% CI 2.6%, 9.3%; *P* = .0005), Figure 30. The risk difference of 6% equates to a number-needed-to-treat (NNT) of 17; that is, for every 17 patients who receive C-ADR instead of anterior cervical fusion among patients with the same cervical disease as those in the studies, 1 additional patient will avoid device failure during the first 24 months following surgery.

Figure 30. Device failure for C-ADR (reoperation, revision, or removal of the implant)



Complications or adverse events

The Prestige ST FDA SSED reported five cases of hardware removal in the C-ADR group (1.8%) compared with nine cases in the ACDF group (3.5%). There were four (1.4%) reoperations in the C-ADR group, two for unresolved neck pain, one for unresolved arm pain and one for both neck and arm pain. The ACDF group sustained five revisions (2%), eight supplemental fixations (3%), and two reoperations (1%). Device related or device/surgical procedure related adverse events occurred less frequently in the C-ADR group (3.3%) compared with the ACDF group (9.8%), risk difference of 7% (95% CI 2%, 11%), Table 11.

The Prodisc-C FDA SSED reported two implant related adverse events in two C-ADR patients and nine implant related adverse events in seven ACDF patients. There were no statistical difference between C-ADR and ACDF with respect to all adverse events (P=1.0), device-related adverse events (P = .17) or surgery-related adverse events (P = .41). Major complications (severe or life threaten adverse events) occurred less frequently in the C-ADR group (15.5%) compared with ACDF group (30.2%), risk difference of 15% (95% CI 3%, 26%), Table 11. Heterotopic ossification resulting in loss of motion (<2°) was found in three Prodisc-C patients.

The Bryan FDA Panel Executive Summary reported similar proportions of serious adverse events (WHO grade 3 or 4) between the C-ADR and ACDF groups, 26.4% versus 24.9%. Implant or surgical procedure related serious adverse events occurred in 1.7% of the C-ADR group and 3.2% in the ACDF group. Subsequent surgical interventions and implant migration/failure related adverse events were reported in 2.5% and 2.9% in the C-ADR group, and 4.1% and 5.4% in the ACDF group, respectively.

Additional detail of complications for the five clinical trials is found in Appendix F.

Table 20. Risk of all, device related and major adverse events/complications for the three FDA randomized controlled trials comparing C-ADR with fusion

	Prestige ST FDA trial			Prodisc FDA trial			Bryan FDA trial*		
Adverse events/complications	ADR (n = 276) no. (%)	Fusion (n = 265) no. (%)	Risk difference† (95% CI)	ADR (n = 103) no. (%)	Fusion (n = 106) no. (%)	Risk difference† (95% CI)	ADR (n = 242) no. (%)	Fusion (n = 221) no. (%)	Risk difference† (95% CI)
All irrespective of relationship to treatment	226 (81.9)	212 (80.0)	0.01 (-0.04, 0.07)	84 (81.6)	86 (81.1)	-0.0 (-0.10, 0.11)	202 (83.5)	174 (78.7)	0.05 (-0.02, 0.12)
Major complications (severe or life threatening)	NR	NR	NR	16 (15.5)	32 (30.2)	-0.15 (-0.26, -0.03)	64 (26.4)	55 (24.9)	0.02 (-0.06, 0.10)
Device related or device/surgical procedure related	9 (3.3)	26 (9.8)	-.07 (-0.11, -0.02)	13 (12.6)	23 (21.7)	-0.09 (-0.19, 0.01)	7 (2.9)	12 (5.4)	-0.03 (-0.06, 0.01)

NR = not reported.

*As reported in the FDA Executive Summary for the full enrolled population, even though the primary analysis focused on 300 who had completed 24 months follow-up.

†A negative risk difference signifies a benefit for C-ADR. There is a statistical difference between C-ADR and fusion groups in for device related adverse events for the Prestige ST trial and for major complications for the Prodisc trial in favor of C-ADR.

Complications from case-series

Other complications reported in case-series (Table 21)
Complications following cervical ADR were reported for 950 patients from 22 case-series. Complication rates were calculated using the number of patients at follow-up when available. When follow-up data was not available, rates were calculated using the number of patients at the start of the study, which may underestimate the actual rate of complications for some studies. Mean follow-up ranged from 4 to 48 months.

Increased or new pain was reported in 42 patients in eight of the studies[50,66,125,128,137,145,147,162] ranging from 1.3%[137] to 33.3%.[162] Hematomas were observed in nine patients over eight studies[19,23,66,74,84,125,137,166] ranging from 0%[19,23] to 4.0%.[84] Dysphonia or other vocal cord problems were reported in six patients in four of the studies[50,90,93,162] ranging from 0%[90] to 13.3%.[162] Dysphagia was also noted in 51 patients in three studies[50,84,90] ranging from 0%[90] to 100%.[84] Heterotopic ossification was reported in 23 patients (grades 1 and 2 in ten; grades 3 and 4 in 13) over six studies[12,19,74,98,125,165] ranging from 0%[12,19,165] to 17.8%[98] and in 48 levels/segments (all grades 1 and 2) in two studies, rate of disease ranging from 0% to 62.2%.[74,113]

Device migration or suspected migration was observed in seven patients in eight of the studies[19,23,50,55,66,74,125,127] ranging from 0%[19,23,55,74] to 4.1%.[125] Revision decompression surgery was necessary in three patients over two studies ranging from 1.4%[66] to 1.6%.[147] Removal of the artificial disc and subsequent fusion was reported in four patients over four studies[128,136,137,162] ranging from 1.3%[137] to 10.0%.[128] Adjacent level surgery was performed in three patients over three studies[66,137,162] ranging from 1.3%[137] to 6.7%.[162]

Since case-series do not include comparisons to other treatments, have variable lengths of follow-up, often do not provide adequate information on loss to follow-up and may be subject to bias, rates should be interpreted with some caution.

Table 21. Complications following C-ADR reported from case-series

Complication	No. of studies	No. of patients with complication	Range of rates reported
New or residual pain	8[50,66,125,128,137,145,147,162]	42	1.3%-33.3%
Hematoma	8[19,23,66,74,84,125,137,166]	9	0%-4.0%
Dysphonia	4[50,90,93,162]	6	0%-13.3%
Dysphagia	3[50,84,90]	51	0%-100%
Heterotopic ossification	7[12,19,74,98,113,125,165]	23	0%-17.8% 62.2%*
Migration or suspected migration of the device	8[19,23,50,55,66,74,125,127]	7	0%-4.1%
Revision decompression surgery	2[66,147]	3	1.4%-1.6%
Device removal	4[128,136,137,162]	4	1.3%-10.0%
Adjacent level surgery	3[66,137,162]	3	1.3%-6.7%

*Proportion based on number of segments with signs of ossification

FDA's Manufacturer and User Facility Device Experience (MAUDE)
The FDA's MAUDE data base of adverse events (updated on March 27, 2008) was searched. Approximately 500 adverse event reports have been made related to artificial discs overall. Report initiators include manufacturers, clinical users/providers, attorneys, and patients. It is unclear how many are unique reports. Some provide information regarding the severity, type, and resolution of adverse events while others do not. Summary and categorization of these is beyond the scope of this report and since no denominator information is available to provide rate information, it is not possible to put these reports into a meaningful context.

3.3 Key Question 3 - What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

Lumbar
Three reports were found evaluating the L-ADR in subpopulations: the elderly (> 60 years of age), athletes, and smokers. No studies were found evaluating L-ADR in workers compensation populations. Due to the nature of the study design (two case-series and one cohort study), the size of the populations and the length of follow-up, no firm conclusions can be drawn with respect to L-ADR in special populations.

The elderly (> 60 years of age)
Bertagnoli et al[22] reported on 22 patients with mean age of 63 years (range 61-71 years) presenting with discogenic low back pain (LBP) with or without radicular pain. Patients had no evidence of spinal stenosis and minimal or no facet joint degeneration. Seventeen patients received single-level replacement, four two-level replacement, and one three-level replacement. Statistical improvements in VAS, ODI, and patient satisfaction scores were observed at early (3 months postoperatively) and late (24 month postoperatively) time periods. Patient satisfaction was reported by 94% of the patients at 24 months. There were two cases involving neurological deterioration; both occurred in patients in whom there was evidence of circumferential spinal stenosis before surgery. There were two cases of implant subsidence and no thromboembolic phenomena. The investigators cautiously recommend the use of artificial disc replacement in the treatment of chronic discogenic LBP in patients older than age 60 years in whom bone quality is adequate in the absence of circumferential spinal stenosis.

Athletes
Siepe et al[150] evaluated the results of Prodisc-L in 39 patients involved in high level athletics or extreme sport. Significant pain relief was attained following L-ADR with a mean follow-up of 26.3 months (range 9-50.7 months). Thirty-seven patients (94.9%) resumed their sporting activity, most improving their performance significantly. Minor subsidence was observed in 13 patients (30%). Preoperative participation in sport was strong positive predictor for highly satisfactory postoperative outcome. The investigators concluded that due to the young age of the patients and significant load increase exerted during athletic activities, a longer follow-up will be required to assess the effectiveness of L-ADR in this population.

Smokers
Bertagnoli et al[21] conducted a prospective cohort study in 104 patients with disabling discogenic low back pain treated with single-level Prodisc-L ADR. Smokers and nonsmokers were assessed before surgery and after surgery using patient satisfaction, Oswestry, and Visual Analog Scores. There were no differences between smokers and nonsmokers at two year follow-up with respect to any of the effectiveness outcomes. There were no cases of loosening, dislodgment, mechanical failure, infection, or fusion of the affected segment in either group. The authors concluded that smokers do equally well compared with nonsmokers when Prodisc-L ADR is used in the treatment of debilitating lumbar spondylosis.

Cervical

No studies evaluating C-ADR within special populations or subpopulations were identified.

3.4 Key Question 4: What are the cost implications and cost effectiveness for ADR?

Critical Appraisal, lumbar

Two studies comparing arthroplasty costs with fusion costs as a competing alternative were included.[68,100] Neither is a full economic evaluation. Critical appraisal, based on the items of the Quality of Health Economic Studies (QHES) instrument and epidemiologic principles, indicates that there are insufficient data for full economic evaluation or extensive conclusions and that potential biases should be considered in the interpretation of these studies. Weighted QHES scores were low at 57 and 59 [possible score 0 (worst) to 100 (best)] for Guyer and Levin respectively.

Both papers are costing studies, not cost-effectiveness or cost-utility analyses, and therefore are considered partial economic analyses. It is well accepted that cost analyses are not considered full economic evaluations. Theoretically, a cost-minimization study (one that compares costs of the alternatives assuming equal effectiveness) might provide a complete economic evaluation, but because of uncertainty around costs and quality of life outcomes that likely differ between alternative interventions this is rarely possible.[49] In addition, when data from trials using a non-inferiority design are used to establish equivalence, the choice of outcome, methods of evaluating outcome proportions and determination of statistical power need to be considered in the design of cost-minimization studies.[153]

Both papers make the assumption that L-ADR and any type of fusion have equivalent clinical outcomes. Both studies, however mention that outcomes for different types of fusion may be different. The assumption of equivalent outcomes, even if appropriate on some outcome measures, prohibits a rigorous examination of qualitative differences between treatment alternatives considering patient experience and long-term clinical outcomes. Neither paper provides a transparent assessment of how, and for which outcomes, they established equivalence. These two papers do provide data that begin to describe the cost of lumbar ADR in the short term. However, neither paper adequately describes the cost of longer-term complications (eg, adjacent segment disease) or lost productivity and other quality of life considerations. Neither study was designed to provide an incremental analysis of the overall *value* of L-ADR, measured

as a cost per clinical outcome achieved, compared with fusion in the context of patient-reported outcomes.

The Levin study provides cost data only for operating room, devices, and physician (surgeon and anesthesiologist) Medicare fees at the time of the index procedure. Since the long-term effects of ADR as a surgical treatment alternative for DDD could vary significantly and could involve hospital charges, a model that includes an appropriate time horizon would provide a more complete picture of costs and should be linked to specific patient outcomes. The Guyer study provides a series of direct cost models from hospital or payer perspectives, and assumes equivalent clinical benefit for each alternative. Costs for single-level L-ADR are compared with different fusion options which included an unknown number of multilevel fusions, Table 22. Although the authors made an adjustment which they believe would adjust the fusion costs downward, it is unclear what the true effect may be. In addition, the patient population used in building these models was not clearly described, so the comparability of patients, generalizability, and potential for selection bias are unknown. Both report mean costs (without ranges or standard deviations), which may or may not reflect the typical values as costs frequently have skewed distributions.

Table 22. Overview of included partial economic analyses comparing lumbar ADR and fusion

	Design	Data sources and Population	Primary Strengths	Primary Limitations
Levin	▪ Cost analysis ▪ Hospital perspective ▪ 2006 USD (inflation corrected) ▪ Authors indicate no funding received for study	▪ Hospital charges ▪ Physician Medicare reimbursement scale used ▪ Demographics N = 53 Female: 38%; Age 39 (22-55); BMI mean 26.9	▪ Prospective design ▪ Data from RCT (FDA IDE trial) ▪ Provided demographic information and inclusion/exclusion criteria	▪ Inpatient costs not reported ▪ Small sample size (N = 53) particularly when divided into 1 and 2 level procedures. ▪ Sample reflects data from one site of multicenter trial ▪ Only short term costs included (index operation only) ▪ Did not compare effectiveness of alternatives ▪ Sensitivity analyses not reported
Guyer	▪ Cost minimization analysis ▪ Hospital and payer perspectives ▪ 2006 USD ▪ Authors acknowledge financial relationship with DePuy and use of DePuy consultant for the study	▪ Commercial payers claims data from hospital and Milliman Database ▪ Demographics: Not reported	▪ Description of included costs and assumptions is reasonably complete ▪ Provision of several models based on different perspectives and different types of fusion ▪ Authors attempted to adjust for inconsistencies in cost related to number of levels.	▪ No demographic description of patient populations to evaluate comparability or generalizability ▪ Method of selecting patients and claims data unclear ▪ Fusion costs included unknown numbers of multi-level procedures while ADR is single-level ▪ Discounting of costs beyond one year not reported ▪ Comparison of outcomes, effectiveness of alternatives not reported ▪ Sensitivity analyses not reported

Results:

Both studies suggest that mean L-ADR costs may be lower or at least similar to those for fusion, depending on the levels compared, types of fusion, and perspective. However, the limitations of the studies should be borne in mind.

From a hospital cost perspective, both studies suggest that L-ADR may be less costly than fusion.

- In one study, one-level L-ADR had significantly lower mean total cost compared with one-level fusion (difference, $10,688 or 23% less) while there was no statistically significant difference between groups when two-level procedures were compared. Mean totals are based on a sum of mean charges for operating room and implants with Medicare-based fees for surgeon and anesthesiologist (Figure 31).[100]
- Total costs for lumbar single-level L-ADR were also less by 12%-36% (difference, $1995-$6087) compared with various fusion options in the other study (Figure 32).[68] Cost included facility, therapy, devices/medications/supplies, diagnostic tests, and other costs. Costs for fusion include an unknown number of multilevel procedures and authors adjusted the estimates downward by a factor of 0.78 to account for this.

Figure 31. Comparison of mean total hospital charges for ProDisc-L ADR and circumferential fusion based on numbers of levels involved[100]

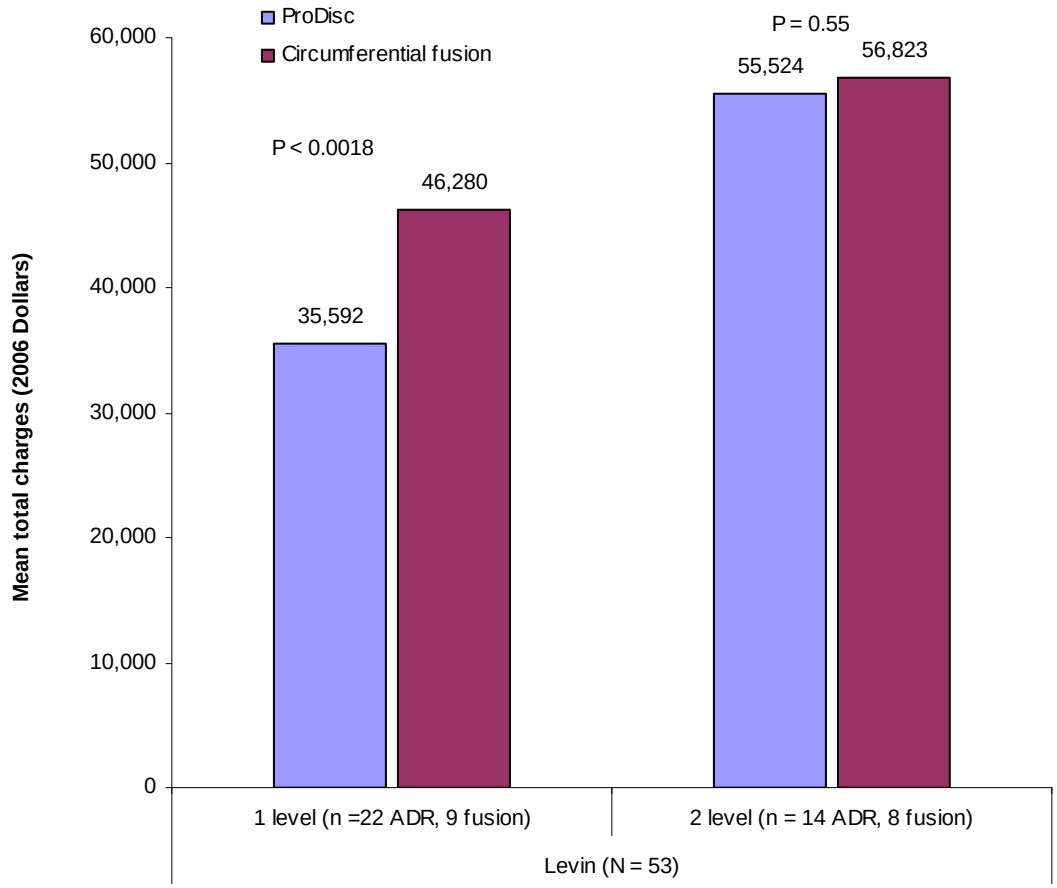
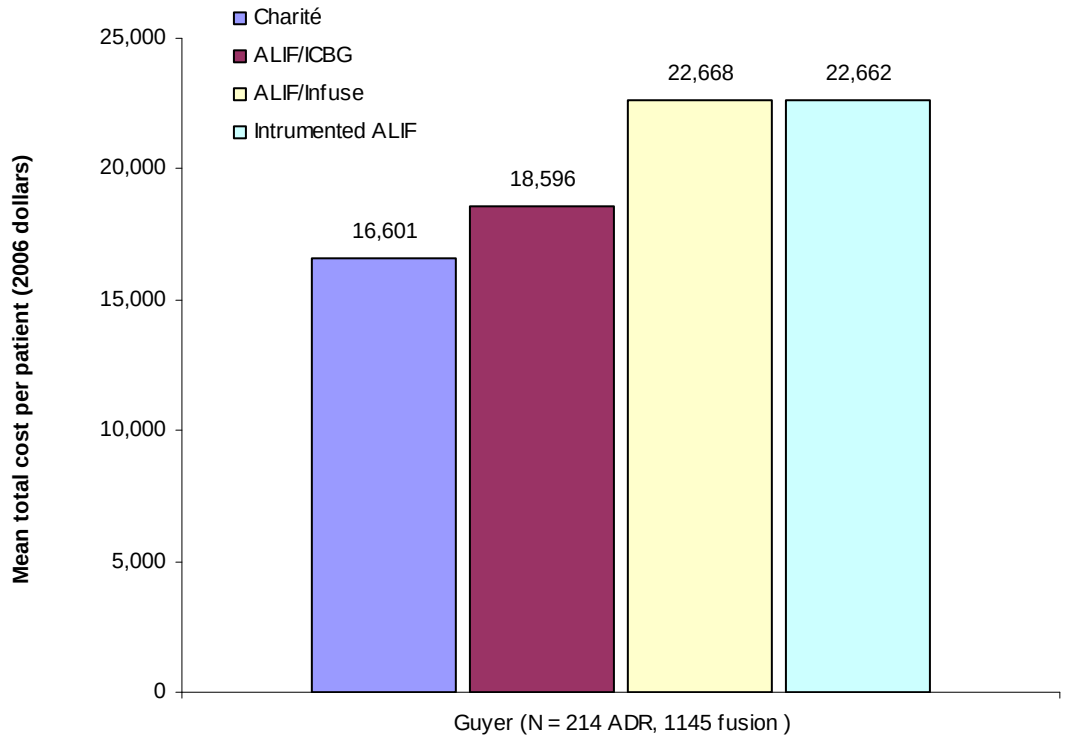


Figure 32. Comparison of mean total costs from hospital perspective (per diem and DRG payment arms) for Charité L-ADR and various fusion procedures[68]



The Guyer study demonstrates that different perspectives can provide different cost estimates (see table 23). The only difference between the perspectives is in the cost of the index procedure implant, with the other cost estimates remaining the same (including follow-up care, revision surgery, and complications). The per diem methodology is based on payer costs using a pre-established, fixed payment for a patient care-day and 100% of implant costs. Compared with ALIF with Infuse or ALIF with instrumentation, the Charité L-ADR total costs were lower in both scenarios.

Table 23. Summary of mean total costs (2006 USD) from different payer perspectives as reported by Guyer for L-ADR

	Payer perspective: DRG arm				Payer perspective: Per diem payment			
Cost Category	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**	**Charité**	**ALIF/ICBG**	**ALIF/Infuse**	**PLIF/Instrument**
Index Procedure	9611	22,338 22,	165	24,663	16,822	13,156 18,	861	21,231
Other costs	8002	10,621 10,	031	10,389	8002	10,621 10,	031	10,389
Total per patient cost	17,614	32,960 32,	196	35,,052	24, 885	23,778 18,	892	31,620
Compared with Charité (%)	- +	87%	+82.8%	+99.0%	-	-.4.4	+16.1	+27.1

ALIF = anterior lumbar interbody fusion.
ICBG = iliac crest bone graft.
PLIF = posterior lumbar interbody fusion.

Levin describes mean length of hospital stay, estimated blood loss, and average length of surgery but does not describe in terms of a cost analysis or impact. No significant differences were reported with regard to mean length of stay with L-ADR patients averaging 4.78 days versus 4.32 days for fusion. Mean estimated blood loss was significantly higher in the L-ADR group (794 mL) compared with fusion (412 mL, $P = .0058$) however the length of surgery for L-ADR was significantly less (185 minutes) compared with fusion (344 minutes, $P < .0001$).[100]

Research recommendations:

These papers could be considered a starting point for full economic evaluation as they present data on hospital charges that may be useful in the development of a more complete model of the cost-effectiveness for L-ADR compared with fusion. Such a model would include a clear statement of perspective, time horizon, and quality-adjusted outcome measures. The downstream outcomes for both ADR and fusion need to be articulated and the potential influence of different types of fusion needs to be more fully considered. In addition, specification of patient populations is needed. Sensitivity analyses incorporating the ranges of various costs and examining the various assumptions are necessary as well to examine the stability of estimates.

Economic analyses from other HTAs

Two previously performed HTAs, one from Ontario and one from Australia provided economic analyses. Differences in health care systems, practice patterns and reimbursement mechanisms need to be considered when reviewing the results. For example, in Ontario, diffusion of artificial discs is controlled by hospitals based on global budgets.

The most thorough evaluation was reported by the Medical Services Advisory Committee (MSAC) of the Commonwealth of Australia. Direct costs (discounted at 5% per annum) for hospital care, prostheses, and medical fees for both public and private hospitals were used to compare the Charité device (based on the index RCT) with two different fusion methods (screw and rod/plate or interbody fusion). Overall clinical success as defined in the Charité trial was used as the best comparator of clinical effectiveness and equivalence of L-ADR and fusion was

assumed for this outcome. However, not all randomized patients had completed the 24 month follow-up and it is not clear what denominator may have been used for success rates (ie, intention to treat or other). In addition to a base case scenario, one-way sensitivity analyses which first assumed a lower devices price and then the higher device prices from price ranges provided by manufacturers. An incremental increase in cost of L-ADR was estimated at $1054 (Australian Dollars) when all fusion methods were included up to a higher estimate of $7570 based on sensitivity analysis. When interbody fusion alone was considered as the competing alternative, a cost *savings* of $3458 for L-ADR was projected as a base case ranging to an increased cost of $262 based on sensitivity analysis. The prosthesis costs were the primary driver of the differences.

The Ontario assessment estimates an incremental increase of $4060 (Canadian Dollars) for use of L-ADR verses fusion, based on a mean prosthesis costs obtained from manufacturers, professional fee schedules, and median hospital costs for 148 fusion cases and five L-ADR cases.[155] Discounting of 3%-5% is mentioned in the standardized methods description. Sensitivity analyses, method of case selection and fusion methods compared are not reported. In addition, a very small number of ADR cases (5) were used for analyses.

Both reports suggest that approximately 5% of those patients eligible for lumbar fusion would be candidates for L-ADR based on indications and contraindications for the use of L-ADR,[112,155] an assumption also made by Huang and colleagues.[81] Assuming 5% substitution of L-ADR in lieu of fusion, estimated incremental costs incurred by the health sector ranged from $218,618 to $1,570,151(Australian Dollars) in the MSAC report. Budgetary impacts from these HTAs are difficult to interpret since long-term benefits and effectiveness are not well delineated.

The following limitations to the evaluations need to be considered:

- Data for some estimates may not be of the highest quality for either L-ADR or fusion
- Data on benefits and safety beyond 24 months are sparse and are of poor quality such that downstream costs cannot be determined. For example there are insufficient data on the rates of adjacent segment disease (ASD) and the extent to which they may differ for ADR compared with fusion or what the influence of follow-up care for graft site pain or use of synthetic proteins in fusion patients may have on estimates. In addition, it is unclear how L-ADR device failure in the long term may influence revision options and costs.
- The impact of rehabilitation following surgery was not included.
- The relative long term advantages of either procedure compared with nonsurgical treatment are not clear.

Implications of economic analyses:

The costing studies by Guyer and Levin suggest that L-ADR costs may be at least similar and perhaps less than those for fusion. This seems to be supported by the MSAC assessment if interbody fusion only is considered as the alternative; however it is not supported by the findings of the Ontario assessment. The fusion method used may influence cost and therefore differences in cost compared with L-ADR. Again the limitations of all of these evaluations need to be considered.

Within Washington State, the Comprehensive Hospital Abstract Reporting System (CHARS) contains hospital inpatient discharge information[10] including diagnostic and procedural information as well as billed charges based on DRGs (diagnosis-related groups). The data below provide a gross estimate of the numbers of ADR procedures since 2005 and costs. These charges include facility and ancillary charges but generally do *not* include physician charges.

Table 24. Summary of the number of lumbar ADR procedures performed and total charges for Washington State 2005-2007 based on CHARS data (DRG basis)

	L-ADR	
	number performed	**mean total charges x 0.50***
2005	29	$20,091
2006	44	$16,805
2007	16	$29,249
total	89	$20,113

*the multiplier of 50% provides a crude estimate of paid charges.

A number of limitations to these data need to be considered. First, this is not a formal economic analysis and is based on available data from CHARS. Second, there are a number of general limitations to the use of administrative data which include differences in coding practices across hospitals, possible miscoding of procedures and misclassification of diagnoses and the possibility of incomplete coding. Coding is primarily geared toward reimbursement. The ICD-9 CM codes capture conditions based on physician documentation and codes which may not relate to reimbursement may not be represented completely. While it is assumed that the primary diagnosis code is the most relevant to the respective procedures, this may not always be the case. Thus, numbers of unique cases may be underestimated.

With regard to actual device costs (or ranges) and diffusion of the technology, particularly in Washington State, Medtronic, DePuy, and Synthes were contacted but declined the opportunity to provide data.

Cervical

No formal economic analyses were found during the systematic literature search of peer-reviewed literature.

Economic analyses from other HTAs

One previously done assessment (Medical Services Advisory Committee (MSAC) of the Commonwealth of Australia) did provide an assessment for cervical arthroplasty.[112] Differences in health care systems, practice patterns and reimbursement mechanisms need to be considered when reviewing the results.

The analysis assumed that hospital costs for fusion and C-ADR were the same. The estimated incremental cost increase of $9,438 (range, $9,438 to $13,346) was attributed to the higher cost of the prosthesis when compared with any type of fusion. When interbody fusion only was the comparator, the incremental cost of C-ADR was slightly less at $8413 (range, $8,413 to $11,696). Although the report describes incremental cost for specific measures (e.g. quality

adjusted life year, QALY), data for outcomes were taken from a preliminary report of the Prestige-II disc randomized controlled trial representing four trial sites. Only 16% of the study population had reached 24 months of follow-up at the time of publication and thus, the evidence base for the determination is questionable.

Based on the assumption that 40% of cervical fusion patients would have C-ADR instead, estimated incremental costs incurred by the health sector ranged from $3,184,940 to $4,503,730 (Australian Dollars) based on sensitivity analyses around the lowest and highest ranges for C-ADR device costs. Budgetary impacts from this HTA are difficult to interpret since long-term benefits and effectiveness are not well delineated. In addition, there are a number of differences in health care delivery and reimbursement practices compared to the United States.

The following limitations to the evaluation need to be considered:

- Data for outcomes are from incomplete trial data supplied by sponsors
- Data on benefits and safety beyond 24 months are sparse and are of poor quality such that downstream costs cannot be determined. For example there are insufficient data on the rates of adjacent segment disease (ASD) and the extent to which they may differ for C-ADR compared with fusion over the long-term.
- The impact of rehabilitation following surgery was not included.

C-ADR in Washington State

Within Washington State, the Comprehensive Hospital Abstract Reporting System (CHARS) contains hospital inpatient discharge information[10] including diagnostic and procedural information as well as billed charges based on DRGs (diagnosis-related groups). The data below provide a gross estimate of the numbers of ADR procedures since 2005 and costs. These charges include facility and ancillary charges but generally do *not* include physician charges.

Table 25. Summary of the number of cervical ADR procedures performed and total charges for Washington State 2005-2007 based on CHARS data (DRG basis)

	C-ADR	
	number performed	**mean total charges x 0.50***
2005	17	$11,399
2006	14	$7,896
2007	25	$10,394
total	56	$14,344

*The multiplier of 50% provides a crude estimate of paid charges.

A number of limitations to these data need to be considered. First, this is not a formal economic analysis and is based on available data from CHARS. Second, there are a number of general limitations to the use of administrative data which include differences in coding practices across hospitals, possible miscoding of procedures and misclassification of diagnoses and the possibility of incomplete coding. Coding is primarily geared toward reimbursement. The ICD-9 CM codes capture conditions based on physician documentation and codes which may not relate to reimbursement may not be represented completely. While it is assumed that the primary

diagnosis code is the most relevant to the respective procedures, this may not always be the case. Thus, numbers of unique cases may be underestimated. Data may include patients who were part of IDE trials. The type of device or number of levels is unknown.

With regard to actual device costs (or ranges) and diffusion of the technology, particularly in Washington State, Medtronic, DePuy, and Synthes were contacted but declined the opportunity to provide data.

Summary and Implications

A summary of the overall strength of evidence for each key question can be found in Tables 26 and 27 below.

1. Efficacy/effectiveness of artificial disc replacement (ADR)

- Findings contained in this technology assessment reflect the use of lumbar or cervical ADR in patients who have failed conservative treatment. For the lumbar spine, conservative treatment for at least six months was required prior to study enrollment. For the cervical spine, six weeks of conservative treatment or a progression of neurological signs was an indication for ADR. Neither the type of conservative treatment nor the level of patient compliance with pre-study conservative treatment was detailed in the published studies used in this technology assessment and therefore, unknown.
- There is insufficient evidence to draw extensive efficacy/effectiveness conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the efficacy/effectiveness of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion. One study is underway that includes three surgical treatment arms for cervical radiculopathy: C-ADR versus anterior cervical discectomy without fusion versus anterior cervical discectomy with fusion (ACDF).
- With respect to the comparison of L-ADR and fusion, there is moderate evidence that the efficacy/effectiveness of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery. This evidence is based on two moderate quality randomized controlled trials conducted as FDA Investigational Device Exemption non-inferiority trials. Overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving L-ADR and 48% receiving lumbar fusion. Though the results suggest that 24 month outcomes for L-ADR are similar to lumbar fusion, it should be noted that a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question.
- There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index, and pain up to two years following surgery. The evidence is based on two moderate quality randomized controlled FDA Investigational Device Exemption non-inferiority trials. An

interim analysis of approximately 65% of a third RCT was reported in an FDA Panel Executive Summary. If the results following completion of the trial are similar to the interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase.

- There is evidence that segmental motion is maintained or improved up to three years in the L-ADR patients and up to four years in C-ADR patients compared with preoperative motion. It is unclear the true extent to which preserving segmental motion by using ADR instead of fusion influences rates of adjacent segment disease (ASD). Whether ASD is a continuation of a disease process necessitating fusion or a result of fusion continues to be disputed. Furthermore, there continues to be debate on whether the presence of ASD is clinically important given that patients with marked radiographic ASD often have no symptoms.

2. Safety of artificial disc replacement (ADR)

- There is insufficient evidence to draw extensive safety conclusions comparing ADR with a broad range of treatment options. There are no direct comparisons of either lumbar or cervical ADR with continued conservative nonoperative care. Other than spinal fusion, there are currently no direct comparison studies to assess the safety of either lumbar or cervical ADR compared with other forms of surgical intervention such as discectomy without fusion.

- There is moderate evidence that L-ADR is as safe as lumbar anterior or circumferential fusion, and that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery.
- There is insufficient data at this time to determine the longer term safety of both L-ADR and C-ADR.

3. Special or subpopulations

- There is insufficient evidence to draw conclusions regarding the safety and efficacy of L-ADR in the few special populations studied (elderly, smokers, athletes). No studies or sub-analyses were found on the use of C-ADR in special or subpopulations.

4. Economic implications

- There are inadequate data from partial economic studies reflecting short time horizons for L-ADR and no economic studies for C-ADR to truly assess the potential cost-effectiveness of ADR technology. One report and one previously done HTA suggest that the type of fusion may influence complication rates and therefore costs.

5. Additional implications

- The studies primarily reflect outcomes measured up to 24 months and therefore questions remain regarding the longer term safety and efficacy of L-ADR or C-ADR compared with fusion. This is an important matter, particularly in those receiving C-ADR where the

average age is near 45 years. Since these are mechanical devices, future failure is a possibility and may influence complication rates and costs in the longer-term.

- Findings contained in this report primarily reflect use of ADR at a single level and it may not be appropriate to extrapolate the results to patients with ADR at multiple levels or for indications other than those evaluated during the FDA trials. As diffusion of these devices increases and they are used for additional indications, the safety and efficacy profiles may change.
- Studies which met the inclusion criteria for this report encompassed only two biomechanical types, an unconstrained device and a semiconstrained device. While it was deemed reasonable to pool information from trials despite difference in device design, it is probably appropriate to consider that such differences may influence longer term outcomes. There are a variety of different biomechanical designs for ADR. There is limited data which directly compare outcomes and complications for different devices in the short-term or longer term and thus, the influence of different designs is unknown.
- One study suggests that surgeons and institutions with a high volume of L-ADR cases have shorter operating time and hospital stay, and lower complication rates which may have an economic effect. No effect on clinical outcomes was reported between high and low volume surgeons or institutions.

Table 26. Summary of overall strength of evidence for key questions pertaining to L-ADR

Key Question 1: Efficacy/effectiveness of L-ADR compared with nonoperative care, lumbar fusion, other surgical procedures					
		Domain Criterion Quality: ≥ 80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
L-ADR versus:	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Nonoperative care	**No evidence**	• There is no evidence from studies directly comparing L-ADR with non-operative care for degenerative disc disease	none	no	ne	none
2. Lumbar fusion • Overall clinical success • ODI • Pain • Neurological success • SF-36 • Patient satisfaction • Preservation of motion	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that L-ADR is as good or slightly better than lumbar fusion with respect to overall clinical success, functional improvement (ODI), pain reduction, neurological success, SF-36 improvement, and patient satisfaction two years following surgery • Motion at the index segment for L-ADR is maintained or improved compared with preoperative levels up to 3 years following surgery, and in two small studies, similar to asymptomatic controls >10 years following surgery • There are no long-term follow-up data assessing efficacy/effectiveness from the two index RCTs at this time	+	–	+
3. Other surgical procedures	**No evidence**	• There is no evidence from studies directly comparing L-ADR with surgical procedures other than lumbar fusion for degenerative disc disease	none	no	ne	none
Key Question 2: What is the evidence related to the L-ADR safety profile (including device failure, reoperation)?					
1. Device failure	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that the frequency of device failure (reoperation, revision or removal of the implant) among patients receiving L-ADR (< 6%) is similar to device failure among those receiving lumbar fusion (≤ 8%) • There is insufficient data at this time to determine the longer term safety of L-ADR.	+	–	+
2. Complications or adverse events	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that L-ADR results in a similar proportion of device-related complications (7 to 18%) compared with lumbar fusion (4 to 20%) • There is moderate evidence that L-ADR results in a similar proportion of major complications (0 to 1%) compared with lumbar fusion (0 to 1%) • There are no long-term follow-up data assessing safety from the two index RCTs at this time	+	–	+

Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations?					
		Domain Criterion Quality: ≥80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Age	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that L-ADR may be effective in select patients (those with good bone quality and absent circumferential spinal stenosis) older than 60 years	–	–	–
2. Athletes	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that L-ADR may be effective in high level athletes in the short term among those who were athletic participants preoperatively	–	–	–
3. Smokers	**Very low** (Any effect estimate is uncertain)	• There is very low evidence to suggest that smoking status may not affect the short term results of L-ADR	–	–	–
Study Question 4: What are the cost implications and cost effectiveness for ADR?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Hospital perspective	**Very low** (Any effect estimate is uncertain)	• There is very low evidence from 2 costing reports (partial economic studies) to suggest that mean L-ADR costs may be less than those for fusion from a hospital perspective for the index procedure	–	–	+
2. Payer perspective	**Very low** (Any effect estimate is uncertain)	• There is very low evidence from 1 costing report to suggest that L-ADR costs may be lower than any type of fusion based DRGs • There is very low evidence from the same report that incremental cost savings from L-ADR may depend on type of fusion using a per diem approach • The time horizon of 2 years may be too short to adequately assess downstream costs or benefits • Analyses from previous HTAs in other countries had conflicting results and suggest that type of fusion may influence cost evaluations	–	–	–

*Majority of characteristics for high quality, full economic studies, and modeling as described in Appendix B are met.

Table 27. Summary of overall strength of evidence for key questions pertaining to C-ADR

Key Question 1: Efficacy/effectiveness of C-ADR compared with nonoperative care, cervical fusion, other surgical procedures					
		Domain Criterion Quality: ≥ 80% of studies LoE I or II Quantity: 3+ studies adequately powered Consistency: Results lead to similar conclusions			
C-ADR versus:	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Nonoperative care	**No evidence**	• There is no evidence from studies directly comparing C-ADR with non-operative care for degenerative disc disease	none no	ne	none
2. Anterior fusion • Overall clinical success • NDI • Pain • Neurological success • SF-36 • Patient satisfaction • Preservation of motion	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence that the proportion of patients achieving overall clinical success and neurological success at 24 months for C-ADR was significantly higher compared with patients receiving anterior cervical fusion (77% vs. 68% for clinical success, 92% vs. 86% for neurological success). This result is based on FDA criteria for overall success and pooled estimates from two completed trials and an interim FDA analysis of a 3rd trial. • Patients receiving either C-ADR or ACDF can expect reduced neck and arm pain following surgery compared with baseline pain status. There is no statistical difference between those receiving C-ADR and those receiving ACDF with respect to intensity or frequency of neck or arm pain • Improvement in disability (≥ 15 points over baseline in the NDI) was achieved by a similar proportion of patients receiving C-ADR and ACDF. • Segmental flexion-extension at the level of instrumentation was generally similar after C-ADR comparing preoperative motion with postoperative motion from 6–48 months following surgery. • The effect of C-ADR on adjacent segment disease remains unanswered. Studies with similar definitions of symptomatic adjacent segment disease with longer follow-up than two years will need to be conducted to answer this question. • There are no long-term follow-up data assessing efficacy/effectiveness from the 5 RCTs at this time	+	–	+
3. Other surgical procedures	**No evidence**	• There is no evidence from studies directly comparing C-ADR with surgical procedures other than cervical fusion for degenerative disc disease	none no	ne	none

Key Question 2: What is the evidence related to the C-ADR safety profile (including device failure, reoperation)?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Device failure	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• There is moderate evidence to suggest that C-ADR is safer than anterior cervical discectomy and fusion as measured by the risk of device failure or device/surgical procedure related adverse events or complications up to two years following surgery. • Device failure defined as reoperation, revision or removal of the implant, was less common among C-ADR recipients (3%) than anterior fusion patients (9%) within the 24 month trial period. • There is insufficient data at this time to determine the longer term safety of C-ADR.	+	–	+
2. Complications or adverse events	**Moderate evidence** (Further research likely to have an important impact on confidence in estimate and *may* change the estimate)	• Complication rates varied among the studies but generally device related or device/surgical procedure related complications or adverse events occurred less frequently among the C-ADR patients (5%) than anterior fusion patients (10%). • There are no long-term follow-up data assessing safety from the five index RCTs at this time	+	–	+
Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Special populations	**No evidence**	• There were no studies or sub-analyses found which describe the efficacy or safety in special populations	none	none	none
Study Question 4: What are the cost implications and cost effectiveness for ADR?					
	Strength of evidence	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Economic analyses	**No Evidence**	• There were no formal economic analyses found in the peer-reviewed literature	none	none	none

*Majority of characteristics for high quality, full economic studies, and modeling as described in Appendix B are met.

APPENDIX A. Search Strategies

Database: MEDLINE
Search Strategy: lumbar spine

For Key Question 1

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(CHARITÉ OR PRODISC* OR MAVERICK OR FLEXICORE OR MOBIDISC)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Lumbar Vertebrae"[Mesh] OR Lumbar[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8 LIMIT:	RCT

For Key Questions 2, 3

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(CHARITÉ OR PRODISC* OR MAVERICK OR FLEXICORE OR MOBIDISC)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Lumbar Vertebrae"[Mesh] OR Lumbar[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	#7 NOT (cadaver* OR case report OR finite element OR in vitro)
9	#8 NOT “Review “[Publication Type]
10	#9 NOT RCT
11	Limit: items with abstracts
12	English AND Human

Search Strategy: cervical spine

For Key Question 1

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(PRODISC* OR PRESTIGE OR Bryan OR porous coated motion OR PCM) OR mobi-c OR Kineflex* OR CerviCore or Discover)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Cervical Vertebrae"[Mesh] OR CERVICAL[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	LIMIT: RCT

For Key Questions 2, 3

1	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR replacement[TI] or arthroplasty[TI]
2	"Prosthesis Implantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Replacement"[Mesh] OR "Implants, Experimental"[Mesh]
3	(PRODISC* OR PRESTIGE OR Bryan OR porous coated motion OR PCM) OR mobi-c OR Kineflex* OR CerviCore or Discover)
4	Disk*[TI] OR Disc*[TI] OR "Intervertebral Disk"[Mesh]
5	"Cervical Vertebrae"[Mesh] OR CERVICAL[TI]
6	(#1 OR #2 OR #3)
7	#4 AND #5 AND #6
8	#7 NOT (cadaver* OR case report OR finite element OR in vitro)
9	#8 NOT “Review “[Publication Type]
10	Limit: items with abstracts

Database: EMBASE
Search Strategy: lumbar spine

1	exp Intervertebral Disk Degeneration/ or degenerative disc disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	exp Spine Fusion/
3	exp intervertebral disk/ or exp lumbar disk/ or exp lumbar vertebra/ or exp vertebra/
4	exp Spine Disease/
5	exp Lumbar Spine/ or exp Cervical Spine/
6	exp Backache/
7	exp intervertebral diskectomy/
8 or/1-7	
9	(dis$ adj1 (prosthe$ or artificial or replacement$ or arthrodesis or arthroplasty)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10	exp joint prosthesis/
11	exp bone prosthesis/
12	exp arthroplasty/
13 or/9-12	
14	8 and 13
15	(sb Charité or Prodisc or (Maverick adj1 disc) or (bryan adj1 disc) or active-l).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16	14 or 15 (802)
17	limit 16 to (human and english language and yr="2003 - 2008")
18	limit 17 to (editorial or letter or note)
19	Case Report/
20	17 not (18 or 19)

Search Strategy: cervical spine

1	exp Intervertebral Disk Degeneration/ or degenerative disc disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2	exp Spine Fusion/
3	exp intervertebral disk/ or exp cervical disk/ or exp cervical vertebra/ or exp vertebra/
4	exp Spine Disease/
5	exp Cervical Spine/
6	exp Neckache/
7	exp intervertebral diskectomy/
8 or/1-7	
9	(dis$ adj1 (prosthe$ or artificial or replacement$ or arthrodesis or arthroplasty)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10	exp joint prosthesis/
11	exp bone prosthesis/

12	exp arthroplasty/
13	or/9-12
14	8 and 13
15	(sb Prestige or Prodisc or (bryan adj1 disc) or active-l).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16	14 or 15 (802)
17	limit 16 to (human and english language and yr="2003 - 2008")
18	limit 17 to (editorial or letter or note)
19	Case Report/
20	17 not (18 or 19)

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches

The following databases have been searched for relevant information:
Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews (through 2007, Issue 2)
Cochrane Registry of Clinical Trials (CENTRAL) (through 2007, Issue 2)
Cochrane Review Methodology Database (through 2007, Issue 2)
Computer Retrieval of Information on Scientific Projects (CRISP)
Database of Reviews of Effectiveness (Cochrane Library) (through 2007, Issue 2)
EMBASE (1985 through April 15, 2007)
PubMed (1975 through April 15, 2007)
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database (Cochrane Library through 2007, Issue 2)
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ- Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX B. Level of Evidence Determination

Methods for critical appraisal and level of evidence assessment

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine,[123] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[16] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[160] Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Procedures for determining adherence to level of evidence (LoE) criteria

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table. For therapeutic articles, the criteria are listed in the Table below and an example is given. All criteria met are marked. A blank for the criterion indicates that the criterion was not met, could not be determined or was not reported by the author.

Table B.1. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size
II	Moderate or Poor quality RCT	• Violation of any of the criteria for good quality RCT
	Good quality Cohort	• Blind or independent assessment in a prospective study or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size • Controlling for possible confounding†
III	Moderate or Poor quality Cohort	• Violation of any of the criteria for good quality cohort
	Case Control	
IV	Case Series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Table B.2. Example of methods evaluation for articles on therapy

Methodological Principle	Author 1	Author 2	Author 3	Author 4
Study design				
Randomized controlled trial	■	■		
Cohort Study			■	
Case-series				■
Statement of concealed allocation*	■	■		
Intention to treat*	■	■		
Independent or blind assessment	■		■	
Co-interventions applied equally	■	■	■	
Complete follow-up of ≥85%	■			■
Adequate sample size	■	■	■	
Controlling for possible confounding	■	■	■	
Evidence Level	**I**	**II**	**III**	**IV**

* Applies to randomized controlled trials only.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence for diagnostic studies are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ.[160]

The following definitions are used by SRI to determine whether or not the body of evidence meets the criteria for each domain:

Domain	Definition/Criterion
Quality	• At least 80% of the studies are LoE I or II
Quantity	• There are at least three studies which are adequately powered to answer the study question
Consistency	• Study results would lead to a similar conclusion (similar values, in the same direction) in at least 70% of the studies

Based on the criteria described above, the possible scenarios that would be encountered are described below. Each scenario is ranked according to the impact that future research is likely to have on both the overall estimates of an effect and the confidence in the estimate. This ranking describes the overall "Strength of Evidence" (SoE) for the body of literature on a specific topic. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group[16] for the development of clinical guidelines.

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	**High**	Very unlikely to change confidence in effect estimate	+	+	+
2	**Moderate**	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	**Low**	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	**Very Low**	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al.[119] QHES embodies the primary components relevant for critical appraisal of economic studies.[36,119] It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention

comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (eg, complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (eg, were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:
- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument[119] **Study** _____

Questions	Points	Yes	No
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**		
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**		
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**		
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**		
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**		
6. Was incremental analysis performed between alternatives for resources and costs?	**6**		
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**		
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**		
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**		
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**		
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**		
16. Was there a statement disclosing the source of funding for the study?	**3**		
TOTAL POINTS	**100**		

APPENDIX C. Inclusion and Exclusion Criteria for the Index Randomized Controlled Trials Assessing ADR

Inclusion and Exclusion Criteria for the Two Index Randomized Controlled Trials Assessing L-ADR

Blumenthal et al (Charité L-ADR)

INCLUSION	EXCLUSION
• Male or female • Age 18 to 60 years • Symptomatic degenerative disc disease with objective evidence of lumbar DDD by CT or MR scan, followed by discogram • Single level disease at L4-L5 or L5-SI • Minimum of 6 months of unsuccessful conservative treatment • Oswestry Low Back Pain Disability Questionnaire ≥30 points • Patient a surgical candidate for an anterior approach to the lumbar spine (<3 abdominal surgeries) • Back pain at the operative level only (by discogram) • Leg pain and/or back pain in the absence of nerve root compression, per MRI or CT scan, without prolapse or narrowing of the lateral recess. • VAS ≥40mm • Able to comply with protocol • Informed consent • DDD is defined as discogenic back pain with degeneration of the disc as confirmed by history and radiographic studies with one or more of the following factors: • Contained herniated nucleus pulposus • Facet joint degeneration/changes • Decreased disc height by >2mm, and/or • Scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule	• Previous or other spinal surgery at any level, except prior discectomy, laminotomy, laminectomy, or nucleolysis at the same level • Multiple level degeneration • Previous trauma to the L4, L5, or S1 levels in compression or burst • Non-contained or extruded herniated nucleus pulposus • Mid-sagittal stenosis of <8mm (by CT or MR) • Spondylolisthesis >3mm • Lumbar scoliosis (>11º sagittal plane deformity) • Spinal tumor • Active systemic or surgical site infection • Facet joint arthrosis • Arachnoiditis • Isthmic spondylolisthesis • Chronic steroid use • Metal allergy • Pregnancy • Autoimmune disorders • Psychosocial disorders • Morbid obesity (BMI >40) • Bone growth stimulator use in spine • Investigational drug or device use within 30 days • Osteoporosis or osteopenia or metabolic bone disease • Positive single or bilateral straight leg raising test

Zigler et al (Prodisc-L ADR)

INCLUSION	EXCLUSION
• Degenerative Disc Disease (DDD) in one vertebral level between L3 and S1. Diagnosis of DDD requires back and/or leg (radicular pain); and radiographic confirmation of any 1 of the following by CT, MRI, discography, plain film, myelography and/or flexion/extension films: o Instability (≥ 3mm translation or ≥ 5° angulation); o Decreased disc height > 2mm; o Scarring/thickening of annulus fibrosis; o Herniated nucleus pulposus; or o Vacuum phenomenon • Age between 18 and 60 years • Failed at least 6 months of conservative treatment • Oswestry Low Back Pain Disability Questionnaire score of at least 20/50 (40%) (Interpreted as moderate/severe disability) • Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements and filling out of forms • Signed informed consent	• No more than 1 vertebral level may have DDD, and all diseased levels must be treated • Patients with involved vertebral endplates dimensionally smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions • Known allergy to titanium, polyethylene, cobalt, chromium or molybdenum • Prior fusion surgery at any vertebral level • Clinically compromised vertebral bodies at the affected level due to current or past trauma • Radiographic confirmation of facet joint disease or degeneration • Lytic spondylolisthesis or spinal stenosis • Degenerative spondylolisthesis of grade > 1 • Back or leg pain of unknown etiology • Osteopenia or osteoporosis: A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients to determine if a DEXA scan is required. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score < -2.5. • Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis which is addressed above) • Morbid obesity defined as a body mass index > 40 or a weight more than 100 lbs. over ideal body weight • Pregnant or interested in becoming pregnant in the next 3 years • Active infection – systemic or local • Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids) • Rheumatoid arthritis or other autoimmune disease • Systemic disease including AIDS, HIV, Hepatitis • Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years

Inclusion and Exclusion Criteria for the Five Index Randomized Controlled Trials Assessing C-ADR

Bryan Panel meeting (Bryan C-ADR)

INCLUSION	EXCLUSION
• DDD at single level between C3 and C7 • Disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy • 6 weeks minimum unsuccessful conservative unless myelopathy requiring immediate treatment • CT, myelography and CT, and/or MRI demonstration of need for surgical treatment • ≥21 years old • Preoperative NDI ≥ 30 and minimum one clinical sign associated with level to be treated • Willing to sign informed consent and comply with protocol	• Significant cervical anatomical deformity • Moderate to advanced spondylosis • Any combination of bridging osteophytes, marked reduction or absence of motion • Collapse of intervertebral disc space of > 50% normal height, radiographic signs of subluxation > 3.5 mm, angulation of disc space > 11° greater than adjacent segments, significant kyphotic deformity or reversal or lordosis • Axial neck pain as solitary symptom • Previous cervical spine surgery • Metabolic bone disease • Active systemic infection or infection at operative site • Known allergy to components of titanium, polyurethane, ethylene oxide residuals • Concomitant conditions requiring steroid treatment • Daily insulin management • Extreme obesity • Medical condition which may interfere with postop management program or may result in death prior to study completion • Pregnancy • Current or recent alcohol and/or drug abuser • Signs of being geographically unstable

Mummaneni et al (Prestige C-ADR)

INCLUSION	EXCLUSION
• adults >18 years of age • single level symptomatic DDD between C3-7 • intractable radiculopathy, myelopathy or both • NDI scores ≥ 30 • VAS neck pain scores ≥ 20 • preserved motion at the symptomatic level found in all included patients • unresponsive to ≥ 6 weeks conservative treatment or progressive neurological worsening despite conservative treatment • no previous procedures at the operative level • negative for several radiographic findings, medications, and diagnoses	• multilevel symptomatic DDD or evidence of cervical instability • sagittal plane translation of greater than 3.5 mm or sagittal plane angulation of greater than 20 degrees at a single level • symptomatic C2-C3 or C7-T1 disc disease • previous surgery at the involved level • severe facet joint disease at the involved level • history of discitis • osteoporosis • metastases • medical condition that required long-term use of medication such as steroid or nonsteroidal antiinflammatory drugs that could affect bone quality and fusion rates

Nabhan et al (Prodisc C-ADR)

INCLUSION	EXCLUSION
• monosegmental cervical DDD between C3-C7 • unresponsive to conservative treatment or presence of signs of nerve root compression with paresis • soft disc herniation • no myelopathy • age between 20-60 years • negative for specific radiographic findings, medications, and diagnoses • signed informed consent	• marked cervical instability on resting or flexion-extension radiographs • >11 of angulations • translation >3 mm • more than one level pathology • myelopathy • radiographic confirmation of severe facet joint degeneration • hard disc disease • osteoporosis, infection, rheumatiod arthritis • spondylodiscitis and active infection • malignant disease • system disease, eg hepatitis, HIV, AIDS • known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • traumatic injury of spine • pregnant or possible pregnancy in the next 3 years

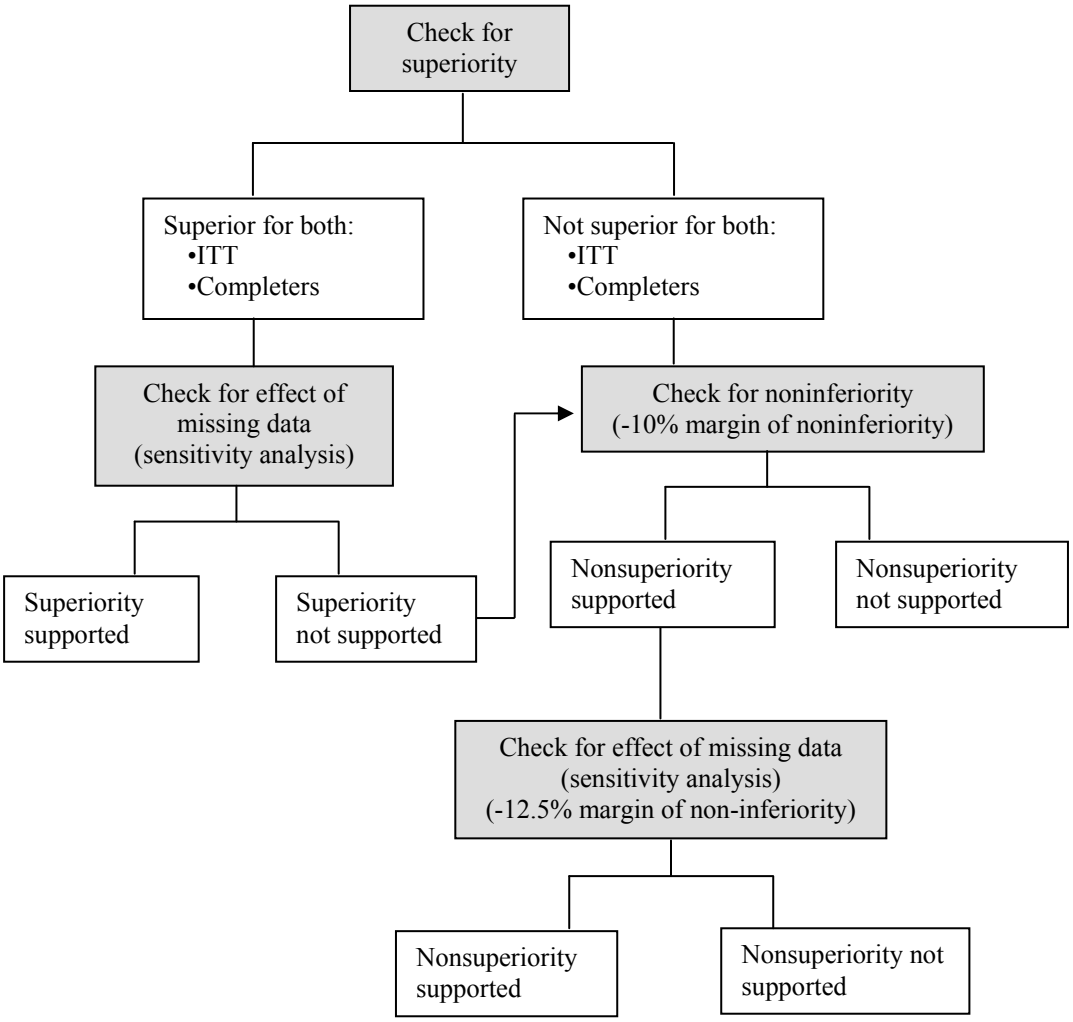
Sun Peng-Fei et al (C-ADR)

INCLUSION	EXCLUSION
• single C5-6 intervertebral disc hernia • failed conservative treatment w/ worsening symptoms	• NR

Prodisc C FDA (Prodisc C-ADR)

INCLUSION	EXCLUSION
• Symptomatic cervical disc disease (SCDD) in one level between C3-C7 • Age 18-60 years • Unresponsive to nonoperative treatment for six weeks or progressive symptoms • NDI ≥ 15/50 (30%) • Able to comply with protocol • Informed consent	• More than one vertebral level requiring treatment • Marked cervical instability ; translation > 3 mm or > 11° rotational difference • Fused level adjacent to level to be treated • Radiographically confirmed severe facet joint disease or degeneration • Allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • Clinically compromised vertebral bodies at affected level due to trauma • Prior surgery at level to be treated • Severe spondylosis at level to be treated • Neck or arm pain of unknown etiology • Osteoporosis • Metabolic bone disease • Daily insulin management • Pregnancy • Active infection, systemic or local • Medications or drug known to potentially interfere with healing (steroids) • Autoimmune disease including RA • Systemic disease including AIDS, HIV, hepatitis • Active malignancy within last 5 years

APPENDIX D. Decision Tree in Assessing Results for Clinical Success



APPENDIX E. Data Used for ADR Meta-Analysis

Spectrum Research, Inc. uses the statistical program STATA for meta-analysis. The following tables list the data used for meta-analyses.

LUMBAR ADR

1) Overall success at 24 months

1.1) Using baseline sample size as reference (ITT analysis)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	107	98	99	44	55
2	Zigler	161	79	82	75	29	46

1.2) Using completers only

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	184	107	77	81	44	37
2	Zigler	148	79	69	71	29	42

2) ODI success at 24 months

2.1) Using baseline sample size as reference (ITT analysis)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	117	88	99	47	52
2	Zigler	161	101	60	75	39	36

2.1) Using data for completers only

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	184	117	67	81	47	34
2	Zigler	149	101	48	71	39	32

3) Device Success at 24 months (relative to baseline sample size, ITT analysis only)

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	194	11	99	91	8
2	Zigler	161	155	6	75	73	2

4) Neurological success at 24 months (relative to baseline sample size, ITT analysis only)

4.1) Using baseline sample size as reference

stu~m	studname	ADR N	ADR succ	ADR fail	ACDF N	ACDF succ	ACDF fail
1	Blumenthal	205	169	36	99	78	21
2	Zigler	161	135	26	75	57	18

CERVICAL ADR

1) Overall Clinical Success (FDA ≥ 15 point) at 24 months –

1.1) Using the baseline sample size as reference for ITT analysis.

	studname	ADR succ	ADR fail	ACDF succ	ACDF fail
1.	Mummaneni	177	99	134	131
5.	Bryan FDA report	129	.	99	.
6.	Prodisc-C FDA report	73	30	69	37

1.2) Using the sample size at 24 months follow-up as reference.- **completers**

Clinical outcome using the sample size at 24 months follow-up as reference. 101 = n for ACDF

	studname	ADR succ	ADR fail	ACDF succ	ACDF fail
1.	Mummaneni	177	46	134	64
2.	Prodisc-C FDA report	73	28	69	32
3.	Bryan FDA report	129	31	99	41

2) NDI success (FDA ≥ 15 point) at 24 months of follow-up

2.1) Data used for the meta analysis are shown in the next two tables. – ITT analysis uses baseline N and "completer" analysis uses 24 month N

Table for ADR

	studnum	studname	base N	24mo N	Succ24 (base N)	Fail24 (base N)	Fail24 (24mo N)
1.	1	Mummaneni	276	223	185	91	38
2.	6	Prodisc FDA report	103	99	79	24	20
3.	5	Bryan FDA report	242	160	134	.	26

Table for ACDF

	studnum	studname	base N	24mo N	Succ24 (base N)	Fail24 (base N)	Fail24 (24mo N)
1.	1	Mummaneni	265	198	159	106	39
2.	6	Prodisc FDA report	106	92	72	34	20
3.	5	Bryan FDA report	221	140	106	.	34

3) Neurological Success-

3.1) ITT analysis

Table for ADR group

	studnum	studname	ADRbaseN	ADR_ne~e	ADR_ne~s
1.	1	Mummaneni	276	69	207
3.	6	Prodisc FDA report	103	13	90

Table for ACDF Group

	studnum	studname	ACDFba~N	ACDF_n~e	ACDF_n~s
1.	1	Mummaneni	265	98	167
3.	6	Prodisc FDA report	106	25	81

3.2) Completer analysis

Table for ADR group

	studnum	studname	N at 24mo	Failures	Successes
1.	1	Mummaneni	223	16	207
2.	5	Bryan FDA report	160	10	150
3.	6	Prodisc FDA report	99	9	90

Table for ACDF

	studnum	studname	N at 24mo	Failures	Successes
1.	1	Mummaneni	198	31	167
2.	5	Bryan FDA report	140	12	128
3.	6	Prodisc FDA report	92	11	81

4) Device Success-

4.1) ITT analysis

Table for ADR – ITT analysis

	stu~m	studname	ADR..	ADR..
1.	1	Mummaneni	267	9
2.	6	Prodisc FDA report	101	2

Table for ACDF – ITT analysis

	stu~m	studname	ACD..	ACD..
1.	1	Mummaneni	241	24
2.	6	Prodisc FDA report	97	9

APPENDIX F. A List of Adverse Events/Complications Given for the Randomized Controlled Studies

Adverse events comparing the Charité L-ADR with lumbar spinal fusion*

Adverse event	L-ADR (n = 205) No. (%)	Spinal fusion (n = 99) No. (%)
Adverse events irrespective of relationship to treatment		
Any	156 (76.1)	77 (77.8)
Severe or life-threatening	30 (14.6)	9 (9.1)
Adverse events related to treatment		
Device-related	15 (7.3)	4 (4.0)
Device failures	10 (4.9)	8 (8.1)
Adverse events irrespective of relationship to treatment		
Pain (back or lower extremity)	107 (52.2)	52 (52.5)
Pain (other)	27 (13.2)	9 (9.1)
Neurological	34 (16.6)	17 (17.2)
Infection 25	(12.2)	6 (6.1)
Approach problems (abdominal)	18 (8.8)	8 (8.1)
DDD progression, natural history	6 (2.9)	4 (4.0)
Additional surgery, index level	10 (4.9)	8 (8.1)
Intraoperative complications	2 (1.0)	3 (3.0)
Abnormal bone formation	2 (1.0)	0 (0.0)
Severe or life-threatening adverse events irrespective of relationship to treatment		
Pain (back or lower extremity)	10 (4.9)	5 (5.1)
Other 11	(5.4)	3 (3.0)
Other, cardiovascular	0 (0.0)	1 (1.0)
Infection	3 (1.5)	2 (2.0)
Additional surgery, index level, removal	4 (2.0)	0 (0.0)
Additional surgery, index level, delayed fusion	1 (0.5)	0 (0.0)
Additional surgery, index level, reoperation	1 (0.5)	0 (0.0)
Approach problems (abdominal)	2 (2.0)	1 (1.0)
Approach problems (hernia)	1 (0.5)	0 (0.0)
Approach problems (retrograde ejaculation)	1 (0.5)	1 (1.0)
Additional surgery, unrelated to index level	1 (0.5)	1 (1.0)
Neurological (nerve root injury)	1 (0.5)	0 (0.0)
Device failures		
Reoperation	0 (0.0)	1 (1.0)
Revision	0 (0.0)	1 (1.0)
Removal	2 (1.0)	0 (0.0)
Supplemental fixation	8 (3.9)	6 (6.1)

*From the FDA Clinical Review Report, P040006.

Adverse events comparing the Prodisc-L ADR with lumbar spinal fusion*

Adverse event	L-ADR (n = 162) No. (%)	Spinal fusion (n = 80) No. (%)
All adverse event	136 (84.0)	70 (87.5)
Anemia	6 (3.7)	2 (2.5)
Burning or dysesthetic pain	8 (4.9)	3 (3.8)
Cardiovascular	2 (1.2)	5 (6.3)
Significant blood loss (> 1500 cc)	0 (0.0)	2 (2.5)
Degenerative Disease progression, other lumbar	9 (5.6)	0 (0.0)
Dermatological	6 (3.7)	2 (2.5)
Dermatological drug allergy	2 (1.2)	0 (0.0)
Dizziness	4 (2.5)	3 (3.8)
Drug allergy	2 (1.2)	1 (1.3)
Dural tear	0 (0.0)	2 (2.5)
Edema	8 (4.9)	3 (3.8)
Fever	10 (6.2)	10 (12.5)
Fracture (nonvertebral)	2 (1.2)	0 (0.0)
Gastrointestinal	32 (19.8)	22 (27.5)
Genitourinary 14	(8.6)	4 (5.0)
Headache 11	(6.8)	5 (6.3)
Herniated Nucleus Pulposus	1 (0.6)	0 (0.0)
Incontinence	3 (1.9)	4 (5.0)
Infection (nonwound related)	5 (3.1)	5 (6.3)
Infection (superficial wound with incision site pain)	0 (0.0)	2 (2.5)
Infection (UTI)	0 (0.0)	1 (1.3)
Insomnia	8 (4.9)	4 (5.0)
Migration not requiring surgery	3 (1.9)	1 (1.3)
Migration requiring surgery	4 (2.5)	0 (0.0)
Motor deficit/index level	4 (2.5)	0 (0.0)
Musculoskeletal spasm, back	1 (0.6)	2 (2.5)
Musculoskeletal spasm, back and leg	0 (0.0)	0 (0.0)
Musculoskeletal spasm, leg	2 (1.2)	0 (0.0)
Narcotic use	2 (1.2)	1 (1.3)
Nerve root injury	1 (0.6)	0 (0.0)
Non-specific musculoskeletal spasms	6 (3.7)	1 (1.3)
Numbness index level related	0 (0.0)	1 (1.3)
Numbness peripheral nerve or nonindex level related	17 (10.5)	5 (6.34)
Other musculoskeletal	21 (13.0)	13 (16.3)
Other 11	(6.8)	8 (10.0)
Pain, back	55 (34.0)	27 (33.8)
Pain, back and lower extremities	29 (17.9)	10 (12.5)
Pain, back and lower extremities with burning	3 (1.9)	0 (0.0)
Pain, back and lower extremities with numbness at index	4 (2.5)	4 (5.0)
Pain, back and other	8 (4.9)	5 (6.3)
Pain, groin area	5 (3.1)	0 (0.0)
Pain, incision site	2 (1.2)	6 (7.5)
Pain, lower extremities	32 (19.8)	16 (20.0)
Pain, lower extremities with numbness at index level	3 (1.9)	1 (1.3)
Pain other (not back/hip/leg)	25 (15.4)	12 (15.0)

Pruritus	8 (4.9)	4 (5.0)
Psychological 19	(11.7)	6 (7.5)
Pulmonary infection	0 (0.0)	1 (1.3)
Radiolucency, graft	0 (0.0)	1 (1.3)
Reflex change	1 (0.6)	0 (0.0)
Respiratory	4 (2.5)	0 (0.0)
Retrograde ejaculation	2 (1.2)	1 (1.3)
Subsidence not requiring surgery	2 (1.2)	1 (1.3)
Subsidence requiring surgery	0 (0.0)	0 (0.0)
Surgery, adjacent level	2 (1.2)	1 (1.3)
Surgery, index level (revision)	1 (0.6)	4 (5.0)
Surgery, index level (supplemental fixation)	1 (0.6)	0 (0.0)
Surgery, other	7 (4.3)	3 (3.8)
Thrombosis	0 (0.0)	0 (0.0)
Thrombosis (DVT leg)	2 (1.2)	1 (1.3)
Vessel damage/bleeding, major	1 (0.6)	1 (1.3)
Vessel damage/bleeding, minor	4 (2.5)	5 (6.3)
Wound issues, other	5 (3.1)	7 (8.8)
All device related adverse events	29 (17.9)	16 (20.0)
Pain, back	8 (4.9)	5 (6.3)
Pain, back and lower extremities	6 (3.7)	2 (2.5)
Numbness peripheral nerve or non index level related	4 (2.5)	0 (0.0)
Edema	2 (1.2)	0 (0.0)
Other musculoskeletal	2 (1.2)	3 (3.8)
Degenerative Disease progression, other lumbar	3 (1.9)	0 (0.0)
Burning or dysesthetic pain	1 (0.6)	0 (0.0)
Fracture (non-vertebral)	1 (0.6)	0 (0.0)
Herniated Nucleus Pulposus	1 (0.6)	0 (0.0)
Motor deficit in index level	1 (0.6)	0 (0.0)
Pain, back and lower extremities with burning	1 (0.6)	0 (0.0)
Pain, back and lower extremities with numbness at index level	1 (0.6)	1 (1.3)
Pain, lower extremities with numbness at index level	1 (0.6)	0 (0.0)
Musculoskeletal spasms, back	0 (0.0)	1 (1.3)
Nerve root injury	0 (0.0)	0 (0.0)
Pain other (not back/hip/leg)	0 (0.0)	1 (1.3)
Radiolucency (graft)	0 (0.0)	1 (1.3)
Headache	0 (0.0)	1 (1.3)
Cardiovascular	0 (0.0)	2 (2.5)
Gastrointestinal	0 (0.0)	1 (1.3)
Pruritus	0 (0.0)	1 (1.3)
Other	0 (0.0)	1 (1.3)
Subsidence	2 (1.2)	1 (1.3)
Migration requiring surgery	4 (2.5)	0 (0.0)
Migration not requiring surgery	3 (1.9)	1 (1.3)
Surgery, index level (supplemental fixation)	1 (0.6)	0 (0.0)
Surgery, index level (revision)	1 (0.6)	4 (5.0)

*From the FDA SSED, P050010.

Adverse events comparing the Bryan C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 242) No. (%)	Spinal fusion (n = 221) No. (%)
All adverse events	202 (83.5)	174 (78.7)
Anatomical/technical difficulty	0 (0.0)	1 (0.5)
Cancer	2 (0.8)	0 (0.0)
Cardiovascular	4 (1.7)	2 (0.9)
Carpal tunnel syndrome	12 (5.0)	4 (1.8)
Death	0 (0.0)	1 (0.5)
Dysphagia/dysphonia	26 (10.7)	19 (8.6)
Gastrointestinal	9 (3.7)	6 (2.7)
Infection	17 (7.0)	10 (4.5)
Malpositioned implant	2 (0.8)	0 (0.0)
Neck or arm pain	115 (47.5)	96 (43.4)
Neurological	48 (19.8)	46 (20.8)
Nonunion	0 (0.0)	5 (2.3)
Other	59 (24.4)	39 (17.6)
Other pain	49 (20.2)	44 (19.9)
Pending nonunion	0 (0.0)	5 (2.3)
Respiratory	4 (1.7)	6 (2.7)
Spinal event	21 (8.7)	20 (9.0)
Trauma	34 (14.0)	22 (10.0)
Urogenital	6 (2.5)	3 (1.4)
Vascular intra-op	2 (0.8)	3 (1.4)
Subsequent surgical interventions†	6 (2.5)	9 (4.1)

*As reported in the FDA Executive Summary, P060023 based on full study population.
†For purposes of revision, removal, reoperation, or supplemental fixation.

Adverse events comparing the Prestige C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 276) No. (%)	Spinal fusion (n = 265) No. (%)
All perioperative adverse events	17 (6.2)	11 (4.2)
Neurological (numbness, paresthesia, back and leg, paresthesia/pain in arm, Lhermitte phenomenon)	4 (1.4)	1 (0.4)
Pain (bursitis, headaches, neck and/or arm pain)	3 (1.1)	2 (0.8)
Venous bleeding	1 (0.4)	0 (0.0)
Infections (UTI and sinusitis)	2 (0.7)	0 (0.0)
CSF leaks	0 (0.0)	2 (0.8)
Spinal fluid leak	1 (0.4)	0 (0.0)
Respiratory (sleep apnea)	1 (0.4)	0 (0.0)
Dysphagia/dysphonia	2 (0.7)	3 (1.1)
Anatomical/technical (screw fixation) difficulty	1 (0.4)	0 (0.0)
Hematoma	2 (0.7)	0 (0.0)
Low bone density	1 (0.4)	0 (0.0)
Nausea	0 (0.0)	1 (0.4)
Vomiting	0 (0.0)	1 (0.4)
Device failure		
Revisions	0 (0.0)	5 (1.9)
Hardware removals	5 (1.8)	9 (3.4)
Supplemental fixations	0 (0.0)	8 (3.4)

*Data from Mummaneni et al report.

Adverse events comparing Prodisc C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 25) No. (%)	Spinal fusion (n = 24) No. (%)
Mortality during surgery	1 (4.0)	0 (0.0)

*Data from Nabhan et al report.

Adverse events comparing C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 12) No. (%)	Spinal fusion (n = 12) No. (%)
All adverse event	0 (0.0)	0 (0.0)

*Data from Sun Peng-Fei report, Bryan disc used.

Adverse events comparing the Prodisc C-ADR with cervical spinal fusion*

Adverse event	C-ADR (n = 103) No. (%)	Spinal fusion (n = 106) No. (%)
All adverse events	84 (81.6)	86 (81.1)
Adjacent level DDD or DJD	0 (0.0)	4 (3.8)
Burning or dysesthetic pain	1 (1.0)	0 (0.0)
Cancer	1 (1.0)	0 (0.0)
Cardiovascular	5 (4.9)	7 (6.6)
DDD progression, non-cervical	1 (1.0)	1 (0.9)
Dermatological	1 (1.0)	1 (0.9)
Dizziness	1 (1.0)	0 (0.0)
Dural tear	1 (1.0)	0 (0.0)
Dysphagia	6 (5.8)	9 (8.5)
Dysphonia	0 (0.0)	1 (0.9)
Edema	2 (1.9)	1 (0.9)
Fatigue	1 (1.0)	0 (0.0)
Fracture, vertebral	0 (0.0)	1 (0.9)
Gastrointestinal	16 (15.5)	15 (14.2)
Genitourinary	5 (4.9)	3 (2.8)
Headache	18 (17.5)	12 (11.3)
Infection, non-wound	2 (1.9)	6 (5.7)
Infection, superficial wound	0 (0.0)	1 (0.9)
Insomnia	6 (5.8)	3 (2.8)
Musculoskeletal	18 (17.5)	16 (15.1)
Musculoskeletal, back spasms	1 (1.0)	1 (0.9)
Musculoskeletal, neck spasms	3 (2.9)	5 (4.7)
Musculoskeletal, non-specific	3 (2.9)	4 (3.8)
Narcotics use	1 (1.0)	0 (0.0)
Neurological	4 (3.9)	1 (0.9)
Numbness, index level	0 (0.0)	2 (1.9)

Numbness, nonindex level	11 (10.7)	7 (6.6)
Ossification	1 (1.0)	0 (0.0)
Other	4 (3.9)	6 (5.7)
Pain, back	11 (10.7)	8 (7.5)
Pain, back and lower extremities	4 (3.9)	2 (1.9)
Pain, incision site	1 (1.0)	1 (0.9)
Pain, neck	16 (15.5)	22 (20.8)
Pain, neck and other	1 (1.0)	0 (0.0)
Pain, neck and shoulder	7 (6.8)	6 (5.7)
Pain, neck and upper extremities	3 (2.9)	6 (5.7)
Pain, neck and upper extremities with numbness	6 (5.8)	6 (5.7)
Pain, other	5 (4.9)	7 (6.6)
Pain, shoulder	9 (8.7)	9 (8.5)
Pain, upper extremities	8 (7.8)	5 (4.7)
Pain, upper extremities with numbness	4 (3.9)	5 (4.7)
Pseudoarthrosis	0 (0.0)	2 (1.9)
Psychological	4 (3.9)	5 (4.7)
Pulmonary infection	1 (1.0)	0 (0.0)
Puritis	0 (0.0)	2 (1.9)
Reflex change	1 (1.0)	0 (0.0)
Respiratory	4 (3.9)	3 (2.8)
Seizures	0 (0.0)	2 (1.9)
Sore throat	1 (1.0)	1 (0.9)
Surgery, index level	2 (1.9)	10 (9.4)
Surgery, other	12 (11.7)	21 (19.8)
Wound issues, other	3 (2.9)	2 (1.9)
All implant related adverse events	2 (1.9)	7 (6.6)
Dysphagia	0 (0.0)	1 (0.9)
Infection (superficial wound)	0 (0.0)	1 (0.9)
Musculoskeletal	0 (0.0)	1 (0.9)
Pain (neck)	0 (0.0)	1 (0.9)
Surgery (index level)	2 (1.9)	5 (4.7)
All surgery related adverse events	11 (10.7)	16 (15.1)
DDD progression (other cervical)	0 (0.0)	1 (0.9)
Dural tear	1 (1.0)	0 (0.0)
Dysphagia	2 (1.9)	4 (3.8)
Edema	1 (1.0)	0 (0.0)
Gastrointestinal	6 (5.8)	4 (3.8)
Genitourinary	1 (1.0)	0 (0.0)
Pain (back)	1 (1.0)	0 (0.0)
Pain (neck)	0 (0.0)	1 (0.9)
Pain (neck and upper extremities)	0 (0.0)	2 (1.9)
Pain (upper extremities)	2 (1.9)	0 (0.0)
Pseudoarthrosis	0 (0.0)	2 (1.9)
Surgery (index level)	0 (0.0)	2 (1.9)
Wound issues (other)	0 (0.0)	2 (1.9)
All severe or life-threatening adverse events	16 (15.5)	32 (30.2)
Cardiovascular	0 (0.0)	1 (0.9)
Dermatological	1 (1.0)	0 (0.0)
Dural tear	1 (1.0)	0 (0.0)
Gastrointestinal	0 (0.0)	1 (0.9)
Infection (non-wound)	0 (0.0)	1 (0.9)
Infection (superficial wound)	0 (0.0)	1 (0.9)

Other	0 (0.0)	1 (0.9)
Surgery (index level)	2 (1.9)	10 (9.4)
Surgery (other)	13 (12.6)	21 (19.8

*Data from the FDA Summary of Safety and Effectiveness Data, P-070001 .

APPENDIX G. Evidence Tables: Demographics, Study Design, and Characteristics of Included Studies for ADR

Table G1. Demographics and characteristics of included RCTs for L-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Blumenthal (2005) ‡ McAfee (2005) ‡ Geisler (2004) ‡ Statistical Review for Expedited PMA (2004) ‡ Summary of Safety and Effectiveness (2004) ‡	RCT (II) • assignment via central computer • 2:1 allocation • noninferiority • multicenter prospective cohort (II)	N = 304 n = 205 (ADR) n = 99 (fusion) male %: 51.6 mean age: years (sd) ADR: 39.6 (8.2) fusion: 39.6 (9.1)	duration: 24 months *24 months* including out of window: F/U % : 82.2 (250/304) § ADR: 85.9 (176/205) fusion: 74.7 (74/99) per protocol: F/U %: 74.7 (227/304) ADR: 78.5 (161/205) fusion: 66.7 (66/99) *12 months* F/U%: 87.2 (265/304) ADR: 89.8 (184/205) fusion: 81.8 (81/99)	• age 18-60 years • symptomatic DDD confirmed by discogram • single level L4-5 (n = 61) or L5-S1 (n = 144) • ODI ≥ 30 • VAS pain ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive list of medications and diagnoses • able to comply • informed consent	• prior fusion • current or prior fracture L4, L5 or S1 • other spinal surgery at the affected level • symptomatic multilevel degeneration • allergies • noncontained herniation • facet disease • spondylosis • spondylolisthesis > 3 mm or midsagittal stenosis > 8 mm • scoliosis > 11° • osteoporosis or osteopenia • positive straight leg raise or established nerve root compression	• Charite artificial disc via the anterior retroperitoneal approach • ALIF with BAK cages at 1 or 2 contiguous levels	• binary clinical success score based on meeting four criteria • pain using VAS • narcotic use • function using ODI • QoL using SF-36 • neurological status • radiological evaluation • satisfaction questionnaire • work status • complications • intraoperative parameters	• industry funds received to support work • 1 or more authors has or will receive benefits from commercial party related to the subject of the manuscript

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					• additional diagnoses: spinal tumor, metabolic bone disease, infection, psychosocial disorder, morbid obesity, arachnoiditis, autoimmune disease, pregnancy • additional perscriptions: chronic steroids, bone growth stimulator • participation in another study			
Zigler (2007)	RCT (II) • randomization held by sponsor until individual enrolled • 2:1 allocation • noninferiority • multicenter	N = 236 (paper) n = 161 (ADR) n = 75 (fusion) male %: 49.2 mean age: years (sd) ADR: 40.4 (7.6) fusion: 38.7 (8.0) FDA report N = 292 n = 162 (ADR) n = 80 (fusion) n = 50 (nonrandomized	duration : 24 months F/U % : 98.2%** ADR : 98.6% (159/161) fusion : 97.1% (73/75) with complete data (paper) : ADR : 91% (147/161) fusion : 88.5% (66/75)	• age 18-60 years • symptomatic DDD confirmed by any of several radiographic confirmations • single level L3-S1 • ODI ≥ 40 • failed ≥ 6 months conservative treatment • negative for extensive	• prior fusion • no DDD > 1 • allergies • small endplates • compromised vertebral bodies • facet disease • lytic spondylolisthesis or spinal stenosis • osteopo	• Prodisc-L total disc replacement per IDE No. G010133 • circumferential fusion	• binary clinical success score based on meeting 10 primary endpoints • 1.function using ODI • 2.QoL using SF-36 • 3. neurologic exam • 4. “device success” • 5-10. radiographic endpoints • pain using	• no industry funds received to support work • 1 or more authors has or will receive benefits from commercial party related to the subject of the manuscript

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
		ADR) male %: 50 mean age: years (sd) ADR: 39.6 (8.0) fusion: 40.2 (7.6)	FDA report : ADR : 91% (148/162) fusion : 88.5% (71/80)	list of diagnoses • able to comply • informed consent	rosis • back or leg pain of unknown etiology • metabolic bone disease (long list)		VAS • narcotic use • satisfaction using VAS • would have again • work status • recreation status • complications • intraoperative parameters	

BMI = body mass index.
DDD = degenerative disc disease.
ODI = Oswestry Disability Index.
NR = not reported.
QoL = quality of life.
VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡These three published studies and two FDA reports all refer to a single RCT. Blumenthal was used for most information included in the assessments, except for neurological outcomes and one subgroup analysis.
§These percentages include all individuals followed-up at ≥ 24 months, including 15 in ADR group and 8 in control group evaluated after the window specified in the protocol.
**Percentage that followed-up at 24 months for which complete data are available is less; ADR: 91% and fusion: 88.5%.

Table G2. Demographics and characteristics of included nonrandomized studies for L-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Bertagnoli (2006)	prospective cohort (III) multicenter	N = 22 male%: 41 age: 63 years (61-71)	mean F/U: 2.9 years (1-4.7) F/U %: NR	• DDD (n = 19) or failed disc surgery syndrome (n = 3) • discogenic LBP with or without radiculopathy	• Prodisc II ADR • number of levels monolevel: n = 17 bilevel: n = 4 trilevel: n = 3	• ODI • VAS for back pain • patient satisfaction • general back pain • radicular pain • medication usage • complications • radiography: disc heights of affected and adjacent levels, disc motion, subsidence	• NA
Bertagnoli (2006)	case-series (IV)	N = 110 male%: NR ‡mean age: smokers: 45 years (30-60) nonsmokers: 49 years (29-60)	duration of F/U: 24 months mean F/U: smokers: 33 months (24-49) nonsmokers: 34 months (24-47) F/U %: 94.5	• age 18-60 years • disabling discogenic back pain • minimal radicular pain • failed ≥ 9 months conservative treatment • no spinal stenosis, osteoporosis, chronic infections, metal allergies, facet arthrosis, neuromuscular disease, pregnancy, Worker's Compensation, litigation, isthmic or degenerative spondylolisthesis greater than Grade 1 • BMI < or = 35 • adequate vertebral endplate size	• ADR with Prodisc • number of levels monolevel: all • spinal segments L3-4: n = 7 L4-5: n = 17 L5-S1: n = 76 L5-6: n = 5	• ODI • VAS • patient satisfaction • general back pain • radicular pain • medication use • several radiological outcomes (not ROM or segmental disease) • complications	• smokers v. nonsmokers

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Cakir (2005)	case-series (IV) Germany	N = 29 male %: 34 mean age ± sd: 40.8 years ± 6.4 (29-56)	mean F/U: 15.3 months (12-35) F/U%: 100	• symptomatic DDD (n = 21) or postdiscectomy syndrome (n = 8) • low back pain ≥ 12 months • failed ≥ 6 months conservative treatment	• Prodisc ADR via retroperitoneal approach using a pararectal incision for level L3-4 and L4-5 or a horizontal incision for level L5-S1 • number of levels: monosegmental: all	• ODI • SF-36 • evaluation of the segmental lordosis at the operated level and the total lumbar lordosis using standard Cobb measurements before and after surgery • segmental/lumbar lordosis classified as: insufficient (< 16°/< 41°); normative (16°-30°/41°-75°); excessive (> 30°/> 75°)	• NA
Caspi (2003)	case-series (IV) Israel	N = 20 male %: 55 age range: 24–50 years	duration of F/U: 48 months F/U %: NR	• low back pain with or without radicular pain • mean duration of disease = 5 years	• Charite SB III ADR via anterior retroperitoneal approach • number of levels: monolevel: n = 17 bilevel: n = 3	• clinical results rated as poor, fair, good, or excellent • return to work • radiological assessment	• NA
Chung (2006)	retrospective cohort (III) Seoul, Korea	N = 26 male %: 44 mean age: 44.2 years (30-57)	mean F/U: 30 months (24-36) F/U %: 100	• age 18-60 years • symptomatic DDD confirmed by any of several radiographic criteria • no radicular leg pain or claudication • primary complaint of back pain • disc height ≥ 4mm • ODI ≥ 40 • failed ≥ 6	• ADR with Prodisc • number of levels monolevel: n = 19 bilevel: n = 7 • spinal segment L3-4: n = 2 L4-5: n = 18 L5-S1: n = 13	• radiological evaluation: lumbar lordosis, sacral tilt, pelvic tilt, ROM	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
				months conservative treatment			
Chung (2006)	case-series (IV) Seoul, Korea	N = 38 ‡male %: 44.4 ‡mean age: 43 years (25-58)	mean F/U: 37 months (25-42) F/U %: 94.7	• 18-60 years of age • symptomatic DDD at 1 or 2 levels • primary complaint of back pain • disc height ≥ 4mm • ODI ≥ 40 • failed ≥ 6 months conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 25 bilevel: n = 11 • spinal segments L3-4: n = 2 L4-5: n = 24 L5-S1: n = 25	• VAS for back and leg pain • ODI • work status • medication usage • segmental ROM and intervertebral disc height via anteroposterior, lateral, and flexion-extension radiographs	• age • gender • body mass index • single or double level • previous operations on the same level (discectomy) • estimated blood loss during surgery • operation time • segmental ROM • prosthesis position

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
David (2007)	case-series (IV) Bois-Bernard, France	N = 108 male %: 41.7 mean age: 36.4 years (23-50)	mean F/U: 13.2 years (10.0-16.8) F/U%: 98.1	• single level DDD with (n = 68) or without (n = 44) radiculopathy • failed ≥ 6 months conservative treatment	• ADR with SB Charite III via anterior retroperitoneal approach • spinal segment: L3-4: n = 1 L4-5: n = 25 L5-S1: n = 82	• modified Stauffer-Coventry • return to work among previously employed, divided into heavy and light/sendentary labor • complications • ROM	• NA
Fraser (2004)	case-series (IV) Adelaide, Australia	N = 28 AcroFlex I: n = 11 AcroFlex II: n = 17 male%: 50 mean age: 41years (30-54)	duration of F/U: 24 months F/U %: NR	• 30-55 years of age • symptomatic DDD, with or without leg symptoms, confirmed by discography • failed ≥ 6 months conservative treatment • consenting, able to f/u • no previous lumbar surgery • lumbosacral angle not too steep • no significant lateral or recess spinal stenosis • no spondylolisthesis, systemic disease that would limit ability to assess in f/u, morbid obesity, EtOH or drug abuse, structural scoliosis • < 3 positive	• ADR with AcroFlex via direct anterior retroperitoneal approach • number of levels monolevel: n = 24 bilevel: n = 4 • spinal segments L4-5: n = 9 L5-S1: n = 23	• ODI • low back outcome score • complications • operative characteristics	• genera tion of AcroFlex disc

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
				Waddell signs • no major psych disorder or other condition limiting ability to comply • no current litigation			
Kim (2007)	prospective cohort (III) Seoul, Korea	N = 32 ‡male %: 40% ‡mean age: 38.9 years (24-60)	mean F/U: 30.2 months (24-41) F/U %: 93.8 (30/32)	• 18-60 years • DDD confirmed by any of several radiographic criteria • axial back pain, back + buttock or thigh pain, or back + leg pain • failed ≥ 6 months conservative treatment • no spinal stenosis, advanced facet arthrosis, osteoporosis, prior fusion, obesity, instability, deformity, chronic infection or pregnancy • excluded if moderate facet arthrosis treated with facet block and pain went away	• ADR with Prodisc II via median retroperitoneal approach • number of levels: monolevel: n = 19 bilevel: n = 11	• global lumbar lordosis • segmental lordosis at affected level • ROM	• gender • age • BMI • preoperative ROM • spinal segment • position and size of prosthesis

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Le Huec (2005)	case-series (IV) France	N = 64 male %: 39 mean age: 44 years (20-60)	mean F/U: 18 months (12-26) F/U%: 100	• chronic back pain • failed ≥ 12 months conservative treatment • received medical and rheumatologic follow-up and rehabilitation physiotherapy	• Maverick ADR via mini-invasive anterior approach • number of levels monolevel: all • spinal segment: L5-S1 (n = 35) L4-5 (n = 27) L3-4 (n = 2)	• clinical success§ • ODI • VAS for pain • neurological function • use of analgesics • SF-36 • patient satisfaction	• NA
Leivseth (2006)	prospective cohort (III) multicenter trial	N = 41 male %: 46.3 median age: 45 years (31-60)	mean F/U: 2 years F/U%: 100	• DDD or postdiscetomy syndrome • low back and/or leg pain > 1 year • failed conservative treatment	• Prodisc II • spinal segment: L1-2 (n = 1) L2-3 (n = 4) L3-4 (n = 7) L4-5 (n = 21) L5-S1 (n = 23)	• ODI • ROM • disc space height	• NA
Lemaire (2005)	case-series (IV) prospective cohort (III) France	N = 107 ‡male %: 41 ‡mean age: 39.6 years (24-51)	mean F/U: 11.3 years (10.0-13.4) F/U %: 93.4 (100/107)	• DDD with intractable low back pain • failed nonsurgical treatment • mean duration of disease = 6 years	• Charité SB III ADR via the anterior retroperitoneal approach • number of levels: monolevel: n = 54 bilevel: n = 45 trilevel: n = 1 • spinal segment: L3-4: n = 6 L4-5: n = 69 L5-S1: n = 72	• clinical evaluation: modified Stauffer Coventry score • radiological evaluation: disc height, sagittal alignment, ROM	• NA

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Mayer, (2002)**	case-series (IV) Munich, Germany	N = 26 ADR male %: 42 mean age (range): 44 years (25.2-65)	average F/U: 6 months (3-18) F/U%: NR	• DDD with discogenic lower back pain	• ADR with Prodisc II • spinal segment L5-S1: n = 24 L5-6: n = 2	• ODI • VAS pain • operative parameters • complications	• NA
Putzier (2006)	case-series (IV) Berlin, Germany	N = 71 (84 segments) male %: 38 (after loss to f/u) age 44 years (30-59) (after loss to f/u)	mean F/U: 17.3 years (14.5-19.2) F/U%: patients 74.6% (53/71) segments 75.0% (63/84)	• DDD at 1 or 2 levels • moderate to severe osteochondrosis • some with previous disc surgery or history of spondylolisthesis	• ADR with Charite total disc prosthesis Type I, II or III • Type I: n = 15 Type II: n = 22 Type III: n = 16 • number of levels monolevel: n = 43 bilevel: n = 10 • spinal segments L3-4: n = 2 L4-5: n = 25 L5-S1: n = 16 L4-S1: n = 10 Type I: n = 16 Type II: n = 25 Type III: n = 22	• ODI • VAS pain • perception of overall outcome • radiological parameters: segmental mobility, heterotopic ossification, implant failure, adjacent segment disease (disc height and dynamic translation), subsidence, dislocation • secondary surgery for implant fracture, subsidence, dislocation or persistent pain	• genera tion of Charite

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
SariAli (2006)	retrospective cohort (III) Paris, France	N = 23 ††male %: 52.9 ††mean age ± sd: 38.6 ± 9 (25-47)	mean F/U: 12.4 years ± 1 (10.8-14.3) F/U %: NR	• severe discopathy OR • healthy controls with no history of lumbalgia	*In patients* • ADR with SB Charite III (n = 17) • number of levels monolevel: n = 5 bilevel: n = 12 • spinal segment L4-5: n = 17 L5-S1: n = 12 OR *In healthy controls* • none (n = 6)	• degree of right axial motion • occurrence of increased right axial motion	• DDD patients receiving ADR vs. healthy controls
Shim (2007)	retrospective cohort (III) Seoul, Korea	N = 61 Charite: n = 33 Prodisc: n = 24 (data available on 57 patients followed) male %: 52.6 Charite: 51.5 Prodisc: 54.2 mean age Charite: 44.4 years (31-63) Prodisc: 44 years (31-66)	mean F/U Charite: 41 months (36-48) Prodisc: 38 months (36-40) clinical F/U %: 93 (57/61) radiographic F/U %: 91.2 (52/57)	• DDD • low back pain • failed conservative treatment ≥ 6 months • disc herniation and significant space narrowing	• ADR with Charite or Prodisc • number of levels monolevel: n = 50 bilevel: n = 7 • spinal segment L4-5: n = 36 L5-S1: n = 14 L4-5/L5-S1: n = 7	• ODI • VAS back pain • subjective improvement rate • satisfaction rate • clinical success rate • ROM of L4-5 and L5-S1 • complications	• ADR with Charite vs. Prodisc

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Siepe (2007)	case-series (IV) Munich, Germany	N = 99 male %: NR mean age: NR	F/U: ≥ 12 months F/U %: NR	• DDD without accompanying pathologies or transitional vertebrae • low back pain > sciatica • failed conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 79 bilevel: n = 20 • spinal segment L4-5: n = 42 L5-S1: n = 77 • fluoroscopically guided spine infiltration (in some pts.)	• ODI • VAS pain • clinical and radiographic parameters • patient satisfaction rating • would do again • return to work • intraoperative parameters • complications • pain relief with fluoroscopically guided spine infiltrations	• number of levels • spinal segment
Siepe (2007)	prospective cohort (III) Munich, Germany	N = 39 male %: 53.8 mean age: 39.8 years (26-58) athlete active in contact or professional sport at least twice per week	F/U: 2.2 years F/U%: 97.4	• DDD at one or more levels • no accompanying pathologies or transitional vertebrae • low back pain > sciatica • failed conservative treatment	• ADR with Prodisc II • number of levels monolevel: n = 36 bilevel: n = 3 • fluoroscopically guided spine infiltration	• ODI • VAS pain • clinical and radiographic parameters • sports related issues questionnaire • patient satisfaction rating • return to work • return to sports • range of motion • complications	• preoperative participation in sport
Tortolani (2007) ‡‡ Regan (2006) ‡‡	case-series within an RCT multicenter trial	N = 276 **n = 205 trial (late)** ---------- n = 91 high-volume surgeon n = 114 low-volume surgeon	Duration of F/U: 24 months *Tortolani* F/U %: NR *Regan* trial: 90.7% pretrial: 85.6%	• age 18-60 years • symptomatic DDD confirmed by discogram • ODI ≥ 30 • VAS pain ≥ 40 • failed ≥ 6 months conservative treatment • prior fusion,	• Charite ADR via the anterior retroperitoneal approach	*Tortolani* • heterotropic ossification classification • segmental range of motion • ODI • VAS pain *Regan* • surgical	• high vs. low-volume surgeon • high vs. low-volume institution • early (pretrial) vs. late (trial)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
		---------- n = 120 high-volume institution n = 85 low-volume institution ---------- **n = 71 pretrial (early)** male %: 55.8% mean age, range: 39.3 (18-60)		current or prior fracture L4, L5 or S1, other spinal surgery at the affected level, symptomatic multilevel degeneration, allergies, noncontained herniation, facet disease, spondylosis, spondylolisthesis, scoliosis, osteoporosis or osteopenia, positive straight leg raise or established nerve root compression, several additional dx or rx, or participation in another study		parameters • adverse events • ODI • VAS pain • neurologic status • patient satisfaction • work status • range of motion flexion-extension	experience
Tropiano (2003)	prospective case-series (IV) multicenter trial	N = 53 male %: 34 mean age: 45 years (28-67)	F/U: 1.4 years (1-2) F/U %: 100	• DDD (n = 33) or failed spine surgery (n = 20) • 6 months severe back pain • failed conservative treatment	• Prodisc II • approach retroperitoneal: n = 48 transperitoneal: n = 5 • number of levels monolevel: n = 40 bilevel: n = 11 trilevel: n = 2 • spinal segment L3-4: n = 4 L4-5: n = 26 L5-S1: n = 38	• VAS for back and leg pain • Oswestry Disability Questionnaire • qualitative scales for quality of life, return to work, and patient satisfaction • radiography: Cobb angle, implant position, interface ingrowth, angular motion, and degenerative changes in adjacent motion segments	• single vs. multilevel surgery • previous lumbar surgery vs. none

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Characteristics	Interventions	Outcomes	Variables evaluated
Tropiano (2005) §§ Huang (2006) §§	case-series (IV) Caselnau-le-Lez, France	N = 64 ‡male %: 54.5% ‡mean age: 46 years (25-65)	mean F/U ± sd (range): 8.7 years ± 1 (6.9 – 10.7) F/U %: overall: 85.9% with complete ASD and ROM data: 65.6%	• symptomatic DDD confirmed by any of several radiographic criteria • discogenic back pain • failed ≥ 6 months conservative treatment • no facet arthrosis, central or lateral recess stenosis, osteoporosis, sagittal or coronal plane deformity, absence of posterior elements, sequestrated herniated nucleus	• ADR with first-generation Prodisc • approach retroperitoneal: n = 45 transperitoneal: n = 10 • number of levels monolevel: n = 35 bilevel: n = 17 trilevel: n = 3 • spinal segment L3-4: n = 8 L4-5: n = 43 L5-S1: n = 28	• category of relative improvement for 20-point modified Stauffer-Coventry score • 3-point scales for low-back pain, lower-limb pain, and ability to perform work, and ADLs • satisfaction • radiography: periprosthetic radiolucent lines, implant migration, mechanical failure, wear of bearing, height of polyethylene core, ASD, ROM	• gender • age • previous surgery • multilevel surgery • ROM
Xu (2004)	case-series (IV) China	N = 34 male %: 59 mean age: 41.1 years (21-65)	mean F/U: 18.6 months (3-28) F/U %: 100	• DDD	• Charite SB III ADR via anterior extra-peritoneal approach • number of levels: monolevel: n = 27 bilevel: n = 7 • spinal segment: L3-5: n = 2 L4-5: n = 18 L5-S1: n = 7 L3-4, L4-5: n = 1 L4-5, L5-S1: n = 6	• radiological evaluation: lumbar spine stability, angle between superior and inferior endplates in flexion and extension, intervertebral space height, and intervertebral foramen size	• NA

ADL = activities of daily living.
BMI = body mass index.
DDD = degenerative disc disease.
NA = not applicable.

ODI = Oswestry Disability Index.
ROM = range of motion.
VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡Demographics reported in this study are after loss to follow-up.
§"Clinical success" = improvement on ODI of ≥ 25%.
**Mayer and Wiechart also report on a series of patients receiving fusion surgeries for other indications (spondylolisthesis, spinal stenosis, and more), but only DDD patients receiving ADR are included here.
††Demographic information is given only for patients, not healthy controls.
‡‡Tortolani et al and Regan et al studied subjects in the RCT reported by Blumenthal et al and McAfee et al that were randomized to receive ADR (n = 205) plus all subjects in the nonrandomized, pretrial study (n = 71). Tortolani et al evaluated whether heterotopic ossification is associated with ODI, VAS pain, or range of motion. Regan et al evaluated whether surgery or hospital experience was associated with ADR and whether ADR was associated with other outcomes.
§§Tropiano et al and Huang et al studied the same patients. Tropiano et al evaluated whether gender, age, previous surgery or multiple levels were associated with clinical and radiographic outcomes. Huang et al reported the frequency of ASD and whether it was associated with ROM or clinical outcome. Not all patients in the entire series reported by Tropiano et al had complete ASD and ROM data to be included in Huang et al's analysis, but distribution of age, gender, number of levels and segment treated were similar in both reports.

Table G3. Demographics and characteristics of included RCTs for C-ADR

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Bryan Panel meeting 2007	• RCT (II) • Multisite; up to 35 sites approved number of sites represented in the report are not clear	N = 463 n = 242 (ADR) n = 221 (ACDF) male %: 48% age: 44.5 (25-78) ADR: 44.4 (25-78) ACDf: 44.7 (27-68) mean weight: ADR: 173 lbs (108-312) ACDF: 180 (100-285) worker's comp: ADR: 15 (16.2%) ACDF: 11 (5.0%) tobacco user: ADR: 61 (25.5%) ACDF: 53 (24.0%)	Duration: 24 months; % NR ‡	• DDD at single level between C3 and C7 • Disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy • 6 weeks minimum unsuccessful conservative unless myelopathy requiring immediate treatment • CT, myelography and CT, and/or MRI demonstration of need for surgical treatment • ≥21 years old • Preopearative NDI ≥ 30 and minimum one clinical sign associated with level to be treated • Willing to sign informed consent and comply with protocol	• Significant cervical anatomical deformity • Moderate to advanced spondylosis • Any combination of bridging osteophytes, marked reduction or absence of motion • Collapse of intervertebral disc space of > 50% normal height, radiographic signs of subluxation > 3.5 mm, angulation of disc space > 11° greater than adjacent segments, significant kyphotic deformity or reversal or lordosis • Axial neck pain as solitary symptom • Previous cervical spine surgery • Metabolic bone disease • Active	• BRYAN Cervical Disc • Standard anterior cervical discectomy and fusion (ACDF) using allograft and MEDTRONIC Sofamor Danek ATLANTIS Cervical Plate system • Treatment levels: C3-4 n = 3 C4-5 n = 29 C5-6 n = 250 C6-7 n = 181	• Overall success defined as improvement of at least 15 points on NDI, maintenance or improvement in neurological status, no serious adverse event which was implant associated or implant-surgical procedure associated, and no additional surgical procedure classified as "failure" • Overall neuro status • NDI score • Neck pain score • Arm pain score • SF-36 health survey • FSU (functional spinal unit) height/implant subsidence • AP implant migration • Angular motion • Translation • Radiographic success • Bending at target level • Fusion status • Angular motion at adjacent levels • Gait • Patient satisfaction	• (Medtronic)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					systemic infection or infection at operative site • Known allergy to components of titanium, polyurethane, ethylene oxide residuals • Concomitant conditions requiring steroid treatment • Daily insulin management • Extreme obesity • Medical condition which may interfere with postop management program or may result in death prior to study completion • Pregnancy • Current or recent alcohol and/or drug abuser • Signs of being geographically unstable		• Adverse events	

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Mummaneni (2007)	• RCT (II) • multisite (32 sites) • patients given sequential clinical trial number then randomly assigned according to randomization schedule using Plan Procedure in Statistical Analysis System (version 6.12 or higher, SAS) • treatment 1:1 on a site basis	N = 541 n = 276 (ADR) n = 265 (ACDF) male %: 46.2 age: 43.6 years (22-73) ADR: 43.3 (25-72) ACDF: 43.9 (22-73)	duration: 24 months 24 month F/U %: 79% ADR: 80% (n = 223/276) ACDF: 75% (n = 198/265) 12 month F/U: ADR: 96% (265/276) ACDF: 86% (228/265) 6 month F/U: ADR 94% ACDF: 88% 3 month F/U: ADR 93% ACDF: 91% 1.5 month F/U: ADR: 99% ACDF: 97%	• adults >18 years of age • single level symptomatic DDD between C3-7 • intractable radiculopathy, myelopathy or both • NDI scores ≥ 30 • VAS neck pain scores ≥ 20 • preserved motion at the symptomatic level found in all included patients • unresponsive to ≥ 6 weeks conservative treatment or progressive neurological worsening despite conservative treatment • no previous procedures at the operative level • negative for several radiographic findings, medications, and diagnoses	• multilevel symptomatic DDD or evidence of cervical instability • sagittal plane translation of greater than 3.5 mm or sagittal plane angulation of greater than 20 degrees at a single level • symptomatic C2-C3 or C7-T1 disc disease • previous surgery at the involved level • severe facet joint disease at the involved level • history of discitis • osteoporosis • metastases • medical condition that required long-term use of medication such as steroid or nonsteroidal antiinflammatory drugs that could affect bone quality and fusion rates	• ADR: Prestige ST Cervical Disc System prosthesis • ACDF: interbody fusion with cortical ring allograft spacers and Atlantis Cervical Plate System	• SF-36 • NDI • neck pain (VAS) • arm pain (VAS) • neurological status • work status • angulation • sagittal plane angulation • secondary surgical procedures including for adjacent segment disease • adverse events • overall success	• "Authors have or will receive benefits for personal or professional use Medtronek Sofamor Danek in relation to products named in this article."

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
Nabhan (2007)	• RCT (II) • drawing cards in sealed envelops • single site	N = 49 n = 25 (disc) n = 24 (ACDF) 8 patients excluded after randomization due to markers obscured (n = 5 of disc group, n = 3 of ACDF group) which leaves: N = 41 n = 20 (disc) n = 21 (ACDF) male %: 56 age: 44 years	duration: 52 weeks F/U % at 52 weeks: 82% (40/49)	• monosegmental cervical DDD between C3-C7 • unresponsive to conservative treatment or presence of signs of nerve root compression with paresis • soft disc herniation • no myelopathy • age between 20-60 years • negative for specific radiographic findings, medications, and diagnoses • signed informed consent	• marked cervical instability on resting or flexion-extension radiographs • >11 of angulations • translation >3 mm • more than one level pathology • myelopathy • radiographic confirmation of severe facet joint degeneration • hard disc disease • osteoporosis, infection, rheumatiod arthritis • spondylodiscitis and active infection • malignant disease • system disease, eg hepatitis, HIV, AIDS • known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene • traumatic injury of spine	• Prodisc-C prosthesis implant: metal polyethylene ball-in-socket design with 2 metal fins; interface UHMW polyethylene inlay, and cobalt-chrome alloy with titanium surface superior and inferior plate (Synthes) • ACDF with “Solis” cage (PEEK) and nonconstrained plate for anterior osteosynthesis	• neck pain (VAS) • arm pain (VAS) • intervertebral mobility (translation) • complications	• no funds received in support of the work • no benefits in any form from a commercial party

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
					• pregnant or possible pregnancy in the next 3 years			
Sun Peng-Fei (2008)	• RCT (II) • single site	N = 24 n = 12 (ADR) n = 12 (ACDF) male %: 70.8 age: 42 years (24-53)	average: 17 months (range, 10-35) F/U %: NR	• single C5-6 intervertebral disc hernia • failed conservative treatment w/ worsening symptoms	• NR •	Bryan ADR • interbody ACDF	• JOA score • ROM of adjacent space • degree of alleviation of clinical symptoms according to the Odom criteria • neurological or vascular complications • mechanical failure	• NR

Prodisc-C FDA report (2007)	RCT (II)
	multisite (13)
	non-inferiority study
		N = 209
		n = 103 (ADR)
		n = 106 (ACDF)
		
		% male: 45
		ADR: 44.7%
		ACDF: 46.2%
		
		mean age: 43 years
		ADR: 42.1 years
		ACDF: 43.5 years
		
		smoking status:
		former:
		n = 38 (18%);
		ADR n = 18 (18%);
		ACDF n = 20 (19%)
		current:
		n = 71 (34%);
		ADR n = 34 (33%);
		ACDF n = 37 (35%)
		
		weight:
			duration 24 months
			
			ADR: 96.1% (99/103) §
			
			ACDF: 86.8% (92/106) §
				• Symptomatic cervical disc disease (SCDD) in one level between C3-C7
				• Age 18-60 years
				• Unresponsive to nonop treatment for six weeks or progressive symptoms
				• NDI ≥ 15/50 (30%)
				• Able to comply with protocol
				• Informed consent
					• More than one vertebral level requiring treatment
					• Marked cervical instability ; translation > 3 mm or > 11° rotational difference
					• Fused level adjacent to level to be treated
					• Radiographically confirmed severe facet joint disease or degeneration
					• Allergy to cobalt, chromium, molybdenum, titanium, or
						• ADR: Prodisc-C
						• ACDF
						• Treatment levels:
						C3-C4 n = 4
						C4-C5 n = 16
						C5-C6 n = 119
						C6-C7 n = 70
							• Overall clinical success
							• NDI > 20% improvement
							• NDI > 15 point improvement
							• SF-36
							• VAS pain intensity
							• device failure
							• neurological failure
								• (Synthes Spine)

Author (year)	Study design (LoE)*	Demographics†	Follow-up	Inclusion criteria	Exclusion criteria	Interventions	Outcomes	Funding
		ADR 171 lbs; ACDF 180 lbs			polyethylene • Clinically compromised vertebral bodies at affected level due to trauma • Prior surgery at level to be treated • Severe spondylosis at level to be treated • Neck or arm pain of unknown etiology • Osteoporosis • Metabolic bone disease • Daily insulin management • Pregnancy • Active infection, systemic or local • Medications or drug known to potentially interfere with healing (steroids) • Autoimmune disease including RA • Systemic disease including AIDS, HIV, hepatitis • Active malignancy within last 5 years			

ACDF = anterior cervical decompression and fusion.

DDD = degenerative disc disease.
NDI = Neck Disability Index.
NR = not reported.
SF-36 = Short Form 36.
VAS = visual analog scale.
*Study design is determined relative to the exposures being compared.
†Demographics are before loss to follow-up, unless otherwise noted.
‡Patients included are those with 24 months of follow-up at time of paper preparation; of the original group, 160 of 168 ADR and 140 of 165 ACDF patients had passed the 24 month point in the course of their treatment.
§Follow-up n's are from table 13 of report (based on number of patients who complete trial); percent is calculated from those n's.