

Artificial Disc Replacement – Re-review

Draft report: Appendices

October 18, 2016

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Artificial Disc Replacement – Re-review

Provided by:



Spectrum Research, Inc.

**Draft Report
APPENDICES**

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TABLE OF CONTENTS

APPENDICES

APPENDIX A. ALGORITHM FOR ARTICLE SELECTION.....1

APPENDIX B. SEARCH STRATEGIES2

APPENDIX C. EXCLUDED ARTICLES4

APPENDIX D. CLASS OF EVIDENCE, STRENGTH OF EVIDENCE, AND QHES DETERMINATION.....9

APPENDIX E. STUDY QUALITY: RISK OF BIAS AND QHES EVALUATION17

APPENDIX F. DEVICES.....30

 LUMBAR ADR (C-ADR) DEVICES 30

 CERVICAL ADR (C-ADR) DEVICES 32

APPENDIX G. L-ADR STUDY CHARACTERISTICS DATA ABSTRACTION TABLES.34

 L-ADR VS. FUSION (1-LEVEL) 34

 L-ADR VS. FUSION (2-LEVEL) 41

 L-ADR VS. FUSION (1- OR 2-LEVEL) 44

 L-ADR VS. MULTIDISCIPLINARY REHABILITATION 50

APPENDIX H. C-ADR STUDY CHARACTERISTICS DATA ABSTRACTION TABLES.52

 C-ADR VS. ACDF (1-LEVEL) 52

 C-ADR VS. ACDF (2-LEVEL) 80

 C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3-LEVEL)) 86

 C-ADR VS. ACDF WITH A ZERO-PROFILE DEVICE (2 NONCONTIGUOUS LEVELS) 94

APPENDIX I. L-ADR EFFICACY AND EFFECTIVENESS RESULTS.95

 L-ADR VS. ACDF (1-LEVEL) 95

 L-ADR VS. FUSION (2-LEVEL) 101

 L-ADR VS. FUSION (1- OR 2-LEVEL) 103

 L-ADR VS. MULTIDISCIPLINARY REHABILITATION 108

APPENDIX J. C-ADR EFFICACY AND EFFECTIVENESS RESULTS..... 112

 C-ADR VS. ACDF (1-LEVEL) 112

 C-ADR VS. ACDF (2-LEVEL) 134

 C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3-LEVELS)) 140

 C-ADR VS. ACDF WITH A ZERO-PROFILE DEVICE (2 NON-CONTIGUOUS LEVELS) 145

APPENDIX K. L-ADR SUMMARY SAFETY TABLES. 146

 L-ADR VS. FUSION (1-LEVEL) 146

 L-ADR VS. FUSION (2-LEVEL) 158

 L-ADR VS. FUSION (1- TO 2-LEVEL) 161

 L-ADR VS. MULTIDISCIPLINARY REHABILITATION 166

APPENDIX L. L-ADR SAFETY DATA ABSTRACTION TABLES..... 169

 L-ADR VS. FUSION (1-LEVEL) 169

 L-ADR VS. FUSION (2-LEVEL) 175

L-ADR VS. FUSION (1- OR 2-LEVEL)	177
L-ADR VS. MULTIDISCIPLINARY REHABILITATION	179
APPENDIX M. C-ADR SUMMARY SAFETY TABLES.....	181
C-ADR VS. ACDF (1-LEVEL)	181
C-ADR VS. ACDF (2-LEVEL)	194
C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3 LEVEL))	197
APPENDIX N. C-ADR SAFETY DATA ABSTRACTION TABLES.	198
C-ADR VS. ACDF (1-LEVEL)	198
C-ADR VS. ACDF (2-LEVEL)	234
C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3-LEVEL))	241
C-ADR VS. ACDF WITH A ZERO-PROFILE DEVICE (2 NON-CONTIGUOUS LEVELS)	245
APPENDIX O. ONGOING CLINICAL TRIALS.....	246
APPENDIX P. CLINICAL EXPERTS.....	249

TABLES

TABLE D1. DEFINITION OF THE RISK OF BIAS FOR STUDIES ON THERAPY.....	9
TABLE D2. EXAMPLE METHODOLOGY OUTLINE FOR DETERMINING OVERALL STRENGTH OF EVIDENCE (SOE):.....	11
TABLE D3. CHECKLIST FOR EVALUATING THE QUALITY OF ADMINISTRATIVE DATABASE STUDIES.	12
TABLE E1. L-ADR RISK OF BIAS EVALUATION: RCTS	17
APPENDIX TABLE E2. L-ADR RISK OF BIAS EVALUATION: NON-RANDOMIZED COMPARATIVE STUDIES (COHORTS).....	18
APPENDIX TABLE E3. L-ADR RISK OF BIAS EVALUATION: REGISTRY STUDIES	19
APPENDIX TABLE E4. L-ADR RISK OF BIAS EVALUATION: ADMINISTRATIVE DATABASE STUDIES	20
APPENDIX TABLE E5. C-ADR RISK OF BIAS EVALUATION: RCTS	21
TABLE E6. C-ADR RISK OF BIAS EVALUATION: NON-RANDOMIZED COMPARATIVE STUDIES.....	24
TABLE E7. C-ADR RISK OF BIAS EVALUATION: REGISTRY STUDIES	25
TABLE E8. C-ADR RISK OF BIAS EVALUATION: ADMINISTRATIVE DATABASE STUDIES	26
TABLE E9. QUALITY OF HEALTH ECONOMIC STUDIES (QHES) SCORES: L-ADR ECONOMIC STUDIES	27
TABLE E10. QUALITY OF HEALTH ECONOMIC STUDIES (QHES) SCORES: C-ADR ECONOMIC STUDIES.....	28
APPENDIX TABLE F1. BIOMECHANICAL CLASSIFICATION OF FDA APPROVED L-ADR PROSTHESES	30
APPENDIX TABLE F2. BIOMECHANICAL CLASSIFICATION OF L-ADR PROSTHESES THAT DO NOT HAVE FDA APPROVAL.....	31
APPENDIX TABLE F3. BIOMECHANICAL CLASSIFICATION OF FDA APPROVED C-ADR PROSTHESES.....	32
APPENDIX TABLE F4. BIOMECHANICAL CLASSIFICATION OF C-ADR PROSTHESES THAT DO NOT HAVE FDA APPROVAL.	33
APPENDIX TABLE G1. L-ADR VS. ACDF (1-LEVEL): RCTS.....	34
APPENDIX TABLE G2. L-ADR VS. ACDF (1-LEVEL): NONRANDOMIZED COMPARATIVE STUDIES	39
APPENDIX TABLE G3. L-ADR VS. ACDF (1-LEVEL): RCTS.....	41
APPENDIX TABLE G4. L-ADR VS. ACDF (1 OR 2-LEVEL): RCTS.....	44
APPENDIX TABLE G5. L-ADR VS. ACDF (1-LEVEL): NONRANDOMIZED COMPARATIVE STUDIES	46
APPENDIX TABLE G6. L-ADR VS. MULTIDISCIPLINARY REHABILITATION: RCTS	50
APPENDIX TABLE H1. C-ADR VS. ACDF (1-LEVEL): RCTS	52
TABLE H2. C-ADR VS. ACDF (1-LEVEL): COHORT STUDIES	73
TABLE H3. C-ADR VS. ACDF (2-LEVEL): RCTS.....	80
TABLE H4. C-ADR VS. ACDF (2-LEVEL): COHORT STUDIES	84
TABLE H5. C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3-LEVEL)): RCTS	86
TABLE H6. C-ADR VS. ACDF (MIXED LEVELS (1-, 2-, OR 3-LEVEL)): COHORT STUDIES.....	90
TABLE H7. C-ADR VS. ACDF WITH A ZERO-PROFILE DEVICE (2 NONCONTIGUOUS LEVELS): RCTS	94

TABLE I1. L-ADR vs. FUSION (1-LEVEL) RCT DATA: OVERALL SUCCESS95

TABLE I2. L-ADR vs. FUSION (1-LEVEL) RCT DATA: ODI, NEUROLOGICAL, AND SF-36 SUCCESS97

TABLE I3. L-ADR vs. FUSION (1-LEVEL) RCT DATA: PATIENT SATISFACTION, WORK STATUS, AND NARCOTIC USE98

TABLE I4. L-ADR vs. FUSION (1-LEVEL) RCT DATA: SF-36, ODI, AND VAS PAIN SCORES.....100

TABLE I5. L-ADR vs. FUSION (2-LEVELS) RCT DATA: OVERALL AND NEUROLOGICAL SUCCESS101

TABLE I6. L-ADR vs. FUSION (2-LEVELS) RCT DATA: ODI, VAS, AND SF-36 SCORES102

TABLE I7. L-ADR vs. FUSION (2-LEVELS) RCT DATA: NARCOTIC USE, WORK AND RECREATIONAL ACTIVITY STATUS, AND PATIENT SATISFACTION.....102

TABLE I8. L-ADR vs. FUSION (1- OR 2-LEVELS) RCT DATA: OVERALL AND ODI SUCCESS103

TABLE I9. L-ADR vs. FUSION (1- OR 2-LEVELS) RCT DATA: GLOBAL ASSESSMENT OF PAIN (OTHER THAN INCLUDED FOR OVERALL SUCCESS)104

TABLE I10. L-ADR vs. FUSION (1- OR 2-LEVELS) RCT DATA: OTHER PAIN, FUNCTION, AND QUALITY OF LIFE SCORES.....104

TABLE I11. L-ADR vs. FUSION (1- OR 2-LEVELS) RCT DATA: PATIENT SATISFACTION, WORK STATUS AND ANALGESIC CONSUMPTION. ..105

TABLE I12. L-ADR vs. FUSION (1- OR 2-LEVELS) RCT DATA: SEX LIFE OUTCOMES BASED ON ODI ITEM 8.106

TABLE I13. L-ADR vs. FUSION (1- OR 2-LEVEL) NON-RANDOMIZED REGISTRY DATA: PAIN, DISABILITY, QUALITY OF LIFE, WORK STATUS, AND PATIENT SATISFACTION.....107

TABLE I14. L-ADR vs. MULTIDISCIPLINARY REHABILITATION: ODI SUCCESS108

TABLE I15. L-ADR vs. MULTIDISCIPLINARY REHABILITATION: TREATMENT FAILURE – REHABILITATION GROUP ONLY108

TABLE I16. L-ADR vs. MULTIDISCIPLINARY REHABILITATION: ODI, VAS PAIN, SF-36, AND EQ-5D SCORES.....108

TABLE I17. L-ADR vs. MULTIDISCIPLINARY REHABILITATION: WORK STATUS, PATIENT SATISFACTION, AND MEDICATION USE110

TABLE I18. L-ADR vs. MULTIDISCIPLINARY REHABILITATION: OTHER SECONDARY OUTCOMES.....110

TABLE J1. C-ADR vs. ACDF (1-LEVEL) RCT DATA: OVERALL SUCCESS112

TABLE J2. C-ADR vs. ACDF (1-LEVEL) RCT DATA: NDI SUCCESS.....115

TABLE J3. C-ADR vs. ACDF (1-LEVEL) RCT DATA: NDI SCORES116

TABLE J4. CERVICAL ADR vs. ACDF AT 1-LEVEL RCT DATA: EFFICACY OUTCOMES: NEUROLOGICAL SUCCESS118

TABLE J5. C-ADR vs. ACDF (1-LEVEL) RCT DATA: ARM PAIN SUCCESS119

TABLE J6. C-ADR vs. ACDF (1-LEVEL) RCT DATA: ARM PAIN VAS/NRS SCORES119

TABLE J7. C-ADR vs. ACDF (1-LEVEL) RCT DATA: NECK OR ARM PAIN SUCCESS121

TABLE J8. C-ADR vs. ACDF (1-LEVEL): NECK PAIN SUCCESS121

TABLE J9. C-ADR vs. ACDF (1-LEVEL) RCT DATA: NECK PAIN VAS/NRS SCORES122

TABLE J10. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SF-36 PCS AND MCS SUCCESS124

TABLE J11. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SF-36 PCS SCORES125

TABLE J12. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SF-36 MCS SCORES126

TABLE J13. C-ADR vs. ACDF (1-LEVEL) RCT DATA: PATIENT SATISFACTION.....127

TABLE J14. C-ADR vs. ACDF (1-LEVEL) RCT DATA: PATIENT SATISFACTION VAS SCORES.....128

TABLE J15. C-ADR vs. ACDF (1-LEVEL) RCT DATA: ODOM’S CRITERIA128

TABLE J16. C-ADR vs. ACDF (1-LEVEL) RCT DATA: RETURN TO WORK129

TABLE J17. C-ADR vs. ACDF (1-LEVEL) RCT DATA: TIME TO RETURN TO WORK130

TABLE J18. C-ADR vs. ACDF (1-LEVEL) RCT DATA: NURICK GRADE130

TABLE J19. C-ADR vs. ACDF (1-LEVEL) RCT DATA: JOA SCORES130

TABLE J20. C-ADR vs. ACDF (1-LEVEL) RCT DATA: MEDICATION USAGE131

TABLE J21. C-ADR vs. ACDF (1-LEVEL) NON-RANDOMIZED STUDY DATA: FUNCTION AND PAIN SCORES.....132

TABLE J22. C-ADR vs. ACDF (1-LEVEL) NON-RANDOMIZED STUDY DATA: RESPONDER OUTCOMES133

TABLE J23. C-ADR vs. ACDF (2-LEVEL) RCT DATA: OVERALL SUCCESS134

TABLE J24. C-ADR vs. ACDF (2-LEVEL) RCT DATA: NDI SUCCESS.....134

TABLE J25. C-ADR vs. ACDF (2-LEVEL) RCT DATA: NDI SCORES135

TABLE J26. C-ADR vs. ACDF (2-LEVEL) RCT DATA: NEUROLOGICAL SUCCESS.....135

TABLE J27. C-ADR vs. ACDF (2-LEVEL) RCT DATA: ARM PAIN VAS SCORES135

TABLE J28. C-ADR vs. ACDF (2-LEVEL) RCT DATA: NECK PAIN VAS SCORES136

TABLE J29. C-ADR vs. ACDF (2-LEVEL) RCT DATA: SF-36 PCS SCORES136

TABLE J30. C-ADR vs. ACDF (2-LEVEL) RCT DATA: PATIENT SATISFACTION.....138

TABLE J31. C-ADR vs. ACDF (2-LEVEL) RCT DATA: ODOM’S CRITERIA138

TABLE J32. C-ADR vs. ACDF (2-LEVEL) RCT DATA: TIME TO RETURN TO WORK138

TABLE J33. C-ADR vs. ACDF (2-LEVEL) NON-RANDOMIZED STUDY DATA: FUNCTION AND PAIN SCORES.....139

TABLE J34. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: NDI SCORES.....140

TABLE J35. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: ARM PAIN VAS SCORES.....140

TABLE J36. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: NECK PAIN VAS SCORES.....140

TABLE J37. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: QUALITY OF LIFE SCORES.....141

TABLE J38. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: ODOM’S CRITERIA.....141

TABLE J39. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: TIME TO RETURN TO WORK.....141

TABLE J40. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: JOA SCORES.....142

TABLE J41. C-ADR vs. ACDF (MIXED LEVELS) NON-RANDOMIZED STUDY DATA: OUTCOME SCORES.....142

TABLE J42. C-ADR vs. ACDF (MIXED LEVELS) NON-RANDOMIZED STUDY DATA: RESPONDER OUTCOMES.....144

TABLE J43. C-ADR vs. ACDF WITH A ZERO-PROFILE DEVICE (2-LEVEL) RCT DATA: NDI SCORES.....145

TABLE J44. C-ADR vs. ACDF WITH A ZERO-PROFILE DEVICE (2-LEVEL) RCT DATA: JOA SCORES.....145

TABLE K1. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: MAJOR, DEVICE-RELATED, AND ANY ADVERSE EVENTS.....146

TABLE K2. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: SUBSEQUENT SURGERY AT THE INDEX LEVEL.....148

TABLE K3. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: APPROACH-RELATED ADVERSE EVENTS.....149

TABLE K4. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: INFECTION.....151

TABLE K5. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: TREATMENT-SPECIFIC ADVERSE EVENTS.....153

TABLE K6. L-ADR vs. FUSION (1 LEVEL) RCTs SAFETY DATA: OTHER ADVERSE EVENTS AND ADJACENT LEVEL SURGERY.....154

TABLE K7. L-ADR vs. FUSION (1-LEVEL) ADVERSE EVENTS DATA FROM THE CHARITE IDE TRIAL RANDOMIZED PATIENTS PLUS ADDITIONAL TRAINING CASES – COHORT ANALYSIS.....155

TABLE K8. L-ADR vs. FUSION (1-LEVEL) NON-RANDOMIZED STUDY DATA: ADVERSE EVENTS.....156

TABLE K9. L-ADR vs. FUSION (2 LEVELS) RCTs SAFETY DATA: SUBSEQUENT SURGERY AT THE INDEX LEVEL.....158

TABLE K10. L-ADR vs. FUSION (2 LEVELS) RCTs SAFETY DATA: MAJOR ADVERSE EVENTS.....159

TABLE K11. L-ADR vs. FUSION (2 LEVELS) RCTs SAFETY DATA: OTHER REPORTED COMPLICATIONS.....160

TABLE K12. L-ADR vs. FUSION (1- OR 2- LEVELS) RCTs SAFETY DATA: COMPLICATIONS.....161

TABLE K13. L-ADR vs. FUSION (1- OR 2- LEVELS) RCTs SAFETY DATA: SUBSEQUENT SURGERY AT THE INDEX AND ADJACENT LEVEL AND ADDITIONAL INTERVENTIONS.....163

TABLE K14. L-ADR vs. FUSION (2 LEVELS) NONRANDOMIZED SAFETY DATA: REOPERATIONS.....165

TABLE K15. L-ADR vs. MULTIDISCIPLINARY REHABILITATION RCTs SAFETY DATA: MAJOR AND ANY COMPLICATION.....166

TABLE K16. L-ADR vs. MULTIDISCIPLINARY REHABILITATION RCTs SAFETY DATA: SUBSEQUENT SURGERY AT THE INDEX LEVEL.....168

TABLE L1. L-ADR vs. FUSION (1 LEVEL) RCT DATA: SAFETY DATA ABSTRACTION – CHARITE IDE TRIAL.....169

TABLE L2. L-ADR vs. FUSION (1 LEVEL) RCT DATA: SAFETY DATA ABSTRACTION – PRODISC-L IDE TRIAL.....172

TABLE K3. L-ADR vs. FUSION (2 LEVELS) RCTs SAFETY DATA: PRODISC-L (2 LEVEL) IDE TRIAL.....175

TABLE L4. L-ADR vs. FUSION (1 OR 2 LEVELS): SAFETY DATA ABSTRACTION – BERG 2009 RCT.....177

TABLE L5. L-ADR vs. MULTIDISCIPLINARY REHABILITATION (1 TO 2 LEVELS) RCTs SAFETY DATA: HELLUM 2011.....179

TABLE M1. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SECONDARY SURGERY INVOLVING THE INDEX LEVEL*.....181

TABLE M2. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SERIOUS ADVERSE EVENTS.....186

TABLE M3. C-ADR vs. ACDF (1-LEVEL) RCT DATA: DEATH.....187

TABLE M4. C-ADR vs. ACDF (1-LEVEL) RCT DATA: DEVICE-RELATED ADVERSE EVENTS.....188

TABLE M5. C-ADR vs. ACDF (1-LEVEL) RCT DATA: SECONDARY SURGERY INVOLVING AN ADJACENT LEVEL.....189

TABLE M6. C-ADR vs. ACDF (1-LEVEL) RCT DATA: ANY ADVERSE EVENT.....191

TABLE M7. C-ADR vs. ACDF (1-LEVEL): ADVERSE EVENTS REPORTED BY ONE OR MORE RCTs TO BE SIGNIFICANTLY MORE COMMON WITH C-ADR.....192

TABLE M8. C-ADR vs. ACDF (1-LEVEL): ADVERSE EVENTS REPORTED BY ONE OR MORE RCTs TO BE SIGNIFICANTLY MORE COMMON WITH C-ADR.....193

TABLE M9. C-ADR vs. ACDF (2-LEVEL) RCT DATA: SECONDARY SURGERY INVOLVING THE INDEX LEVEL*.....194

TABLE M10. C-ADR vs. ACDF (2-LEVEL) RCT DATA: SERIOUS ADVERSE EVENTS.....195

TABLE M11. C-ADR vs. ACDF (2-LEVEL) RCT DATA: DEVICE-RELATED ADVERSE EVENTS.....195

TABLE M12. C-ADR vs. ACDF (2-LEVEL) RCT DATA: SECONDARY SURGERY INVOLVING AN ADJACENT LEVEL.....196

TABLE M13. C-ADR vs. ACDF (2-LEVEL) RCT DATA: ANY ADVERSE EVENT.....196

TABLE M14. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: SECONDARY SURGERY INVOLVING THE INDEX LEVEL.....197

TABLE M15. C-ADR vs. ACDF (MIXED LEVELS) RCT DATA: SECONDARY SURGERY INVOLVING AN ADJACENT LEVEL.....197

TABLE N1. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- PRESTIGE ST IDE TRIAL.....198

TABLE N2. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- BRYAN ST IDE TRIAL202

TABLE N3. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- PCM IDE TRIAL208

TABLE N4. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- MOBI-C IDE TRIAL.....212

TABLE N5. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- PRODISC-C IDE TRIAL217

TABLE N6. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- SECURE-C IDE TRIAL221

TABLE N7. ADR vs. ACDF (1-LEVEL): SAFETY DATA ABSTRACTION- RCTS OTHER THAN IDE TRIALS230

TABLE N8. C-ADR vs. ACDF (1-LEVEL) NON-RANDOMIZED STUDY DATA: ADVERSE EVENTS232

TABLE N9. ADR vs. ACDF (2-LEVEL): SAFETY DATA ABSTRACTION- MOBI-C (2-LEVEL) IDE TRIAL.....234

TABLE N10. ADR vs. ACDF (2-LEVEL): SAFETY DATA ABSTRACTION- RCTS OTHER THAN IDE TRIALS240

TABLE N11. C-ADR vs. ACDF (1-LEVEL) NON-RANDOMIZED STUDY DATA: ADVERSE EVENTS240

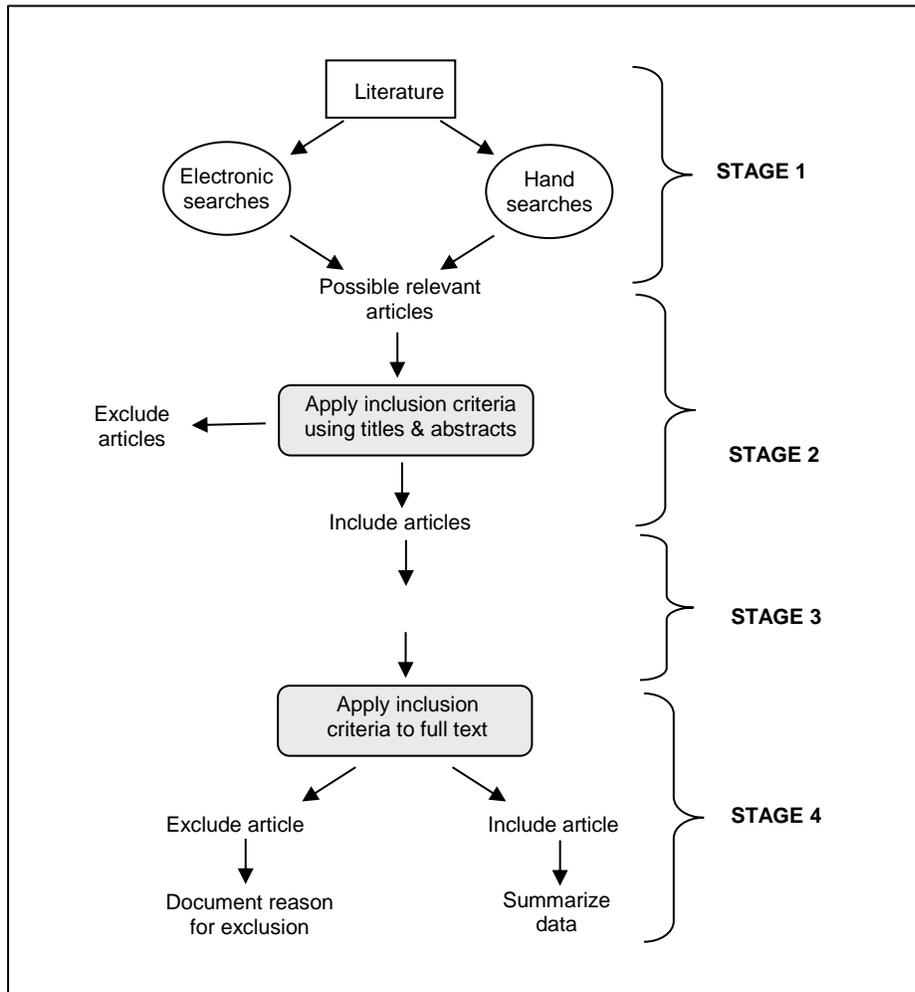
TABLE N12. ADR vs. ACDF (MIXED LEVELS (1-, 2-, OR 3- LEVEL): SAFETY DATA ABSTRACTION- RCTS241

TABLE N13. C-ADR vs. ACDF (MIXED LEVELS (1-, 2-, OR 3- LEVEL) NON-RANDOMIZED STUDY DATA: ADVERSE EVENTS243

TABLE N14. ADR vs. ACDF WITH ZERO-PROFILE DEVICE (2 NON-CONTIGUOUS LEVELS): SAFETY DATA ABSTRACTION- RCTS245

TABLE O1. ONGOING CLINICAL TRIALS.....246

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)

Search date: 5/16/2016

Filters: Abstract available, English, Publication date from 2008/01/01

	Search terms	Citations
1.	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR total[TI] OR replacement*[TI]	58,721
2.	Disk*[TI] OR Disc[TI] OR Discs[TI] OR Intervertebral Disk[Mesh]	9200
3.	#1 AND #2	613
4.	Total Disc Replacement[MeSH] OR arthroplasty[TI]	13,017
5.	#3 OR #4	13,362
	LUMBAR	
6.	Lumbar Vertebrae[Mesh] OR Low Back Pain[Mesh] OR intervertebral disc degeneration[Mesh] OR "low back"[TIAB] OR Lumbar[TI]	24,944
7.	#5 AND #6	487
8.	#7 NOT (Disease Models, Animal[MeSH] OR mice[TI] OR mouse[TI] OR murine[TI] OR rat[TI] OR animal[TI] Case Reports[Publication Type] OR Comment[Publication Type] OR hip[TI] OR femoral[TI])	456
	CERVICAL	
9.	Cervical Vertebrae[Mesh] OR Neck Pain[Mesh] OR intervertebral disc degeneration[Mesh] OR Neck[TI] OR Cervical[TI]	47,159
10.	#5 AND #9	688
11.	#10 NOT (Disease Models, Animal[MeSH] OR mice[TI] OR mouse[TI] OR murine[TI] OR rat[TI] OR animal[TI] Case Reports[Publication Type] OR Comment[Publication Type] OR hip[TI] OR femoral[TI])	548
12.	BOTH LUMBAR AND CERVICAL	
13.	#8 OR #11	803
14.	artificial[TI] OR prosthetic*[TI] OR prosthes*[TI] OR total[TI] OR replacement*[TI]	58,721
15.	Disk*[TI] OR Disc[TI] OR Discs[TI] OR Intervertebral Disk[Mesh]	9200
16.	#1 AND #2	613
17.	Total Disc Replacement[MeSH] OR arthroplasty[TI]	13,017
18.	#3 OR #4	13,362
	LUMBAR	
19.	Lumbar Vertebrae[Mesh] OR Low Back Pain[Mesh] OR intervertebral disc degeneration[Mesh] OR "low back"[TIAB] OR Lumbar[TI]	38,912
20.	#5 AND #6	565
21.	#7 NOT (Disease Models, Animal[MeSH] OR mice[TI] OR mouse[TI] OR murine[TI] OR rat[TI] OR animal[TI] Case Reports[Publication Type] OR Comment[Publication Type] OR hip[TI] OR femoral[TI])	511
	CERVICAL	
22.	Cervical Vertebrae[Mesh] OR Neck Pain[Mesh] OR intervertebral disc	112,443

	Search terms	Citations
	degeneration[Mesh] OR Neck[TI] OR Cervical[TI]	
23.	#5 AND #9	1052
24.	#10 NOT (Disease Models, Animal[MeSH] OR mice[TI] OR mouse[TI] OR murine[TI] OR rat[TI] OR animal[TI] Case Reports[Publication Type] OR Comment[Publication Type] OR hip[TI] OR femoral[TI])	629
25.	BOTH LUMBAR AND CERVICAL	
26.	#8 OR #11	921

Parallel strategies were used to search the Cochrane Library, EMBASE, and others listed below. Keyword searches were conducted in the other listed resources. In addition, handsearching of included studies was performed.

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
- Cochrane Registry of Clinical Trials (CENTRAL)
- Cochrane Review Methodology Database
- Database of Reviews of Effectiveness (Cochrane Library)
- EMBASE
- PubMed
- Informational Network of Agencies for Health Technology Assessment (INAHTA)
- NHS Economic Evaluation Database
- 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 C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

	Citation	Reason for exclusion after full-text review
LUMBAR		
1.	Auerbach JD, Jones KJ, Milby AH, Anakwenze OA, Balderston RA. Segmental contribution toward total lumbar range of motion in disc replacement and fusions: a comparison of operative and adjacent levels. <i>Spine</i> 2009;34:2510-7.	Not primary outcomes of interest (ROM and radiographic parameters)
2.	Berg S. On total disc replacement. <i>Acta orthopaedica Supplementum</i> 2011;82:1-	Review of separate studies on this trial/using primary citations
3.	Berg S, Tropp HT, Leivseth G. Disc height and motion patterns in the lumbar spine in patients operated with total disc replacement or fusion for discogenic back pain. Results from a randomized controlled trial. <i>The spine journal : official journal of the North American Spine Society</i> 2011;11:991-8.	Not a primary outcomes of interest (disc height, ROM)
4.	Burkus JK, Dryer RF, Peloza JH. Retrograde ejaculation following single-level anterior lumbar surgery with or without recombinant human bone morphogenetic protein-2 in 5 randomized controlled trials: clinical article. <i>Journal of neurosurgery Spine</i> 2013;18:112-21.	Of the 5 included RCTs, only one compared ADR to ALIF and a non-FDA approved device (Maverick) was used
5.	Buttacavoli FA, Delamarter RB, Kanim LE. Cost comparison of patients with 3-level artificial total lumbar disc replacements versus 360 degrees fusion at 3 contiguous lumbar vertebral levels: an analysis of compassionate use at 1 site of the US investigational device exemption clinical trial. <i>SAS J.</i> 2010;4(4):107-114.	Costing study only; not a full economic evaluation
6.	Geisler FH, Guyer RD, Blumenthal SL, et al. Patient selection for lumbar arthroplasty and arthrodesis: the effect of revision surgery in a controlled, multicenter, randomized study. <i>Journal of neurosurgery Spine</i> 2008;8:13-6.	Not a comparison of interest; comparison of those who did/didn't have subsequent revision surgery
7.	Geisler FH, McAfee PC, Banco RJ, et al. Prospective, Randomized, Multicenter FDA IDE Study of CHARITE Artificial Disc versus Lumbar Fusion: Effect at 5-year Follow-up of Prior Surgery and Prior Discectomy on Clinical Outcomes Following Lumbar Arthroplasty. <i>SAS journal</i> 2009;3:17-25	Not comparator of interest, subgroup analysis of those who had had prior fusion or discectomy only not full trial population
8.	Hellum C, Berg L, Gjertsen Ø, Johnsen LG, Neckelmann G, Storheim K, Keller A, Grundnes O, Espeland A; Norwegian Spine Study Group. Adjacent level degeneration and facet arthropathy after disc prosthesis surgery or rehabilitation in patients with chronic low back pain and degenerative disc: second report of a randomized study. <i>Spine (Phila Pa 1976)</i> . 2012 Dec 1;37(25):2063-73. doi: 10.1097/BRS.0b013e318263cc46.	Not outcomes of interest (Facet arthropathy, radiographic features);subanalysis of 67% of patient population
9.	Johnsen LG, Brinckmann P, Hellum C, Rossvoll I, Leivseth G. Segmental mobility, disc height and patient-reported outcomes after surgery for degenerative disc disease: a prospective randomised trial comparing disc replacement and multidisciplinary rehabilitation. <i>Bone Joint J.</i> 2013 Jan;95-B(1):81-9. doi: 10.1302/0301-620X.95B1.29829.	Not a primary outcomes of interest (disc height, ROM); subanalysis of 69% of patient population

	Citation	Reason for exclusion after full-text review
10.	Leahy M, Zigler JE, Ohnmeiss DD, Rashbaum RF, Sachs BL. Comparison of results of total disc replacement in postdiscectomy patients versus patients with no previous lumbar surgery. <i>Spine</i> 2008;33:1690-3; discussion 4-5.	Not population of interest
11.	Ohnmeiss DD, Bodemer W, Zigler JE. Effect of adverse events on low back surgery outcome: twenty-four-month follow-up results from a Food And Drug Administration investigational device exemption trial. <i>Spine</i> 2010;35:835-8.	Wrong study design (prognostic study evaluating impact of post-treatment AEs on clinical outcomes; data not stratified by treatment group)
12.	Oktenoglu T, Ozer AF, Sasani M, Ataker Y, Gomleksiz C, Celebi I. Posterior Transpedicular Dynamic Stabilization versus Total Disc Replacement in the Treatment of Lumbar Painful Degenerative Disc Disease: A Comparison of Clinical Results. <i>Advances in orthopedics</i> . 2013;2013:874090.	Device not FDA approved/not listed as available (Maverick)
13.	Rischke B, Zimmers KB, Smith E. Viscoelastic Disc Arthroplasty Provides Superior Back and Leg Pain Relief in Patients with Lumbar Disc Degeneration Compared to Anterior Lumbar Interbody Fusion. <i>International journal of spine surgery</i> . 2015;9:26.	Device not FDA approved/not listed as available (FREEDOM)
14.	Strube P, Putzier M, Streitparth F, Hoff EK, Hartwig T. Postoperative posterior lumbar muscle changes and their relationship to segmental motion preservation or restriction: a randomized prospective study. <i>J Neurosurg Spine</i> . 2016 Jan;24(1):25-31.	Device not FDA approved/not listed as available (Maverick)
CERVICAL		
15.	Anakwenze OA, Auerbach JD, Milby AH, Lonner BS, Balderston RA. Sagittal cervical alignment after cervical disc arthroplasty and anterior cervical discectomy and fusion: results of a prospective, randomized, controlled trial. <i>Spine</i> 2009;34:2001-7.	Wrong outcome (lordosis only)
16.	Arts MP, Brand R, van den Akker E, Koes BW, Peul WC. The Netherlands Cervical Kinematics (NECK) trial. Cost-effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blind randomised multicenter study. <i>BMC musculoskeletal disorders</i> 2010;11:122.	Wrong study type (protocol only, no publications of results data identified)
17.	Auerbach JD, Anakwenze OA, Milby AH, Lonner BS, Balderston RA. Segmental contribution toward total cervical range of motion: a comparison of cervical disc arthroplasty and fusion. <i>Spine</i> 2011;36:E1593-9.	Wrong outcome (total cervical ROM, no primary outcomes reported)
18.	Bhadra AK, Raman AS, Casey AT, Crawford RJ. Single-level cervical radiculopathy: clinical outcome and cost-effectiveness of four techniques of anterior cervical discectomy and fusion and disc arthroplasty. <i>European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society</i> 2009;18:232-7.	Not a formal economic study (cost not directly linked to outcomes)
19.	Boselie TF, van Mameren H, de Bie RA, van Santbrink H. Cervical spine kinematics after anterior cervical discectomy with or without implantation of a mobile cervical disc prosthesis; an RCT. <i>BMC musculoskeletal disorders</i> 2015;16:34.	Wrong study type (protocol only, no publications of results data identified)

	Citation	Reason for exclusion after full-text review
20.	Buchowski JM, Anderson PA, Sekhon L, Riew KD. Cervical disc arthroplasty compared with arthrodesis for the treatment of myelopathy. Surgical technique. The Journal of bone and joint surgery American volume 2009;91 Suppl 2:223-32.	Wrong outcome (no outcomes of interest; description of surgical technique only)
21.	Davis RJ, Hoffman GA, Bae HW, et al. Cervical disc arthroplasty results in fewer secondary surgeries through 48 months compared to ACDF: results for a prospective randomized IDE study for two-level use. The spine journal : official journal of the North American Spine Society 2013;13:S164-5.	Wrong study type (conference abstract)
22.	Ghori A, Konopka JF, Makanji H, Cha TD, Bono CM. Long Term Societal Costs of Anterior Discectomy and Fusion (ACDF) versus Cervical Disc Arthroplasty (CDA) for Treatment of Cervical Radiculopathy. International journal of spine surgery 2016;10:1.	Not a formal economic study (cost not directly linked to outcomes)
23.	Kelly MP, Anderson PA, Sasso RC, Riew KD. Preoperative opioid strength may not affect outcomes of anterior cervical procedures: a post hoc analysis of 2 prospective, randomized trials. Journal of neurosurgery Spine 2015;23:484-9.	Wrong study design (outcomes not stratified by treatment group)
24.	Kelly MP, Mok JM, Frisch RF, Tay BK. Adjacent segment motion after anterior cervical discectomy and fusion versus Prodisc-c cervical total disk arthroplasty: analysis from a randomized, controlled trial. Spine 2011;36:1171-9.	Wrong outcome (motion only)
25.	Maldonado CV, Paz RD, Martin CB. Adjacent-level degeneration after cervical disc arthroplasty versus fusion. European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2011;20 Suppl 3:403-7.	Wrong disc (Discocerv disc excluded from scope; the percentage of patients who received this disc was not reported)
26.	Menzin J, Zhang B, Neumann PJ, et al. A Health-economic Assessment of Cervical Disc Arthroplasty Compared With Allograft Fusion. Techniques in Orthopaedics 2010:133-7.	Not a formal economic study (cost not directly linked to outcomes)
27.	Nandyala SV, Marquez-Lara A, Fineberg SJ, Singh K. Comparison of revision surgeries for one- to two-level cervical TDR and ACDF from 2002 to 2011. The spine journal : official journal of the North American Spine Society 2014;14:2841-6.	Wrong population (patients undergoing revision ADR)
28.	Nunley PD, Jawahar A, Kerr EJ, 3rd, et al. Factors affecting the incidence of symptomatic adjacent-level disease in cervical spine after total disc arthroplasty: 2- to 4-year follow-up of 3 prospective randomized trials. Spine 2012;37:445-51.	Wrong outcomes (reports ASD but no primary outcomes of interest)
29.	Park DK, Lin EL, Phillips FM. Index and adjacent level kinematics after cervical disc replacement and anterior fusion: in vivo quantitative radiographic analysis. Spine 2011;36:721-30.	Wrong outcome (no primary outcomes)
30.	Patel SA, Ackerman C, Gandhi SD, Rihn JA. Cost-effectiveness of treatments for cervical disc herniation. Seminars in spine surgery 2016;28:123-7.	Not a formal economic study (narrative review)

Citation		Reason for exclusion after full-text review
31.	Qureshi S, Goz V, McAnany S, et al. Health state utility of patients with single-level cervical degenerative disc disease: comparison of anterior cervical discectomy and fusion with cervical disc arthroplasty. <i>Journal of neurosurgery Spine</i> 2014;20:475-9.	Wrong outcome (health state utility, which was derived by converting SF-36 (reported in other studies) to SF-6 scores)
32.	Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. <i>Spine</i> 2015;40:521-9.	Not a formal economic study (cost not directly linked to outcomes)
33.	Richardson SS, Berven S. The development of a model for translation of the Neck Disability Index to utility scores for cost-utility analysis in cervical disorders. <i>The spine journal : official journal of the North American Spine Society</i> 2012;12:55-62.	Wrong outcome (no primary outcomes)
34.	Riina J, Patel A, Dietz JW, Hoskins JS, Trammell TR, Schwartz DD. Comparison of single-level cervical fusion and a metal-on-metal cervical disc replacement device. <i>American journal of orthopedics (Belle Mead, NJ)</i> 2008;37:E71-7.	Wrong study design (single site results of multicenter trial)
35.	Sasso RC, Best NM. Cervical kinematics after fusion and bryan disc arthroplasty. <i>Journal of spinal disorders & techniques</i> 2008;21:19-22.	Wrong study design (single site results of multicenter trial)
36.	Sasso RC, Best NM, Metcalf NH, Anderson PA. Motion analysis of bryan cervical disc arthroplasty versus anterior discectomy and fusion: results from a prospective, randomized, multicenter, clinical trial. <i>Journal of spinal disorders & techniques</i> 2008;21:393-9.	Wrong outcome (motion only, no primary outcomes)
37.	Shichang L, Yueming S, Limin L, et al. Clinical and radiologic comparison of dynamic cervical implant arthroplasty and cervical total disc replacement for single-level cervical degenerative disc disease. <i>Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia</i> 2016;27:102-9.	Comparator group device not FDA-approved (dynamic cervical implant (name NR) from Scient'x/Alphatec Spine; this manufacturer does not have any devices with PMA listed on the FDA website as of 7/15/16 (searched http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm))
38.	Sundseth J, Jacobsen EA, Kolstad F, et al. Heterotopic ossification and clinical outcome in nonconstrained cervical arthroplasty 2 years after surgery: the Norwegian Cervical Arthroplasty Trial (NORCAT). <i>European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society</i> 2016.	Wrong study design (single site results of multicenter trial)
39.	Tracey RW, Kang DG, Cody JP, Wagner SC, Rosner MK, Lehman RA, Jr. Outcomes of single-level cervical disc arthroplasty versus anterior cervical discectomy and fusion. <i>Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia</i> 2014;21:1905-8.	Wrong population: 23.9% of ACDF patients were undergoing revision surgery
40.	Warren D, Andres T, Hoelscher C, Ricart-Hoffiz P, Bendo J, Goldstein J. Cost-utility analysis modeling at 2-year follow-up for cervical disc arthroplasty versus anterior cervical discectomy and fusion: A single-	CUA uses single site results from multicenter trial to calculate clinical outcomes (including

	Citation	Reason for exclusion after full-text review
	center contribution to the randomized controlled trial. International journal of spine surgery 2013;7:e58-66.	health utility values); 5-year results from the full trial (Murrey trial) were used in another included CUA (McAnany et al.))
41.	Wiedenhofer B, Nacke J, Stephan M, Richter W, Carstens C, Eichler M. Is Total Disc Replacement a Cost Effective Treatment for Cervical Degenerative Disc Disease? Clinical spine surgery 2016.	Excluded from KQ4: not a formal economic study (cost not directly linked to outcomes); Excluded from KQ1/2 as no data for primary outcomes were reported.

APPENDIX D. Class of Evidence, Strength of Evidence, and QHES Determination

Each study is rated against pre-set criteria that resulted in a Risk of Bias (RoB) assessment and presented in a table. The criteria are listed in the Tables below.

Table D1. Definition of the risk of bias for studies on therapy

Risk of Bias	Studies of Therapy*	
	Study design	Criteria*
<p>Low risk:</p> <p>Study adheres to commonly held tenets of high quality design, execution and avoidance of bias</p>	Good quality RCT	<ul style="list-style-type: none"> • Random sequence generation • Statement of allocation concealment • Intent-to-treat analysis • Blind or independent assessment for primary outcome(s) • Co-interventions applied equally • F/U rate of 80%+ and <10% difference in F/U between groups • Controlling for possible confounding‡
<p>Moderately low risk:</p> <p>Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias</p>	Moderate quality RCT	<ul style="list-style-type: none"> • Violation of one or two of the criteria for good quality RCT
	Good quality cohort	<ul style="list-style-type: none"> • Blind or independent assessment for primary outcome(s) • Co-interventions applied equally • F/U rate of 80%+ and <10% difference in F/U between groups • Controlling for possible confounding‡
<p>Moderately High risk:</p> <p>Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results</p>	Poor quality RCT	<ul style="list-style-type: none"> • Violation of three or more of the criteria for good quality RCT
	Moderate or poor quality cohort	<ul style="list-style-type: none"> • Violation of any of the criteria for good quality cohort
	Case-control	<ul style="list-style-type: none"> • Any case-control design
<p>High risk:</p> <p>Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes</p>	Case series	<ul style="list-style-type: none"> • Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt⁴:

- Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
- Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a smaller number tested?

- † Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.
- ‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Quality of Evidence

Following the assessment of the quality of each individual study included in the report, an overall “quality of evidence” for the relevant question or topic is determined. Methods for determining the overall quality of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI’s method incorporates the primary domains of quality (risk of bias), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

All AHRQ “required” and “additional” domains (risk of bias, consistency, directness, precision, publication bias) are assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Table D2. Example methodology outline for determining overall strength of evidence (SoE):

<p>All AHRQ “required” and “additional” domains* are assessed. Only those that influence the baseline grade are listed in table.</p> <p><u>Baseline strength</u>: HIGH = majority of articles RCTs. LOW = majority of articles cohort studies.</p> <p><u>DOWNGRADE</u>: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated <i>a priori</i> and no test for interaction (2)</p> <p><u>UPGRADE</u>: Large magnitude of effect (1 or 2); Dose response gradient (1)</p>					
Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	HIGH	Summary of findings	HIGH RCTs	NO consistent, direct, and precise estimates	NO
Outcome	MODERATE	Summary of findings	LOW Cohort studies	NO consistent, direct, and precise estimates	YES Large effect
Outcome	LOW	Summary of findings	HIGH RCTs	YES (2) Inconsistent Indirect	NO

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.

**Single study = “consistency unknown”, not downgraded

Administrative Database Study evaluation

What constitutes a high quality administrative database study? What criteria?

Although the precise guidelines that should govern high quality administrative database studies are still under development,² a number of criteria that should be met in a high quality administrative database study have been suggested.^{2,5} The checklist below highlights many of these qualities as was used to provide an initial assessment of administrative data studies. Individual report topics may have unique aspects of coding, requirements for developing algorithms for subject identification and potential for misclassification that need to be considered as part of an assessment of bias risk and study limitations.

Table D3. Checklist for evaluating the quality of administrative database studies.

Methodological Principle	Author 1 (2004)	Author 2 (2006)	Author (2008)
Study design			
Administrative database comparative study			
Administrative database case-control study			
Administrative database case series			
Why database created clearly stated			
Description of database’s inclusion/exclusion criteria			
Description of methods for reducing bias in database			
Codes and search algorithms reported			
Rationale for coding algorithm reported			
Code accuracy reported			
Code validity reported			
Clinical significance assessed			
Is the period of data consistent with the outcome data?			
Statement regarding whether data stems from single or multiple hospital admissions			
Statement regarding whether data stems from single or multiple procedures			
Accounting for clustering			
Number of criteria met (maximum: 12)			

Below is a description of criteria used to evaluate administrative database studies.

Robust descriptions of the data set

High quality administrative database studies will include clear descriptions of the data set used for the study.^{2,5}

- Why the database was created should be clearly stated.
- How the administrative database was created should be clearly stated, including:
 - Description of the database's inclusion and exclusion criteria.
 - Description of the methods by which the data sets are created so that the potential for biased or missing information can be assessed.⁵

Code accuracy

- The diagnostic and/or procedural codes used in the search algorithm should be clearly stated.
- The rationale for coding algorithm reported.
- Code accuracy should be clearly reported. Code accuracy allows one to estimate the percentage of misclassified data as well as the degree of resulting bias. There are several different types of studies used to measure code accuracy, and the design will affect the reliability of the results.
 - “Ecological” studies compare outcomes measured by the code to those from another more reliable method. Because these studies do not evaluate accuracy at the patient level, they are at risk for “ecological bias” and should be considered to be a relatively crude measure of code accuracy.⁵
 - “Reabstraction” studies reabstract a set of individual medical records and check them against the code(s) entered into the database for that patient. The reliability of statistics from reabstraction studies can be affected by missed cases (due to incorrect diagnosis or unrecorded information in the chart) as well as by misinterpreted cases (diagnosed and recorded correctly but misinterpreted by the person translating that information into code in the database).
 - “Gold standard” studies are the most reliable type of validation studies and compare the code to some gold standard, such as a set of standard clinical or laboratory criteria required for diagnosis or an accurate population-based disease registry.⁵
- The validity of the codes should be clearly stated as it provides information as to whether the code or combination of used actually represent the diagnosis or outcome of interest. The validity of the database study is dependent on a statistically significant association between degree to which the diagnostic or procedural code is associated with the actual diagnosis or procedure, so that the reader has confidence that the code actually represents the diagnosis or procedure under study. Note that code validity statistics are commonly reported in one of two ways:
 - PPV (positive predictive value) is most frequently used, and reflects the percentage of patients identified by the code that are “true positives”, or actually have the condition (or underwent the procedure) of interest. However, this statistic bears a major drawback: its accuracy decreases with decreasing disease prevalence. While validation studies are typically done on a population of patients with the code, and

thus have a high prevalence of disease, the prevalence of the disease within the database population is typically going to be much lower. Thus, the probability of a patient in the database study having the disease represented by the code is likely to be lower than the PPV reported in the validation study suggests.⁵

- Sensitivity and specificity may be used, and tend to be more accurate measures of code accuracy than PPV as they don't vary as much with disease prevalence.
- Positive likelihood ratio can be calculated from sensitivity and specificity. Positive likelihood ratio can also be combined with the baseline odds of disease to determine the likelihood that a patient identified by the code actually has the disease. Disease prevalence within the study population must be estimated in order to perform such a calculation, and is best done using data from a gold standard validation study.⁵

Clinical significance

- Results should not solely be based on p-values, but should be interpreted based on clinical relevance.
 - This is because in large database studies, very small differences between groups can result in statistically significant differences, but these differences may not be clinically relevant.⁵
 - Remember that additional zeroes in a p-value does not imply a more meaningful result.
 - Instead, the significance of the results should be interpreted by evaluating the absolute and relative differences between treatment groups.
 - Determining whether there is overlap in the 95% confidence intervals between groups can help the reader determine whether a result may be clinically significant, as they highlight the differences in results between the treatment groups.⁵

Time-dependent bias

- Is the period of data consistent with the outcome data? That is, if looking at hospital discharge data (like NIS), then is the reported follow-up period for outcomes of interest reflective of that?
- Does the data set specify whether it includes data from the initial hospital admission only, or were data from repeat admissions included?
- Does the data set specify whether it includes data from the first procedure only, or were data from repeat procedures included?

Clustering

- The administrative database study should properly account for clustering that may be present in the data set.
 - Patient populations in health administrative data sets are often clustered (ie., within a health care provider), and outcomes for those within the same cluster tend to be more similar than those patients in a different cluster even after adjusting for potentially confounding variables using conventional regression analysis. Multilevel (or hierarchical, random effects, or mixed effects) regression models allow the user to account for patient clustering (e.g., within health care providers and facilities) when evaluating clustered data. Inaccurate conclusions may result if the appropriate methods to account for clustering are not used.⁵

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 al³. QHES embodies the primary components relevant for critical appraisal of economic studies^{1,3}. 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 (e.g., 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 (e.g., 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 (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., 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? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Definitions of the different levels of evidence for registry studies

Risk of Bias	Study design	Criteria
Moderately low risk: Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias	Good quality registry	<ul style="list-style-type: none"> • Designed specifically for conditions evaluated • Includes prospective data only • Validation of completeness and quality of data • Patients followed long enough for outcomes to occur • Independent outcome assessment* • Complete follow-up of $\geq 85\%$ • Controlling for possible confounding† • Accounting for time at risk‡
Moderately high risk: Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate quality cohort	<ul style="list-style-type: none"> • Prospective data from registry designed specifically for conditions evaluated with violation of 2 of the rest of the criteria in level II
High risk: Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality cohort	<ul style="list-style-type: none"> • Prospective data from registry designed specifically for conditions evaluated with violation of 3 or more of the rest of the criteria in level II • Retrospective data or data from a registry not designed specifically for conditions evaluated

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Economic Studies

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature.

References

1. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. *Med Care* 2003;41:32-44.
2. Langan SM, Benchimol EI, Guttman A, et al. Setting the RECORD straight: developing a guideline for the REporting of studies Conducted using Observational Routinely collected Data. *Clin Epidemiol* 2013;5:29-31.
3. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm* 2003;9:53-61.
4. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med* 1992;116:78-84.
5. van Walraven C, Austin P. Administrative database research has unique characteristics that can risk biased results. *J Clin Epidemiol* 2012;65:126-31.

APPENDIX E. Study quality: Risk of bias and QHES evaluation

Table E1. L-ADR Risk of Bias Evaluation: RCTs

Study year	Random sequence generation	Allocation concealment	Intention to treat	Blind outcome assessment	Co-interventions applied equally	Complete F/U of ≥80%*	<10% difference in F/U between groups*	Controlling for confounding	Risk of Bias
L-ADR vs. Fusion: 1-level									
Charite IDE trial (Blumenthal 2005)	Yes	Yes	Unclear	No	Yes	24 mos.: Yes† (87.2%; 265/304) 60 mos.: No† (43.8%; 133/304)	24 mos.: Yes† [89.8%; (184/205) vs. 81.8% (81/99)] 60 mos.: Yes† [43.9%; (90/205) vs. 43.4% (43/99)]	No	Mod High
ProDisc-L IDE trial (Zigler 2007, 2012)	Yes	Yes	No	No	Yes	24 mos.: No‡ (79.3%; 219/276) 60 mos.: No (67.4% 186/276)	24 mos.: Yes‡ [80.9%; (148/183) vs. 76.3% (71/93)] 60 mos.: No [73.2%; (134/183) vs. 55.9% (52/93)]	Yes	Mod High
L-ADR vs. Fusion: 2-levels									
ProDisc-L IDE trial (Delamarter 2011)	Yes	Yes	No	No	Unclear	24 mos.: Yes (84.0%; 215/256)§	24 mos.: Yes [85.1%; (148/174) vs. 81.7% (67/82)]	Yes	Mod High
L-ADR vs. Fusion: 1- or 2-levels									
Berg 2009	No	Yes	Unclear	No	Yes	24 mos.: Yes† (100%; 152/152) 60 mos.: Yes† (99%; 151/152)	24 mos.: Yes† [100% (80/80) vs. 100% (72/72)]** 60 mos.: Yes† [100% (80/80) vs. 98.6% (71/72)]**	No	Mod High
L-ADR vs. Rehabilitation									
Hellum 2011	Yes	Yes	No	No	Yes	24 mos.: No 77.7% (139/179)	24 mos.: Yes [82.0% (73/89) vs. 73.3% (66/90)]	No	Mod High

F/U: follow-up; L-ADR: lumbar artificial disc replacement.

* Assessed for study’s primary outcome unless otherwise indicated; denominator used was the number of patients randomized

† It is not clear if there were randomized patients who did not receive the allotted treatment and we used number reported for baseline for the denominator.

‡ Assessment based on trial information published in 2012 publication and FDA SSED documentation; 2007 publication did not account for patients who were randomized but did not receive the intervention.

§ Based on author’s text; flow/consort diagram indicates 203/256.

Unclear: no information provided unless otherwise noted below.

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Chartite IDE trial (Blumenthal 2005): ITT: patient accounting was poorly described in the publications and SSED; authors report on number of patients randomized who receive treatment and completed evaluations but do not describe whether there were randomized subjects who did not receive allocated treatment; Blinding:

statement that blinding of patients/physicians not performed; Confounding: mean patient weight was significantly different between groups at baseline and not controlled for, 77.5 kg vs. 81.7 kg, p=0.03; also, activity level at enrollment (active/moderate) was very different between groups although the difference did not reach statistical significance: 17.1% vs. 6.1%, p=0.064.

- ProDisc-L IDE trial (Zigler 2008, 2012 and SSED): ITT and follow-up: 183 were originally enrolled for ADR, 93 for fusion, however 22 in the ADR group and 18 in the fusion group did not receive the intervention and not accounted for in analysis so credit not given for ITT and calculated follow-up is lower than reported by authors. Blinding: statement that blinding of patients/physicians not performed; Coninterventions: authors (Zigler 2007) state that there were differences in the postoperative management (brace immobilization for fusion patients vs. early mobilization for the ADR group).
- ProDisc-L IDE trial – 2 levels (Delamarter 2011): Intention-to-treat: 10 Fusion patients and 9 ADR patients did not received the treatment they were randomized to and they are not accounted for in any analysis; no statement of ITT provided (Figure 1); Blinding: statement that blinding of patients/physicians not performed.
- Berg trial: Randomization: randomization method not specified; ITT: patient accounting was poorly described in the publications and SSED; authors report on number of patients randomized who receive treatment and completed evaluations but do not describe whether there were randomized subjects who did not receive allocated treatment; Blinding: Both the surgeon and patient were informed of the randomization when they arrived at the hospital for surgery; Confounding: VAS leg pain was significantly different between groups at baseline (32.8 vs. 43.7, p=0.016) and was not controlled for.
- Hellum 2011: Intention-to-treat: Six patients (3 in each group) were excluded shortly after randomization and not accounted for in the studies ITT analysis (Figure 1); Blinding: patients/treating staff informed about the allocation shortly after randomization; Controlling for confounding: Low back pain score and SF-36 mental health subscores were significantly worse in the rehabilitation group than in the surgery group – authors state that significantly different baseline scores were not controlled for.
-

Appendix Table E2. L-ADR Risk of Bias Evaluation: Non-randomized Comparative Studies (Cohorts)

Study year	Blind outcome assessment	Co-interventions applied equally	Complete F/U of ≥80%	<10% difference in F/U between groups	Controlling for confounding	Risk of Bias
1-level						
Lee 2015	Unclear	Unclear	No (73.0% (54/74))*	Yes (70.4% (38/54) vs. 80.0% (16/20))*	No	Moderately High
1 + levels (number of levels unclear)						
Lindley 2012	Unclear	Unclear	No (78.9% (75/95))†	No (70.7% (29/41) vs. 85.2 (46/54))†	No	Moderately High

F/U: follow-up; L-ADR: lumbar artificial disc replacement.

*Only patients with ≥2 years follow-up were included.

†Reflects the number of patients that were reachable by phone after discharge in order to confirm diagnosis and update medical records.

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Lee 2015: Confounding: mean age of the patients in the ADR group was significantly lower than that of the patients in the fusion group (34 years vs. 52 years; p < 0.05); mean f/u durations were also different: 4.92 (range 2.1–9.3) vs. 7.43 (range 3.7–10.2); no statement that specific factors were controlled for.
- Lindley 2012: patients treated with fusion were significantly older (P < 0.001) than the patients treated with ADR (49 vs. 35 yrs., respectively); no statement that specific factors were controlled for.

Appendix Table E3. L-ADR Risk of Bias Evaluation: Registry studies

	1- or 2-levels
Methodological principle	Berg 2010
Designed specifically for conditions evaluated	+
Includes prospective data only	+
Validation of completeness and quality of data	–
Patients followed long enough for outcomes to occur	+
Independent outcome assessment*	+
Complete follow-up of $\geq 85\%$	–
Controlling for possible confounding†	–
Accounting for time at risk‡	+
Evidence class	Moderately High

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Data quality: no indication that this was done.
- Follow-up: 12 months, 61.3% (279/455) and 24 months, 30.1% (137/455).
- Confounding: the following characteristics were significantly different between the ADR and the fusion groups, respectively: age 39.8 vs. 42.7 years ($p < 0.0002$), ODI 41 vs. 45 ($p < 0.005$), and smoking (fewer smokers in the ADR group, $p < 0.041$); these differences were not controlled for.

Appendix Table E4. L-ADR Risk of Bias Evaluation: Administrative database studies

	1-level	1-, 2-, or 3- levels
Methodological Principle	Eliasberg (2016)	Kurtz (2010)
Study design		
Administrative database comparative study	✓	✓
Administrative database case-control study		
Administrative database case series		
Why database created clearly stated	✓	✓
Description of database’s inclusion/exclusion criteria		✓
Description of methods for reducing bias in database		
Codes and search algorithms reported	✓	✓
Rationale for coding algorithm reported	✓	✓
Code accuracy reported		
Code validity reported		
Clinical significance assessed		✓
Is the period of data consistent with the outcome data?	✓	✓
Statement regarding whether data stems from single or multiple hospital admissions	✓	✓
Statement regarding whether data stems from single or multiple procedures	✓	✓
Accounting for clustering		✓
Number of criteria met (maximum: 12)	6	9

Appendix Table E5. C-ADR Risk of Bias Evaluation: RCTs

Study year	Random sequence generation	Allocation concealment	Intention to treat	Blind outcome assessment	Co-interventions applied equally	Complete F/U of $\geq 80\%^*$	<10% difference in F/U between groups*	Controlling for confounding	Risk of Bias
1-level									
BRYAN IDE trial	Yes	Yes	No	No	Yes	24 mos.: No (72.9%) 48 mos. No (54.8%)	24 mos.: No (79.3% vs. 66.4%) 48 mos.: No (62.4% vs. 47.3%)	Yes	Mod High
Prestige ST IDE trial	Yes	Unclear‡	Yes	No	Yes	24 mos. Yes† (87.4%) 60 mos.: No† (75.2%) 84 mos.: No† (72.5%)	24 mos.: Yes† (91.7% vs. 83.0%) 60 mos.: Yes† (79.3% vs. 70.9%) 84 mos.: Yes† (76.4% vs. 68.3%)	Yes	Mod Low (24 mos.); Mod High (60, 84 mos.)
ProDisc-C IDE trial	Yes	Yes	Yes	No	Yes	24 mos. Yes (88.6%) 48 mos.: No† (50.0%) 84 mos.: No† (66.7%)	24 mos.: Yes (91.0% vs. 86.3%) 48 mos.: No† (58.6% vs. 41.9%) 84 mos.: Yes† (71.2% vs. 62.4%)	Yes	Mod Low
PCM IDE trial	Unclear‡	Unclear‡	No	No	Unclear‡	24 mos.: Yes (81.7%) 60 mos. No† (70.4%)	24 mos.: Yes (84.4% vs. 78.6%) 60 mos.: Yes† (72.8% vs. 67.7%)	No	Mod High
Mobi-C (1-level) IDE trial	Yes	Yes	Yes‡	No	Yes	24 mos.: Yes‡ (90.2%) 60 mos.: No‡ (79.7%)	24 mos.: Yes‡ (92.3% vs. 86%) 60 mos.: Yes‡ (82.8% vs. 74%)	Yes	Mod Low
SECURE-C IDE trial	Unclear‡	Yes‡	Yes	Unclear‡	Yes	24 mos.: Yes‡ (81.1%)	24 mos.: No‡ (91.4% vs. 70%)	Yes	Mod High
Karabag 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Mod High
Nabhan 2007	Yes	Unclear	Yes	Unclear	Unclear	12 mos.: Yes† (82%) 36 mos.: Yes† (80%)	12 mos.: No† (76% vs. 88%) 36 mos.: Yes† (76% vs. 83%)	Unclear	Mod High
Nabhan 2011	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Mod High
Peng-Fei 2008	Unclear	Unclear	Unclear	Unclear	Unclear	17 mos. (mean): Yes (100%)	17 mos. (mean): Yes (100% vs. 100%)	Unclear	Mod High
Rozankovic 2016	Yes	Unclear	Unclear	Unclear	Unclear	24 mos.: Yes (96.2%)	24 mos.: Yes (98% vs. 94%)	Unclear	Mod High
Zhang 2012	Yes	Unclear	Yes	Unclear	No	24 mos.: Yes (90.8%)	24 mos.: Yes (93% vs. 88%)	Yes	Mod High
Zhang 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Mod High

Study year	Random sequence generation	Allocation concealment	Intention to treat	Blind outcome assessment	Co-interventions applied equally	Complete F/U of $\geq 80\%^*$	$<10\%$ difference in F/U between groups*	Controlling for confounding	Risk of Bias
2-level									
Mobi-C (2-level) IDE trial	Yes	Yes	No	No	Yes	24 mos.: Yes (92.2%) 60 mos. Yes (85.6%)	24 mos.: Yes (95.3% vs. 86.1%) 60 mos.: Yes (87.9% vs. 80.9%)	Yes	Mod Low
Cheng 2009	Unclear	Unclear	Yes	Unclear	Unclear	24 mos.: Yes† (95.4%)	24 mos.: Yes† (97% vs. 94%)	Yes	Mod High
Qizhi 2016	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Mod High
1-, 2-, or 3-levels									
Skeppholm 2015	Yes	Yes§	No	No	Yes	24 mos.: Yes (89.5%)	24 mos.: Yes (92% vs. 87%)	No	Mod High
Cheng 2011	Yes	Unclear	Yes	No	Yes	24 mos.: Yes† (98%)	24 mos.: Yes† (100% vs. 95%)	Unclear	Mod High
Rohl 2009**	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Mod High
2 non-contiguous levels									
Qizhi 2016	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Mod High

n/a: not applicable;

* Assessed for study’s primary outcome unless otherwise indicated; denominator used was the number of patients randomized

† % f/u was based on the number of patients with data available for the following outcome:

- Prestige ST trials: NDI scores (see Burkus 2014 Table 2) because the number of patients with data available was not reported for the primary outcome (overall success)
- ProDisc-C (48, 84 months): NDI follow-up score because the primary outcome was not evaluated past 24 months
- Nabhan: Neck pain VAS because the primary outcome was segmental motion (and not included in this report)
- Cheng 2009: NDI because the primary outcome was not stated
- Cheng 2011: NDI because the primary outcome was not stated

‡ Assessment based on trial information published in the peer-reviewed journal and in the FDA SSED documentation

§Skeppholm: although treatment allocation was placed in a sealed envelope without mention of the envelope being opaque, credit was given as the study went to great lengths to describe how allocation concealment was maintained

**Rohl 2009: number of levels not reported

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- BRYAN trial: Intention to treat: after randomization, 13 patients switched treatment groups (12 patients randomized to C-ADR converted to the fusion group; 1 patient randomized to fusion converted to the C-ADR group), no other details were reported; Blinding: statement that blinding of physicians/patients not continued post-

surgery; Co-interventions: Although C-ADR received two-week NSAID treatment (to inhibit heterotopic ossification formation) and ACDF did not (as NSAIDs inhibit bone formation), the difference is to some degree is within the realm of standard practice and is not likely to impact results at 24 months or later.

- Prestige ST trial: Blinding: statement that blinding of patients/physicians not performed
- ProDisc-C trial: Blinding: statement that physicians not blinded and blinding of patients not continued post-surgery
- PCM trial: Intention to treat: after randomization but before treatment, 13 patients were not treated and it was not stated whether they withdrew or were excluded; Blinding: Statement that physicians not blinded and blinding of patients not continued post-surgery; Follow-up: because the number of patients randomized was not reported, we were unable to calculate the percent follow-up based on the number of patients randomized, however the study reported percent follow-up based on the number of patients randomized and treated (24 mos.: 93.9%; 60 mos.: 83.3%); (C-ADR versus fusion: 24 mos.: 94.5% vs. 92.6%; 60 months: 85.5% vs. 78.9%); Confounding: there were potentially clinically relevant differences between C-ADR and fusion groups in baseline neurological symptoms that were not controlled for (radiculopathy and myelopathy: 15.1% vs. 24.3%; radiculopathy only: 84.4% vs. 75.7%)
- Mobi-C (1-level) trial: Blinding: Statement that physicians not blinded and blinding of patients not continued post-surgery
- SECURE-C trial: Blinding: The FDA SSED states that “The applicant is not aware of any randomized patient who was unblinded to their treatment.” Follow-up: while the study stated that 87.1% of patients were available for follow-up, this included both randomized and non-randomized patients – the complete follow-up rate for the randomized patients only was not reported
- Karabag 2014: Very few details methodological details reported, including the number of patients randomized; Confounding: important patient characteristics such as sex or duration of symptoms were not reported
- Nabhan 2011: Very few details methodological details reported, including the number of patients randomized; Confounding: very few patient characteristics were reported
- Peng-Fei 2008: Very few details methodological details reported
- Mobi-C (2-level) trial: Intention to treat: the CONSORT flow chart (Radcliff 2016) shows that after randomization, 5 patients withdrew but 12 were not treated for “other” (unspecified) reasons – it isn’t clear whether they withdrew or were excluded; Blinding: Statement that blinding not continued post-surgery
- Qizhi 2016: Very few details methodological details reported; Confounding: very few patient characteristics were reported
- Rozankovic 2016: Very few details methodological details reported; Confounding: very few patient characteristics were reported
- Zhang 2012: Confounding: C-ADR but not ACDF patients were given a home-exercise program
- Skeppholm: Intention to treat: after allocation, 2 patients were excluded from the ADR group during surgery because of technical problems encountered; Blinding: allocation blinded to physicians and patients only up to implantation; Co-interventions: Although C-ADR received 10-day ketorolac treatment (to inhibit heterotopic ossification formation) and ACDF did not (as ketorolac inhibits bone formation), the difference is to some degree is within the realm of standard practice and is not likely to impact results at 24 months or later; Confounding: there were potentially clinically relevant differences between C-ADR and fusion groups in symptom duration that were not controlled for (neck pain duration >2 years: 57% vs. 42%; arm pain duration 1-2 years: 38% vs. 27%)
- Cheng 2011: Blinding: Statement that blinding was not performed at any time
- Rohl 2009: Very few details methodological details reported

Table E6. C-ADR Risk of Bias Evaluation: Non-randomized Comparative Studies

Study year	Blind outcome assessment	Co-interventions applied equally	Complete F/U of $\geq 80\%^*$	<10% difference in F/U between groups*	Controlling for confounding	Risk of Bias
1-level						
Kim 2009 (1-level data)	Unclear	Unclear	Unclear (% NR)	Unclear (% NR)	No	Mod High
Hou 2014 (1-level data)	Unclear	Unclear	Yes (89.3%)	Yes (89.7% vs. 88.9%)	No	Mod High
2-level						
Kim 2009 (2-level data)	Unclear	Unclear	Unclear (% NR)	Unclear (% NR)	No	Mod High
Hou 2014 (2-level data)	Unclear	Unclear	Yes (92.5%)	Yes (90.6% vs. 93.2%)	No	Mod High
Mixed levels (1-, 2-, or 3-level)						
Cappelletto 2013	Unclear	Unclear	Unclear (% NR)	Unclear (% NR)	No	Mod High
Peng 2011	Unclear	Yes	Unclear (% NR)	Unclear (% NR)	No	Mod High

Unclear: no information provided unless otherwise noted below

Reasons for No credit (or unclear credit if for reason other than no info provided):

- Kim 2009: no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for
- Hou 2014: % f/u NR (number of patients enrolled not reported); no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for
- Cappelletto 2013: % f/u NR (number of patients eligible for enrollment not clearly reported); no explicit statement that either (a) factors that could affect outcomes were evaluated as potential confounders or (b) specific factors were controlled for

Table E7. C-ADR Risk of Bias Evaluation: Registry Studies

Methodological principle	Staub 2016 Matching sub-study	Staub 2016 Atypical sub-study	Staub 2016 Long-term sub-study	Grob 2010
Designed specifically for conditions evaluated	Yes	Yes	Yes	Yes
Includes prospective data only	Yes	Yes	Yes	Yes
Validation of completeness and quality of data	Yes	Yes	Yes	No
Patients followed long enough for outcomes to occur	Yes	Yes	Yes	No§
Independent outcome assessment*	No	No	No	Unclear
Complete follow-up of $\geq 85\%$	Unclear	Unclear	Unclear	No
Controlling for possible confounding†	Yes	Yes	Yes	Yes
Accounting for time at risk‡	Yes	No	Yes	No
Evidence class	Mod High	Mod High	Mod High	Mod High

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

§ Of the 342 patients included in the study, only 284 had reached 12 month follow-up, and only 178 had reached 24 month follow-up.

Table E8. C-ADR Risk of Bias Evaluation: Administrative Database Studies

Methodological Principle	Radcliff 2015	Nandyala 2013
Study design		
Administrative database comparative study	X	X
Administrative database case-control study		
Administrative database case series		
Why database created clearly stated	Yes	Yes
Description of database’s inclusion/exclusion criteria	Yes	Yes
Description of methods for reducing bias in database	No	No
Codes and search algorithms reported	No	Yes
Rationale for coding algorithm reported	No	Yes
Code accuracy reported	No	No
Code validity reported	No	No
Clinical significance assessed	No	No
Is the period of data consistent with the outcome data?	Yes	Yes
Statement regarding whether data stems from single or multiple hospital admissions	No	Yes*
Statement regarding whether data stems from single or multiple procedures	No	No
Accounting for clustering	No	No
Number of criteria met (maximum: 12)	3/12	6/12

*Implied, since one factor the study controlled for was hospital characteristics.

Table E9. Quality of Health Economic Studies (QHEs) scores: L-ADR economic studies

QHEs Question (points possible)	Fritzell 2011	Parkinson 2013	Johnsen 2013
1. Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	7	7	7
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	4	4	4
3. Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	8	8	8
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1	1	1
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	9	9	9
6. Was incremental analysis performed between alternatives for resources and costs? (6 pts)	6	6	6
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	5	5	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 pts)	0	0	0
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	8	8	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 pts)	6	0	0
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 pts)	7	7	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 pts)	8	8	8
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	0	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	6	0	6
15. Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	8	8	8
16. Was there a statement disclosing the source of funding for the study? (3 pts)	3	3	3
Total score:	86	81	87

Table E10. Quality of Health Economic Studies (QHES) scores: C-ADR economic studies

QHES Question (points possible)	Radcliff 2016	Quereshi 2013	McAnany 2014	Lewis 2014	Ament 2014	Ament 2016
17. Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	7	7	7	7	7	7
18. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	4	0	4	0	4	4
19. Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	8	8	8	0	8	8
20. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1	1	1	1	1	1
21. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	9	9	9	9	9	9
22. Was incremental analysis performed between alternatives for resources and costs? (6 pts)	6	6	6	0	6	6
23. Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	5	0	0	5	5	5
24. 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 pts)	7	7	7	0	7	7
25. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	8	8	0	8	8	8
26. 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 pts)	0	6	6	0	6	6
27. 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 pts)	7	0	7	7	7	7
28. 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 pts)	8	0	8	8	8	8
29. Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	7	7	7	0	7	7
30. Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	6	6	6	6	6	6
31. Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	8	8	8	8	8	8

QHES Question (points possible)	Radcliff 2016	Quereshi 2013	McAnany 2014	Lewis 2014	Ament 2014	Ament 2016
32. Was there a statement disclosing the source of funding for the study? (3 pts)	0	0	3	3	3	3
Total score:	91	73	87	62	100	100

APPENDIX F. Devices**Lumbar ADR (C-ADR) Devices****Appendix Table F1. Biomechanical classification of FDA approved L-ADR prostheses**

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
InMotion (formerly known as SB Charité III)	unconstrained	mobile	CoCrMo UHMWPE	metal on polymer	2	small fins/ bone ingrowth
Prodisc-L (also called Prodisc II in European literature)	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	1	keel
Activ-L	semiconstrained	mobile	CoCrMo UHMWPT	metal on polymer	NR	spike or keel*/ bone ingrowth

COR: center of rotation; CoCrMo: cobalt-chromium-molybdenum alloy; FDA: Food and Drug Administration; NR: not reported; UHMWPE: ultra-high molecular weight polyethylene

* Activ-L achieves initial fixation either through spiked or a keel endplate, but both versions achieve long term fixation through bone ingrowth.

Appendix Table F2. Biomechanical classification of L-ADR prostheses that do not have FDA approval.

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
Triumph	semiconstrained	mobile	CoCrMo	NR	NR	bone ingrowth
XL TDR eXtreme	NR	mobile	CoCrMo	NR	NR	serrated teeth
Freedom (Lumbar)	semiconstrained	NR	Titanium	metal on polymer	1	rails and bead-coated
Maverick	semiconstrained	fixed	CoCrMo	metal on metal	1	keel
Kineflex-L	unconstrained	mobile	CoCrMo	metal on polymer	1	Anchored with keels
Cadisc-L	NR	fixed	polycarbonate-polyurethane	NR	0	NR
M6-L	semiconstrained	mobile	CoCrMo UHMWPE	NR	2	keels/bone ingrowth
FlexiCore	fully constrained	fixed	CoCrMo	metal on metal	1	small fins/bone ingrowth

COR: center of rotation; CoCrMo: cobalt-chromium-molybdenum alloy; FDA: Food and Drug Administration; NR: not reported; UHMWPE: ultra-high molecular weight polyethylene

Cervical ADR (C-ADR) Devices**Appendix Table F3. Biomechanical classification of FDA approved C-ADR prostheses**

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
Prestige (Frenchay)	semiconstrained	mobile	stainless steel	metal on metal	1	dual rails/ bone ingrowth
Prestige LP	semiconstrained	NR	titanium ceramic composite	metal on metal	2	dual rails/ bone ingrowth
Prodisc-C	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	1	keel/bone ingrowth
Bryan	unconstrained	mobile	titanium alloy polyurethane	metal on polymer	2	milled cavities/ bone ingrowth
Mobi-C (indicated for both 1 and 2-level replacement)	semiconstrained	mobile	titanium UHMWPE	metal on polymer	2	dual rails/ bone ingrowth
PCM	semiconstrained	fixed	CoCrMo UHMWPE	metal on polymer	2	dual rails/ bone ingrowth
Secure-C	semiconstrained	mobile	CoCrMo UHMWPE	metal on polymer	2	keel
Discover	NR	NR	Titanium alloy polyethylene	metal on polymer	1	dual rails/ bone ingrowth

COR: center of rotation; CoCrMo: cobalt-chromium-molybdenum alloy; FDA: Food and Drug Administration; HA: hydroxyapatite; NR: not reported; TPS: porous titanium plasma spray; UHMWPE: ultra-high molecular weight polyethylene.

Appendix Table F4. Biomechanical classification of C-ADR prostheses that do not have FDA approval.

Device name	Constraint	COR	Material	Bearing surface	Articulating surfaces	Fixation
Freedom (Cervical)	semiconstrained	NR	Titanium	metal on polymer	1	rails and bead-coated
Simplify	unconstrained	mobile	PEEK and ceramic	Polymer on ceramic	2	bone ingrowth
NuNec	semiconstrained	mobile	PEEK	Polymer on polymer	NR	rotating cams
M6-C	semiconstrained	mobile	Titanium and polymer	Metal on polymer	2	tri-keel
CerPass	semiconstrained	NR	Titanium and ceramic	Ceramic on ceramic	NR	spikes
NeoDisc	NR	NR	Polymer	NR	NR	screws
Advent	NR	NR	NR	Metal on polymer	NR	NR
Bryan ACCEL	unconstrained	mobile	titanium alloy polyurethane	metal on polymer	2	milled cavities/ bone ingrowth
Discocerv	semiconstrained		Metal and ceramic	Metal on ceramic		
Kineflex-C	unconstrained	NR	CoCrMo	metal on metal	NR	keel/ bone ingrowth
Cadisc-C	NR	fixed	polycarbonate- polyurethane	NR	0	NR
Cervicore	unconstrained	NR	CoCrMo	metal on metal	NR	dual rails/ bone ingrowth

COR: center of rotation; CoCrMo: cobalt-chromium-molybdenum alloy; FDA: Food and Drug Administration; HA: hydroxyapatite; NR: not reported; PEEK: polyetherether-ketone; TPS: porous titanium plasma spray; UHMWPE: ultra-high molecular weight polyethylene.

APPENDIX G. L-ADR Study Characteristics Data Abstraction Tables.

L-ADR vs. Fusion (1-level)

Appendix Table G1. L-ADR vs. ACDF (1-level): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Charité IDE trial Index study: Blumenthal 2005 FDA SSED 2004 Follow-up studies: Guyer 2009 RCT United States	304 treated (no. randomized NR)*	<p>L-ADR (n=205): ADR with Charité via an open anterior retroperitoneal approach</p> <p>Arthrodesis (n=99): 1- or 2-level fusion using iliac crest autograft and BAK cages, via an open anterior retroperitoneal approach</p>	<p>Inclusion: Age 18 to 60 years; Symptomatic DDD confirmed by discography; Single-level DDD at L4–L5 or L5-S1; Oswestry score ≥ 30; VAS score ≥ 40 (of 100); Failed ≥ 6 mos of appropriate non-operative care; Back and/or leg pain with no nerve root compression; Able to tolerate anterior approach; Able and willing to comply with follow-up schedule; Willing to give written informed consent</p> <p>Exclusion: Previous thoracic or lumbar fusion; Current or prior fracture at L4, L5, or S1; Symptomatic multilevel degeneration; Noncontained herniated nucleus pulposus; Spondylosis;</p>	<p><i>L-ADR vs Arthrodesis</i></p> <ul style="list-style-type: none"> • % Female: 44.9% (92/205) vs 55.6% (55/99) • Age, mean ± SD: 39.6 ± 8.2 vs 39.6 ± 9.1 • Race: <ul style="list-style-type: none"> - Caucasian: 91.7% (188/205) vs. 87.9% (87/99) - African American: 3.9% (8/205) vs. 5% (5/99) - Other: 4.4% (9/205) vs. 7.1% (7/99) • BMI, mean ± SD: 26 ± 4.2 vs 27 ± 4.8 • Previous spinal surgery: 34.1% (70/205) vs. 33.3% (33/99) • Normal activity level (prior to experiencing back pain) – Active: 91.7% (188/205) vs. 86.9% (86/99) • Activity level at enrollment – Active: 4.4% (9/205) vs. 1.0% (1/99) 	<p><i>L-ADR vs. Arthrodesis</i></p> <p>24 months <u>% F/U</u> Overall: 87.2% (265/304); L-ADR: 89.8% (184/205); Fusion: 81.8% (81/99)</p> <p>60 months <u>% F/U</u> Overall: 43.8% (133/304); L-ADR: 43.9% (90/205); Fusion: 43.4% (43/99)</p>	<p>Overall success (a; 4 criteria must be met):</p> <ol style="list-style-type: none"> 1. ≥25% improvement in ODI score compared with the preoperative score 2. No device failure 3. No major complications 4. No neurological deterioration compared to preoperative status. <p>ODI, 0-100 (worst)</p> <p>ODI success (≥25% improvement from baseline)</p> <p>ODI success (≥15 point improvement from baseline – FDA criteria)</p> <p>Neurological success (no neurological</p>	Corporate/ Industry funds

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			Spondylolisthesis >3 mm; Scoliosis >11°; Midsagittal stenosis <8 mm; Positive straight leg raise; Spinal tumor; Osteoporosis, osteopenia, or metabolic bone disease; Infection; Facet joint arthrosis Psychosocial disorder; Morbid obesity; Metal allergy; Use of a bone growth stimulator; Participation in another study; Arachnoiditis; Chronic steroid use; Autoimmune disorder; Pregnancy; Other spinal surgery at affected level (except discectomy, laminotomy/ectomy, without accompanying facetotomy or nucleolysis at the same level to be treated)	<ul style="list-style-type: none"> • Pre-op work status (% working): 53.2% (109/205) vs. 57.6% (57/99) • Treatment levels <ul style="list-style-type: none"> - L4-L5: 29.8% (61/205) vs. 32.3% (32/99) - L5-S1: 70.2% (144/205) vs. 67.7% (67/99) • Intraoperative blood loss (ml), mean ± SD: 205 ± 212 vs. 209 ± 284 • Operating time (mins.) mean ± SD: 111 ± 48 vs. 114 ± 68 • Length of hospital stay (days), mean ± SD: 3.7 ± 1.2 vs. 4.2 ± 2.0; p=0.004 		deterioration compared to preoperative status) VAS pain, 0-100 (worst) SF-36, 0-100 (best) Patient satisfaction – satisfied with outcome Patient satisfaction – would undergo the same treatment again Narcotic use Work status Complications	
ProDisc-L IDE trial Index study: Zigler 2007 FDA SSED	276 randomized; 236 treated	L-ADR (n=183): ADR with ProDisc-L at 1 diseased level (L3-S1) via a standard mini-open anterior retroperitoneal	Inclusion: Age 18–60 years; Single-level DDD at L3–S1. Diagnosis of DDD requires: 1. Back and/or leg (radicular) pain; and 2. Radiographic confirmation of any 1 of	<i>L-ADR vs Arthrodesis</i> <ul style="list-style-type: none"> • % Female: 49.1% (79/161) vs 54.7% (41/75) • Age, mean ± SD: 38.7 ± 8.0 vs 40.4 ± 7.6 • Race: 	<i>L-ADR vs. Arthrodesis</i> 24 months % F/U Overall: 79.3% (219/276); L-	Overall success (a; 4 criteria must be met): 1. ≥25% improvement in ODI score compared with the preoperative score 2. No device failure 3. No major	Authors state that no funds were received in support of this work; Spectrum Research, Inc. assumes that

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
2006 Follow-up studies: Zigler 2012 (5-year results); Zigler 2012 (5-year adjacent level) RCT United States		approach. Arthrodesis (n=93): Circumferential arthrodesis: 2-level, anterior lumbar interbody fusion using a femoral ring allograft and posterior fusion with autogenous iliac crest bone graft in combination with pedicle screw instrumentation)	the following by computed tomography magnetic resonance imaging, diskography, plain film, myelography, and/ or flexion/extension films: i. Instability (≥ 3 mm translation or $\geq 5^\circ$ angulation); ii. Decreased disc height > 2 mm; iii. Scarring/thickening of annulus fibrosus; iv. Herniated nucleus pulposus; or v. Vacuum phenomenon. Oswestry Low Back Pain Disability Questionnaire score ≥ 40 (20/50); Failed ≥ 6 mo of conservative treatment; Psychosocially, mentally, and physically able to comply fully with protocol, including adhering to follow-up schedule and requirements, and filling out forms; Willing to give written informed consent Exclusion: > 1 vertebral	- Caucasian: 82.6% (133/161) vs. 78.7% (59/75) - African American: 3.1% (5/161) vs. 6.7% (5/75) - Hispanic: 11.2% (18/161) vs. 13.3% (10/75) - Other: 3.1% (5/161) vs. 7.1% (1/75) • BMI, mean \pm SD: 26.7 \pm 4.2 vs. 27.3 \pm 4.3 • Smoking status, %: - Never: 54.0% (87/161) vs 30.7% (23/75) - Former: 24.8% (40/161) vs 22.7% (17/75) - Current: 21.1% (34/161) vs 32.0% (24/75) • Previous surgical treatment: 35.4% (57/161) vs 30.7% (23/75) • - Discectomy: 16.1% (26/161) vs 16.0% (12/75) • - Intradiscal electrothermal therapy: 11.2% (18/161) vs. 6.7% (5/75) • - Laminectomy: 9.3% (15/161) vs 6.7% (5/75) • - Laminotomy:	ADR: 80.9% (148/183); Fusion: 76.3% (71/93) 60 months % F/U Overall: 67.4% (186/276); L-ADR: 73.2% (134/183); Fusion: 55.9% (52/93)	complications 4. No neurological deterioration compared to preoperative status. ODI, 0-100 (worst) ODI success ($\geq 25\%$ improvement from baseline) ODI success (≥ 15 point improvement from baseline – FDA criteria) Neurological success (no neurological deterioration compared to preoperative status) VAS pain, 0-10 (worst) SF-36, 0-100 (best) Patient satisfaction on VAS, 0-10 (best) Patient satisfaction – would undergo the same treatment	corporate/ industry provided some funds since it was an FDA IDE trial for approval.

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			level with DDD; involved endplates smaller than 34.5 mm in the medial-lateral and/or 27mm in the anterior-posterior direction; Known allergy to titanium, polyethylene, cobalt, chromium, or molybdenum; Prior fusion at any vertebral levels; 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; Osteoporosis; Back or leg pain of unknown etiology; Paget’s disease, osteomalacia, or any other metabolic bone disease (excluding osteoporosis addressed above); Degenerative spondylolisthesis of grade >1; Morbid obesity defined as a body	2.5% (4/161) vs 2.7% (2/75) <ul style="list-style-type: none"> • - Other: 7.5% (12/161) vs. 4.0% (3/75) • Treatment levels <ul style="list-style-type: none"> - L3-L4: 1.9% (3/161) vs. 4.0% (3/75) - L4-L5: 33.5% (54/161) vs. 29.3% (22/75) - L5-S1: 64.6% (104/161) vs. 66.7% (50/75) • Intraoperative blood loss (ml), mean ± SD: 204 ± 231 vs. 465 ± 440; p<0.0001 • Operating time (mins.) mean ± SD: 121 ± 59 vs. 229 ± 76; p<0.0001 • Length of hospital stay (days), mean ± SD: 3.5 ± 1.3 vs. 4.4 ± 1.5; p=0.0001 		again Narcotic use Work and recreation status Complications	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			mass index >40 or a weight more than 100 lbs. over an ideal body weight; Pregnant or interested in becoming pregnant over the next 3 years; Active infection—systemic or local; Taking 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 treated with curative intent and there has been no clinical signs or symptoms of the malignancy >5 years				

DDD: degenerative disc disease; EQ5D: EuroQoL 5 dimensions; FABQ: fear avoidance belief questionnaire; FDA: Food and Drug Administration; F/U: follow-up; HSCL-25: Hopkins symptom checklist; L-ADR: lumbar artificial disc replacement; NR: not report; ODI: Oswestry disability index; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 questionnaire; SSED: Summary of Safety and Effectiveness Data; VAS: visual analog scale.

*Authors report on number of patients randomized who received treatment but did not describe whether there were randomized subjects who did not receive allocated treatment.

Appendix Table G2. L-ADR vs. ACDF (1-level): Nonrandomized comparative studies

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Cohort studies							
Lee 2015 Retrospective cohort study Singapore Note: Study is in an exclusively Asian population	74	<p>L-ADR (n = 54): 1-level ADR with ProDisc-L (Synthes)</p> <p>Fusion (n = 20): 1-level TLIF with screws and LIF cage filled with local autogenous bone graft</p>	<p>Inclusion: Patients with lumbar DDD and pure chronic lower back pain without radiculopathy that involved only the L4/5 spinal level or L5/S1 spinal level, with discogram demonstrating concordant pain at operated level. Isolated discogenic back pain with no clinical and magnetic resonance imaging evidence of facet disease.</p> <p>Exclusion: Concordant discogram pain at more than one level; suffer from traumatic spine injuries, scoliosis, spondylolithesis, tumor and infection, and/or had surgeries involving spinal levels other than L4/5 and L5/S1.</p>	<p>L-ADR vs. Fusion</p> <p><u>Mean (range)</u> (unless otherwise indicated): Age: 34 (21-55) vs. 52 (37-70) Female: 24.1% (13/54) vs. 50.0% (10/20) Implant level, L4-L5: 38.9% (21/54) vs. 70.0% (14/20) Implant level, L5-S1: 61.1% (33/54) vs. 30.0% (6/20)</p>	<p>L-ADR vs. Fusion</p> <p>Follow-up ≥2 years: 70.3% (38/54) vs. 80.0% (16/20)</p> <p>Follow-up time (mean [range]): 4.92 (2.1-9.3) vs. 7.43 (3.7-10.2) years</p>	<p>Surgical approach-related complications</p> <p>Complications</p> <p>Revision surgery</p>	NR
Administrative database studies							
Eliasberg 2016 Administrati	52, 877	<p>L-ADR (n = 2415): 1-level ADR, device(s)</p> <p>NR</p>	<p>Inclusion: Aged 18-65 with degenerative disc disease undergoing lumbar TDA (ICD-9 84.65)</p>	<p>L-ADR vs. Fusion</p> <p><u>Mean ± SD</u> (unless otherwise indicated):</p>	<p>3 months (for acute complications)</p>	<p>Acute complications (<90 days of index procedure)</p>	<p>“No funds were received in support of this work.”</p>

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
ve Database (California Office of Statewide Health Planning and Development) United States		Fusion (n = 50462): 1-level fusion, device details NR	or fusion (ICD-9 81.06, 81.07, or 81.08). Exclusion: Traumatic injury, pathologic fracture or malignant neoplasm, congenital musculoskeletal disorder; inflammatory arthritides; revision procedure as first procedure within the study period; procedures on multiple sections of the spine; multilevel surgeries	Age: 47.2 ± 8.8 vs. 51.8 ± 9.1, p < 0.05 Female: 43.06% (1040/2415) vs. 49.24% (24847/50462) Race, White‡: 84.55% (2042/2415) vs. 80.88% (40814/50462) Race, Black‡: 3.69% (89/2415) vs. 5.22% (2634/50462) Race, Native American‡: 0.25% (6/2415) vs. 0.33% (167/50462) Race, Asian/Pacific Islander‡: 2.69% (65/2415) vs. 2.71% (1368/50462) Race, Other‡: 6.92% (167/2415) vs. 9.61% (4849/50462) Unknown race‡: 1.9% (46/2415) vs. 1.25% (631/50462) Receiving workers' compensation: 45.52% (1099/2415) vs. 28.93% (14599/50462) Number of comorbidities per patient: 0.4605 vs. 0.8207, p < 0.05	12, 36, and 60 months (for rates of subsequent lumbar surgery) % F/U: NR	All-cause readmissions Rates of subsequent lumbar surgery	Relevant financial activities outside the submitted work: grants.”

BMP: Bone morphogenetic protein; CT: Computed tomography; DDD: Degenerative disc disease; F/U: Follow-up; L-ADR: Lumbar artificial disc replacement; MRI: Magnetic resonance imaging; SD: Standard deviation; TDA: Total disc arthroplasty; TLIF: Transforaminal lumbar interbody fusion

* The surgical database originates at a single, tertiary care military treatment facility.

† Regarding military branch, the L-ADR treatment group was composed of 1 Navy SEAL, 1 Explosive Ordnance Disposal Technician, and 1 Marine infantryman.

‡ p < 0.05 between groups for race.

L-ADR vs. Fusion (2-level)

Appendix Table G3. L-ADR vs. ACDF (1-level): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
ProDisc-L 2-level IDE trial Index study: Delamarter 2011 RCT United States	256 randomized, 237 treated	L-ADR: ADR with ProDisc-L at 2 diseased levels (L3-L5 or L4-S1) via a standard mini-open anterior retroperitoneal approach. Arthrodesis: Circumferential arthrodesis: 2-level, anterior lumbar interbody fusion using a femoral ring allograft and	Inclusion: DDD at two contiguous vertebral levels from L3 to S1 with or without leg pain; ≥6 months unsuccessful non-operative treatment; and ODI score ≥40. (Flexion-extension radiographs, computed tomography, magnetic resonance imaging, discography, and/or myelography were used to confirm diseased disc levels). Exclusion: major exclusion criteria included spondylolisthesis	<i>L-ADR vs Arthrodesis</i> <ul style="list-style-type: none"> Female: 42.4% (70/165) vs 45.8% (33/72) Age, mean ± SD: 41.8 ± 7.73 vs 41.8 ± 7.81 BMI, mean ± SD: 27.0 ± 4.52 vs 27.1 ± 4.05 Smoking status, %: <ul style="list-style-type: none"> - Never: 52.4% (86/165) vs 40.3% (29/72) - Former: 18.9% (31/165) vs 29.2% (21/72) - Current: 28.7% (47/165) vs 30.6% (22/72) Previous surgical treatment: 41.8% (69/165) vs 40.3% (29/72) - Discectomy: 	<i>L-ADR vs. Arthrodesis</i> 24 months <u>% F/U</u> Overall: 84.0% (215/256); L-ADR: 85.1% (148/174); Fusion: 81.7% (67/82)	Composite end point (10 criteria): 1. ≥15% improvement in ODI compared with baseline 2. Improvement in SF-36 PCS compared with baseline 3. Neurological status improved or maintained from baseline 4. No secondary surgical procedures to remove or modify the total disc replacement implant or arthrodesis implant/site 5. No subsidence >3 mm	Synthes USA Products, LLC

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		posterior fusion with autogenous iliac crest bone graft in combination with pedicle screw instrumentation)	classified as greater than grade I; DDD at more than 2 levels; previous arthrodesis; and inability to comply with study protocol.	<p>19.4% (32/165) vs 18.1% (13/72)</p> <ul style="list-style-type: none"> • - Intradiscal electrothermic therapy: 10.3% (17/165) vs. 9.7% (7/72) • - Laminectomy: 18.8% (31/165) vs 12.5% (9/72) • - Laminotomy: 2.4% (4/165) vs 2.8% (2/72) • - Other: 7.3% (12/165) vs. 11.1% (8/72) • Previous conservative treatment: <ul style="list-style-type: none"> • - Injection: 77.0% (127/165) vs 72.2 • - Physical therapy: 81.8% (135/165) vs. 84.7% (61/72) • - Corset/brace: 41.2% (68/165) vs 38.9% (28/72) • - Chiropractic: 36.4% (60/165) vs 38.9% (28/72) • - Other: 21.2% (35/165) vs. 16.7% (12/72) • Duration of pain in the back/leg: <ul style="list-style-type: none"> • - <6 mos.: 0.6% 		<p>6. No migration >3 mm</p> <p>7. No radiolucency/loosening</p> <p>8. No loss of disc height >3 mm</p> <p>9. Total disc replacement: range of motion improved or maintained from baseline</p> <p>10. Arthrodesis: no motion (<10_ angulation, total for two levels combined) on flexion and extension radiographs</p> <p>ODI, 0-100 (worst)</p> <p>SF-36 PCS, 0-100 (best)</p> <p>Neurological Success (maintenance or improvement of motor status, sensory status, reflexes, and a straight leg raise test)</p> <p>Secondary Surgical Procedure</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				<p>(1/165) vs. 0% (0/72)</p> <ul style="list-style-type: none"> • - 6 mos. to 1 yr.: 9.7% (16/165) vs. 5.6% (4/72) • - >1 year: 89.7% (148/165) vs. 94.4% (68/72) • Implant level: <ul style="list-style-type: none"> • - L3-L5: 8.5% (14/165) vs. 11.1% (8/72) • - L4-S1: 91.5% (151/165) vs. 88.9% (64/72) • ODI, mean ± SD: 64.7 ± 11.4 vs 64.8 ± 9.5 • SF-36 PCS, mean ± SD: 29.5 ± 5.4 vs 30.1 ± 6.7 • VAS Pain score, mean ± SD: 75.7 ± 16.0 vs. 74.7 ± 13.6 • % Narcotic Use: 69.1% (114/165) vs 63.9% (46/72) • % employment: 79.4% (131/165) vs 83.3% (60/72) <ul style="list-style-type: none"> • % participating in recreational activities: 36.4% (60/165) vs 43.7% (31/71) • Operative time (mins.), mean ± SD: 160.2 ± 73.30 vs. 272.8 ± 81.68; 		<p>VAS for pain, 0-100 (worst)</p> <p>VAS for Patient Satisfaction and Willingness to Undergo Surgery, 0-100 (best)</p> <p>Narcotic Use</p> <p>Work and Recreation Status</p> <p>Complications</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				<p>p<0.0001</p> <ul style="list-style-type: none"> Estimated blood loss (ml), mean ± SD: 398.1 ± 451.48 vs. 569.3 ± 466.63; p=0.0013 Length of hospital stay (days), mean ± SD: 3.8 ± 1.53 vs. 5.0 ± 1.93; p<0.0001 			

DDD: degenerative disc disease; EQ5D: EuroQoL 5 dimensions; FDA: Food and Drug Administration; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not report; ODI: Oswestry disability index; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 questionnaire; SSED: Summary of Safety and Effectiveness Data; VAS: visual analog scale.

*Authors report on number of patients randomized who received treatment but did not describe whether there were randomized subjects who did not receive allocated treatment.

L-ADR vs. Fusion (1- or 2-level)

Appendix Table G4. L-ADR vs. ACDF (1 or 2-level): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
<p>Berg 2009</p> <p>Follow-up studies: Skold 2013; Berg 2009 (sex life)</p> <p>RCT</p> <p>Sweden</p>	<p>152 treated (no. randomized NR)*</p>	<p>L-ADR (n=80): ADR with Charite, ProDisc-L, or Maverick at 1- or 2-levels via the anterior retroperitoneal approach (graft source and instrument-</p>	<p>Inclusion: LBP) with or without leg pain for > 1 year (If leg pain occurred, then LBP should dominate); Failure of conservative treatment scheduled for >3 months; Confirmation of disc degeneration on MRI; Age 20–55 years; ODI</p>	<p><i>L-ADR vs Arthrodesis</i></p> <ul style="list-style-type: none"> % Female: 60% (48/80) vs 58% (42/72) Age, mean ± SD: 40.2 ± 8.1 vs 38.5 ± 7.8 Smokers: 10% (8/80) vs. 11% (8/72) Previous spinal surgery: 12% (10/80) vs. 11% (8/72) 	<p><i>L-ADR vs. Arthrodesis</i></p> <p>24 months % F/U</p> <p>Overall: 100% (152/152); L-ADR: 100% (80/80); Fusion: 100% (72/72)</p>	<p>ODI, 0-100 (worst)</p> <p>ODI success (≥25% improvement from baseline)</p> <p>Global Assessment of Pain: totally pain-free, much better, better, unchanged, or worse</p>	<p>NR</p>

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		ation NR) Arthrodesis (n=72): 1- or 2-level posterolateral fusion (PLF) or posterior lumbar interbody fusion (PLIF) (without complementary PLF) (method at the discretion of the treating surgeon)	score over 30 or back pain (VAS) score over 50/100 the week before Inclusion; Signed informed consent; Open mind to the two treatment options Exclusion: Spinal stenosis requiring decompression; Moderate or worse facet joint arthritis; ≥3 painful levels at clinical examination; No obvious painful level, or levels, at diagnostic injection evaluation (if done); Isthmic spondylolysis/ olisthesis; Degenerative spondylolisthesis >3 mm; Major deformity; Manifest osteoporosis; Previous lumbar fusion or decompression with Postoperative instability (e.g. facet joint damage or wide laminectomy); Compromised vertebral body; Previous spinal infection or tumor; Inability to understand information due to	<ul style="list-style-type: none"> • Back pain VAS, mean ± SD: 62.3 ± 20.8 vs. 58.5 ± 21.7 • Leg pain VAS, mean ± SD: 32.8 ± 26.4 vs. 43.7 ± 28.2 • EQ5D, mean ± SD: 0.42 ± 0.31 vs. 0.36 ± 0.33 • ODI (%), mean ± SD: 41.8 ± 11.8 vs. 41.2 ± 14.6 • Duration of LBP ≥2 years: 79% vs. 87% • 1-level surgery: 56% (45/80) vs 46% (33/72) • Intraoperative blood loss (ml), mean ± SD: 560 ± 400 vs. 444 ± 228 • Operating time (hrs.), mean ± SD: 2.3 ± 0.8 vs. 2.7 ± 0.6; p=0.0008 • Length of hospital stay (days), mean ± SD: 4.4 ± 1.6 vs. 5.9 ± 1.2; p<0.0000 	60 months <u>% F/U</u> Overall: 99% (151/152); L-ADR: 100% (80/80); Fusion: 98.6% (71/72)	Low back pain: VAS, 0-100 (worst) Leg pain: VAS, 0-100 (worst) SF-36, 0-100 (best) EQ-5D, -0.59 to 1 (best) Patient satisfaction Reoperations Complications (major and minor; “The Swedish Spine Study” grading was used)	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			abuse, psychological or medical reasons; Language difficulties with inability to understand follow-up instruments; Pregnancy or other medical condition that would be a contraindication to surgery				

DDD: degenerative disc disease; EQ5D: EuroQoL 5 dimensions; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not report; ODI: Oswestry disability index; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 questionnaire; VAS: visual analog scale.

*Authors report on number of patients randomized who received treatment but did not describe whether there were randomized subjects who did not receive allocated treatment.

Appendix Table G5. L-ADR vs. ACDF (1-level): Nonrandomized comparative studies

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Cohort studies							
Lindley 2012 Retrospective cohort study United States Note: In an exclusively male population	95	L-ADR (n = 40): Prodisc-L (Synthes) or Activ-L (Aesculap Implant Systems) Fusion with BMP (n = 54): ALIF with BMP with anterior plate with 4 screws (ATB	Inclusion: Patients were included if their received ALIF or ADR procedures on at least the L5-S1 level. Exclusion: Underwent revision surgery for previous anterior spine procedures.	L-ADR vs. Fusion <u>Mean (range):</u> Age: 35 (23-59) vs. 49 (24-76), p < 0.01 Female: 0% vs. 0% Primary diagnosis, DDD (w/ or w/out stenosis): 97.6% (40/41) vs. 72.2% (39/54), p < 0.01 Primary diagnosis, spondylolisthesis: 2.4% (1/41) vs. 9.3%	NR	Retrograde ejaculation Other sexual dysfunction	“No funds were received in support of this work”; ≥1 author has or will receive benefits for personal or professional use related directly or indirectly to the subject of this

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		Plate from Synthes) and femoral ring allograft, or an integrated cage/plate device with 4 screws (SynFix-L from Synthes). Interbody devices contained 1-2 sponges of rhBMP-2 (Small Kit, 4.2 mg rhBMP-2 from Medtronic Sofamor Danek)		(5/54) Primary diagnosis, degenerative scoliosis: 0% (0/41) vs. 3.7% (2/54) Primary diagnosis, pseudoarthrosis: 0% (0/41) vs. 14.8% (8/54), p < 0.05 Single-level L5-S1: 52.8% (24/41) vs. 31.5% (17/54), p < 0.05 Anterior surgery only: 100% (41/41) vs. 50% (27/54)			manuscript
Registry studies							
Berg 2010 Retrospective registry study Sweden	455	L-ADR (n = 229): 1- or 2-level ADR Fusion (n = 226): 1- or 2-level fusion, device details NR	Inclusion: Back pain diagnosed as mechanical and discogenic in origin with interspinous tenderness on examination, disc narrowing on radiographs, and signs of degeneration on magnetic resonance imaging. Low-grade facet joint arthritis at the index level, as well as low-grade degeneration at other levels, was accepted. Patients who fulfilled the	L-ADR vs. Fusion <u>Mean*</u> (unless otherwise indicated): Age: 39 vs. 43 Female: 49% (80/163) vs. 54% (96/178) Smokers: 11% (18/163) vs. 19% (34/178), p < 0.05	>12 mos.: 61.3% (279/455) >24 mos.: 30.1% (137/455)	Back pain VAS (0-100 (worst)) Back pain improvement ODI (0-100 (worst)) ODI improvement EQ-5D (-0.59-1 (best))	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>inclusion criteria at the primary consultation but scored lower on the ODI and VAS at the time of surgery were not excluded. Patients with a strong belief that one treatment option was superior to the other were not included in the RCT but could be included in the non-RCT group.</p> <p>Exclusion: Spinal stenosis requiring decompression; moderate or worse facet joint arthritis; three or more painful levels at clinical examination; no obvious painful level(s) at diagnostic injection evaluation (if done); isthmic spondylolysis/spondylolisthesis; degenerative spondylolisthesis >3 mm; major deformity; manifest osteoporosis—if osteoporosis was suspected because of gender and age (women aged >50 years), illness, or medication, osteoporosis should be evaluated and excluded before inclusion; previous lumbar fusion or decompression with potential instability (e.g., facet joint damage or wide laminectomy); compromised</p>	<p>Prior surgery: 26% (42/163) vs. 31% (55/178), p < 0.05 1-level surgery: 60% (98/163) vs. 60% (107/178) 2-level surgery: 40% vs. 40%</p>		<p>EQ-5D improvement</p> <p>EQ-VAS (0-100 (worst))</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			vertebral body; previous spinal infection or tumor; inability to understand information because of abuse or for psychological or medical reasons; language difficulties with inability to understand follow-up instruments; pregnancy or other medical condition that would be a contraindication to surgery.				
Administrative database studies							
Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States	Kurtz 2010 Administrative database study (National Inpatient Service (NIS)) United States

L-ADR vs. Multidisciplinary Rehabilitation

Appendix Table G6. L-ADR vs. Multidisciplinary Rehabilitation: RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Hellum 2011 RCT Norway	179 randomized, 157 treated	<p>L-ADR (n = 89) ADR with ProDisc II at L4-L5 or L5-S1 (single level) or both (multilevel) via the anterior retroperitoneal approach</p> <p>Multidisciplinary Rehabilitation (n=90): Cognitive approach and supervised physical exercise (based on the treatment model described by Brox et al.); 60 hours over 3-5 to weeks; physical exercise included daily endurance, strength and</p>	<p>Inclusion: Age 25 to 55; LBP primary symptom for ≥1 year; inadequate response to ≥6 months’ structured physiotherapy or chiropractic treatment; ODI score ≥30; and degenerative changes in the intervertebral disc in one or both of the lower lumbar levels (L4/L5 or L5/S1)</p> <p>Exclusion: symptoms of nerve root involvement; degeneration established in ≥2 levels; symptoms of spinal stenosis; generalized chronic pain; disc protrusion or recess stenosis with involvement of nerve roots; spondylosis with or without spondylolisthesis; arthritis; former fracture of L1-S1; ongoing psychiatric or somatic disease that excluded either one or both</p>	<p><i>L-ADR vs. rehabilitation:</i></p> <p><u>Mean ± SD</u> (unless indicated):</p> <ul style="list-style-type: none"> • Age: 41.1 ± 7.1 vs 40.8 ± 7.1 • Female: 47% (40/86) vs 59% (51/86) • Duration of pain: 76 ± 72 vs 85 ± 74 mos. • BMI: 25.6 ± 3.1 vs 25.5 ± 3.5 • Current smokers: 49% (42/86) vs 43% (37/86) • Daily consumption of narcotics: 27% (23/86) vs 20% (17/86) • Previous surgery: 27% (23/86) vs 29% (25/86) • ODI score: 41.8 ± 9.1 vs 42.8 ± 9.3 • Low back pain score: 64.9 ± 15.3 vs 73.6 ± 13.9 • SF-36 Physical Function: 52.7 ± 17.6 vs. 50.6 ± 17.7 • SF-36 Role Physical: 25.3 ± 24.2 vs. 23.9 ± 18.7 • SF-36 Bodily Pain: 24.9 ± 16.54 vs. 24.4 ± 12.1 • SF-36 General Health: 	<p><i>L-ADR vs. rehabilitation</i></p> <p>24 months</p> <p><u>%F/U:</u> Overall: 77.7%, (139/179); L-ADR: 82.0%, (73/89); Rehab: 73.3%, (66/90)</p> <p>Cross over from rehab to surgery: 7.5% (6/80 [denominator reflects the no. who were treated]);</p>	<p>ODI, 0-100 (worst)</p> <p>Back performance scale, 0-15 (worst)</p> <p>Low back pain: VAS, 0-100 (worst)</p> <p>SF-36, 0-100 (best)</p> <p>EQ-5D, -0.59 to 1 (best)</p> <p>HSCL-25 (emotional distress), 1-4 (worst)</p> <p>FABQ for work (0-42 [worst]), and physical activity (0-24 [worst])</p> <p>Self-efficacy beliefs for pain, score range from 1-10 and are summarized and divided by 5 (lower score = uncertainty managing pain)</p> <p>Return to Work (net back to work rate)</p>	<p>South Eastern Norway Regional Health Authority; EXTRA funds from the Norwegian Foundation for Health and Rehabilitation, through the Norwegian Back Pain Association</p>

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		coordination workouts, and specific training of the abdominal muscles and the lumbar multifidus muscles); cognitive approach included education, coping skills, support relating to family, social and work life	treatment alternatives; not able to understand Norwegian, spoken or written; drug abuse; osteoporosis; and congenital or acquired deformity.	57.9 ± 19.7 vs. 55.9 ± 19.9 •SF-36 Vitality: 37.8 ± 20.2 vs. 33.1 ± 19.9 •SF-36 Social Function: 53.0 ± 30.6 vs 57.6 ± 26.7 •SF-36 Role Emotion: 72.5 ± 33.3 vs. 67.6 ± 32.7 •SF-36 Mental Health: 71.7 ± 18.0 vs. 65.8 ± 18.9 •SF-36 Physical Component Summary score: 30.5 ± 7.1 vs. 30.8 ± 6.5 •SF-36 Mental component summary score: 47.7 ± 13.0 vs 45.2 ± 13.2 •HSCL-25: 1.8 ± 0.5 vs 1.9 ± 0.5 •FABQ work: 25.9 ± 11.3 vs 27.4 ± 9.9 •FABQ physical: 14.1 ± 5.8 vs. 12.0 ± 5.5	fusion (n=1)	Prolo scale, 2-10 (best) Patient satisfaction with outcome, 7 point Likert scale (1=completely recovered, 2=much recovered to 7=vastly worsened); slightly improved not included as satisfied with outcome) Patient satisfaction with care (4 point global rating scale, not including slightly satisfied as satisfied with care)	

DDD: degenerative disc disease; EQ5D: EuroQoL 5 dimensions; FABQ: fear avoidance belief questionnaire; FDA: Food and Drug Administration; F/U: follow-up; HSCL-25: Hopkins symptom checklist; L-ADR: lumbar artificial disc replacement; NR: not report; ODI: Oswestry disability index; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form-36 questionnaire; SSED: Summary of Safety and Effectiveness Data; VAS: visual analog scale.

*Authors report on number of patients randomized who received treatment but did not describe whether there were randomized subjects who did not receive allocated treatment.

APPENDIX H. C-ADR Study Characteristics Data Abstraction Tables.

C-ADR vs. ACDF (1-level)

Appendix Table H1. C-ADR vs. ACDF (1-level): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
BRYAN IDE trial RCT United States	582	<p>C-ADR (n = 290): BRYAN Cervical Disc (Medtronic Sofamor Danek)</p> <p>ACDF (n = 292): Commercially available allograft and plating system were used (details NR, but plate is manufactured by Medtronic Sofamor Danek).</p>	<p>Inclusion: At least 21-year-old with radiculopathy or myelopathy from single-level cervical disc disease secondary to disc herniation that had not responded to at least 6 weeks of nonoperative management, with the exception of cases of myelopathy requiring immediate treatment.</p> <p>Exclusion: Marked spondylosis; marked reduction or absence of motion or collapse of the intervertebral disc space of greater than 50% of its normal height; facet joint arthrosis; segmental instability or cervical kyphosis; active infection; metabolic bone disease, such as osteoporosis; known allergy to titanium, polyurethane, or ethylene</p>	<p>C-ADR vs. ACDF</p> <p><u>Mean ± SD</u> (unless otherwise indicated)*: Age: 44.4 ± 7.9 (range: 25-78) vs. 44.7 ± 8.6 (27-68) BMI (kg/m²): 26.6 ± 4.8 vs. 27.6 ± 5.0 Male: 45.5% (110/242) vs. 51.1% (113/221) Currently working: 64.5% (156/242) vs. 65.0% (144/221) C3-C4/C4-C5/C5-C6/C6-C7: 1.2%/5.0%/57.9%/36.0% vs. 0%/7.7%/49.8%/42.5% Worker’s compensation: 6.2% vs. 5.06.2% Unresolved spine-related litigation: 2.5% vs. 2.7% Current tobacco use: 25.5% vs. 24.0%</p>	<p>24 mos.: 72.9% (424/582)</p> <p>48 mos.: 54.8% (319/582)</p> <p>Cross-overs (post-randomization, prior to initial surgery): 4.1% (12/290) vs. 0.3% (1/292)</p> <p>Randomized but not treated: 12.8% (37/290) vs. 28.1% (82/292)</p>	<p>Overall success[†]</p> <p>Neck Disability Index (NDI) score, 0-100 (worst)</p> <p>SF-36 PCS, 0-100 (best)</p> <p>SF-36 MCS, 0-100 (best)</p> <p>Neck pain via NRS, 0-100 (worst)</p> <p>Arm pain via NRS, 0-100 (worst)</p> <p>Neurologic success[‡]</p> <p>Return to work</p> <p>Secondary surgical procedures</p> <p>Adverse events</p>	<p>Medtronic Sofamor Danek</p>

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			oxide residuals; concomitant conditions requiring steroid treatment; diabetes mellitus; extreme obesity; pregnancy; inflammatory spondyloarthropathies, such as ankylosing spondylitis or rheumatoid arthritis, and previous cervical spine surgery.				
Prestige ST IDE trial RCT United States	541	C-ADR (n = 276): Prestige ST Cervical Disc System (Medtronic Sofamor Danek) ACDF (n = 265): Allograft intradiscal spacer (details NR) plus Atlantis Cervical Plate System (Medtronic Sofamor Danek)	Inclusion: 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.	C-ADR vs. ACDF: <u>Mean ± SD</u> (unless otherwise indicated): Age: 43.3 ± 7.6 (range 25-72) vs. 43.9 ± 8.8 (22-73) Male %: 46.4% (128/276) vs. 46.0% (122/265) Workers' compensation: 11.6% (32/276) vs. 13.2% (35/276) Involved in litigation: 10.9% (31/276) vs. 12.1% (32/265) Alcohol use: 43.5% (120/276) vs. 53.2% (141/265), p < 0.05 Tobacco use: 34.4% (95/276) vs. 34.7% (92/265) C3-C4/C4-C5/C5-C6/C6-C7: 2.5%/5.1%/51.4%/40.9% vs. 3.8%/5.7%/56.2%/34.3%	24 mos.: 87.4% (473/541) 60 mos.: 75.2% (407/541) 84 mos.: 72.5% (392/541) Cross-overs: 0% (0/276) vs. 0% (0/265) Randomized but not treated: 0% (0/276) vs. 0% (0/265)	Overall success† SF-36 PCS, 0-100 (best) SF-36 MCS, 0-100 (best) Neck Disability Index (NDI), 0-100 (worst) NDI Success§ Neck and arm pain via NRS, 0-10 (worst) Composite neck and arm pain score, 0-100 (worst)** Neurological status†† Work status	“Authors have or will receive benefits for personal or professional use Medtronic Sofamor Danek in relation to products named in this article.”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>Exclusion: 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 anti-inflammatory drugs that could affect bone quality and fusion rates.</p>			<p>Secondary surgical procedures including for adjacent segment disease</p> <p>Adverse events</p>	
<p>Prodisc-C IDE trial</p> <p>RCT</p> <p>United States</p>	228	<p>C-ADR (n = 111): ProDisc-C total disc replacement (Synthes)</p> <p>ACDF (n = 117): Allograft spacers (commercially available or prepared by the surgeon), fixed</p>	<p>Inclusion: Age 18-60 years; SCDD in only one vertebral level between C3-C7 requiring neck or arm (radicular pain), and/or functional/neurological deficit confirmed by imaging of at least one of the following: herniated nucleus pulposus,</p>	<p>C-ADR vs. ACDF:</p> <p><u>Mean ± SD</u> (unless otherwise indicated):</p> <p>Age: 42.1 ± 8.4 vs. 43.5 ± 7.1</p> <p>Female: 55.3% (57/103) vs. 53.8% (57/106)</p> <p>Race, Caucasian: 85.4% (88/103) vs. 91.5% (97/106)</p> <p>Race, African American: 3.9% (4/103) vs. 0.9%</p>	<p>24 mos.: 88.6% (102/228)</p> <p>48 mos.: 50.0% (114/228)</p> <p>84 mos.: 66.7% (152/228)</p> <p>Cross-overs: 2.7% (3/111)</p>	<p>Overall success^{††}</p> <p>Neck pain and intensity via VAS, 0-100 mm (worst)</p> <p>Arm pain and intensity via VAS, 0-100 mm (worst)</p> <p>VAS satisfaction, 0-100</p>	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		angle plate, device details NR	<p>spondylosis (defined by the presence of osteophytes), or loss of disc height; unresponsive to non-operative treatment for at least six weeks or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment; NDI score ≥15-50 (30%); psychosocially, mentally, and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements, and filling out forms; signed informed consent.</p> <p>Exclusion: More than one vertebral level requiring treatment; marked cervical instability on resting lateral or flexion-extension radiographics: translation >3 mm, and/or more than 11° of rotational difference to that of either adjacent level; has a fused level adjacent to the level to be</p>	<p>(1/106) Race, Hispanic: 4.9% (5/103) vs. 4.7% (5/106) Race, Asian American: 4.9% (5/103) vs. 0% (0/106) Race, Other: 2.9% (3/103) vs. 2.8% (3/106) BMI (kg/m²): 26.4 ± 5.3 vs. 27.3 ± 5.5 Smoking Status, never: 49.5% (51/103) vs. 46.2% (49/106) Smoking status, former: 17.5% (18/103) vs. 18.9% (20/106) Smoking status, current: 33.0% (34/103) vs. 34.9% (37/106) Any prior surgical treatment: 10.7% (11/103) vs. 9.4% (10/106) Prior discectomy: 3.9% (4/103) vs. 2.8% (3/106) Prior laminectomy: 1.9% (2/103) vs. 4.7% (5/106) Other prior surgery: 6.8% (7/103) vs. 3.8% (4/106) Implant level, C3-C4: 2.9% (3/103) vs. 0.9% (1/106) Implant level, C4-C5: 9.7% (10/103) vs. 5.7% (6/106) Implant level, C5-C6: 56.3% (58/103) vs. 57.5% (61/106) Implant level, C6-C7: 31.1%</p>	<p>vs. 0% (0/117) Randomized but not treated: 7.2% (8/111) vs. 9.4% (11/117)</p>	<p>mm (worst) Neck Disability Index (NDI), 0-100 (worst) SF-36 MCS, 0-100 (best) SF-36 PCS, 0-100 (best) Reoperation§§ Neurologic success*** Device success Narcotic use Work status Adverse events Dysphagia Psychological Outcomes Patient Satisfaction/ Surgery Again††† Health-related Quality of Life (HRQL)‡‡‡</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			treated; radiographic confirmation of severe facet joint disease or degeneration; known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene; prior surgery at the level to be treated; neck or arm pain of unknown etiology; clinically compromised vertebral bodies at the affected level as a result of current or past trauma, e.g., by the radiographic appearance of fracture callus, malunion, or nonunion; active infection– systemic or local; severe spondylosis at the level to be treated as characterized by any of the following: 1. bridging osteophytes, 2. loss of disc height >50%, 3. absence of motion (<2°); Paget’s (dual energy X-ray absorptiometry) disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis discussed below); severe diabetes mellitus requiring daily insulin	(32/103) vs. 35.8% (38/106)			

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			management; pregnant or interested in becoming pregnant in the next three years; rheumatoid arthritis or other autoimmune disease; systemic disease including AIDS, HIV, or hepatitis; <i>osteoporosis</i> : a screening questionnaire for osteoporosis, SCORE, will be used to screen patients who require a DEXA bone mineral density measurement. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score ≤ -2.5 (the World Health Organization definition of osteoporosis); taking medications or any drug known to potentially interfere with bone/soft-tissue healing (e.g., steroids); history of any invasive malignancy (except nonmelanoma skin cancer), unless treated with curative intent and there have been no clinical signs or symptoms of the malignancy for ≥ 5 years.				

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
PCM IDE trial RCT United States	416	<p>C-ADR (n = 224): Porous Coated Motion (PCM) Cervical Disc (NuVasive)</p> <p>ACDF (n = 192): ACDF construct (tricortical allograft and CSLP [Synthes Spine]) or Slim Loc (DePuy Spine)</p>	<p>Inclusion: Age 18-65 years; diagnosis of single-level radiculopathy and/or myelopathy; symptomatic at only 1 level C3-C4 through C7-T1 (inclusive); symptoms of 1 or more of the following: arm/shoulder pain (≥30 mm on 100-mm scale), abnormal motor strength, sensation and/or reflexes, myelopathy symptoms; radiographically determined pathology at level to be treated correlating to primary symptoms, including at least decreased disc height, degenerative spondylosis on computed tomography scan or magnetic resonance image, disc herniation; baseline NDI score of ≥30/100; unresponsive to nonoperative treatment for 6 weeks, or progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment.</p>	<p>C-ADR vs. ACDF</p> <p><u>Mean ± SD</u> (unless otherwise indicated)*: Age: 45.3 ± 9.0 vs. 43.7 ± 8.3 Female: 48.2% (105/218) vs. 48.1% (89/185) Race, White: 92.7% (202/218) vs. 91.9% (170/185) Race, Black: 4.6% (10/218) vs. 3.8% (7/185) Race, Asian: 0% (0/218) vs. 2.7% (5/185) Race, Hispanic: 1.4% (3/218) vs. 1.1% (2/185) Race, Other: 1.4% (3/218) vs. 0.5% (1/185) BMI (kg/m²): 28.2 ± 4.6 vs. 27.3 ± 4.8, p < 0.05 Current tobacco use: 51.8% (113/218) vs. 48.6% (90/185) Receiving worker's compensation: 11.9% (26/218) vs. 11.4% (21/185) Prior laminoforaminotomy without facetectomy: 0.5% (1/218) vs. 1.6% (3/185) Prior laminoforaminotomy with facetectomy: 0.5% (1/218) vs. 2.2% (4/185) Prior fusion at adjacent level: 11.5% (25/218) vs.</p>	<p>24 mos.: 81.7% (340/416)</p> <p>60 mos.: 70.4% (293/416)</p> <p>Cross-overs: 1.8% (4/224) vs. 0% (0/192)</p> <p>Randomized but not treated: 2.7% (6/224) vs. 3.6% (7/192)</p>	<p>Overall success\$\$\$</p> <p>Success neck and worst arm pain****</p> <p>Neck and worst arm pain via VAS, 0-100 (worst)</p> <p>Neck pain VAS, ≥20-mm improvement; 0-100 mm (worst)</p> <p>Worst arm pain VAS, ≥20 mm improvement; 0-100 mm (worst)</p> <p>Neck Disability Index (NDI) score, 0-100 (worst)</p> <p>Neck Disability Index (NDI) success, ≥20% improvement</p> <p>Neck Disability Index (NDI) success, ≥15-point improvement</p> <p>SF-36 PCS and MCS scores, 0-100 (best)</p> <p>SF-36 PCS success,</p>	NuVasive

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>Exclusion: Prior failed cervical fusion (prior decompressions and adjacent and nonadjacent fusions allowed); previous cervical trauma resulting in significant bony or discoligamentous cervical spinal injury; marked cervical instability demonstrated by >3.5 mm translation and/or >11° angular difference to that of either adjacent level; congenital canal stenosis resulting in a canal diameter of <10mm; radiographically confirmed facet joint pathology; severe myelopathy to the extent that the patient is wheelchair bound; rheumatoid arthritis and other musculoskeletal autoimmune disorders; osteoporosis and other metabolic bone diseases; infection (local or systemic); diabetes mellitus; morbid obesity; malignancy/metastases; known allergies to device materials.</p>	<p>10.3% (19/218) Prior fusion at nonadjacent level: 1.8% (4/218) vs. 0.5% (1/185) Neurological symptoms, radiculopathy and myelopathy++++: 15.1% (33/218) vs. 24.3% (45/185) Neurological symptoms, radiculopathy only++++: 84.4% (184/218) vs. 75.7% (140/185) Neurological symptoms, myelopathy only++++: 0.4% (1/218) vs. 0.0% (0/185) Radiographic evidence of herniated nucleus pulposus: 80.7% (176/218) vs. 83.8% (155/185) Radiographic evidence of spondylosis: 18.8% (41/218) vs. 15.1% (28/185) Radiographic evidence of loss of disc height: 17.9% (39/218) vs. 28.6% (53/185) Treated level, C3-C4: 0% (0/218) vs. 4.3% (8/185), p < 0.05 Treated level, C4-C5: 14.2% (31/218) vs. 9.2% (17/185) Treated level, C5-C6: 50.0% (109/218) vs. 53.0% (98/185) Treated level, C7-T1: 0.9%</p>		<p>≥15% improvement SF-36 MCS success, ≥15% improvement Neurological success‡ Dysphagia via VAS, 0-100 (worst) Myelopathy maintenance or improvement Odom’s Criteria‡‡‡ Heterotopic ossification Adjacent level degeneration Adverse events Secondary surgical interventions Psychological Outcomes Questionnaire for patient satisfaction Patient satisfaction via</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				(2/218) vs. 0.0% (0/185)		VAS, 0-100 (worst)	
Mobi-C (1-level) IDE trial RCT United States	256	1-level C-ADR (n = 169): Mobi-C (LDR Medical) 1-level ACDF (n = 87): Corticocancellous allograft bone and plate (Slim-Loc Anterior Cervical Plate System (DePuy), Sofamor Danek Atlantis (Medtronic), or Atlantis Vision Anterior Cervical Plate Systems)(Medtronic)	Inclusion: Age 18-69 years; symptomatic cervical degenerative disc disease in only one level between C3-C7 with: neck and/or arm pain, and/or decreased muscle strength, and/or abnormal sensation, and/or abnormal reflexes; deficit confirmed by imaging (CT, MRI, or X-ray); NDI score of ≥ 30 ; unresponsive to non-operative, conservative treatment for at least 6 weeks or presence of progressive symptoms or signs of nerve root/spinal cord; compression despite continued non-operative treatment; no prior surgery at the operative level and no prior cervical fusion procedure at any level; physically and mentally able and willing to comply with the protocol; signed informed consent; willingness to discontinue all use of non-	C-ADR vs. ACDF <u>Mean \pm SD</u> (unless otherwise indicated)§§§§: Age: 43.3 \pm 9.23 vs. 44.0 \pm 8.21 Female: 52.4% (86/164) vs. 55.6% (45/81) Ethnicity, Hispanic or Latino: 1.8% (3/164) vs. 2.5% (2/81) Ethnicity, not Hispanic or Latino: 98.2% (161/164) vs. 97.5% (79/81) Race, American Indian Alaska Native: 1.2% (2/164) vs. 6.7% (1/15) Race, Caucasian: 92.7% (152/164) vs. 85.2% (69/81) Race, Asian: 1.8% (3/164) vs. 1.2% (1/81) Race, Black or African American: 2.4% (4/164) vs. 0% (0/81) Race, Native Hawaiian/other Pacific Islander: 0.6% (1/64) vs. 0% (0/81) Race, Other: 1.2% (2/164) vs. 0% (0/81) BMI (kg/m ²): 27.28 \pm 4.42 (range: 17.91-37.88) vs. 27.39 \pm 4.18 (range: 17.23-39.15)	24 mos.: 90.2% (231/256) 60 mos.: 79.7% (204/256) Cross-overs: 0% (0/169) vs. 0% (0/87) Randomized but not treated: 3.0% (5/169) vs. 6.9% (6/87)	Overall success***** Neck Disability Index, 0-100 (worst) SF-12 Physical Component Score, 0-100 (best) SF-12 Mental Component Score, 0-100 (best) Neck pain via VAS, 0-100 (worst) Arm pain (left and right) via VAS, 0-100 (worst) Adverse events Subsequent surgical interventions Adjacent level degeneration Neurological status++++ Neurological success‡	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			steroidal anti-inflammatory drugs (NSAIDs) from one week before surgery until 3 months after surgery. Exclusion: More than one vertebral level requiring treatment/immobile level between C1 and C7 from any cause; any prior spine surgery at operative level of any prior cervical fusion at any level; disc height less than 3 mm; T-score less than -1.5 (osteoporosis evaluation); Paget’s disease, osteomalacia, or any other metabolic bone disease other than osteoporosis; active systemic infection of surgical site or history of or anticipated treatment for systemic infection including HIV/Hepatitis C; active malignancy: a history of any invasive malignancy (except non-melanoma skin cancer), unless treated with curative intent and there had been no clinical signs	Pain medication: 92.7% (152/164) vs. 91.4% (79/81), p < 0.05 Opioid use, opium alkaloid: 14% (23/164) vs. 6.2% (5/81) Opioid use, semi-synthetic opioid derivative: 53% (87/164) vs. 54.3% (44/81) Opioid use, synthetic opioid: 12.2% (20/164) vs. 8.6% (7/81) Physical therapy: 38.4% (63/164) vs. 42% (34/81) Collar: (11.6% (19/164) vs. 13.6% (11/81) Chiropractic: 26.2% (43/164) vs. 19.8% (16/81) Cervical traction: 22.6% (37/164) vs. 21% (17/81) Bedrest/immobilization: 53% (87/164) vs. 46.9% (38/81) Acupuncture: 5.5% (9/164) vs. 6.2% (5/81) Able to work: 65.9% (180/164) vs. 56.8% (46/81) Able to drive: 94.5% (155/164) vs. 97.5% (79/81) C3-C4/C4-C5/C5-C6/C6-C7: 0.6%/6.7%/56.1%/36.6% vs. 4.9%/2.5%/56.8%/35.8%		Psychological Outcomes Patient satisfaction	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			or symptoms of the malignancy > 5 years; marked cervical instability on resting lateral or flexion-extension radiographs; known allergy to cobalt, chromium, molybdenum, or polyethylene; segmental angulation of greater than 11° at treatment or adjacent levels; rheumatoid arthritis, lupus, or other autoimmune disease; any diseases or conditions that would preclude accurate clinical evaluation; daily, high-dose oral and/or inhaled steroids or a history of chronic use of high dose steroids; BMI > 40 kg/m ² ; use of any other investigational drug or medical device within 30 days prior to surgery; pending personal litigation relating to spinal injury (worker's compensation not included); smoking more than one pack of cigarettes per day;				

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			reported to have mental illness or belonged to a vulnerable population.				
Secure-C IDE trial RCT United States	291	<p>C-ADR (n = 151): SECURE-C Cervical Artificial Disc (Globus Medical)</p> <p>ACDF (n = 140): Allograft interbody spacer (details NR) plus ASSURE Anterior Cervical Plate (Globus Medical).</p>	<p>Inclusion: SCDD in one vertebral level between C3–C7, defined as neck or arm (radicular) pain, or functional or neurological deficit and radiographical confirmation (by CT, MRI, radiography, etc.) of any of the following: herniated nucleus pulposus; radiculopathy or myelopathy; spondylosis (defined by the presence of osteophytes); or loss of disc height. Age between 18 and 60 years; failed at least 6 weeks of conservative treatment; NDI Questionnaire score of at least 30 (as percentage of 50-point total); able to understand and sign informed consent form; psychosocially, mentally, and physically able to fully comply with this protocol including adhering to follow-up schedule and filling out forms; able to</p>	<p>C-ADR vs. ACDF</p> <p><u>Mean ± SD</u> (unless otherwise indicated): Age: 43.4 ± 7.5 vs. 44.4 ± 7.86 Female: 46.4% (70/151) vs. 51.4% (72/140) Race, Caucasian: 90.1% (136/151) vs. 90.0% (126/140) Race, African American: 6.6% (10/151) vs. 7.1% (10/140) Race, Asian: 0.0% (0/151) vs. 0.0% (0/140) Race, Hispanic: 1.3% (2/151) vs. 2.1% (3/140) Race, Other: 2.0% (3/151) vs. 0.7% (1/140) BMI (kg/m²): 28.9 ± 5.53 vs. 29.0 ± 5.47 Current tobacco user: 33.8% (51/151) vs. 37.9% (53/140) Symptom duration, months: 16.6 ± 27 vs. 19.8 ± 40.0 History of non-operative care: 97.4% (147/151) vs. 98.6% (138/140) History of prior surgery: 1.3% (2/151) vs. 2.9%</p>	<p>24 mos.: 81.1% (236/291)</p> <p>Cross-overs: 2.6% (4/151) vs. 0% (0/140)</p> <p>Randomized but not treated: 0% (0/151) vs. 0% (0/140)</p>	<p>Overall success++++</p> <p>No device failures requiring revision, re-operation, or removal</p> <p>Absence of major complications</p> <p>Neck Disability Index (NDI) Scores, 0-100 (worst)</p> <p>Neck Disability Index (NDI), ≥25% improvement from baseline</p> <p>Neck pain via VAS, 0-100 (worst)</p> <p>Right and left arm pain via VAS, 0-100 (worst)</p> <p>Neck pain VAS, 20 mm improvement from baseline; 0-100 mm (worst)</p> <p>Right and left arm pain VAS, 20 mm</p>	<p>“No funds were received in support of this work.”</p>

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>meet the proposed follow-up schedule at 6 weeks, 3 mos., 6 mos., 12 mos., and 24 mos.; able to follow postoperative management program</p> <p>Exclusion: More than one vertebral level requiring treatment; prior fusion surgery adjacent to the vertebral level being treated; prior surgery at the level to be treated; clinically compromised vertebral bodies at the affected level(s) due to current or past trauma; radiographical confirmation of facet joint disease or degeneration, defined as apparent sclerosis and/or hypertrophy of the facets demonstrated on AP radiographs as a disruption of the normally smooth facet curve; marked cervical instability on resting lateral or flexion-extension radiographs: translation greater than 3 mm, and/or more than 11 ° of</p>	<p>(4/140) C3-C4/C4-C5/C5-C6/C6-C7: 3.3%/5.3%/49.7%/41.7% vs. 2.9%/7.9%/50.0%/39.3%</p>		<p>improvement from baseline; 0-100 mm (worst)</p> <p>SF-36 MCS score, 0-100 (best)</p> <p>SF-36 PCS score, 0-100 (best)</p> <p>SF-36 MCS, 15% improvement from baseline</p> <p>SF-36 PCS, 15% improvement from baseline</p> <p>Neurological status (maintenance, worsening, or improvement)</p> <p>Device displacement or migration >3 mm</p> <p>Return to work</p> <p>Adverse events</p> <p>Psychological outcomes</p> <p>Patient satisfaction</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			rotational difference from that of either adjacent level. Severe spondylosis at the level to be treated as characterized by any of the following: bridging osteophytes; a loss of disc height greater than 50%; or absence of motion (<2°). Neck or arm pain of unknown etiology; osteoporosis, osteopenia, Paget disease, osteomalacia, or any other metabolic bone disease; pregnant or interested in becoming pregnant in the next 2 years; active systemic or local infection; known allergy to titanium, polyethylene, cobalt, chromium, or molybdenum; 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				

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			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; neuromuscular disorders such as muscular dystrophy, spinal muscular atrophy, amyotrophic lateral sclerosis, etc.; acute mental illness or substance abuse; use of bone growth stimulator within past 30 days; participation in other investigational device or drug clinical trials <30 days of surgery; is a prisoners				
Karabag 2014 RCT Turkey	42 treated	C-ADR (n = 19 treated): Bryan ACDF (n = 23 treated): polyetheretherketone (PEEK) cage; no other details reported	Inclusion: Single-level disc disorder between C4-C7 with no improvement from previous medical treatment. Exclusion: NR	C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated): Age: 43.1 ± 6.1 vs. 46.2 ± 4.7 Implant level, C4-C5: 15.7% (3/19) vs. 13.0% (3/23) Implant level, C5-C6: 52.6% (10/19) vs. 47.8% (11/23) Implant level, C6-C7: 31.5%	Unclear (Note: number of patients randomized not clearly stated)	Odom’s Criteria Neck Disability Index (NDI) score, 0-50 or 100 (worst)\$\$\$\$\$ VAS, 0-10 (worst)*****	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				(6/19) vs. 39.0% (9/23)			
<p>Nabhan 2007</p> <p>RCT</p> <p>Germany</p> <p>(NOTE: There is no patient overlap between Nabhan 2007 and Nabhan 2011 based on the dates of patient enrollment given in the studies.)</p>	49	<p>C-ADR (n = 25): Prodisc-C prosthetic implant (Synthes)</p> <p>ACDF (n = 24): Bone graft (details NR) plus Solis (PEEK) cage (Stryker Howmedia GmbH) and nonconstrained plate</p>	<p>Inclusion: 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.</p> <p>Exclusion: 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, rheumatoid arthritis; spondylodiscitis and active infection; malignant disease; system disease (e.g., hepatitis,</p>	<p>C-ADR vs. ACDF</p> <p><u>Mean ± SD</u> (unless otherwise indicated): Male: 56% (23/41 treated) No other demographic details reported</p>	<p>13 mos.: 82% (40/49)</p> <p>36 mos.: 80% (39/49)</p> <p>Cross-overs: 0% (0/25) vs. 0% (0/24)</p> <p>Randomized but not treated: 20% (5/25) vs. 12.5% (3/24)</p>	<p>Neck pain via VAS, 0-10 (worst)</p> <p>Arm pain via VAS, 0-10 (worst)</p> <p>Adverse events</p>	Synthes Spine

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			HIV, AIDS); known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene; traumatic injury of spine; pregnant or possible pregnancy in the next 3 years.				
Nabhan 2011 RCT Germany (NOTE: There is no patient overlap between Nabhan 2007 and Nabhan 2011 based on the dates of patient enrollment given in the studies.)	20 treated	C-ADR (n = 10 treated): Prodisc-C (Synthes) ACDF (n = 10 treated): Graft NR, Solis (PEEK) cage (Stryker Howmedia GmbH) with ABC titanium alloy plate (Aesculap AG, AM Aesculap-Platz)	Inclusion: Suffering from symptomatic degenerative soft disc disease with single-level radiculopathy, not responsive to a trial of conservative treatment. Exclusion: Details NR	Entire group (C-ADR and ACDF) <u>Mean ± SD</u> (unless otherwise indicated): Age: 43.0 ± 7 Women: 35% (7/20)	Unclear (Note: number of patients randomized not clearly stated)	Brachial pain via VAS, 0-10 (worst) Cervical pain via Neck Disability Index (NDI) scale, 0-1 (worst)	NR
Peng-Fei 2008 RCT China	24	C-ADR (n = 12): Bryan Interbody fusion (n = 12): Iliac bone plus fixation device (device	Inclusion: Intervertebral disc hernia at C5-C6. Failed conservative treatment with worsening symptoms. Exclusion: NR	Entire group (C-ADR and ACDF) <u>Mean (range):</u> Age: 42 (range: 24-53) Female: 29.1% (7/24) Course of disease (mos.): 18	17 mos. (mean): 100% (24/24) Cross-overs: 0% (0/12) vs. 0% (0/12)	Japanese Orthopedic Association (JOA) scale, 0-17 (best) Odom’s Criteria Prosthesis subsidence	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		details NR)		(range: 3-48)	Randomized but not treated: 0% (0/12) vs. 0% (0/12)	or extrusion Neurological or vascular complications	
Rozan-kovic 2016 RCT Croatia	105	C-ADR (n = 54): Discover Artificial Cervical Disc (DePuy) ACDF (n = 51): DuoCage allograft (SBM)	Inclusion: Patients with single-level cervical disc disease from C3-C7 presenting with radiculopathy and/or myelopathy with failure of conservative treatment for ≥12 weeks; NDI score ≤30%. Exclusion: Presence of significant anatomic deformity such as severe spondylosis and radiographic signs of instability or previous procedures at the operative level; ROM <2 degrees measured at the dynamic cervical X-rays by independent radiologist.	C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated)*: Age: 41.32 ± 8.8 vs. 41.94 ± 9.36 Symptom duration (mos.): 14.12 ± 12.67 vs. 14.38 ± 10.77 Female: 51% (26/51) vs. 50% (25/50) Implant level, C3-C4: 2.0% (1/51) vs. 2.0% (1/50) Implant level, C4-C5: 8.0% (4/51) vs. 10% (5/50) Implant level, C6-C6: 53% (27/51) vs. 52% (26/50) Implant level, C6-C7: 37% (19/51) vs. 36% (18/50)	24 mos.: 96.2% (101/105) Cross-overs: 0% (0/54) vs. 0% (0/51) Randomized but not treated: 0% (0/54) vs. 0% (0/51)	Neck pain via VAS, 0-10 (worst) Arm pain via VAS, 0-10 (worst) Neck Disability Index (NDI) score, 0-100 Neurological status Adverse events Reoperations Prosthesis migration Heterotopic ossification	None
Zhang 2012 RCT China	120	C-ADR (n = 60): Bryan cervical disc prosthesis (Medtronic Sofamor Danek)	Inclusion: Patients with symptomatic mild degenerative disc disease at 1 cervical level, including disc herniation with radiculopathy caused	C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated) Age: 44.77 ± 5.6 vs. 45.57 ± 5.83	24 mos.: 90.8% (109/120) Cross-overs: 0% (0/60) vs. 0% (0/60)	Neck Disability Index (NDI), 0-100 (worst) Neck pain via VAS, 0-100 (worst)	Chinese Medical Doctor Association

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
(NOTE: There is no patient overlap between Zhang 2012 and Zhang 2014 based on the dates of patient enrollment given in the studies.)		ACDF (n = 60): Fibular allograft; plating performed (device NR)	by foraminal osteophytes, soft disc herniation, or myelopathy, who had not responded to at least 6 weeks of conservative treatment. Exclusion: Patients with axial neck pain as a solitary symptom were not eligible for cervical spine arthroplasty. Other exclusion criteria include contraindications for TDR, including incompetent posterior elements, instability or severe facet arthrosis, insufficient cervical motion at the index level, bridging osteophytes, collapse of intervertebral disc space of more than 50% of normal height, and severe osteoporosis.	Female: 41.7% (25/60) vs. 46.7% (28/60) Implant level, C3-C4: 11.7% (7/60) vs. 6.7% (4/60) Implant level, C4-C5: 31.7% (19/60) vs. 33.3% (20/60) Implant level, C5-C6: 43.3% (26/60) vs. 41.6% (25/60) Implant level, C6-C7: 13.3% (8/60) vs. 18.3% (11/60)	Randomized but not treated: 6.7% (4/60) vs. 11.7% (7/60)	Arm pain via VAS, 0-100 (worst) Adverse events	
Zhang 2014 RCT China NOTE: There is no patient overlap	111	C-ADR (n = 55): Mobi-C (LDR Medical) ACDF (n = 56): Autologous graft (from iliac crest or clavicle) plus plate/cage (details	Inclusion: Age 18-68; diagnosis of degenerative cervical spondylosis of one segmental level that was supported by clinical symptoms and imaging data and with no significant improvement after conservative	C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated): Age: 44.8 vs. 46.7 Male: 45% (25/55) vs. 46% (26/56) BMI (kg/m ²): 25.3 vs. 26.5 Implant level, C3-C4: 18.1%	Unclear Cross-overs: 0% (0/55) vs. 0% (0/56) Randomized but not treated:	Japanese Orthopedic Association (JOA) Scores, 0-17 (best) VAS, 0-10 (worst)***** Neck Disability Index (NDI), 0-50 or 100	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
between Zhang 2012 and Zhang 2014 based on the dates of patient enrollment given in the studies.)		NR)	treatment for at least three months before surgery. Exclusion: Multisegmental-level cervical diseases, severe facet-joint degeneration, osteoporosis, cervical instability, spinal-canal stenosis, ossification of the posterior longitudinal ligament, tumor, infection or metal allergies.	(10/55) vs. 21.4% (12/56) Implant level, C4-C5: 30.9% (17/55) vs. 32.1% (18/56) Implant level, C5-C6: 29.1% (16/55) vs. 28.5% (16/56) Implant level, C6-C7: 21.8% (12/55) vs. 21.4% (12/56)	0% (0/55) vs. 0% (0/56)	(worst)§§§§§ Secondary surgery Heterotopic ossification Secondary surgery Adverse events	

ACDF: Anterior cervical discectomy and fusion; AIDS: Acquired immune deficiency syndrome; BMI: Body mass index; C-ADR: Cervical artificial disc replacement; DDD: Degenerative Disc Disease; DEXA: Dual-energy x-ray absorptiometry; F/U: Follow-up; HIV: Human immunodeficiency virus; HRQOL: Health-related Quality of Life; IDE: Investigational Device Exemption; NDI: Neck Disability Index; NRS: Numerical Rating Scale; RCT: Randomized controlled trial; SCDD: Symptomatic Cervical Disc Disease; SD: Standard deviation; SF-36 MCS/PCS: Short Form-36 Mental Component Summary/Physical Component Summary; VAS: Visual Analog Scale

- * Patients dropped out after randomization; denominators indicate the number of patients actually receiving treatment.
- † Overall success comprised the primary effectiveness and safety measures. To be considered an overall success, patients had to achieve all of the following: a ≥15-point improvement in their NDI scores, maintenance or improvement in their neurologic status, no serious adverse events related to the implant or implant/surgical procedure, and no subsequent surgery or intervention that is classified as “failure.”
- ‡ Neurologic success required maintenance or improvement of all 3 neurologic parameters (motor, sensory, and reflexes).
- § The NDI success criterion is based on the improvement in relation to the preoperative NDI score. A 15-point or greater NDI score improvement after surgery was required for the classification of a successful outcome.
- ** The composite neck pain score was derived by multiplying the intensity (0-10) and duration (0-10) scores. By this method, the composite score could range from 0 to 100.
- †† The neurological status of the patients was determined by measuring motor function, sensory function, and deep tendon reflexes. The neurological success for each of these three indicators was based on a postoperative maintenance or improvement in condition compared with the preoperative status. Overall neurological status success was based on the maintenance or improvement in all three indicators.

‡‡ Overall success for each patient is determined by four-component endpoints: NDI success, neurological success, device success, and absence of adverse events related to the implant or its implantation. The overall study success rate is defined as the percentage of individual patients achieving success in all four-component endpoints.

§§ Reoperation included any subsequent surgical procedure to the cervical spine, including posterior procedures such as a decompressive laminectomy or foraminotomy.

*** Neurologic success was defined as maintenance or improvement in each of the neurologic evaluations including sensory, motor, and reflex functions.

††† Patients were asked whether they would have the same surgical treatment again.

‡‡‡ The HRQOL endpoints consist of six-component endpoints to determine overall success for each patient: NDI success, patient satisfaction measured by willingness to have the same surgery again, absence of device failure, absence of pseudoarthrosis (fusion)/absence of fusion (ProDisc-C), visual analog scale (VAS) neck or arm pain improvement, and absence of strong narcotic or muscle relaxant use. The success rate is defined as the percentage of individual patients achieving success in all six-component endpoints.

§§§ Includes minimum 20% NDI improvement, no major complications, no neurological worsening, no secondary surgical procedures, and meeting radiographical criteria of motion for PCM and fusion for ACDF.

**** Success defined as 20 mm improvement over preoperative score.

†††† For all combined neurological symptoms, $p < 0.05$ between groups.

‡‡‡‡ Defined as the operative surgeon's overall assessment of outcome. Assessed only at 24 months F/U.

§§§§ Reported data from the Mobi-C SSED (Table 7); only demographics and baseline characteristics on primary analysis population were provided.

***** To be considered a success a patient had to be successful in each of the following three measures: 1) NDI success, a 30 point improvement in score if baseline NDI score was greater than or equal to 60, or a 50% of baseline score improvement in NDI score if baseline NDI scores were less than 60, 2) No device related subsequent surgical intervention at the index level (defined as removal, revision, supplemental fixation, or reoperation), and 3) No study defined major complications which were defined as radiographic failure, neurologic deterioration, and adverse events determined to be major complications by an independent Clinical Events Committee (CEC).

††††† Diminished neurological status was defined as a decrease in two points when compared to baseline in any of the treated level motor or reflex assessments or a decrease of one point when compared to baseline of the treated level sensory tests.

‡‡‡‡‡ An individual patient was considered a success if the protocol-specified criteria were met at 24 months: Pain/disability improvement of at least 25% in neck disability index (NDI) compared with baseline; no device failures requiring revision, removal, reoperation, or supplemental fixation; absence of major complications defined as major vessel injury, neurological damage, or nerve injury; and for patients who underwent ACDF only, radiographic fusion, as defined by the presence of bridging trabecular bone, without evidence of pseudoarthrosis (defined radiographically as no apparent bridging trabecular bone and range of motion >3 mm in translation and $>2^\circ$ in rotation). Additionally, the FDA requested additional criteria (FDA-defined) for overall success at 24 months: Pain/disability improvement of at least 15 points in NDI compared with baseline; no secondary surgery at the index level including revision, removal, reoperation, or supplemental fixation; no potentially device-

related adverse events; maintenance or improvement in all components of neurological status, and no SECURE-C intraoperative changes in treatment.

§§§§§ It is unclear if authors utilized 0-50 or 0-100% NDI scale.

***** It is unclear if VAS was evaluated for neck and/or arm pain.

Table H2. C-ADR vs. ACDF (1-level): Cohort studies

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Kim 2009 Prospective cohort study South Korea Note: 1-level only, 2-level data in relevant table	65	<p>C-ADR (n = 39): 1-level C-ADR with Bryan Cervical Disc Prosthesis (Medtronic Sofamor Danek)</p> <p>Fusion (n = 26): 1-level ACDF with autograft (details NR) and plate (ABC plate (Aesculap) or Atlantas plate (Medtronic) or cage (Blackstone (Blackstone Medical) or Solis (Stryker Spine))</p>	<p>Inclusion: Symptomatic 1- or 2-level cervical disc disease.</p> <p>Exclusion: NR</p>	<p>C-ADR vs. Fusion</p> <p><u>Mean (range)</u> (unless otherwise indicated): Age: 43.6 (24-74) vs. 47.4 (33-74) Male: 51.3% (21/39) vs. unclear (the study reported that there were 17 males and 19 females in the ACDF group, however there were only 26 patients in this group.) Clinical diagnosis, radiculopathy: 92.3% (36/39) vs. 84.6% (22/26) Clinical diagnosis, myelopathy: 7.7% (3/39) vs. 15.4% (4/26) Implant level, C3-C4: 7.7% (3/39) vs. 19.2% (5/26) Implant level, C4-C5: 10.3% (4/39) vs. 15.4% (4/26) Implant level, C5-C6: 61.5% (24/39) vs. 50.0% (13/26) Implant level, C6-C7:</p>	<p>Mean 18 (range 13-40) vs. 17 (range 12-36) mos.</p> <p>% f/u NR</p>	<p>VAS (0-10 (worst))</p> <p>Neck Disability Index (NDI) scale (0-50 or 100 (worst))*</p>	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				20.5% (8/39) vs. 15.4% (4/26)			
Hou 2014 Prospective cohort study China Note: 1-level only, 2-level data in relevant table	225	C-ADR (n = 117): 1-level C-ADR with Discover Fusion (n = 108): 1-level ACDF with autogenous bone and various anterior cervical plates or stand-alone cages (details NR)	Inclusion: Symptoms of radiculopathy and/or myelopathy, not responding to conservative treatment for greater than or equal to 6 weeks and objective evidence of cervical disc disease at one or two vertebral levels between C3–C7. Exclusion: Congenital or post-traumatic deformity, infection, tumor, metabolic bone disease, severe multilevel cervical disc degeneration, medical history of fusion procedure at any level (C1–C7), allergy to the metal alloy or polyethylene, and any serious general illness (e.g., heart failure, HIV) and a follow-up period less than 12 months. Patients with cervical instability (translation >3mm and/or >11° rotational difference to that or either adjacent level), facet joint	C-ADR vs. ACDF (1-level) <u>Mean (range):</u> Age: 45.6 (31-70) vs. 44.1 (30-74) Male (%): 56.4% (66/117) vs. 55.6% (60/108) Myelopathy: 27.4% (32/117) vs. 28.7% (31/108) Radiculopathy: 43.6% (51/117) vs. 36.1% (39/108) Myelopathy and radiculopathy: 29.1% (34/117) vs. 35.2% (38/108)	3 mos: 100% (225/225) 6 mos.: 100% (225/225) 12 mos.: 100% (225/225) 18 mos.: 95.5% (215/225) 24 mos.: 89.3% (201/225)	Neck Disability Index (NDI) score (0-100 (worst)) VAS (0-10 (worst))	“No funding was received for this study”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			degeneration, severe spondylosis (bridging osteophytes, disc height loss >50%, and absence of motion <2°), and osteoporosis/osteopenia were considered inappropriate for the artificial disc replacement.				
Radcliff 2015 Retrospective database study§ United States	6962	C-ADR (n = 327)**: 1-level C-ADR, device NR Fusion (n = 6635): 1-level ACDF, device NR	Inclusion: Aged 18-60, continuously enrolled and treated surgically with either C-ADR or ACDF between January 2008 and December 2009 for single-level degenerative disc disease, with at least 6 weeks of conservative care and without history of cervical surgery. Exclusion: NR	C-ADR vs. Fusion <u>Mean</u> (unless otherwise indicated): Age††: 45.46 vs. 46.91 Male: 53.85% vs. 44.97% Existing comorbidity‡‡: 23.08% (75/327) vs. 27.37% (1816/6635) % using BMP in procedure: 0.0% (0/327) vs. 2.79% (185/6635)	C-ADR vs. Fusion F/U time (mean): 26.01 vs. 25.67 mos. F/U % NR	Adverse events§§ Readmission Reoperations	Grant from Synthes
Staub 2016 Matching study Retrospective registry Switzerland	380	C-ADR (n = 190): 1-level C-ADR, device NR Fusion (n = 190): 1-level anterior cervical interbody fusion, device NR	Inclusion: Most severely affected segment between C3–C4 and C7–T1, inclusive; no previous surgical treatment of the spine; a baseline COMI; and at least one follow-up COMI completed between 3 months and 2 years postoperatively. Exclusion: Undergone posterior surgical	C-ADR vs. Fusion <u>Mean ± SD</u> (unless otherwise indicated): Age: 44.4 ± 7.5 vs. 44.2 ± 7.7 Female: 53.7% (102/190) vs. 55.3% (105/190) Degenerative disc: 24.7% (47/190) vs. 22.1% (42/190) Disc herniation: 92.6% (175/190) vs. 87.9%	C-ADR vs. Fusion: Follow-up time (mean ± SD): 16.8 ± 8.1 vs. 16.7 ± 7.8 mos. F/U % NR	Neck and Arm pain Neck and Arm pain relief Core Outcome Measures Index (COMI) score (0-10 (worst)) COMI score improvement	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			procedures or whose ASA status was marked as “unknown” in the surgery form. Age ≥60 years, follow-up time >2 years, treated segment C7–T1, diagnosis of spondylosis, trauma, facet joint degeneration, or spondylolisthesis.	(167/190) No previous treatment: 9.5% (18/190) vs. 9.0% (17/190) <6 mos. conservative treatment: 60.0% (114/190) vs. 60.5% (115/190) 6-12 mos. conservative treatment: 15.3% (29/190) vs. 15.8% (30/190) >12 mos. conservative treatment: 15.3% (29/190) vs. 14.7% (28/190) Implant level, C3-C4: 1.1% (2/190) vs. 2.6% (5/190) Implant level, C4-C5: 4.2% (8/190) vs. 5.8% (11/190) Implant level, C5-C6: 48.4% (92/190) vs. 49.5% (94/190) Implant level, C6-C7: 46.3% (99/190) vs. 42.1% (80/190)		MCIC responder	
Staub 2016 Atypical patients study Retrospective registry	248	C-ADR (n = 27): 1-level C-ADR, device NR Fusion (n = 221): 1-level anterior cervical interbody fusion, device NR	Inclusion: Most severely affected segment between C3–C4 and C7-T1, inclusive; no previous surgical treatment of the spine; a baseline COMI; and at least one follow-up COMI completed between 3 months and 2 years	C-ADR vs. Fusion <u>Mean ± SD</u> (unless otherwise indicated): Age: 53.8 ± 12.8 vs. 61.1 ± 11.5, p <0.05 Female: 33.3% vs. 48.4% Degenerative disc: 51.9% vs. 39.8%	C-ADR vs. Fusion Follow-up time (mean ± SD): 17.5 ± 7.5 vs. 14.2 ± 8.0	Neck and Arm pain Neck and Arm pain relief Core Outcome Measures Index (COMI) score (0-10 (worst))	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Switzerland			<p>postoperatively. Also included all (atypical) patients from the overall cohort that were not used in the matching study because they had one or more of the exclusion criteria*** defined in the matching patients study.</p> <p>Exclusion: Undergone posterior surgical procedures or whose ASA status was marked as “unknown” in the surgery form.</p>	<p>Disc herniation: 70.4% vs. 78.7%</p> <p>No previous treatment: 11.1% vs. 14.0%</p> <p><6 mos. conservative treatment: 33.3% vs. 40.7%</p> <p>6-12 mos. conservative treatment: 18.5% vs. 22.2%</p> <p>>12 mos. conservative treatment: 37.0% (10/27) vs. 23.1% (51/221)</p> <p>Implant level, C3-C4: NR vs. 1.0% (2/221), p < 0.05</p> <p>Implant level, C4-C5: 7.4% (2/27) vs. 11.8% (26/221), p < 0.05</p> <p>Implant level, C5-C6: 63.0% (17/27) vs. 33.5% (74/221), p < 0.05</p> <p>Implant level, C6-C7: 18.5% (5/27) vs. 24.4% (54/221), p < 0.05</p> <p>Implant level, C7-T1: 11.1% (3/27) vs. 20.4% (45/221), p < 0.05</p> <p>Excluded from matching study due to age ≥60 years: 40.7% (11/27) vs. 65.6% (145/221), p < 0.05</p> <p>Excluded from matching study due to spondylosis: 50.0% (14/27) vs. 41.9% (93/221)</p>	F/U % NR	COMI score improvement	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				Excluded from matching study due to facet joint arthritis: NR vs. 11.5% (25/221) Excluded from matching study due to trauma: 3.7% (1/27) vs. NR			
Staub 2016 Long-term study Retrospective registry Switzerland	149	C-ADR (n = 55): 1-level C-ADR, device NR Fusion (n = 95): 1-level anterior cervical interbody fusion, device NR	Inclusion: Most severely affected segment between C3–C4 and C7–T1, inclusive; no previous surgical treatment of the spine; a baseline COMI; and at least one follow-up COMI completed between 3 months and 2 years postoperatively. Patients had additional longer-term follow-up, defined as at least 2 years post-operation. Exclusion: Undergone posterior surgical procedures or whose ASA status was marked as “unknown” in the surgery form.	C-ADR vs. Fusion: <u>Mean ± SD</u> (unless otherwise indicated): Age 44.3 ± 8.7 vs. 50.6 ± 10.9, p < 0.05 Female: 50.9% (28/55) vs. 56.4% Degenerative disc: 38.2% (21/55) vs. 37.2% (35/94) Disc herniation: 80% (44/55) vs. 79.8% (75/94) No previous treatment: 5.5% (3/55) vs. 8.5% (8/94) <6 mos. conservative treatment: 50.9% (28/55) vs. 44.7% (42/94) 6-12 mos. conservative treatment: 18.2% (10/55) vs. 17.0% (16/94) >12 mos. conservative treatment: 25.5% vs. 29.8% Implant level, C3-C4: NR vs. 3.2% Implant level, C4-C5: 3.6% vs. 6.4%	Follow-up duration: ≥2 years (mean) F/U % NR	Neck pain (0-10 (worst)) Arm pain (0-10 (worst)) Neck and Arm pain relief Core Outcome Measures Index (COMI) score (0-10 (worst)) COMI score improvement	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
				Implant level, C5-C6: 56.4% vs. 44.7% Implant level, C6-C7: 40.0% vs. 41.5% Implant level, C7-T1: NR vs. 4.3%			

ACDF: Anterior cervical discectomy and fusion; ASA: American Society of Anesthesiologists; C-ADR: Cervical artificial disc replacement; COMI: Core Outcome Measures Index; CT: Computed tomography; F/U: Follow-up; MCIC: Minimum clinically important change; MRI: Magnetic resonance imaging; NDI: Neck disability index; NR: Not reported; SD: Standard deviation; VAS: Visual analog scale

* It is unclear what NDI scale was used in this study.

† The surgical database originates at a single, tertiary care military treatment facility.

‡ Regarding military branch, seven patients in the cervical arthroplasty group were Navy SEALs, another 2 were highly trained operators (1 Marine and 1 landing craft air cushion engineer), and the remaining 3 were high-ranking officers.

§ Blue Health Intelligence (BHI) national claims database, a national, prospectively collected database of 110 million patients enrolled in 18 of the BlueCross BlueShield Association plans across the United States, and it includes all inpatient, outpatient, and office-setting care reported by procedure and diagnosis codes.

** Authors speculate that based on the years of the study distribution, the majority of patients underwent ProDisc-C, Prestige, or Bryan disc arthroplasty.

†† There is a discrepancy between the ages reported in Table 2 and in the results. Have reported Table 2 ages.

‡‡ There is a discrepancy between Table 2 and results section reporting on incidence of comorbidities; have reported Table 2 incidences here. Comorbidities include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, neurologic, renal disease, any malignancy (except neoplasm of skin), moderate or severe liver disease, metastatic solid tumor, AIDS/HIV, myocardial infarction and/or congestive heart failure and/or peripheral vascular disease and/or cerebrovascular disease, metastatic solid tumor and/or any malignancy (except neoplasm of skin), diabetes without chronic complication and/or diabetes with chronic complication. Further details provided in Supplemental Digital Content Table 1.

§§ Adverse events (AEs) were determined by reviewing study population patients' claims for subsequent care, which contained the presence of specific International Classification of Diseases, Ninth Revision (ICD-9) diagnosis or procedure coding.

*** Exclusion criteria include age ≥60 years, follow-up time >2 years, treated segment C7–T1, diagnosis of spondylosis, trauma, facet joint degeneration, or spondylolisthesis.

C-ADR vs. ACDF (2-level)

Table H3. C-ADR vs. ACDF (2-level): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Mobi-C (2-level) IDE trial RCT United States	347	C-ADR (n = 232): Mobi-C (LDR) ACDF (n = 115): Cortico-cancellous allograft plus plate (Slim-Loc Anterior Cervical Plate System (DePuy Spine), Sofarmor Danek Atlantis (Medtronic), or Atlantis Vision Anterior Cervical Plate Systems (Medtronic Sofamor Danek))	Inclusion: Age 18-69 years; symptomatic cervical DDD at 2 contiguous levels between C3 and C7 with neck and/or arm pain, and/or decreased muscle strength, and/or abnormal sensation, and/or abnormal reflexes; diagnosis confirmed by imaging (CT, MRI, or radiography); NDI score ≥30; unresponsive to nonoperative, conservative treatment for at least 6 weeks or presence of progressive symptoms or signs of nerve root/spinal cord compression despite continued nonoperative treatment; no prior surgery at the operative level and no prior cervical fusion procedure at any level; physically and mentally able and willing to comply with the protocol; willingness	C-ADR vs. Fusion <u>Mean ± SD</u> (unless otherwise indicated)*: Age: 45.3 ± 8.1 vs. 46.2 ± 7.9 Female: 49.8% (112/225) vs. 57.1% (60/105) Ethnicity, Hispanic: 6.2% (14/225) vs. 6.7% (4/105) Ethnicity, non-Hispanic: 93.8% (211/225) vs. 93.3% (98/105) Race, American Indian: 1.3% (3/225) vs. 1.0% (1/105) Race, Caucasian: 94.2% (212/225) vs. 94.3% (99/105) Race, Asian: 1.8% (4/225) vs. 0% (0/105) Race, Black or African American: 2.2% (5/225) vs. 3.8% (4/105) Race, Native Other: 0.4% (1/225) vs. 1.0% (1/105) BMI (kg/m ²): 27.6 ± 4.5 vs. 28.1 ± 4.2 Pain medication: 92.4% (208/225) vs. 95.2% (100/105)	C-ADR vs. ACDF 24 mos.: 92.2% (320/347) 60 mos.: 85.6% (297/347) Cross-overs: 0% (0/232) vs. 0% (0/115) Randomized but not treated: 3.0% (7/232) vs. 8.7% (10/115)	Overall study success† SF-12 PCS, 0-100 (best) SF-12 MCS, 0-100 (best) Neck pain via VAS, 0-100 (worst) Arm pain (left and right) via VAS, 0-100 (worst) Neck Disability Index (NDI) score, 0-100 (worst) Neck Disability Index (NDI) Success‡ Subsequent surgical intervention§ Adverse events** Maintenance of improvement in neurological function	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>to discontinue all use of NSAIDs from 1 week before surgery until 3 months after surgery; signed informed consent.</p> <p>Exclusion: More than 2 vertebral levels requiring treatment/immobile level between C1 and C7 from any cause; any prior spine surgery at operative level or any prior cervical fusion at any level; disc height <3 mm; T score <-1.5 (osteoporosis evaluation); Paget disease, osteomalacia, or any metabolic bone disease other than osteoporosis; active malignancy—a history of any invasive malignancy (except nonmelanoma skin cancer), unless treated with curative intent and with no clinical signs or symptoms of the malignancy for >5 years; marked cervical instability on resting lateral or flexion</p>	<p>Opioid use, opium alkaloid: 12.0% (27/225) vs. 6.7% (7/105) Opioid use, semisynthetic opioid derivative: 52.9% (119/225) vs. 57.1% (60/105) Opioid use, synthetic opioid: 8% (18/225) vs. 17.1% (18/105) Physical therapy: 48.9% (110/225) vs. 46.7% (49/105) Collar: 12% (27/225) vs. 14.3% (15/105) Chiropractic: 27.1% (61/225) vs. 21.9% (23/105) Cervical traction: 20% (45/225) vs. 20% (21/105) Bed rest/immobilization: 48.9% (110/225) vs. 46.7% (49/105) Acupuncture: 8% (18/225) vs. 5.7% (6/105) Able to work: 62.7% (141/225) vs. 61% (64/105) Able to drive: 93.3% (210/225) vs. 97.1% (105/105) Receiving worker's compensation: 4.9% (11/225) vs. 6.7% (7/105) Levels treated (C3-4,C4-/C4-C, C5-6/</p>		<p>Adjacent segment degeneration</p> <p>Heterotopic ossification</p> <p>Psychological Outcomes</p> <p>Patient satisfaction</p>	

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			extension radiographs; known allergy to cobalt, chromium, molybdenum, or polyethylene; segmental angulation >11° at treatment or adjacent levels; any diseases or conditions that would preclude accurate clinical evaluation; daily, high-dose oral and/or inhaled steroids or a history of chronic use of high-dose steroids; BMI >40 kg/m ² ; use of any other investigational drug or medical device w/30 days prior to surgery; pending personal litigation relating to spinal injury (workers' compensation not included); smoking >1 pack of cigarettes/day; reported to have mental illness or belonged to a vulnerable population.	C5-6, C6-7) (%): 0.4%/26.7%/72.9% vs. 1.9%/21.9%/76.2%			
Cheng 2009 RCT China (NOTE: There	65	C-ADR (n = 31): Bryan Cervical Disc replacement (Medtronic Sofamor Danek) ACDF (n = 34):	Inclusion: Intractable cervical radiculopathy or myelopathy resulting from a disc herniation or stenosis at two adjacent levels from C3-4 to C6-7, and failure of	C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated): Age: 45 vs. 47 Men: 51.6% (16/31) vs. 50.0% (17/34)	24 mos.: 95.4% (62/65) Cross-overs: 0% (0/31) vs. 0% (0/34)	Arm pain score via VAS, 0-10 (worst) Neck pain score via VAS, 0-10 (worst) SF-36 PCS, 0-100	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
is likely to be patient overlap between Cheng 2009 (2-level) and Cheng 2011 (mixed number of levels) based on the dates of patient enrollment given in the studies.)		Iliac crest autograft plus plating (Orion Cervical Plate System (Medtronic Sofamor Danek))	conservative care for 12 weeks. Exclusion: Presence of significant anatomical deformity and previous cervical procedure and patients with severe osteoporosis or spinal infection.	Divorced: 6.3% (2/31) vs. 5.8% (2/34) Married: 93.7% (19/31) vs. 94.2% (32/34) Smokers: 19.7% (6/31) vs. 20.6% (7/34)	Randomized but not treated: 0% (0/31) vs. 0% (0/34)	(best) SF-36 MCS, 0-100 (best) Neck Disability Index (NDI) score, 0-100 (worst) Odom’s Criteria Adverse events	

ACDF: Anterior cervical discectomy and fusion; BMI: Body mass index; C-ADR: Cervical artificial disc replacement; CT: Computed Tomography; DDD: Degenerative Disc Disease; DEXA: Dual-energy x-ray absorptiometry; F/U: Follow-up; IDE: Investigational Device Exemption; MRI: Magnetic Resonance Imaging; NDI: Neck Disability Index; NSAIDs: Nonsteroidal anti-inflammatory drugs; RCT: Randomized controlled trial; SD: Standard deviation; SF-12/36 MCS/PCS: Short Form-12/36 Mental Component Summary/Physical Component Summary; VAS: Visual Analog Scale

* Patients dropped out after randomization; denominators indicate the number of patients actually receiving treatment.

† Overall study success was a composite measure of NDI success, no subsequent surgical intervention at the index level or levels, no adverse events assessed, maintenance or improvement in neurological function, and radiographic success.

‡ NDI success defined as improvement of ≥30 points for patients with baseline NDI of ≥60, or as an improvement of ≥50% from baseline with patients with baseline NDI <60.

§ Subsequent surgical interventions defined as any surgery falling into categories of removal, revision, supplemental fixation, or reoperation AND operation that occurred at the initial treatment level or at adjacent levels after the primary operation.

** Defined as any clinically adverse sign, symptom, syndrome, or illness that occurred or worsened during the operative and postoperative period, regardless of causality. All AEs were evaluated and classified by the clinical events committee, composed of two orthopedic surgeons and one neurosurgeon

Table H4. C-ADR vs. ACDF (2-level): Cohort studies

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Hou 2014 Prospective cohort study China Note: 2-level only, 1-level data in relevant table	120	C-ADR (n = 32): 2-level C-ADR with Discover Fusion (n = 88): 2-level ACDF with autogenous bone and various anterior cervical plates or stand-alone cages	Inclusion: Symptoms of radiculopathy and/or myelopathy, not responding to conservative treatment for greater than or equal to 6 weeks and objective evidence of cervical disc disease at one or two vertebral levels between C3–C7. Exclusion: Congenital or post-traumatic deformity, infection, tumor, metabolic bone disease, severe multilevel cervical disc degeneration, medical history of fusion procedure at any level (C1–C7), allergy to the metal alloy or polyethylene, and any serious general illness (e.g., heart failure, HIV) and a follow-up period less than 12 months. Patients with cervical instability (translation >3 mm and/or >11° rotational difference to that or either adjacent level), facet joint degeneration, severe	1- or 2-level C-ADR vs. 1- or 2-level ACDF <u>Mean (range):</u> Age: 45.8 (range: 30-70) Myelopathy: 25.5% (38/149) vs. 28.1% (55/196) Radiculopathy: 44.3% (66/149) vs. 39.3% (77/196) Myelopathy and radiculopathy: 30.2% (45/149) vs. 32.7% (64/196)	3 mos.: 100% (120/120) 6 mos.: 100% (120/120) 12 mos.: 100% (120/120) 18 mos.: 95.0% (114/120) 24 mos.: 92.5% (111/120)	Neck Disability Index (NDI) score (0-100 (worst)) VAS (0-10 (worst))	“No funding was received for this study”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			spondylosis (bridging osteophytes, disc height loss >50%, and absence of motion <2°), and osteoporosis/osteopenia were considered inappropriate for the artificial disc replacement.				
Kim 2009 Prospective cohort study South Korea Note: 2-level only, 1-level demographics in relevant table	40	C-ADR (n = 12): 2-level ADR with Bryan Cervical Disc Prosthesis (Medtronic Sofamor Danek) Fusion (n = 28): 2-level ACDF with autogenous bone graft	Inclusion: NR Exclusion: NR	C-ADR vs. Fusion <u>Mean (range)</u> (unless otherwise indicated): Age: 46.91 (30-58) vs. 52.7 (30-78) Female: 33.3% (4/12) vs. 39.3% (11/28) Clinical diagnosis, radiculopathy: 83.3% (10/12) vs. 85.7% (24/28) Clinical diagnosis, myelopathy: 16.7% (2/12) vs. 14.3% (4/28) Implant level, C4-C5-C6: 33.3% (4/12) vs. 46.4% (13/28) Implant level, C5-C6-C7: 66.6% (8/12) vs. 53.6% (15/28)	1- or 2-level C-ADR vs. 1- or 2-level Fusion F/U time (mos.): 19 (range 12-38) vs. 20 (range: 12/40) FU % NR	VAS (0-10 (worst)) Neck Disability Index (NDI) scale (0-50 or 0-100 (worst))*	NR

ACDF: Anterior cervical discectomy and fusion; C-ADR: Cervical artificial disc replacement; CT: Computed tomography; F/U: Follow-up; HIV: Human immunodeficiency virus; NDI: Neck disability index; NR: Not reported; SD: Standard deviation; TDR: Total disc replacement; VAS: Visual analog scale

* It is unclear what scale was used in this study.

C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3-level))

Table H5. C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3-level)): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Skeppholm 2015 RCT Sweden	153	<p>C-ADR (n = 83): 1- or 2-level C-ADR with Discover artificial disc (DePuy Spine)</p> <p>ACDF (n = 70): 1- or 2-level ACDF with autologous tricortical bone graft from iliac crest; details NR for plate type.</p>	<p>Inclusion: Age 25-60; symptoms of radiating arm pain with a duration of at least 3 mos.; correlating findings on MRI on one or two cervical levels; eligible for both treatments; ability to understand and read Swedish language.</p> <p>Exclusion: Previous cervical spine surgery; more than two cervical levels requiring treatment; visible or severe arthrosis in facet joints evaluated preoperatively on plain x-rays and MRI; marked radiologic signs or symptoms of myelopathy; drug abuse, dementia, or other reason to suspect poor adherence to follow-up; cervical malformation or marked cervical instability; history of whiplash-associated disorder or severe</p>	<p>C-ADR vs. ACDF</p> <p><u>Mean ± SD</u> (unless otherwise indicated)*:</p> <p>Age: 46.7 ± 6.7 vs. 47.0 ± 6.9</p> <p>Women: 50.6% (41/81) vs. 52.9% (37/70)</p> <p>Smoker: 31% (25/81) vs. 31% (21/70)</p> <p>Unemployed: 10% (8/81) vs. 14% (10/70)</p> <p>BMI (kg/m²): 26 vs. 26</p> <p>On full-time sick leave: 38% (31/81) vs. 36% (25/70)</p> <p>On part-time sick leave: 20% (16/81) vs. 17% (12/70)</p> <p>On sick leave for other reason: 7% (6/81) vs. 4% (3/70)</p> <p>Not on sick leave: 35% (28/81) vs. 43% (30/70)</p> <p>Takes analgesics regularly: 42% (34/81) vs. 51% (36/70)</p> <p>Takes analgesics irregularly: 42% (34/81) vs. 36% (25/70)</p> <p>Does not take analgesics: 16% (13/81) vs. 13% (9/70)</p>	<p>24 mos.: 89.5% (137/153)</p> <p>Cross-overs: 0% (0/83) vs. 0% (0/70)</p> <p>Randomized but not treated: 2.4% (2/83) vs. 0% (0/70)</p>	<p>Neck Disability Index (NDI), 0-100 (worst)</p> <p>EQ-5D, -0.59-1 (best)</p> <p>Arm pain VAS, 0-100 (worst)</p> <p>Neck pain VAS, 0-100 (worst)</p> <p>Dysphagia</p> <p>Psychological Outcomes</p> <p>Depression and anxiety via the Hospital Anxiety and Depression (HAD) scale, 0-21 (worst)</p>	DePuy Spine

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			cervical trauma; pregnancy; rheumatoid arthritis, known malignancy, active infection, or other systemic disease; known allergy or hypersensitivity to any of the constituent materials of the implants or to nonsteroidal anti-inflammatory drugs.	Neck pain duration, <3 mos.: 3% (2/81) vs. 1% (1/70) Neck pain duration, 3-12 mos.: 26% (21/81) vs. 34% (24/70) Neck pain duration, 24-48 mos.: 38% (31/81) vs. 27% (19/70) Neck pain duration >24 mos.: 32% (26/81) vs. 34% (24/70)			
Cheng 2011 RCT China (NOTE: There is likely to be patient overlap between Cheng 2009 (2-level) and Cheng 2011 (mixed number of levels) based on the dates of patient enrollment given in the studies.)	83	C-ADR (n = 41)†: 1-, 2- or 3-level Bryan Cervical Disc replacement (Medtronic Sofamor Danek) ACDF (n = 42)‡: 1-, 2-, or 3-level Orion cervical plate system (Medtronic Sofamor Danek)	Inclusion: Intractable cervical myelopathy attributable to disc herniation or stenosis at one, two, or three levels from C3–C4 to C6–C7 and failed nonoperative management for 12 weeks. Patients requiring immediate treatment were not required to meet the inclusion criteria. Immediate treatment was provided if the patients had (1) significant clinical symptoms and unbearable pain, (2) a definite sign of cervical disc prolapse discovered by radiographic examination, and (3) progressive neural	All levels, C-ADR vs. ACDF <u>Mean ± SD</u> (unless otherwise indicated): 47.2 ± 5.7 vs. 47.7 ± 5.8 Female: 48.8% (20/41) vs. 45.2% (19/42) Smokers: 14.6% (6/41) vs. 17.6% (8/42)	24 mos.: 98% (81/83) Cross-overs: 0% (0/41) vs. 0% (0/42) Randomized but not treated: 0% (0/41) vs. 0% (0/42)	Odom’s Criteria SF-36 PCS, 0-100 (best) Japanese Orthopedic Association (JOA) scale, 0-17 (best) Neck Disability Index (NDI) score (Chinese version), 0-100 (worst) Return to work Adverse events Heterotopic ossification	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			<p>damage.</p> <p>Exclusion: Significant anatomic deformity (e.g., ankylosing spondylitis); received a previous cervical procedure; had a spinal infection; or had severe osteoporosis, cervical kyphosis, ankylosing spondylitis, ossification of the posterior longitudinal ligament of the spine, or severe spondylosis (defined as bridging osteophytes) based on preoperative radiographs. Patients also were excluded if they had substantial facet disease or showed no preserved motion on preoperative flexion-extension radiographs.</p>				
<p>Rohl 2009 RCT Germany</p>	24 treated	<p>C-ADR (n = 12 treated)§: Prodisc C (Clinical House)</p> <p>ACDF (n = 12 treated)§: Ventral microscopic decompression</p>	<p>Inclusion: Paraplegia with paralysis level of ASIA A with discopathy and clinical symptoms.</p> <p>Exclusion:</p>	<p>Entire group (C-ADR and ACDF)</p> <p><u>Mean ± SD</u> (unless otherwise indicated): Age: 45.65 (range: 28.4-53.7) Female: 50% (12/24) Level of paralysis, C5**: 25% (6/24)</p>	<p>Unclear</p> <p>(Note: number of patients randomized not clearly stated)</p>	<p>Neck Disability Index (NDI), 0-100 (worst)</p> <p>Spinal Cord Independence Measure (SCIM) III, 0-100 (best)</p> <p>SF-36 MCS, 0-100 (best)</p>	NR

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		and fusion with plate or cage, device NR		Level of paralysis, C6**: 50% (12/24) Level of paralysis, C7**: 50% (12/24)			

ACDF: Anterior cervical discectomy and fusion; BMI: Body mass index; C-ADR: Cervical artificial disc replacement; EQ-5D: EuroQol-5D; F/U: Follow-up; HAD: Hospital Anxiety and Depression; IDE: Investigational Device Exemption; JOA: Japanese Orthopedic Association; MRI: Magnetic Resonance Imaging; NDI: Neck Disability Index; RCT: Randomized controlled trial; SCIM: Spinal Cord Independence Measure; SD: Standard deviation; SF-36 MCS/PCS: Short Form-36 Mental Component Summary/Physical Component Summary; VAS: Visual Analog Scale

* Patients dropped out after randomization; denominators indicate the number of patients actually receiving treatment.

† 1-level C-ADR (n = 24); 2-level C-ADR (n = 14); 3-level C-ADR (n = 3)

‡ 1-level ACDF (n = 21); 2-level ACDF (n = 17); 3-level ACDF (n = 4)

§ It was not indicated if the 24 patients in this study were randomized in a 1:1 ratio. These values are assumed.

** Data is as reported by authors; it is unclear why these values add up to >100%.

Table H6. C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3-level)): Cohort studies

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Cappelletto 2013 Retro-spective cohort study Italy	176	<p>C-ADR (n = 84): 1- or 2-level C-ADR with Bryan prosthesis (Medtronic Sofamor Danek) (n=31) or Discover prosthesis (DePuy Spine, Inc.) (n=53)</p> <p>Fusion (n = 92): 1-, 2-, or 3-level fusion with heterologous bone graft with Unilab Surgibone (Unilab Surgibone, Inc.) and Atlantis plate (Medtronic Sofamor Danek) (n = 28) or interbody fusion cages (n = 28).</p>	<p>Inclusion: Patients who underwent microdiscectomy by the anterior approach for cervico- brachial pain or myelopathy due to cervical herniated disc or spondylosis.</p> <p>Exclusion: NR</p>	<p>C-ADR vs. Fusion</p> <p><u>Mean (range)</u> unless otherwise noted: Age: 42 (25-60) vs. 51 (26-79), p < 0.05 Female: 50% (42/84) vs. 44.6% (41/92) Implant level, C6-C7: 50% (42/84) Implant level. C5-C6: 45.2% (38/84) vs. 43.9% (50/114) Implant level not specified: 4.8% (4/84) vs. 30.7% (35/114) Radiculopathy^{††}: 84.5% (71/84) vs. 55.4% (51/92) Myelopathy^{††}: 5.9% (5/84) vs. 34.8% (32/92) Radiculopathy and myelopathy^{††}: 5.9% (5/84) vs. 7.6% (7/92), p < 0.05 Retired or disabled: 0% (0/84) vs. 19.6% (18/92) Smoking frequency: NR, p NS Current smoker: NR, p NS</p>	12 mos.: % NR	<p>VAS (0-10 (worst))</p> <p>Return to work</p> <p>Neck Disability Index (NDI) score (0-100 or 0-50 (worst))*</p> <p>Neurologic success^{‡‡}</p> <p>Complications</p> <p>Reoperations</p>	NR
Nandyala 2013 Retro-	141,230 cases	<p>C-ADR (n = 1830): 1- or 2-level C-ADR</p> <p>Fusion (n =</p>	<p>Inclusion: Patients who underwent elective one- to two-level (ICD-9 81.62) cervical TDR (84.62) or a one- to two-level ACDF</p>	<p>C-ADR vs. Fusion</p> <p><u>Mean</u> (unless otherwise indicated): Age: 46.4 vs. 51.1, p < 0.05</p>	NR	<p>Complications</p> <p>Mortality</p>	“No funds were received in support of this work”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
pective database analysis (Nationwide Inpatient Sample (NIS database))§§ United States		141,230): 1- or 2-level ACDF	(81.02). Exclusion: Patients younger than 18 years were excluded from the study.	Female: 51.6% (944/1830) vs. 51.9% (73298/141230) Race, Caucasian: 82.2% (1504/1830) vs. 82.5% (116515/141230) Race, African American: 6.4% (117/1830) vs. 8.5% (12005/141230) Race, Hispanic: 5.1% (93/1830) vs. 5.0% (7062/141230) Race, Asian/Pacific Islander: 1.6% (29/1830) vs. 1.2% (1695/141230) Race, Other: 4.6% (84/1830) vs. 2.8% (3954/141230) (p<0.05 between groups for all races) Procedure at a teaching hospital: 45.9% (840/1830) vs. 51.5% (72733/141230), p < 0.05			
Peng 2011 Retro-spective*** cohort study Singapore	115	C-ADR (n = 40) : 1-, 2-, or 3-level ADR with Prestige LP ADR (Medtronic Sofamor Danek) Fusion (n = 75) : Details NR	Inclusion: Patients with radiculopathy and primary symptom of upper limb pain (rather than neck pain). Exclusion: History of trauma, infection, or radiographic evidence of instability. Coexisting	C-ADR vs. Fusion <u>Mean (range)</u> (unless otherwise indicated): Age: 43.9 (16-59) vs. 54.9 (28-77) Female: 52.5% (21/40) vs. 38.6% (29/75) 1-level operation: 62.5% (25/40) vs. 38.7% (29/75)	Mean f/u (years): 2.9 (range: 2.0-3.5) % F/U NR	Japanese Orthopedic Association (JOA) score (0-17 (best)) Modified American Academy of Orthopedic Surgeons (AAOS) score for neck disability (0-6 (worst))	“No funds were received in support of this work.”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
			illnesses such as rheumatoid arthritis, renal failure, osteoporosis, and cancer as well as the use of preoperative corticosteroid medication were considered further exclusion criteria. Patients with no motion at disc space of the operative level were not eligible for ADR.	2-level operation: 27.5% (11/75) vs. 48% (36/75) 3-level operation: 10% (4/40) vs. 13.3% (10/75) Implant level, C3-C4: 5% (3/59 levels) vs. 7.6% (10/131 levels) Implant level, C4-C5: 23.7% (14/59 levels) vs. 27.5% (36/131 levels) Implant level, C5-C6: 56% (33/59 levels) vs. 45% (59/131 levels) Implant level, C6-C7: 15.3% (9/59 levels) vs. 19.8% (26/131 levels) Neural compression from herniated disc: 50% (20/40) vs. 21.3% (16/75) Neural compression from spondylosis: 45% (18/40) vs. 70.7% (53/75) Neural compression due to herniated disc and spondylosis: 5% (2/40) vs. 8% (6/75)		Modified American Academy of Orthopedic Surgeons (AAOS) score for neurogenic symptoms (0-6 (worst)) VAS for neck pain (0-10 (worst)) VAS for leg pain (0-10 (worst)) Neck Disability Index (NDI) score (0-100 (worst))* SF-36 (0-100 (worst))	
Grob 2010 Registry Switzerland	342	C-ADR (n = 73): Prestige II (Medtronic Sofamor Danek), Discover (DePuy), Bryan Cervical Disc (Medtronic),	Inclusion: Patients in Spine Society of Europe Spine Tango Registry who underwent fusion/stabilization or disc arthroplasty for degenerative cervical	<u>Mean ± SD</u> (unless otherwise indicated): Age: 45.8 ± 7.9 vs. 56.1 ± 10.8, p < 0.05 Male: 46.6% (34/73) vs. 50.6% (136/269) 1 affected segment: 68.5%	12 mos.: 77.8% (266/341) 24 mos.: 49.6% (169/341)	Core Outcome Measures Index (COMI) (0-10 (worst))§ Global outcome of surgery (0-5 (worst))	“The study was supported by the Schulthess Klinik Research Fund.”

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
		or Prodisc-C (Medtronic) Fusion (n = 269): Fusion with autologous bone, allogenic bone, combination of both, other material, or no fusion material; anterior stabilization; interbody cage, plates, or combination of both	spinal disease. Fluent in either German or English. Exclusion: Undergone both fusion/stabilization and disc arthroplasty at different levels.	(50/73) vs. 46.5% (125/269) 2-3 affected segments: 32.5% (24/73) vs. 53.5% (142/265) 1 degenerative pathology‡: 68.5% (50/73) vs, 45.7% (123/269) 2 degenerative pathologies‡: 26% (19/73) vs. 33.1% (89/269) >2 degenerative pathologies‡: 5.5% (4/73) vs. 21.2% (57/269) Previous surgery at same level: 4.1% (3/73) vs. 7.4% (20/269)		Satisfaction with treatment (0-5 (worst)) Reoperation Patient-rated complications Spine Tango Surgery form** Morbidity status	

AAOS: American Academy of Orthopedic Surgeons; ACDF: Anterior cervical discectomy and fusion; ADR: Artificial disc replacement; C-ADR: Cervical artificial disc replacement; COMI: Core Outcome Measures Index; CT: Computed tomography; F/U: Follow-up; ICD: International Classification of Diseases; JOA: Japanese Orthopedic Association; NDI: Neck disability index; NR: Not reported; SD: Standard deviation; VAS: Visual analog scale

* Unclear if authors used 0-100 or 0-50 NDI scale.

‡ p < 0.05 between groups for all pathologies.

§ The COMI is a multidimensional index consisting of validated questions covering the domains of pain (neck and arm pain intensity, each measured separately on a 0–10 graphic rating scale), function, symptom-specific well-being, general quality of life, and social and work disability.

**The Spine Tango Surgery form is used to document information regarding the medical history [main pathology, with further indication of the specific type of pathology(ies)], number of affected levels, previous surgery, operation duration (ten categories, from <1 h to >10 h), blood loss (five categories: none, <500, 500–1,000, 1,000– 2,000, >2,000 ml), comorbidity [assessed with the American Society of Anesthesiologists Physical Status Score (ASA Score), from 1 (no disturbance) to 5 (moribund)], surgical details, surgical complications and general complications.

†† Data reported as-is from paper; it is unclear why these values do not add up to 100%.

‡‡ Authors do not clearly describe this outcome, but it appears to involve improvement of pain/resolution of radicular and myelopathy signs.

§§ (NIS) database, which compiles information from more than 1000 hospitals in 45 states, approximating a 20% stratified sample of all hospitals discharges.

*** ACDF pts assessed retrospectively, so study is retrospective rather than prospective as stated in the abstract.

C-ADR vs. ACDF with a zero-profile device (2 noncontiguous levels)

Table H7. C-ADR vs. ACDF with a zero-profile device (2 noncontiguous levels): RCTs

Study Design Country	N	Interventions	Inclusion, Exclusion Criteria	Demographics	F/U, %	Outcomes	Funding
Qizhi 2016 RCT China	30	C-ADR (n = 14): Discover (DePuy) Arthrodesis (n = 16): Zero-P (Synthes)	Inclusion: Patients with 2 noncontiguous levels of cervical spondylosis; the intermediate segment was only 1, that was the degenerative diseases were C3/C4 and C5/C6 or C4/C5 and C6/C7; patients had not responded to conservative treatment for at least 6 weeks. Exclusion criteria: Contiguous multilevel or single-level cervical spondylosis, development of stenosis, ossification of the posterior longitudinal ligament or yellow ligament; previous history of cervical spine surgery; instability of the cervical spine; big osteophyma behind the vertebral body; osteoporosis; infection; tumor; focal or global kyphosis, age >55 years.	C-ADR vs. Arthrodesis <u>Mean ± SD</u> (unless otherwise indicated): Age: 46.79 ± 5.15 vs. 48.13 ± 5.98 Women: 35.7% (5/14) vs. 31.2% (5/16) Implant level, C3/C4 and C5/C6: 57.1% (8/14) vs. 56.2% (9/16) Implant level, C4/C5 and C6/C7: 42.8% (6/14) vs. 43.8% (7/16)	Unclear	Neurological status via Japanese Orthopedic Association (JOA) score, 0-17 (best) Neck function via Neck Disability Index (NDI), 0-50 (worst) Instrument subsidence Heterotopic ossification Adverse events Dysphagia via modified Swallowing of Life (SWAL-QOL) score, 0-100 (best)	NR

C-ADR: Cervical artificial disc replacement; NR: not reported; SD: Standard deviation

APPENDIX I. L-ADR EFFICACY AND EFFECTIVENESS RESULTS.

L-ADR vs. ACDF (1-level)

Table I1. L-ADR vs. Fusion (1-level) RCT data: Overall Success

Analysis	Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
Overall success (ODI ≥15 points)†						
<i>ITT analysis</i>	Charite IDE trial (FDA SSED 2004)	24 mos	52.2% (107/205)	44.4% (44/99)	NR	NR
<i>Completers only</i>	Charite IDE trial (FDA SSED 2004)	24 mos	58.2% (107/184)	54.3% (44/81)	NR	NR
<i>ITT analysis</i>	ProDisc-L IDE trial (Zigler 2007, FDA SSED 2006)	24 mos	43.2% (79/183)	31.2% (29/93)	NR	NR
<i>Completers only</i>	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	53.4% (79/148)	40.8% (29/71)	NR	NR
<i>ITT analysis</i>	Charite IDE trial (Guyer 2009)	60 mos	25.4% (52/205)	22.2% (22/99)	NR	NR
<i>Completer only</i>	Charite IDE trial (Guyer 2009)	60 mos.	57.8% (52/90)	51.2% (22/43)	NR	NR
<i>ITT analysis (excluding early device failure)</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos	39.8% (64/183)‡	28.0% (21/93)‡	NR	NR
<i>Completers only (excluding early device failure)</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	48.1% (64/134)‡	41.1% (21/52)‡	NR	NR
<i>Completer only (including early device failures)</i>	Charite IDE trial (Guyer 2009)	60 mos.	54% (NR)	50% (NR)	NR	NR
Overall success (ODI ≥25%)†						
<i>ITT analysis</i>	Charite IDE trial (Blumenthal 2005, FDA SSED 2004)	24 mos.	57.1% (117/205)	46.5% (46/99)	NR	NR
<i>Completer only</i>	Charite IDE trial (Blumenthal 2005, FDA SSED 2004)	24 mos.	63.6% (117/184)	56.8% (46/81)	NR	<0.0001 0.0004
Overall success (ODI ≥15%)†						
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results, FDA SSED 2006)	24 mos.	63.5% (94/148)	45.1% (32/71)	NR	0.005
<i>ITT analysis LOCF</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	51.8% (84/162)	42.5% (34/80)	NR	0.744
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	53.7% (72/134)§	50.0% (26/52)§	NR	NS

CI: confidence interval; F/U: follow-up; ITT: intention-to-treat; L-ADR: lumbar artificial disc replacement; LOCF: last observation carried forward; NR: not reported; NS: not significant; ODI: Oswestry Disability Index; RD: risk difference.

*As calculated by the study.

†Overall success was defined as having met all the following criteria:

- Charite IDE trial: 1) ≥15-point (FDA criteria) or ≥25% (Protocol criteria) improvement from baseline in ODI score; 2) no device failure (i.e., requiring revision, reoperation, or removal); 3) no major complication (i.e., major vessel injury, neurological damage, nerve root injury, and death), and 4) no neurological change (i.e. defined as lack of neurological deterioration compared with preoperative status, at any point of time).

- ProDisc-L IDE trial: 1) ≥ 15 -point (FDA criteria) or $\geq 15\%$ (Protocol criteria) improvement from baseline in ODI score; 2) no secondary surgical intervention at index level (ADR = no reoperation to remove or modify TDR implant; fusion = no reoperation to modify fusion site or correction complication with an implant); 3) improvement in SF-36 score (i.e., follow-up score – baseline score > 0); 4) neurological status improved or maintained (motor, sensory, reflex, straight leg raise); and 4) radiographic success (i.e., device migration, device subsidence, and loss of disc height ≤ 3 mm for both groups and for ADR only, no radiolucency along implant-bone interface $> 25\%$ of interface's length for each endplate, $\geq 6^\circ$ flexion-extension ROM at L3-4 or L4-5 or $\geq 5^\circ$ at L5-S1 (Protocol criteria) or maintenance or improvement of ROM (FDA criteria, defined as follow-up flexion-extension ROM – preoperative flexion-extension ROM ≥ 0), and no evidence of bony fusion, and for fusion only, no halos or radiolucencies around implant, < 3 mm translation and $< 5^\circ$ angulation for ROM, and strong evidence of fusion, including 50% trabecular bridging bone or bone mass maturation and increased or maintained bone density at site with no visible gaps in fusion mass).

‡For overall success, a ≥ 15 points improvement from baseline in ODI was requested by the FDA and not a planned analysis; thus the authors performed additional analyses (see Alternative Analyses section of Zigler 2012). We used the N's provided for protocol-defined overall success (ODI improvement $\geq 15\%$) and back-calculated the numerators.

§Numerators back-calculated based on percentage and total N provided.

Table I2. L-ADR vs. Fusion (1-level) RCT data: ODI, Neurological, and SF-36 Success

Analysis	Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
ODI success (i.e., ≥15 point improvement)						
<i>ITT</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	57.1% (117/205)	47.5% (47/99)	NR	NR
<i>Completers only</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	63.6% (117/184)	58.0% (47/81)	NR	0.844
<i>ITT</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	62.7% (101/183)	52.0% (39/93)	NR	NR
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	67.8% (101/149)†	54.9% (39/71)†	NR	0.045
<i>ITT</i>	Charite IDE trial (Guyer 2009)	60 mos.	29.8% (61/205)	28.3% (28/99)	NR	NR
<i>Completers only</i>	Charite IDE trial (Guyer 2009)	60 mos.	68% (61/90)	65% (28/43)	NR	0.844
<i>ITT</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	58.4% (94/183)‡	42.7% (32/93)‡	NR	NR
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	74.6% (94/126)‡	62.8% (32/51)‡	NR	0.143
ODI success (i.e., ≥25% improvement)						
<i>ITT analysis</i>	Charite IDE trial (Blumenthal 2005)	24 mos.	63.9% (131/205)	50.5% (50/99)	NR	0.004
<i>Completers only</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	70.7% (130/184)	61.7% (50/81)	NR	NR
ODI Success (i.e., ≥15% improvement)						
<i>Completer only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results, FDA SSED 2006)	24 mos.	77.2% (115/149)	64.8% (46/71)	NR	<0.05
<i>Completer only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	78.6% (99/126)‡	76.5% (39/51)‡	NR	0.842
Neurological success (i.e., status improved or unchanged [motor, sensory, reflex, straight-leg raise])						
<i>ITT</i>	Charite IDE trial (Blumenthal 2005)	24 mos.	82.4% (169/205)	78.8% (78/99)	NR	0.438
<i>Completers only</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	90.8% (167/184)	95.1% (77/81)	NR	NR
<i>ITT</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	73.8% (135/183)	61.3% (57/93)	NR	NR
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results, FDA SSED 2006)	24 mos.	91.2% (135/148)	81.4% (57/70)	NR	0.034
<i>ITT</i>	Charite IDE trial (Guyer 2009)	60 mos.	37.6% (77/205)	36.4% (36/99)	NR	NR
<i>Completers only</i>	Charite IDE trial (Guyer 2009)	60 mos.	86% (77/90)	84% (36/43)	NR	0.799
<i>ITT</i>	ProDisc-L IDE trial (Zigler 2012)	60 mos.	60.7% (111/183)	46.2% (43/93)	NR	NR
<i>Completers only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	88.8% (111/125)	89.6% (43/48)	NR	1.0

Analysis	Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
SF-36 PCS success (i.e., maintained or improved)						
<i>Completer only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results, FDA SSED 2006)	24 mos.	79.2% (118/149)	70.0% (49/70)	NR	0.094
<i>Completer only</i>	ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	81.3% (102/126)§	74.0% (38/51)§	NR	0.305
SF-36 PCS (i.e., ≥15% improvement)						
<i>Completer only</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	72% (132/184)	63% (51/81)	NR	NR
SF-36 MCS (i.e., ≥15% improvement)						
<i>Completer only</i>	Charite IDE trial (FDA SSED 2004)	24 mos.	50% (92/184)	51% (41/81)	NR	NR

CI: confidence interval; F/U: follow-up; ITT: intention-to-treat; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; ODI: Oswestry Disability Index; RD: risk difference; SF-36 MCS: Short-Form 36 questionnaire Mental Component Score; SF-36 PCS: Short-Form 36 questionnaire Physical Component Score.

*As calculated by the study.

†n/N from ProDisc FDA SSED; percentages reported were identical to those reported in Zigler 2012.

‡Numerators back-calculated based on percentages provided in text and total N at 60 months for ODI scores in Table 4 of article.

§Numerators back-calculated based on percentages provided in text and total N at 60 months for SF-36 PCS scores in Table 5 of article.

Table 13. L-ADR vs. Fusion (1-level) RCT data: Patient satisfaction, work status, and narcotic use
Completer analysis only

Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
Patient satisfaction: satisfied					
Charite IDE trial (Blumenthal 2005)	24 mos.	73.7% (119/161)	53.1% (35/66)	NR	0.001
Patient satisfaction: yes, would have same surgery again					
Charite IDE trial (Blumenthal 2005)	24 mos.	69.9% (113/161)	50% (33/66)	NR	0.006
ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	82.5% (113/137)	68.0% (38/56)	NR	0.163
Work status: working full- or part-time					
Charite IDE trial (Blumenthal 2005)	0 mos.	53.2% (109/205)	57.6% (57/99)	NR	0.470
ProDisc-L IDE trial (Zigler 2007)	0 mos.	83.5% (134/161)†	78.1% (59/75)†	NR	NS
Charite IDE trial (Blumenthal 2005)	24 mos.	62.4% (116/186)	65.0% (52/80)	NR	0.633
ProDisc-L IDE trial (Zigler 2007)	24 mos.	92.4% (147/159)	85.1% (62/73)	NR	0.049
Charite IDE trial (Guyer 2009)‡	60 mos.	72.2% (65/90)	58.1% (25/43)	NR	NR
Work status: working full-time					
Charite IDE trial (Blumenthal 2005)	0 mos.	44.9% (92/205)	49.5% (49/99)	NR	NR

Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
Charite IDE trial (Blumenthal 2005)	24 mos.	55.9% (104/186)	52.5% (42/80)	NR	NR
Charite IDE trial (Guyer 2009)‡	60 mos.	65.6% (59/90)†	46.5% (20/43)†	NR	0.040
Work status: working part-time					
Charite IDE trial (Blumenthal 2005)	0 mos.	8.3% (17/205)	8.1% (8/99)	NR	NR
Charite IDE trial (Blumenthal 2005)	24 mos.	6.5% (12/186)	12.5% (10/80)	NR	NR
Charite IDE trial (Guyer 2009)‡	60 mos.	7% (6/90)§	12% (5/43)§	NR	NS
Recreational activity status: participating					
ProDisc-L IDE trial (Zigler 2012 Five- year results)	0 mos.	42.2% (68/161)†	49.3% (37/75)†	NR	NS
ProDisc-L IDE trial (Zigler 2012 Five- year results)	24 mos.	88.4% (130/147)†	78.3% (54/69)†	NR	0.064
ProDisc-L IDE trial (Zigler 2012 Five- year results)	60 mos.	82.4% (103/125)†	90.0% (45/50)†	NR	0.253
Narcotic use					
ProDisc-L IDE trial (Zigler 2012 Five- year results)	0 mos.	84% (135/161)†	76% (57/75)†	NR	NR
Charite IDE trial (Blumenthal 2005)	24 mos.	72.2% (148/184)	85.9% (85/81)	NR	0.008
ProDisc-L IDE trial (Zigler 2012 Five- year results)	24 mos.	44.6% (66/148)†	42.5% (30/70)†	NR	NR
ProDisc-L IDE trial (Zigler 2012 Five- year results)	60 mos.	38.4% (48/125)†	40.0% (20/50)†	NR	NR
Study	F/U	ADR Mean ± SD	Fusion Mean ± SD	MD (95% CI)*	p-value*
Patient satisfaction (VAS, 0-100 mm [best])					
ProDisc-L IDE trial (Zigler 2012 Five- year results)	24 mos.	76.7 ± 29.2 (n=156)**	67.3 ± 31.5 (n=73)**	NR	0.015
ProDisc-L IDE trial (Zigler 2012 Five- year results)	60 mos.	78.3 ± 27.1 (n=137)**	78.1 ± 26.7 (n=56)**	NR	0.620

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement NR: not reported; NS: not significant; RD: risk difference; VAS: visual analog scale.

*As calculated by the study.

†Numerators back-calculated based on percentage and total N provided.

‡Of the 14 initial sites involved in the Charite IDE trial, 6 declined participation in the 60-month continuation study; furthermore, Guyer 2009 reported outcomes only for patients with both 24 and 60 month follow-up, thus data reported is likely not representative of the total number of patients with follow-up at 60 months.

§Estimated from graph and numerators back-calculated.

**N's from Table 2 of article, represent the number of patients followed at 24 and 60 months.

Table I4. L-ADR vs. Fusion (1-level) RCT data: SF-36, ODI, and VAS pain scores*Completers only analysis*

Study	F/U	Mean ± SD		Δ from baseline*		MD (95% CI)*	p-value*
		L-ADR	Fusion	ADR	Control		
SF-36 PCS scores							
ProDisc-L IDE trial (Zigler 2012 Five-year results)	0 mos.	31.1 ± 6.5 (n=158) [†]	30.9 ± 5.6 (n=74) [†]	NA	NA	NA	0.739
Charite IDE trial (Guyer 2009) [‡]	24 mos.	NR (n=NR)	NR (n=NR)	14.2	11.2	NR	NS
ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	42.8 ± 11.1 (n=147) [§] (% change: 39.4 ± 43.5)	38.8 ± 11.3 (n=70) [§] (% change: 29.8 ± 40.9)	NR	NR	NR	0.036
Charite IDE trial (Guyer 2009) [‡]	60 mos.	NR (n=90)	NR (n=43)	12.6	12.3	NR	NS
ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	42.0 ± 11.3 (n=126) (% change: 40.1 ± 43.9)	40.1 ± 13.6 (n=51) (% change: 29.9 ± 43.7)	NR	NR	NR	0.168
ODI scores							
Charite IDE trial (Blumenthal 2005, FDA SSED 2004)	0 mos.	50.6 (n=205)	52.1 (n=99)	NA	NA	NA	NS
ProDisc-L IDE trial (Zigler 2012 Five-year results)	0 mos.	63.4 ± 12.6 (n=161) [†]	62.7 ± 10.3 (n=75) [†]	NA	NA	NA	0.613
Charite IDE trial Blumenthal 2005, FDA SSED 2004)	24 mos.	26.3 (n=185) (48.5% improve baseline)	30.5 (n=82) (42.4% improve baseline)	NR	NR	NR	0.267
ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	34.5 ± 24.5 (n=149) ^{**}	39.8 ± 24.3 (n=71) ^{**}	-47.4 ± 34.8	-37.8 ± 36.0	NR	0.055
Charite IDE trial (Guyer 2009) [‡]	60 mos.	24 ^{††} (n=90)	24 ^{††} (n=43)	NR	NR	NR	NS
ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	34.2 ± 24.3 (n=126)	36.2 ± 25.7 (n=51)	-47.5 ± 34.7	-43.8 ± 37.1	NR	0.455
VAS pain scores (0-100)							
Charite IDE trial Blumenthal 2005, FDA SSED 2004)	0 mos.	72.0 (n=205)	71.8 (n=99)	NA	NA	NA	NS
ProDisc-L IDE	0 mos.	75.9 ± 16.4	74.9 ± 14.7	NA	NA	NA	0.360

Study	F/U	Mean ± SD		Δ from baseline*		MD (95% CI)*	p-value*
		L-ADR	Fusion	ADR	Control		
trial (Zigler 2012 Five-year results)		(n=159) [†]	(n=73) [†]				
Charite IDE trial Blumenthal 2005, FDA SSED 2004)	24 mos.	31.2 (n=186)	37.5 (n=82)	-40.6	-34.1	NR	0.107
ProDisc-L IDE trial (Zigler 2012 Five-year results)	24 mos.	36.6 ± 30.1 (n=149)	43.3 ± 31.6 (n=71)	-49.9 ± 41.9	-42.4 ± 42.9	NR	0.134
Charite IDE trial (Guyer 2009) [‡]	60 mos.	31 ^{††} (n=90)	30 ^{††} (n=43)	NR	NR	NR	NS
ProDisc-L IDE trial (Zigler 2012 Five-year results)	60 mos.	37.1 ± 29.3 (n=125)	40.0 ± 32.1 (n=51)	-48.7 ± 44.6	-47.5 ± 43.8	NR	0.567

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; MD: mean difference; NR: not reported; NS: not significant; ODI: Oswestry Disability Index; SD: standard deviation; SF-36 PCS: Short-Form 36 questionnaire Physical Component Score; VAS: visual analog scale.

*As reported by the study.

[†]N's based on patients treated, not randomized. For the SF-36 and VAS scores, not all patients had baseline data.

[‡]Of the 14 initial sites involved in the Charite IDE trial, 6 declined participation in the 60-month continuation study; furthermore, Guyer 2009 reported outcomes only for patients with both 24 and 60 month follow-up, thus data reported is likely not representative of the total number of patients with follow-up at 60 months.

[§]At 24 mos., some patients had incomplete data sets.

**Patients with device failures were excluded.

^{††}Estimated from graph in the article.

L-ADR vs. Fusion (2-level)

Table 15. L-ADR vs. Fusion (2-levels) RCT data: Overall and Neurological Success

Analysis	Study	F/U	ADR % (n/N)	Fusion% (n/N)	p-value*
Overall success[†]					
<i>ITT</i>	ProDisc-L IDE (Delamarter 2011)	24 mos.	50.0% (87/174)	39.0% (32/82)	NR
<i>Completer only</i>	ProDisc-L IDE (Delamarter 2011)	24 mos.	58.8% (87/148) [‡]	47.8% (32/67) [‡]	0.0874
Neurological success[§]					
<i>ITT</i>	ProDisc-L IDE (Delamarter 2011)	24 mos.	75.7% (132/174)	61.0% (50/82)	NR
<i>Completer only</i>	ProDisc-L IDE (Delamarter 2011)	24 mos.	89.2% (132/148) [‡]	80.6% (50/62) [‡]	NS

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; RD: risk difference.

*As reported in the article.

†Overall success was a FDA-guided endpoint for which patients had to meet all 9 of the following criteria: 1) ≥15% improvement in ODI compared with baseline; 2) Improvement in SF-36 PCS compared with baseline; 3) Neurological status improved or maintained from baseline; 4) No secondary surgical procedures to remove or modify the total disc replacement implant or arthrodesis implant/site; 5) no subsidence >3 mm; 6) no migration >3 mm; 7) no radiolucency/loosening; 8) no loss of disc height >3 mm; 9) for ADR, range of motion improved for maintained from baseline and for Fusion, no motion (<10° angulation, total for two levels combined) on flexion and extension radiographs.

‡There is a discrepancy in the article between the consort diagram and the text regarding the number of patients analyzed at 24 months. We have reported the data as reported in the text; the authors provided the % (n/N) for both outcomes in the text.

§Neurological success was defined as the maintenance or improvement of patient responses to all neurological criteria, including motor status, sensory status, reflexes, and a straight leg raise test.

Table 16. L-ADR vs. Fusion (2-levels) RCT data: ODI, VAS, and SF-36 scores

Completer only analysis

Study	F/U	Mean ± SD		% change from baseline*		p-value*
		ADR	Fusion	ADR	Fusion	
ODI (0-100 [worst])						
ProDisc-L IDE (Delamarter 2011)	0 mos.	64.7 ± 11.4 (n=165)	64.8 ± 9.5 (n=72)	NA	NA	NS
	24 mos.	30.3 ± 24.3 (n=148)†	38.7 ± 24.1 (n=67)†	52.4% ± 38.1%	40.9% ± 36.0%	0.028
VAS pain (0-100 [worst])						
ProDisc-L IDE (Delamarter 2011)	0 mos.	75.7 ± 16.0 (n=165)	74.7 ± 13.6 (n=72)	NA	NA	NS
	24 mos.	31.9 ± 30.5 (n=143)‡	38.4 ± 29.8 (n=60)‡	43.3% ± 33.3%	36.7% ± 30.3%	0.118
SF-36 PCS (0-100 [best])						
ProDisc-L IDE (Delamarter 2011)	0 mos.	29.5 ± 5.4 (n=165)	30.1 ± 6.7 (n=72)	NA	NA	NS
	24 mos.	43.9 ± 11.9 (n=148)	39.2 ± 11.2 (n=67)	54.2% ± 54.6%	36.2% ± 44.9%	0.014

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; MD: mean difference; NA: not applicable; NR: not reported; SD: standard deviation.

*As reported by the study.

†The number of patients providing data for ODI scores at 24 months was not provided; the n’s reported reflect the number of patients who had data for the primary endpoint – overall success – of which the ODI is a component.

‡The number of patients providing data for VAS pain scores at 24 months was not provided; the n’s reported reflect the number of patients with complete data sets at 24 months (this outcome is not part of the composite primary outcome).

Table 17. L-ADR vs. Fusion (2-levels) RCT data: Narcotic use, work and recreational activity status, and patient satisfaction

Completer only analysis

Study	F/U	ADR % (n/N)	Fusion % (n/N)	p-value*
Narcotic use				
ProDisc-L IDE (Delamarter 2011)	0 mos.	69.1% (114/165)	63.9% (46/72)	NS
	24 mos.	36.1% (52/144) (% decrease from	59.3% (35/59) (% decrease from	0.0020†

Study	F/U	ADR % (n/N)	Fusion % (n/N)	p-value*
		baseline: 47.8%)	baseline: 7.2%)	
Work status (working)				
ProDisc-L IDE (Delamarter 2011)	0 mos.	79.4% (131/165)	83.3% (60/72)	0.5928
	24 mos.	80.4% (115/143)	86.0% (49/57)	0.4193
Recreational activity status (participating)				
ProDisc-L IDE (Delamarter 2011)	0 mos.	36.4% (60/165)	43.7% (31/71)	0.3099
	24 mos.	84.6% (121/143)	79.7% (47/59)	0.4121
Patient satisfaction (yes, would have same surgery again)				
ProDisc-L IDE (Delamarter 2011)	24 mos.	78.2% (111/142)	62.1% (36/58)	0.0546
Study	F/U	ADR Mean ± SD	Fusion Mean ± SD	p-value*
Patient satisfaction (VAS, 0-100 mm [best])				
ProDisc-L IDE (Delamarter 2011)	24 mos.	77.70 ± 27.95 (n=143)‡	68.89 ± 30.50 (n=60)‡	0.0126

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; MD: mean difference; NA: not applicable; NR: not reported; RR: risk ratio; SD: standard deviation.

*As reported by the study.

†As calculated by SRI: RR 0.6 (95% CI 0.4, 0.8); p=0.0025.

‡The number of patients providing data for VAS patient satisfaction scores at 24 months was not provided; the n’s reported reflect the number of patients with complete data sets at 24 months (this outcome is not part of the composite primary outcome).

L-ADR vs. Fusion (1- or 2-level)

Table 18. L-ADR vs. Fusion (1- or 2-levels) RCT data: Overall and ODI Success

Analysis	Study	F/U	ADR % (n/N)*	Fusion % (n/N)*	RD (95% CI)†	p-value‡
Clinical success (GA of back pain: totally pain free OR much better)						
<i>ITT (no loss to followup reported)‡</i> <i>ITT analysis</i>	Berg trial (Skold 2013)	24 mos.	70.0% (56/80)	63.9% (46/72)	NR	NS
	Berg trial (Skold 2013)	60 mos.	72.5% (58/80)	66.7% (48/72)	NR	NS
<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	72.5% (58/80)	67.6% (48/71)	NR	NS
Clinical success (GA of back pain: totally pain free)						
<i>ITT (no loss to followup reported)‡</i> <i>ITT analysis</i>	Berg trial (Skold 2013)	24 mos.	30% (24/80)	15% (11/72)	NR	0.031
	Berg trial (Skold 2013)	60 mos.	38% (30/80)	15% (11/72)	NR	NR
<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	38% (30/80)	15% (11/71)	NR	0.002
ODI success (≥25% improvement)						
<i>ITT (no loss to followup reported)‡</i> <i>Completers only</i>	Berg trial (Skold 2013)	24 mos.	64% (51/80)§	55% (40/72)§	NR	0.305
	Berg trial (Skold 2013)	60 mos.	77.5% (62/80)	64.8% (46/71)	NR	0.084

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; GA: global assessment; NR: not reported; NS: not significant; ODI: Oswestry disability index; RD: risk difference.

* For the ITT analysis, it is not clear if there were randomized patients who did not receive the allotted treatment and we used number reported for baseline for the denominator.

† Calculated unless otherwise indicated.

‡ No patient was lost-to-follow-up at 24 months, however, authors do not report on number randomized who may not have received treatment.

§ Numerators were back-calculated based on percentages and denominators provided by the authors.

Table I9. L-ADR vs. Fusion (1- or 2-levels) RCT data: Global Assessment of Pain (other than included for overall success)

Analysis	Study	F/U	ADR % (n/N)*	Fusion % (n/N)*	RD (95% CI)†	p-value‡
GA of back pain (much better)						
<i>ITT (no loss to followup reported)‡</i>	Berg trial (Skold 2013)	24 mos.	40% (32/80)	49% (35/72)	NR	NS
	<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	35% (28/80)	52% (37/71)	NR (-17.1% (-32.7%, -1.5%))
GA of back pain (better)						
<i>ITT (no loss to followup reported)‡</i>	Berg trial (Skold 2013)	24 mos.	18% (14/80)	22% (16/72)	NR	NS
	<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	16% (13/80)	20% (14/71)	NR
GA of back pain (unchanged)						
<i>ITT (no loss to followup reported)‡</i>	Berg trial (Skold 2013)	24 mos.	6% (5/80)	10% (7/72)	NR	NS
	<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	4% (3/80)	8% (6/71)	NR
GA of back pain (worse)						
<i>ITT (no loss to followup reported)‡</i>	Berg trial (Skold 2013)	24 mos.	6% (5/80)	4% (3/72)	NR	NS
	<i>Completers only</i>	Berg trial (Skold 2013)	60 mos.	8% (6/80)	4% (3/71)	NR

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; GA: global assessment; NR: not reported; NS: not significant; ODI: Oswestry disability index; RD: risk difference.

* For the ITT analysis, it is not clear if there were randomized patients who did not receive the allotted treatment and we used number reported for baseline for the denominator.

† Calculated unless otherwise indicated.

‡ No patient was lost-to-follow-up at 24 months, however, authors do not report on number randomized who may not have received treatment.

Table I10. L-ADR vs. Fusion (1- or 2-levels) RCT data: Other pain, function, and quality of life scores Completers only analysis

Study	F/U	Mean ±SD	Fusion	Δ from baseline*	Fusion	MD (95% CI)*	p-value*
		ADR		ADR			
VAS back pain (0-100 [worst])							
Berg trial (Skold 2013)	0 mos.	62.3 ± 20.8 (n=80)	58.5 ± 21.7 (n=72)	NA	NA	NA	0.218

Study	F/U	Mean \pm SD		Δ from baseline*		MD (95% CI)*	p-value*
		ADR	Fusion	ADR	Fusion		
	24 mos.	25.4 \pm 29.8 (n=80)	29.2 \pm 24.6 (n=72)	-36.9 \pm 31.0	-29.3 \pm 31.6	NR	0.056 Δ 0.099
	60 mos.	22.7 \pm 29.2 (n=80)	30.5 \pm 26.9 (n=71)	-39.6 \pm 31.8	-27.5 \pm 32.3	NR	0.009 Δ 0.022
VAS leg pain (0-100 [worst])							
Berg trial (Skold 2013)	0 mos.	32.8 \pm 26.4 (n=80)	43.7 \pm 28.2 (n=72)	NA	NA	NA	0.016
	24 mos.	16.4 \pm 24.5 (n=80)	20.7 \pm 24.3 (n=72)	-21.0 \pm 26.4	-23.2 \pm 28.1	NR	0.037 Δ 0.254
	60 mos.	14.0 \pm 23.1 (n=80)	20.3 \pm 24.7 (n=71)	-18.8 \pm 33.6	-22.6 \pm 28.5	NR	0.037 Δ NS
SF-36 pain (back) subscale (0-100 [best])							
Berg trial (Skold 2013)	60 mos.	67.6 \pm 31.8 (n=80)	56.8 \pm 27.3 (n=71)	39.0	27.8	NR	<0.05 for both
ODI (%)							
Berg trial (Skold 2013)	0 mos.	41.8 \pm 11.8 (n=80)	41.2 \pm 14.6 (n=72)	NA	NA	NA	0.303
	24 mos.	20.0 \pm 19.6 (n=80)	23.0 \pm 17.0 (n=72)	-21.9 \pm 18.9	-18.1 \pm 19.4	NR	0.248 Δ 0.152
	60 mos.	17.3 \pm 19.0 (n=80)	22.5 \pm 17.1 (n=71)	-24.6 \pm 18.1	-18.3 \pm 18.6	NR	0.015 Δ 0.019
EQ-5D (-0.59 to 1 [best])							
Berg trial (Skold 2013)	0 mos.	0.42 \pm 0.31 (n=80)	0.36 \pm 0.33 (n=72)	NA	NA	NA	0.167
	24 mos.	0.67 \pm 0.33 (n=80)	0.69 \pm 0.25 (n=72)	0.25 \pm 0.36	0.33 \pm 0.38	NR	0.740 Δ 0.248
	60 mos.	0.76 \pm 0.30 (n=80)	0.68 \pm 0.30 (n=71)	0.34 \pm 0.35	0.32 \pm 0.39	NR	0.026 Δ NS

Δ indicates p value for change scores.

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; GA: global assessment; MD: mean difference; NR: not reported; NS: not significant; ODI: Oswestry Disability Index; SD: standard deviation; VAS: visual analog scale.

*As reported by the study.

Table I11. L-ADR vs. Fusion (1- or 2-levels) RCT data: Patient satisfaction, work status and analgesic consumption.

Completers only analysis

Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
Patient satisfaction (satisfied)					
Berg trial (Berg 2009 Total disc)	24 mos.	71% (57/80)†	67% (48/72)†	NR	0.586
Berg trial (Skold 2013)	60 mos.	79% (63/80)†	69% (49/71)†	NR	0.14
Work status (return-to-work at full- or part-time)					
Berg trial (Skold 2013)	0 mos.	36.8% (29/80)	47.2% (34/72)	NR	NS

Study	F/U	ADR % (n/N)	Fusion % (n/N)	RD (95% CI)*	p-value*
Berg trial (Berg 2009 Total disc)	24 mos.	76% (61/80)	72% (52/72)	NR	0.750
Berg trial (Skold 2013)	60 mos.	77.5% (62/80)	90% (64/71)	NR	0.04
Sickness benefits (none)					
Berg trial (Skold 2013)	60 mos.	84% (67/80)	83% (57/69)	NR	NS
Analgesic consumption (totally free from pain medication)					
Berg trial (Skold 2013)	60 mos.	59% (47/80)	38% (27/71)	NR	0.01

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; GA: global assessment; NR: not reported; NS: not significant; RD: risk difference.

*As reported by authors.

†Numerators were back-calculated based on percentages and denominators provided by the authors in the text.

Table I12. L-ADR vs. Fusion (1- or 2-levels) RCT data: Sex Life Outcomes based on ODI item 8.
Completers only analysis

Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)*	RD (95% CI)†	p-value‡	
ODI item 8 score (0-5)							
Berg trial (Berg 2009 Sex life)	Score 0: normal, no pain	0 mos.	14.1% (11/78)	14.3% (10/70)	NR	NS	
		24 mos.	61.5% (48/78)	49.3% (34/69)	NR	NS	
	Score 1: normal, some pain	0 mos.	30.8% (24/78)	38.6% (27/70)	NR	NS	
		24 mos.	20.5% (16/78)	36.2% (25/69)	NR	NS	
	Score 2: nearly normal, very painful	0 mos.	20.5% (16/78)	20.0% (14/70)	NR	NS	
		24 mos.	3.8% (3/78)	2.9% (2/69)	NR	NS	
	Score 3: severely restricted by pain	0 mos.	29.5% (23/78)	21.4% (15/70)	NR	NS	
		24 mos.	9.0% (7/78)	7.2% (5/69)	NR	NS	
	Score 4: nearly absent because of pain	0 mos.	2.6% (2/78)	4.3% (3/70)	NR	NS	
		24 mos.	3.8% (3/78)	1.4% (1/69)	NR	NS	
	Score 5: no sex life at all	0 mos.	2.6% (2/78)	1.4% (1/70)	NR	NS	
		24 mos.	1.3% (1/78)	2.9% (2/69)	NR	NS	
	Change from baseline in ODI item 8 score						
	Berg trial (Berg 2009 Sex life)	Improved 5 points	24 mos.	1.3% (1/77)	0% (0/69)	NR	NS
Improved 4 points		24 mos.	1.3%	2.9%	NR	NS	

Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)*	RD (95% CI)†	p-value‡
			(1/77)	(2/69)		
	Improved 3 points	24 mos.	13.0% (10/77)	7.2% (5/69)	NR	NS
	Improved 2 points	24 mos.	24.7% (19/77)	11.6% (8/69)	NR	NS
	Improved 1 point	24 mos.	19.5% (15/77)	36.2% (25/69)	NR	NS
	No improvement	24 mos.	29.9% (23/77)	34.8% (24/69)	NR	NS
	Deteriorated 1 point	24 mos.	6.5% (5/77)	2.9% (2/69)	NR	NS
	Deteriorated 2 points	24 mos.	4.0% (3/77)	4.3% (3/69)	NR	NS

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; NS: not significant; ODI: Oswestry disability index; RD: risk difference.

Table I13. L-ADR vs. Fusion (1- or 2-level) non-randomized registry data: Pain, disability, quality of life, work status, and patient satisfaction.

Study	F/U	L-ADR* Mean ± SD	Fusion* Mean ± SD	p-value‡
Back Pain VAS (0-100 [worst])				
Berg 2010	Baseline	60 ± 20 (n = 163)	63 ± 20 (n = 178)	NR
	12 mos.	27 ± 26 (n = 132)	35 ± 30 (n = 147)	0.031
	24 mos.	22 ± 25 (n = 53)	38 ± 32 (n = 84)	0.002‡
ODI (0-100 [worst])				
Berg 2010	Baseline	41 ± 12 (n = 163)	45 ± 14 (n = 178)	<0.005
	12 mos.	20 ± 17 (n = 132)	30 ± 23 (n = 147)	<0.001
	24 mos.	18 ± 16 (n = 53)	30 ± 21 (n = 84)	<0.001‡
EQ-5D (-0.59 to 1 [perfect health])				
Berg 2010	Baseline	0.39 ± 0.31 (n = 163)	0.34 ± 0.32 (n = 178)	NR
	12 mos.	0.69 ± 0.29 (n = 132)	0.55 ± 0.36 (n = 147)	<0.003
	24 mos.	0.70 ± 0.29 (n = 53)	0.58 ± 0.36 (n = 84)	0.043‡
EQ-VAS (0-100 [worst imaginable health state])				
Berg 2010	Baseline	51 ± 20 (n = 163)	47 ± 21 (n = 178)	NR
	12 mos.	71 ± 22 (n = 132)	62 ± 26 (n = 147)	0.013
	24 mos.	74 ± 21 (n = 53)	62 ± 27 (n = 84)	0.007‡
Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value‡
Global assessment of back pain: totally pain free				
Berg 2010	12 mos.	20% (26/132)	11% (16/147)	0.024
	24 mos.	32% (17/53)	14% (12/84)	0.013‡
Global assessment of back pain: unchanged or worse				
Berg 2010	12 mos.	11% (15/132)	21% (31/147)	0.029‡
	24 mos.	15% (8/53)	21% (18/84)	NS‡
Global assessment of back pain: totally pain free or better				
Berg 2010	12 mos.	89% (117/132)	79% (116/147)	0.029‡
	24 mos.	85% (45/53)	76% (64/84)	NS‡
On full sick-leave				

Berg 2010	12 mos.	24% (32/132)	37% (54/147)	0.024‡
Satisfied with result				
Berg 2010	12 mos.	75% (99/132)	65% (96/147)	NS‡

CI: Confidence interval; EQ5D: EuroQoL; EQ-VAS: EuroQoL Visual Analog Scale; F/U: Follow-up; L-ADR: lumbar artificial disc replacement; NR: Not reported; ODI: Oswestry Disability Index; SD: Standard deviation; VAS: Visual Analog Scale.

*N's/denominators represented the number of patients who responded to the questionnaire at each follow-up point; baseline demographics, including baseline outcome scores, were provided only for those patients with a minimum of 12 months follow-up.

†As reported by the study unless otherwise indicated.

‡Calculated by SRI.

L-ADR vs. Multidisciplinary Rehabilitation

Table I14. L-ADR vs. Multidisciplinary rehabilitation: ODI Success

Outcome	Study	F/U	ADR % (n/N)	Rehab % (n/N)	RD (95% CI)*	p-value*
ODI success (≥15 point improvement)†						
<i>ITT analysis</i>	Hellum 2011	24 mos.	57.3% (51/89)	34.4% (31/90)	NR	NR
<i>Completers only</i>	Hellum 2011	24 mos.	70% (51/73)‡	47% (31/66)‡	NR	0.006

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; ODI: Oswestry Disability Index; RD: risk difference; Rehab: Rehabilitation.

*Calculated unless otherwise indicated.

†This was an unplanned analysis: per-protocol analysis using FDA criteria for ODI success. Subgroup analysis showed no differences in the main outcome variable between centres and level(s) operated on.

‡Denominator back-calculated based on the percentage and number of patients reported.

Table I15. L-ADR vs. Multidisciplinary rehabilitation: Treatment failure – Rehabilitation group only

Outcome	Study	F/U	Rehab % (n/N)	RD (95% CI)*	p-value*
Treatment failure: need for surgical intervention					
ADR (crossed over)	Hellum 2011	24 mos.	6.3% (5/80)	NA	NA
Fusion (crossed over)	Hellum 2011	24 mos.	1.3% (1/80)	NA	NA

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; ODI: Oswestry Disability Index; RD: risk difference; Rehab: Rehabilitation.

*Calculated unless otherwise indicated.

Table I16. L-ADR vs. Multidisciplinary rehabilitation: ODI, VAS pain, SF-36, and EQ-5D scores

Analysis*	Study	F/U	Mean ±SD		Δ from baseline† (95% CI)		MD (95% CI)‡	p-value‡
			ADR	Rehab	ADR	Control		
ODI (0-100 [worst])								
<i>ITT analysis (LOCF)</i>	Hellum 2011	0 mos.	41.8 ± 9.1 (n=86)	42.8 ± 9.3 (n=86)	NA	NA	NA	NR
		24 mos.	21.2 ± 17.1 (n=86)	30.0 ± 16.0 (n=86)	-20.8 (-25.2, -16.4)	-12.4 (-16.3, -8.5)	-8.4 (-13.2, -3.6)	0.001

Analysis*	Study	F/U	Mean ±SD		Δ from baseline† (95% CI)		MD (95% CI)†	p-value†
			ADR	Rehab	ADR	Control		
<i>ITT analysis (Mixed model analysis)</i>	Hellum 2011	0 mos.	41.8 ± 9.1 (n=86)	42.8 ± 9.3 (n=86)	NA	NA	NA	NR
		24 mos.	19.8 ± 16.7 (n=86)	26.7 ± 14.5 (n=86)	-22.5 (-26.4, -18.5)	-15.6 (-19.5, -11.7)	-6.9 (-11.7, -2.1)	0.001
<i>Per protocol analysis (Mixed model analysis)</i>	Hellum 2011	0 mos.	42.2 ± 9.2 (n=77)	42.1 ± 8.3 (n=80)	NA	NA	NA	NR
		24 mos.	18.8 ± 15.8 (n=71)	26.9 ± 13.9 (n=60)	NR	NR	-8.1 (-12.9, -3.2)	0.001
VAS pain (0-100 [worst])								
<i>ITT analysis (LOCF)</i>	Hellum 2011	0 mos.	64.9 ± 15.3 (n=86)	73.6 ± 13.9 (n=86)	NA	NA	NA	<0.05
		24 mos.	35.4 ± 29.1 (n=86)	49.7 ± 28.4 (n=86)	NR	NR	-12.2 (-21.3, -3.1)	0.009
<i>ITT analysis (Mixed model analysis)</i>	Hellum 2011	0 mos.	64.9 ± 15.3 (n=86)	73.6 ± 13.9 (n=86)	NA	NA	NA	<0.05
		24 mos.	32.7 ± 28.8 (n=86)	45.3 ± 28.6 (n=86)	NR	NR	-12.7 (-21.1, -4.2)	<0.001
SF-36 PCS (0-100 [best])								
<i>ITT analysis (LOCF)</i>	Hellum 2011	0 mos.	30.5 ± 7.1 (n=86)	30.8 ± 6.5 (n=86)	NA	NA	NA	NR
		24 mos.	43.3 ± 11.7 (n=86)	37.7 ± 10.1 (n=86)	NR	NR	5.8 (2.5, 9.1)	0.001
SF-36 MCS (0-100 [best])								
<i>ITT analysis (LOCF)</i>	Hellum 2011	0 mos.	47.7 ± 13.0 (n=86)	45.2 ± 13.2 (n=86)	NA	NA	NA	NR
		24 mos.	50.7 ± 11.6 (n=86)	48.6 ± 12.8 (n=86)	NR	NR	1.0 (-2.4, 4.4)	0.50
EQ-5D (-0.59 to 1 [best])								
<i>ITT analysis (LOCF)</i>	Hellum 2011	0 mos.	0.30 ± 0.27 (n=86)	0.27 ± 0.31 (n=86)	NA	NA	NA	NR
		24 mos.	0.69 ± 0.33 (n=86)	0.63 ± 0.28 (n=86)	NR	NR	0.06 (-0.05, 0.18)	0.26

ADR: artificial disc replacement; CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; F/U: follow-up; MD: mean difference; NA: not applicable; NR: not reported; ODI: Oswestry Disability Index; Rehab: rehabilitation; SD: standard deviation; SF-36 PCS and MCS: Short Form-36 Physical and Mental Component Scores; VAS: visual analog scale.

*Analysis were as follows:

- ITT (LOCF): ITT performed with the assumption that patients who dropped out had no improvement after drop-out using last observation carried forward (LOCF) method to account for missing data; author's ITT does not include 6 patients (3 in each group) that were excluded shortly after randomization.

- ITT and Per Protocol (Mixed Model analyses): A mixed model analysis was used to evaluate the effect of each efficacy variable over time and between groups; patients were not excluded from the analysis of an efficacy variable if the variable was missing at some, but not all, time points after baseline. In the additional analysis (categorical or ordinal data at two year followup), missing data were not replaced. Significantly different baseline scores were not adjusted for in the longitudinal model. Each outcome variable was adjusted for the baseline values of the variable.

†As reported by the study.

Table I17. L-ADR vs. Multidisciplinary rehabilitation: Work status, patient satisfaction, and medication use

Completer analysis

Study	F/U	ADR % (n/N)	Rehab % (n/N)	RD (95% CI)*	p-value*
Work status (working; includes part time sick leave)†					
Hellum 2011	0 mos.	28% (24/86)‡	26% (22/86)‡	2.3% (-10.9, 15.6)	0.7312
	24 mos.	31% (21/68)§	23% (15/65)§	7.8% (-7.2, 22.8)	0.3130
Patient satisfaction (satisfied with outcome [i.e., completely recovered or much improved])					
Hellum 2011	24 mos.	63% (46/73)§	39% (26/66)§	23.6% (7.5, 39.8)	0.0056
Patient satisfaction (satisfied with care)					
Hellum 2011	12 mos.	90% (66/73)§	73% (48/66)§	17.7% (5.0, 30.4)	0.0069
Medication usage (daily use)					
Hellum 2011	0 mos.	27% (23/86)‡	20% (17/86)‡	7.0% (-5.6, 19.6)	0.2802
	24 mos.	22% (16/73)§	18% (14/78)§	4.0% (-8.8, 16.7)	0.5426

ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; RD: risk difference; Rehab: Rehabilitation.

*As reported by the study.

†Work status at 24 months represents the “net back to work rate” calculated by subtracting patients who went back to work from patients who stopped working.

‡Numbers at baseline reflect patients who were treated (as opposed to those who were randomized); 6 patients (3 in both groups) were excluded shortly after randomization and 1 patient who underwent rehabilitation that was excluded because of missing baseline and follow-up values.

§Denominators were back-calculated based on the percentage and number of patients reported.

Table I18. L-ADR vs. Multidisciplinary rehabilitation: Other secondary outcomes

*Author ITT analysis**

Study	F/U	Mean ±SD		Δ from baseline†		MD (95% CI)†	p-value†
		ADR	Rehab	ADR	Control		
Back performance scale (0-15 [worst])‡							
Hellum 2011	24 mos.	3.2 ± 3.0 (n=86)	4.0 ± 3.0 (n=86)	NR	NR	-0.8 (-1.8, 0.2)	0.10
Prolo scale (2-10 [best])§							
Hellum 2011	24 mos.	7.0 ± 2.3 (n=86)	6.1 ± 1.9 (n=86)	NR	NR	0.9 (0.1, 1.6)	0.019
Self-efficacy beliefs for pain (0-10 [best])**							
Hellum 2011	0 mos.	3.4 ± 1.5 (n=86)	3.6 ± 1.6 (n=86)	NA	NA	NA	NR
	24 mos.	6.1 ± 2.9 (n=86)	5.3 ± 2.5 (n=86)	NR	NR	1.0 (0.2, 1.9)	0.02
HSCL-25 (1-4 [worst])††							
Hellum 2011	0 mos.	1.81 ± 0.50	1.88 ± 0.51	NA	NA	NA	NR

Study	F/U	Mean \pm SD		Δ from baseline [†]		MD (95% CI) [†]	p-value [†]
		ADR (n=86)	Rehab (n=86)	ADR	Control		
	24 mos.	1.50 \pm 0.44 (n=86)	1.63 \pm 0.52 (n=86)	NR	NR	-0.10 (-0.23, 0.04)	0.20
FABQ physical (0-24 [worst])^{‡‡}							
Hellum 2011	0 mos.	14.0 \pm 5.8 (n=86)	12.5 \pm 5.6 (n=86)	NA	NA	NA	NR
	24 mos.	9.0 \pm 6.8 (n=86)	9.9 \pm 6.0 (n=86)	NR	NR	-1.5 (-3.4, 0.5)	0.10
FABQ work (0-42 [worst])^{‡‡}							
Hellum 2011	0 mos.	25.8 \pm 11.2 (n=86)	27.4 \pm 27.4 (n=86)	NA	NA	NA	NR
	0 mos.	18.1 \pm 13.9 (n=86)	21.2 \pm 12.8 (n=86)	NR	NR	-2.1 (-6.0, 1.7)	0.30

ADR: artificial disc replacement; CI: confidence interval; EQ-5D: EuroQoL 5 Dimensions; FABQ: fear avoidance belief questionnaire; F/U: follow-up; HSCL-25: Hopkins symptom check list; ITT: intention-to-treat; LOCF: last observation carried forward; MD: mean difference; NA: not applicable; NR: not reported; SD: standard deviation; SF-36: Short-Form-36.

*ITT performed with the assumption that patients who dropped out had no improvement after drop-out using last observation carried forward (LOCF) method to account for missing data; author's ITT does not include 6 patients (3 in each group) that were excluded shortly after randomization.

[†]As reported by the study unless otherwise indicated.

[‡]Scale comprises five tests with score ranging from 0 to 15 (worst possible).

[§]Scale comprises functional and economic parts, summed to give worst score of 2 and best score of 10.

**Self-efficacy beliefs for pain scores ranges from 1 to 10 and are summarized and divided by 5. Lower scores indicate that he/she is very uncertain if he/she is able to manage pain.

^{††}The HSCL-25 is a symptom inventory which measures symptoms of anxiety and depression. It consists of 25 items: 10 for anxiety symptoms and 15 for depression symptoms. The scale for each question includes four categories of response ("Not at all," "A little," "Quite a bit," "Extremely," rated 1 to 4, respectively). Two scores are calculated: the total score is the average of all 25 items, while the depression score is the average of the 15 depression items.

^{‡‡}The FABQ consists of 2 subscales: the Physical Activity subscale (items 1-5) and the Work subscale (items 6-16) and is specific to low back pain patients in the clinical setting. This survey can help predict those that have a high pain avoidance behavior.

APPENDIX J. C-ADR EFFICACY AND EFFECTIVENESS RESULTS.

C-ADR vs. ACDF (1-level)

Table J1. C-ADR vs. ACDF (1-level) RCT data: Overall success

Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Overall success (used for meta-analysis): 1) postoperative NDI score improvement of ≥15 points from preoperative 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 a “failure” (removal, revision, or supplemental fixation).					
Prestige ST trial (Burkus 2014)§	24 mos.	78% (197/253)	68% (150/220)	See meta-analysis for calculations	
Bryan trial (Heller 2009)	24 mos.	82.6% (190/230)	72.7% (141/194)		
ProDisc-C trial (Murrey 2009)**	24 mos.	72.3% (73/101)	68.3% (69/101)		
Bryan trial (Sasso 2011)	48 mos.	85.1% (154/181)	72.5% (100/138)		
Prestige ST trial (Burkus 2014)**	60 mos.	78.2% (172/220)	71.8% (136/190)		
Prestige ST trial (Burkus 2014)**	84 mos.	75.0% (159/212)	63.7% (117/183)		
Overall success (used for meta-analysis): 1) NDI improvement of at least 15 points (out of 50) from baseline; 2) No subsequent surgical intervention at the index level or levels; 3) No potentially (possibly or probably) device-related adverse event; 4) Maintenance or improvement in all components of neurological status; and 5) No SECURE-C intraoperative changes in treatment.					
SECURE-C trial (Vaccaro 2013)†	24 mos.	83.8% (109/130)	73.2% (82/112)	See meta-analysis for calculations	
Mobi-C trial (1-level) (Hisey 2016, 60 mos.)‡,**	60 mos.	61.9% (87/140)	52.2% (33/64)		
Overall success (used for meta-analysis): 1) improvement of ≥15 points on the NDI from baseline; 2) no reoperation, revision, or removal; 3) maintenance or improvement in neurological status; 4) no major complications; and 5) meeting radiographic criteria of motion for PCM and fusion for ACDF (i.e., ADR group: ≥2° angular motion in flexion/extension or no evidence of bridging trabecular bone across the disc space; ACDF group: fusion of both treated levels—≤2° of angular motion in flexion/extension and evidence of bridging bone across the disc space and radiolucent lines at no more than 50% of the graft vertebral interfaces).					
PCM trial (Phillips 2013)	24 mos.	72.0% (136/189)	60.9% (92/151)	See meta-analysis for calculations	
Overall success (similar to definitions in above group but not pooled due to differences in NDI score requirements plus no requirement for neurological success): (1) minimum 30-point improvement on the NDI if the baseline score was ≥60, or 50% improvement if the baseline was <60; (2) no device-related subsequent surgery (defined as removal, revision, supplemental fixation, or reoperation); and (3) no major complications defined as neurological deterioration, or adverse events classified as major complications by an independent Clinical Events Committee (CEC).					
Mobi-C trial (1-level)	24 mos.	76.3%	72.0% (54/75)	4.1% (-8.1%, 16.3%)	0.50

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
(Hisey 2014)		(118/155)			
Overall success (same definition used for Mobi-C trial in row directly above but required radiographic success)					
Mobi-C trial (1-level) (Hisey 2014)**	24 mos.	73.7% (114/155)	65.3% (49/75)	8.2% (-4.6%, 21.0%)	0.20
	48 mos.	69.5% (96/138)	58.7% (38/64)	10.2% (-4.1%, 24.5%)	0.15
IN ADDITION TO THE DEFINITIONS REPORTED ABOVE, THE FOLLOWING TRIALS REPORTED ALTERNATIVE DEFINITIONS OF "OVERALL SUCCESS":					
Overall success (with disc height requirement): 1) postoperative NDI score improvement of ≥15 points from preoperative score; 2) maintenance or improvement in neurological status; 3) disc height success (the functional spinal unit [FSU] was measured to assess for any loss of disc height due to subsidence); 4) no serious adverse event classified as implant associated or implant/surgical procedure associated; and 5) no additional surgical procedure classified as a "failure" (removal, revision, or supplemental fixation).					
Prestige ST trial (Burkus 2014)§	24 mos.	78% (197/253)	64% (141/220)	13.8% (5.6%, 21.9%)	<0.01
	60 mos.	71.3% (157/220)	65.2% (124/190)	6.1% (-2.9%, 15.1%)	0.19
	84 mos.	72.6% (154/212)	60.0% (110/183)	12.5% (3.2%, 21.8%)	0.01
Overall success (alternate NDI requirement): 1) improvement of ≥20% on the NDI from baseline; 2) no reoperation, revision, or removal; 3) maintenance or improvement in neurological status; 4) no major complications; and 5) meeting radiographic criteria of motion for PCM and fusion for ACDF (i.e., ADR group: ≥2° angular motion in flexion/extension or no evidence of bridging trabecular bone across the disc space; ACDF group: fusion of both treated levels—≤2° of angular motion in flexion/extension and evidence of bridging bone across the disc space and radiolucent lines at no more than 50% of the graft vertebral interfaces).					
PCM trial (Phillips 2013)	24 mos.	75.1% (142/189)	64.9% (98/151)	10.2% (0.4%, 20.0%)	0.04
Overall success (alternate NDI requirement): 1) NDI success (improvement of ≥20% on the NDI from baseline); 2) device success (no revision, removal or re-operation of the implant or supplemental fixation); 3) neurological exam success (maintenance or improvement in each of the neurologic evaluations including sensory, motor, and reflex functions); 4) adverse events success (absence of adverse events related to the implant or its implantation).					
ProDisc-C trial (Murrey 2009)**	24 mos.	77.2% (78/101)	74.3% (75/101)	3.0% (-8.8%, 14.8%)	0.62
Overall success (alternate NDI requirement, no requirement for neurological status maintenance or improvement, and requiring radiographic fusion in the ACDF group): (1) improvement of ≥25% on the NDI from baseline; (2) no device failures requiring revision, removal, reoperation, or supplemental fixation; (3) absence of major complications defined as major vessel injury, neurological damage, or nerve injury; (4) and for patients who underwent ACDF only, radiographic fusion (presence of bridging trabecular bone, without evidence of pseudarthrosis).					
SECURE-C trial (Vaccaro 2013)	24 mos.	90.1% (127/141)	71.1% (81/114)	19.0% (9.3%, 28.7%)	<0.01
Overall success (MCID defined criteria): 1) NDI success (improvement of ≥20% on the NDI from baseline); 2) patient satisfaction measured by willingness to have the same surgery again; 3) absence of device failure; 4) absence of pseudarthrosis (ACDF group)/absence of fusion (ProDisc-C group); 5) VAS neck or arm pain success (improvement of ≥20% on either neck or arm pain VAS) from baseline; and 6) absence of strong narcotic or muscle relaxant use.					
ProDisc-C trial (Murrey 2009)**	24 mos.	73.5% (74/101)	60.5% (61/101)	12.9% (0.0%, 25.7%)	0.053

*Calculated by SRI

† n/N not reported in Vaccaro 2013 publication so were obtained from the SECURE-C FDA SSED report.

‡ For all outcomes, N for follow-up at 60 months in the Mobi-C trial are calculated based on the percent follow-up provided by authors (85.5% vs. 78.9% for ADR vs. fusion, respectfully), as no patient consort flow chart was provided.

§ Percentages were estimated from graphs; numerators were back-calculated using the estimated percentage.

** Numerators were back-calculated using the percentage reported.

Table J2. C-ADR vs. ACDF (1-level) RCT data: NDI success

Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)‡	p- value‡
NDI success (used for meta-analysis): postoperative NDI score improvement of ≥15 points from the baseline score					
Prestige ST trial (Burkus 2014)*	24 mos.	83% (185/223)	80% (159/198)	See meta-analysis for calculations	
ProDisc-C trial (Murrey 2009)§	24 mos.	79.8% (81/101)	78.3% (79/101)		
Bryan trial (Heller 2009)	24 mos.	85.7% (197/230)	78.9% (153/194)		
SECURE-C trial (Vaccaro 2013)†	24 mos.	89.2% (124/139)	84.5% (98/116)		
PCM trial (Phillips 2013)	24 mos.	79.7% (149/187)	75.5% (114/151)		
Bryan trial (Sasso 2011)	48 mos.	90.6% (164/181)	79.0% (109/138)		
Mobi-C trial (1-level) (Hisey 2016)	60 mos.	68.1% (95/140)	62.1% (40/64)		
Prestige ST trial (Burkus 2014)§	60 mos.	85.4% (188/220)	84.8% (161/190)		
Prestige ST trial (Burkus 2014)§	84 mos.	83.4% (177/212)	80.1% (147/183)		
NDI success: postoperative ≥30-point improvement on the NDI if the baseline score was ≥60, or ≥50% improvement if the baseline score was <60					
Mobi-C trial (1-level) (Hisey 2014)§	24 mos.	79.4% (123/155)	77.1% (58/75)	2.0% (-9.4%, 13.4%)	0.73
Mobi-C trial (1-level) (Hisey 2015)§	48 mos.	80.5% (111/138)	78.2% (50/64)	2.3% (-9.8%, 14.4%)	0.70
NDI success: postoperative ≥20% improvement from the baseline score					
ProDisc-C trial (Murrey 2009)§	24 mos.	84.8% (86/101)	85.9% (87/101)	-1.0% (-10.7%, 8.7%)	0.84
PCM trial (Phillips 2013)	24 mos.	83.4% (156/187)	81.5% (123/151)	2.0% (-6.2%, 10.1%)	0.64
PCM trial (Phillips 2015)*	48 mos.	86.5% (145/168)	78.5% (100/128)	8.2% (-0.7%, 17.0%)	0.07
PCM trial (Phillips 2015)	60 mos.	85.0% (136/160)	74.2% (95/128)	10.8% (1.4%, 20.2%)	0.02
NDI success: postoperative ≥25% improvement from the baseline score					
SECURE-C trial (Vaccaro 2013)†	24 mos.	91.4% (127/139)	87.1% (101/116)	4.3% (-3.4%, 12.0%)	0.27

* Percentages were estimated from graphs; numerators were back-calculated using the estimated percentage and the denominator provided.

† n/N not reported in Vaccaro 2013 publication so were obtained from the SECURE-C FDA SSED report.

‡ Calculated by SRI

§ Numerators were back-calculated using the percentage reported.

Table J3. C-ADR vs. ACDF (1-level) RCT data: NDI scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)§	p-value§
NDI (0-100) higher score = greater disability**					
Prestige ST trial (Burkus 2014)	0 mos.	55.7 ± 14.8 (n=276)	56.4 ± 15.9 (n=264)	NA	NS
Bryan trial (Sasso 2011)	0 mos.	51.4 ± 15.3 (n=242)	50.2 ± 15.9 (n=221)	NA	NS
Mobi-C trial (1 level) (Hisey 2014)	0 mos.	54.0 ± 14.0 (n=164)	54.2 ± 14.6 (n=81)	NA	NS
PCM trial (Phillips 2013)	0 mos.	56 (n=187)	55 (n=151)	NA	NS
ProDisc-C trial (Janssen 2015)	0 mos.	53.9 ± 15.1 (n=103)	52.3 ± 14.5 (n=106)	NR	NS
Karabag 2014	0 mos.	28.2 ± 1.1 (n=19)	29.2 ± 1.0 (n=23)	NA	NS
Rozankovic 2016	0 mos.	50.9 ± 11.5 (n=51)	51.2 ± 8.6 (n=50)	NA	NS
SECURE-C trial (Vaccaro 2013)	0 mos.	51.8 ± 13.8 (n=151)	51.5 ± 14.9 (n=140)	NA	NS
Zhang 2012	0 mos.	51.6 ± 7.2 (n=60)	54.5 ± 8.5 (n=60)	NA	0.055†
Zhang 2014	0 mos.	37.44 (n=55)	37.76 (n=56)	NA	NS
Prestige ST trial (Burkus 2014)	24 mos.	20.0 ± 21.4 (n=253)	22.4 ± 21.5 (n=220)	See meta-analysis for calculations	
ProDisc-C trial (Janssen 2015)‡	24 mos.	Adj. Δ score: -32.0 ± 21.5 (n=101)	Adj. Δ score: -29.8 ± 22.4 (n=101)		
Mobi-C trial (1-level) (Hisey 2016)‡‡	24 mos.	16.6 ± 20.3 (n=155)	12.1 ± 15.6 (n=75)		
Bryan trial (Sasso 2011)	24 mos.	16.2 ± 18.5 (n=229)	19.2 ± 19.3 (n=194)		
PCM trial (Phillips 2013)	24 mos.	21.8 (n=187)	25.5 (n=151)		
Karabag 2014	24 mos.	13.2 ± 1.9 (n=19)	13.6 ± 1.1 (n=23)		
SECURE-C trial (Vaccaro 2013)*	24 mos.	13.2 ± 17.8	16.5 (n=116)		
Zhang 2012	24 mos.	14.9 ± 2.9 (n=56)	15.3 ± 3.8 (n=53)		
Zhang 2014	24 mos.	19.0 (n=55)	19.3 (n=56)		
Rozankovic 2016	24 mos.	11.6 ± 4.4 (n=51)	19.7 ± 6.0 (n=50)		
Bryan trial (Sasso 2011)	48 mos.	13.2 ± 16.1 (n=181)	19.8 ± 20.0 (n=138)	See meta-analysis for calculations	
ProDisc-C trial (Delamarter 2010)	48 mos.	20.3 ± 18.6 (n=65)	21.2 ± 14.9 (n=49)		
Zhang 2014 (48 mos.)	48 mos.	19.6	20.1		

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)§	p-value§
		(n=55)	(n=56)		
Prestige ST trial (Burkus 2014)	60 mos.	17.5 ± 20.4 (n=219)	21.7 ± 20.7 (n=188)		
Mobi-C trial (1-level) (Hisey 2016, 60 mos.)*	60 mos.	16.0 (n=140)	17.0 (n=64)		
PCM trial (Phillips 2015, 60 mos.)*	60 mos.	20.4 (n=160)	28.5 (n=128)		
ProDisc-C trial (Janssen 2015)†	84 mos.	Adj. Δ score: -31.9 ± 20.3 (n=79)	Adj. Δ score: -30.3 ± 20.2 (n=73)	See meta-analysis for calculations	
Prestige ST trial (Burkus 2014)	84 mos.	18.1 ± 20.0 (n=211)	23.8 ± 21.6 (n=181)		

ACDF: anterior cervical discectomy and fusion; ADR: artificial disc replacement; Adj: adjusted; CI: confidence interval; F/U: follow-up; MD: mean difference; NDI: Neck Disability Index; NR: not reported; NS: not significant; SD standard deviation.

* Scores for ACDF were estimated from graphs in the article; patient numbers obtained from the corresponding Secure-C SSED.

† As reported by the study

‡ Mean change scores are used here as they were adjusted for any difference in baseline scores between the groups; the authors reported the adjusted change scores and the corresponding 95% CI (which was converted to SD by SRI)

§ Calculated by SRI

** NDI scale not clearly reported by the majority of studies; the raw score (0-50) should be converted to a final score (0-100), and we assumed this was done (because the baseline scores were commonly >50) unless otherwise indicated.

†† Follow-up scores unless otherwise indicated

‡‡ Data obtained from the Mobi-C (1-level) SSED

Table J4. Cervical ADR vs. ACDF at 1-level RCT data: Efficacy outcomes: NEUROLOGICAL SUCCESS
Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Neurological success: maintenance or improvement (compared with preoperative status) in all 3 of the following clinical findings: motor function, sensory function and deep tendon reflexes.					
Mobi-C trial (1-level) (Hisey 2014)*†	24 mos.	98.1% (152/155)	97.1% (73/75)	See meta-analysis for calculations	
ProDisc-C trial (Janssen 2015)	24 mos.	90.9% (90/99)	88.0% (81/92)		
Prestige ST trial (Burkus 2010)†	24 mos.	91.6% (232/253)	83.6% (184/220)		
Bryan trial (Heller 2009)	24 mos.	93.9% (215/230)	90.2% (175/194)		
PCM trial (Phillips 2013)	24 mos.	94.7% (178/188)	89.5% (137/153)		
SECURE-C trial (Vaccaro 2013)§	24 mos.	96.0% (120/125)	94.9% (93/98)		
ProDisc-C trial (Zigler 2013)†	60 mos.	90.3% (65/72)	91.7% (56/61)	See meta-analysis for calculations	
Bryan trial (Sasso 2011)	48 mos.	92.8% (167/180)	89.9% (124/138)		
Prestige ST trial (Burkus 2014)†	60 mos.	92.2% (203/220)	85.7% (163/190)		
PCM trial (Phillips 2015)	60 mos.	92.4% (146/158)	87.5% (112/128)		
ProDisc-C trial (Janssen 2015)	84 mos.	88% (64/73)	89% (56/63)	See meta-analysis for calculations	
Prestige ST trial (Burkus 2014)†	84 mos.	88.2% (187/212)	79.7% (146/183)		

ACDF: anterior cervical discectomy and fusion; ADR: artificial disc replacement; CI: confidence interval; F/U: follow-up; NR: not reported; NS: not significant; PCM: Porous Coated Motion cervical disc; RD: risk difference.

* As reported by the study.

† Numerators back-calculated based on denominator and percentage given.

§ n/N taken from the SECURE-C SSED

Table J5. C-ADR vs. ACDF (1-level) RCT data: Arm pain success*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Arm (worst) pain success: postoperative ≥20-point improvement on VAS					
PCM trial (Phillips 2013)	24 mos.	79.1% (148/187)	75.3% (113/150)	3.8% (-5.2%, 12.8%)	0.41
PCM trial (Phillips 2015)	60 mos.	80.6% (129/160)	71.1% (91/128)	9.5% (-0.4%, 19.5%)	0.06
Arm pain success: postoperative ≥20-point improvement on VAS					
SECURE-C trial (SECURE-C SSED): Left arm	24 mos.	55.6% (74/133)	50.9% (55/108)	4.7% (-7.9%, 17.4%)	0.47
SECURE-C trial (SECURE-C SSED): Right arm		42.9% (57/133)	45.4% (49/108)	-2.5% (-15.1%, 10.1%)	0.70
Arm pain success: postoperative ≥20-point improvement on VAS or score = 0					
SECURE-C trial (Vaccaro 2013)†: Left arm	24 mos.	75.9% (101/133)	67.6% (73/108)	8.4% (-3.1%, 19.8%)	0.15
SECURE-C trial (Vaccaro 2013)†: Right arm		73.7% (98/133)	70.4% (76/108)	3.3% (-8.1%, 14.7%)	0.57

* Calculated by SRI

†n/N taken from SECURE-C SSED

Table J6. C-ADR vs. ACDF (1-level) RCT data: Arm pain VAS/NRS scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)***	p-value***
VAS/NRS (0-100) higher score = greater pain					
Prestige ST trial (Burkus 2014)*	0 mos.	59.1 ± 29.4 (n=276)	62.4 ± 28.5 (n=264)	NA	NS
ProDisc-C trial (Janssen 2015)	0 mos.	63.9 ± 28.8 (n=103)	61 ± 26.2 (n=104)	NA	NS
Mobi-C trial (1-level) (Hisey 2016)**, §§	0 mos.	71 (n=164)	70.5 (n=81)	NA	NR
Bryan trial (Sasso 2011)†	0 mos.	71.2 ± 19.5 (n=242)	71.2 ± 25.1 (n=221)	NA	NS
PCM trial (Phillips 2013)**	0 mos.	73.5 (n=187)	74.5 (n=150)	NA	NS
SECURE-C trial (Vaccaro 2013)§**	0 mos.	Left arm: 45.1 ± 37.4 (n=151)	Left arm: 39.8 ± 36.3 (n=140)	NA	NS
		Right arm: 33.8 ± 37.0 (n=151)	Right arm: 37.9 ± 37.1 (n=140)	NA	NS
Nabhan 2007‡	0 mos.	73 ± 14 (n=20)	72 ± 15 (n=21)	NA	NS
Rozankovic 2016‡	0 mos.	77 ± 11	77 ± 11	NA	NS

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)***	p-value***
		(n=51)	(n=50)		
Zhang 2012	0 mos.	71.3 ± 7.8 (n=60)	72.1 ± 7.0 (n=60)	NA	NS
Nabhan 2011‡	0 mos.	84 ± 11 (n=10)	82 ± 14 (n=10)	NA	NR
Nabhan 2011‡	12 mos.	12 ± 11 (n=10)	15 ± 13 (n=10)	-3.0 (-14.3, 8.3)	0.58
Prestige ST trial (Burkus 2014)*	24 mos.	13.9 ± 24.6 (n=253)	14.2 ± 24.3 (n=220)	See meta-analysis for calculations	
ProDisc-C trial (Janssen 2015)††	24 mos.	Adj. Δ score: -40.67 ± 29.7 (n=101)	Adj. Δ score: -40.15 ± 31.5 (n=101)		
Mobi-C trial (1-level) (Hisey 2014)§§	24 mos.	13.6 (n=155)	13.5 (n=75)		
Bryan trial (Sasso 2011)†	24 mos.	19.1 ± 27.7 (n=229)	21.5 ± 28.7 (n=194)		
PCM trial (Phillips 2013)**	24 mos.	25 (n=187)	27.5 (n=150)		
SECURE-C trial (Vaccaro 2013)§**, ‡‡	24 mos.	7.5 (n=133)	9.8 (n=108)		
Zhang 2012	24 mos.	16.2 ± 3.8 (n=56)	17.3 ± 4.8 (n=53)		
Nabhan 2007‡	24 mos.	12 ± 3 (n=19)	19 ± 2 (n=20)	-7.0 (-8.7, -5.4)	<0.01
Rozankovic 2016‡	24 mos.	17 ± 8 (n=51)	24 ± 6 (n=50)	-7.0 (-9.8, -4.2)	<0.01
Nabhan 2007‡	36 mos.	12 ± 3 (n=19)	17 ± 2 (n=20)	-5 (-7, -3)	<0.01
ProDisc-C trial (Delamarter 2010)	48 mos.	Δ score: -43.8 (n=65)	Δ score: -40.2 (n=49)	See meta-analysis for calculations	
Mobi-C trial (1-level) (Hisey 2016)**, §§	60 mos.	15.5 (n=140)	15 (n=64)		
Bryan trial (Sasso 2011)†	48 mos.	16.6 ± 24.4 (n=181)	22.4 ± 28.2 (n=138)		
Prestige ST trial (Burkus 2014)*	60 mos.	10.6 ± 21.5 (n=218)	13.6 ± 23.5 (n=189)		
PCM trial (Phillips 2015)**	60 mos.	25.5 (n=160)	31.5 (n=128)		
ProDisc-C trial (Janssen 2015)††	84 mos.	Adj Δ score: -40.72 ± 28.3 (n=79)	Adj Δ score: -38.83 ± 28.6 (n=73)		
Prestige ST trial (Burkus 2014)*	84 mos.	12.7 ± 24.1 (n=210)	15.0 ± 24.9 (n=181)	See meta-analysis for calculations	

* Pain score was calculated by multiplying the duration score (0-10) by the intensity score (0-10)

† Pain measured using the NRS

‡ Score was reported on 0-10 scale; SRI converted the score to a 0-100 scale

§ Study reported individual mean scores (but no SD) from the left and right arm; SRI reported the mean of these scores.

**Scores were estimated from graphs in the articles.

†† Mean change scores are used here as they were adjusted for any difference in baseline scores between the groups; the authors reported the adjusted change scores and the corresponding 95% CI (which was converted to SD by SRI)

‡‡ For the SECURE-C trial (Vaccaro 2013), per FDA, VAS data excludes one site in which some scores were reported verbally.

§§ For the Mobi-C trial, the arm with the worst pain at baseline was followed at each subsequent time-point.

*** Calculated by SRI

Table J7. C-ADR vs. ACDF (1-level) RCT data: Neck OR Arm pain success

Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Neck or arm pain success: postoperative ≥20-point improvement on neck or arm pain VAS					
ProDisc-C trial (Murrey 2009)†	24 mos.	87.9% (89/101)	86.9% (88/101)	1.0% (-8.1%, 10.1%)	0.83

* Calculated by SRI

† Numerators back-calculated based on denominator and percentage given.

Table J8. C-ADR vs. ACDF (1-level): Neck pain success

Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Neck pain success: postoperative ≥20-point improvement on VAS					
PCM trial (Phillips 2013)	24 mos.	74.3% (139/187)	75.3% (113/150)	See meta-analysis for calculations	
SECURE-C trial (SECURE-C SSED)	24 mos.	78.2% (104/133)	70.4% (76/108)		
PCM trial (Phillips 2015)	60 mos.	71.9% (115/160)	75.8% (97/128)	See meta-analysis for calculations	
Neck pain success: postoperative ≥20-point improvement on VAS <u>or</u> score = 0					
SECURE-C trial (Vaccaro 2013)†	24 mos.	81.2% (108/133)	72.2% (78/108)	9.0% (-1.8%, 19.7%)	0.10

* Calculated by SRI

† n/N taken from the SECURE-C SSED

Table J9. C-ADR vs. ACDF (1-level) RCT data: Neck pain VAS/NRS scores
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)\$§	p-value§§
VAS/NRS (0-100) higher score = greater pain					
Prestige ST trial (Burkus 2014)*	0 mos.	68.2 ± 22.7 (n=276)	69.3 ± 21.5 (n=264)	NA	NS
ProDisc-C trial (Janssen 2015)††	0 mos.	73.0 ± 19.5 (n=103)	65.7 ± 21.7 (n=104)	NA	0.012††
Mobi-C trial (1-level) (Hisey 2016)	0 mos.	70.8 ± 22.4 (n=164)	70.1 ± 21.5 (n=81)	NA	NS
Bryan trial (Sasso 2011)†	0 mos.	75.4 ± 19.9 (n=242)	74.8 ± 23.0 (n=221)	NA	NS
PCM trial (Phillips 2013)**	0 mos.	68.5 (n=187)	73.5 (n=150)	NA	0.08
SECURE-C trial (Vaccaro 2013)	0 mos.	65.2 ± 26.8 (n=151)	63.4 ± 27.3 (n=140)	NA	NS
Nabhan 2007‡	0 mos.	60 ± 12 (n=20)	62 ± 09 (n=21)	NA	NS
Rozankovic 2016‡,§	0 mos.	76 ± 14 (n=51)	75 ± 14 (n=50)	NA	NS
Zhang 2012	0 mos.	68.1 ± 8.1 (n=60)	68.8 ± 7.1 (n=60)	NA	NS
Prestige ST trial (Burkus 2014)*	24 mos.	15.6 ± 24.4 (n=253)	16.6 ± 1.62 (n=220)	See meta-analysis for calculations	
ProDisc-C trial (Janssen 2015)††	24 mos.	Adj. Δ score: -44.73 ± 31.3 (n=101)	Adj. Δ score: -42.73 ± 33.0 (n=101)		
Mobi-C trial (1-level) (Hisey 2016)	24 mos.	17.3 (n=155)	19.4 (n=75)		
Bryan trial (Sasso 2011)†	24 mos.	23.0 ± 27.7 (n=229)	30.3 ± 39.7 (n=194)		
PCM trial (Phillips 2013)**	24 mos.	26 (n=187)	30 (n=150)		
SECURE-C trial (Vaccaro 2013)**,‡‡	24 mos.	14.5 (n=133)	20 (n=108)		
Nabhan 2007‡	24 mos.	18 ± 5 (n=19)	27 ± 4 (n=20)		
Rozankovic 2016‡	24 mos.	24 ± 8 (n=51)	35 ± 7 (n=50)		
Zhang 2012	24 mos.	19.1 ± 5.0 (n=56)	21.5 ± 4.9 (n=53)		
Nabhan 2007‡	36 mos.	17 ± 4 (n=19)	25 ± 4 (n=20)		
ProDisc-C trial (Delamarter 2010)	48 mos.	Δ score: -49.3 (n=65)	Δ score: -38.7 (n=49)	See meta-analysis for calculations	
Mobi-C trial (1-level) (Hisey)	60 mos.	19	20		

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)§§	p-value§§
2016)**		(n=140)	(n=64)		
Bryan trial (Sasso 2011)†	48 mos.	20.7 ± 25.3 (n=181)	30.6 ± 30.8 (n=138)		
Prestige ST trial (Burkus 2014)*	60 mos.	12.7 ± 22.4 (n=217)	16.9 ± 24.4 (n=189)		
PCM trial (Phillips 2015)**	60 mos.	25 (n=160)	34 (n=128)		
ProDisc-C trial (Janssen 2015)††	84 mos.	Adj. Δ score: -45.67 ± 29.5 (n=79)	Adj. Δ score: -42.88 ± 29.9 (n=73)	See meta-analysis for calculations	
Prestige ST trial (Burkus 2014)*	84 mos.	13.1 ± 23.3 (n=210)	19.4 ± 24.8 (n=181)		

* Pain score was calculated by multiplying the duration score (0-10) by the intensity score (0-10)

† Pain measured using the NRS

‡ Score was reported on 0-10 scale; SRI converted the score to a 0-100 scale

§ For Rozankovic 2016, baseline scores were reported only after loss to follow-up (N=52 vs. 53 at randomization).

**Scores were estimated from graphs in the articles.

†† Mean change scores at follow-up were reported as they were adjusted for differences in baseline scores between the groups; the authors reported the adjusted change scores and the corresponding 95% CI (which was converted to SD by SRI)

‡‡ For the SECURE-C trial (Vaccaro 2013), per FDA, VAS data excludes one site in which some scores were reported verbally

§§ Calculated by SRI

Table J10. C-ADR vs. ACDF (1-level) RCT data: SF-36 PCS and MCS success*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
SF-36 PCS success: postoperative ≥15% improvement					
PCM trial (Phillips 2013)	24 mos.	71.1% (133/187)	64.9% (98/151)	See meta-analysis for calculations	
SECURE-C trial (Vaccaro 2013)†	24 mos.	79.0% (109/138)	78.1% (89/114)		
ProDisc-C trial (ProDisc SSED)†	24 mos.	51.5% (51/99)	34.4% (31/90)		
PCM trial (Phillips 2015)	60 mos.	73.7% (115/156)	56.7% (72/127)	See meta-analysis for calculations	
SF-36 PCS success: any postoperative improvement from baseline					
ProDisc-C trial (Delamarter 2010)‡	48 mos.	87.1% (57/65)	83.3% (41/49)	4.0% (-9.1%, 17.1%)	0.54
SF-36 MCS success: postoperative ≥15% improvement					
PCM trial (Phillips 2013)	24 mos.	46.5% (87/187)	49.7% (75/151)	See meta-analysis for calculations	
SECURE-C trial (Vaccaro 2013)†	24 mos.	50.7% (70/138)	42.1% (48/114)		
ProDisc-C trial (ProDisc SSED)†	24 mos.	36.4% (36/99)	42.2% (38/90)		
PCM trial (Phillips 2015)	60 mos.	46.2% (72/156)	54.3% (69/127)	See meta-analysis for calculations	
SF-36 MCS success: any postoperative improvement from baseline					
ProDisc-C trial (Delamarter 2010)‡	48 mos.	80.6% (52/65)	73.8% (36/49)	6.5% (-9.2%, 22.3%)	0.41

* Calculated by SRI.

† n/N taken from the FDA SSED

‡ Numerators back-calculated based on denominator and percentage provided.

Table J11. C-ADR vs. ACDF (1-level) RCT data: SF-36 PCS scores

Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
SF-36 PCS (0-100) higher score = less disability					
Prestige ST trial (Burkus 2014)	0 mos.	31.9 ± 7.0 (n=275)	32.0 ± 7.5 (n=263)	NA	NS
Mobi-C trial (1 level)† (Hisey 2014)	0 mos.	32.5 ± 5.9 (n=164)	33.8 ± 6.4 (n=81)	NA	NS
ProDisc-C trial (Janssen 2015)	0 mos.	34.5 ± 7.2 (n=103)	35.2 ± 7.2 (n=104)	NA	NS
Bryan trial (Sasso 2011)	0 mos.	32.6 ± 6.7 (n=242)	31.8 ± 7.2 (n=221)	NA	NS
PCM trial (Phillips 2015)‡	0 mos.	34.5 (n=187)	35 (n=151)	NA	NS
SECURE-C trial (Vaccaro 2013)	0 mos.	33.9 ± 7.4 (n=151)	32.0 ± 6.5 (n=140)	NA	NS
Prestige ST trial (Burkus 2014)	24 mos.	44.6 ± 12.2 (n=248)	44.4 ± 12.0 (n=218)	See meta-analysis for calculations	
Mobi-C trial (1 level)† (Hisey 2014)	24 mos.	48.3 (n=155)	46.5 (n=75)		
ProDisc-C trial (Janssen 2015)§	24 mos.	Adj. Δ score: 13.1 ± 11.8 (n=101)	Adj. Δ score: 10.9 ± 12.4 (n=101)		
Bryan trial (Sasso 2011)	24 mos.	47.9 ± 11.1 (n=229)	46.3 ± 10.8 (n=194)		
PCM trial (Phillips 2015)‡	24 mos.	47 (n=187)	45 (n=151)		
SECURE-C trial (Vaccaro 2013)**	24 mos.	48.5 (n=138)	46.5 (n=115)		
Mobi-C trial (1 level)† (Hisey 2016)	60 mos.	47.6 (n=140)	48.3 (n=64)	See meta-analysis for calculations	
Bryan trial (Sasso 2011)	48 mos.	48.4 ± 10.6 (n=181)	44.9 ± 11.7 (n=138)		
Prestige trial (Burkus 2014)	60 mos.	45.8 ± 11.7 (n=217)	44.7 ± 11.9 (n=187)		
PCM trial (Phillips 2015)	60 mos.	47.5 (n=156)	44 (n=127)		
ProDisc-C trial (Janssen 2015)§	84 mos.	Adj. Δ score: 12.2 ± 10.3 (n=79)	Adj. Δ score: 12.1 ± 10.4 (n=73)		
Prestige trial (Burkus 2014)	84 mos.	45.1 ± 12.0 (n=209)	43.2 ± 12.1 (n=179)	See meta-analysis for calculations	

* Calculated by SRI.

† The Mobi-C trial used the SF-12 PCS.

‡ Scores were estimated from graphs in the articles.

§ Mean change scores were adjusted for any difference in baseline scores between the groups; the authors reported the adjusted change scores and the corresponding 95% CI (which was converted to SD by SRI).

** n/N obtained from the SECURE-C SSED.

Table J12. C-ADR vs. ACDF (1-level) RCT data: SF-36 MCS scores
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
SF-36 MCS (0-100) higher score = less disability					
Prestige ST trial (Burkus 2014)	0 mos.	41.6 (n=276)	42.5 (n=265)	NA	NS
Mobi-C trial (1 level)† (Hisey 2014)	0 mos.	42.1 ± 13.1 (n=164)	42.2 ± 10.4 (n=81)	NA	NS
ProDisc-C trial (Janssen 2015)	0 mos.	40.6 ± 11.7 (n=103)	39.9 ± 12.4 (n=104)	NA	NS
Bryan trial (Sasso 2011)	0 mos.	42.3 ± 12.5 (n=242)	44.6 ± 11.6 (n=221)	NA	0.04††
PCM trial (Phillips 2015)‡	0 mos.	43.5 (n=187)	42 (n=151)	NA	NS
SECURE-C trial (Vaccaro 2013)	0 mos.	44.0 ± 13.2 (n=151)	44.4 ± 12.0 (n=140)	NA	NS
Prestige ST trial (Burkus 2014)	24 mos.	49 (n=223)	50 (n=198)	-1 (NC)	0.56††
Mobi-C trial (1 level)† (Hisey 2014)	24 mos.	51.0 (n=155)	49.2 (n=75)	1.8 (NC)	NR
ProDisc-C trial (Janssen 2015)§	24 mos.	Adj. Δ score: 8.6 ± 13.6 (n=101)	Adj. Δ score: 9.1 ± 14.3 (n=101)	-0.5 (-4.4, 3.4)	0.80
Bryan trial (Sasso 2011)	24 mos.	51.7 (n=230)	51.7 (n=194)	0 (NC)	0.27††
PCM trial (Phillips 2015)‡	24 mos.	50 (n=187)	49 (n=151)	1 (NC)	0.40††
SECURE-C trial (Vaccaro 2013)**	24 mos.	51.5‡ (n=138)	49.5‡ (n=115)	2 (NC)	NR
Mobi-C trial (1 level)† (Hisey 2015)	60 mos.	51‡ (n=148)	51‡ (n=64)	0 (NC)	NS††
PCM trial (Phillips 2015)	60 mos.	52‡ (n=156)	48‡ (n=127)	4 (NC)	<0.01††
ProDisc-C trial (Janssen 2015)§	84 mos.	Adj. Δ score: 8.9 ± 12.1 (n=79)	Adj. Δ score: 6.9 ± 12.3 (n=73)	2.0 (-1.9, 5.9)	0.31

* Calculated by SRI.

† The Mobi-C trial used the SF-12 MCS.

‡ Scores were estimated from graphs in the articles.

§ Mean change scores were adjusted for any difference in baseline scores between the groups; the authors reported the adjusted change scores and the corresponding 95% CI (which was converted to SD by SRI).

** n/N obtained from the SECURE-C SSSED.

†† As reported by the study.

Table J13. C-ADR vs. ACDF (1-level) RCT data: Patient Satisfaction
Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Patient Satisfaction (Very or somewhat satisfied (Mobi-C, PCM trials), Very or somewhat satisfied (60-100 on VAS; ProDisc-C trial); definite or mostly satisfied (SECURE-C trial))					
Mobi-C trial (1-level) (Hisey 2016)†	24 mos.	98% (152/155)	95% (71/75)	See meta-analysis for calculations	
ProDisc-C trial (Delamarter 2010)‡	24 mos.	86.3% (87/101)	83.0% (84/101)		
PCM trial (Phillips 2013)‡	24 mos.	84.4% (160/189)	79.4% (121/153)		
SECURE-C trial (Vaccaro 2013)‡,§	24 mos.	95.7% (133/139)	85.2% (98/115)		
Mobi-C trial (1-level) (Hisey 2016)†	60 mos.	97% (136/140)	96% (61/64)	See meta-analysis for calculations	
ProDisc-C trial (Delamarter 2010)‡	48 mos.	85.7% (56/65)	76.2% (37/49)		
PCM trial (Phillips 2015)‡	60 mos.	88.8% (142/160)	78.7% (101/128)		
Would definitely or probably recommend surgery to a friend					
Mobi-C trial (1-level) (Hisey 2014)**	24 mos.	>93% (n=155)	>93% (n=75)	NR	NR
PCM trial (Phillips 2013)‡	24 mos.	91.9% (174/189)	87.5% (134/153)	4.5% (-2.0%, 11.0%)	0.17
Mobi-C trial (1-level) (Hisey 2016)‡	60 mos.	97.1% (136/140)	91.1% (58/64)	6.5% (-1.1%, 14.2%)	0.046
PCM trial (Phillips 2015)‡	60 mos.	94.4% (151/160)	85.0% (109/128)	9.2% (2.1%, 16.3%)	<0.01
Would undergo the same surgical treatment again					
ProDisc-C trial (Delamarter 2010)‡	24 mos.	85.6% (86/101)	80.9% (82/101)	4.0% (-6.3%, 14.3%)	0.45
ProDisc-C trial (Delamarter 2010)‡	48 mos.	88.9% (58/65)	81.0% (40/49)	7.6% (-5.6%, 20.8%)	0.25

* Calculated by SRI.

† Estimated from graph in article. Numerators back-calculated using estimated percentage.

‡ Numerators back-calculated using estimated percentage.

§ n/N taken from SECURE-C SSED, Table 34.

** No other details reported.

Table J14. C-ADR vs. ACDF (1-level) RCT data: Patient Satisfaction VAS Scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
Patient Satisfaction VAS (0-100) higher score = greater patient satisfaction					
ProDisc-C trial (Janssen 2015)	24 mos.	83.39 ± 24.84 (n=101)	79.99 ± 28.04 (n=101)	See meta-analysis for calculations	
PCM trial (Phillips 2013)	24 mos.	82.8 ± 27.1 (n=189)	81.4 ± 25.7 (n=153)		
ProDisc-C trial (Delamarter 2010)†	48 mos.	85.5 ± 23.7 (n=65)	76.4 ± 30.6 (n=49)	See meta-analysis for calculations	
PCM trial (Phillips 2015)	60 mos.	86.9 ± 21.6 (n=160)	78.3 ± 29.6 (n=128)		
ProDisc-C trial (Janssen 2015)	84 mos.	85.81 ± 23.97 (n=79)	81.81 ± 29.48 (n=73)	See meta-analysis for calculations	

* Calculated by SRI.

† The ProDisc-C trial also reported 60 month data (mean scores, 86.56 vs. 82.74) but no standard deviations were given for this time point.

Table J15. C-ADR vs. ACDF (1-level) RCT data: Odom's Criteria*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Odom's criteria: Excellent					
Peng-Fei 2008	Mean 17 months	50.0% (6/12)	58.3% (7/12)	-8% (-5%, 31%)	0.69
PCM trial (Phillips 2013)	24 mos.	68.6% (129/188)	53.6% (82/153)	15.0% (4.7%, 25.3%)	<0.01
Karabag 2014	24 mos.	21.1% (4/19)	21.7% (5/23)	-1 (-26%, 24%)	0.96
Odom's criteria: Good					
Peng-Fei 2008	Mean 17 months	25.0% (3/12)	25.0% (3/12)	0% (-35%, 35%)	1.0
PCM trial (Phillips 2013)	24 mos.	22.9% (43/188)	32.7% (50/153)	-9.8% (-19.4%, -0.3%)	0.04
Karabag 2014	24 mos.	63.2% (12/19)	60.9% (14/23)	2% (-27%, 32%)	0.88
Odom's criteria: Fair					
Peng-Fei 2008	Mean 17 months	25.0% (3/12)	16.7% (2/12)	8% (24%, 41%)	0.63
PCM trial (Phillips 2013)	24 mos.	8.0% (15/188)	9.8% (15/153)	-1.8% (-7.9%, 4.3%)	0.55
Karabag 2014	24 mos.	10.5% (2/19)	13.0% (3/23)	-3% (-22%, 17%)	0.80
Odom's criteria: Poor					
Peng-Fei 2008	Mean 17 months	0% (0/12)	0% (0/12)	0%	1.0
PCM trial (Phillips 2013)	24 mos.	0.5% (1/188)	3.9% (6/153)	-3.4% (-6.6%, -0.1%)	0.03

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Karabag 2014	24 mos.	5.3% (1/19)	4.3% (1/23)	1% (-12%, 14%)	0.89

* Calculated by SRI.

Table J16. C-ADR vs. ACDF (1-level) RCT data: Return to work
Completer analysis

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Working, not otherwise specified					
Prestige ST trial (Burkus 2014)*§	0 mos.	65.9% (182/276)	62.6% (165/264)	NA	NS
Bryan trial (Sasso 2011)*§	0 mos.	64.5% (156/242)	65.0% (144/221)	NA	NS
ProDisc-C trial (Murrey 2009)†§	0 mos.	82.5% (85/103)	84.9% (90/106)	NA	NS
Prestige ST trial (Mummaneni 2007)*§	24 mos.	75.4% (168/223)	74.7% (148/198)	See meta-analysis for calculations	
Bryan trial (Heller 2009)*§	24 mos.	76.8% (177/230)	73.6% (143/194)		
ProDisc-C trial (Murrey 2009)†§	24 mos.	82.8% (84/101)	80.0% (81/101)		
Skeppholm 2015‡	24 mos.	90.8% (69/76)	85.2% (52/61)		
Bryan trial (Sasso 2011)*§	48 mos.	74.7% (135/181)	67.9% (94/138)	See meta-analysis for calculations	
Prestige ST trial (Burkus 2010)*§	60 mos.	76.3% (110/144)	72.6% (92/127)		
Prestige ST trial (Burkus 2014)*§	84 mos.	73.9% (157/212)	73.1% (132/183)	See meta-analysis for calculations	
Physical labor status: Moderate to heavy work					
ProDisc-C trial (Murrey 2009)	0 mos.	57.1% (59/103)	52.2% (55/106)	NA	NS
ProDisc-C trial (Murrey 2009)	24 mos.	48.1% (49/101)	44.7% (45/101)	4.0% (-9.8%, 17.7%)	0.57

* Working, not otherwise specified

† Working full- or part-time

‡ Working full-time

§ Numerators back-calculated using estimated percentage.

** Calculated by SRI.

Table J17. C-ADR vs. ACDF (1-level) RCT data: Time to Return to Work
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
SECURE-C trial (Vaccaro 2013)	24 mos.	44 ± 74.5 (n=151)	50 ± 72.21 (n=140)	See meta-analysis for calculations	
Mobi-C trial (1-level) (Davis 2014)	24 mos.	30.1 ± 24.6 (n=155) Median 21.0	36.8 ± 40.3 (n=75) Median 22.0		
Prestige ST trial (Mummaneni 2007)	24 mos.	Median 45 (n=223)	Median 61 (n=198)	NC	0.09†
Bryan trial (Heller 2009)	24 mos.	Median 48 (n=230)	Median 61 (n=194)	NC	0.02†
Prestige ST trial (Burkus 2014)	84 mos.	NR (median)	NR (median)	NR	0.02‡; Adj. 0.03†‡, lower in C- ADR group

* Calculated by SRI unless otherwise reported.

† As reported by the study.

‡ Adjusted for preoperative work status.

Table J18. C-ADR vs. ACDF (1-level) RCT data: Nurick Grade
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
Nurick grade (myelopathy): maintained or improved					
PCM trial (Phillips 2013)	24 mos.	100.0% (185/185)	96.7% (148/153)	3.3% (0.5%, 6.1%)	0.01
PCM trial (Phillips 2015)	60 mos.	99.4% (156/157)	96.9% (124/128)	2.5% (-0.8%, 5.6%)	0.11

* Calculated by SRI.

Table J19. C-ADR vs. ACDF (1-level) RCT data: JOA Scores
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
JOA (0-17) higher score = better outcome					
Peng-Fei 2008	0 mos.	8.6 (n=12)	9.0 (n=12)	NA	NR
Zhang 2014	0 mos.	10.86 (n=55)	10.84 (n=56)	NA	NS
Peng-Fei 2008	Mean 17 mos.	15.8 (n=12)	16.2 (n=12)	NR	NS
Zhang 2014	24 mos.	14.8† (n=55)	14.6† (n=56)	NR	NS
Zhang 2014	48 mos.	14.4† (n=55)	14.0† (n=56)	NR	NS

* As reported by the study.

† Estimated from graph in article.

Table J20. C-ADR vs. ACDF (1-level) RCT data: Medication usage
Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
Taking schedule-2 or -3 narcotics					
ProDisc-C trial (Janssen 2015)	0 mos.	48% (49/103)	46% (49/106)	NA	NS
ProDisc-C trial (Murrey 2009)	24 mos.	11.2% (11/101)†	13.0% (13/101)†	-2.0% (-10.9%, 6.9%)	0.66
ProDisc-C trial (Janssen 2015)	84 mos.	12% (9/76)	14% (10/71)	-2.2% (-13.1%, 8.6%)	0.69
Taking muscle relaxants					
ProDisc-C trial (Janssen 2015)	0 mos.	19% (20/103)	22% (23/106)	NA	NS
ProDisc-C trial (Murrey 2009)	24 mos.	8.1% (8/101)†	13.0% (13/101)†	-5.0% (-13.3%, 3.4%)	0.25
ProDisc-C trial (Janssen 2015)	84 mos.	15% (12/79)	11% (8/73)	4.5% (-6.5%, 15.5%)	0.43
Medication use success: absence of strong narcotics and/or muscle relaxants					
ProDisc-C trial (Murrey 2009)	24 mos.	90.0% (91/101)†	79.2% (80/101)†	10.9% (1.1%, 20.7%)	0.03
Medication use success, FDA criteria: absence of strong narcotics					
ProDisc-C trial (Murrey 2009)	24 mos.	98.6% (100/101)†	95.7% (97/101)†	3.0% (-1.3%, 7.2%)	0.18

* Calculated by SRI.

† Numerators were back-calculated using denominators and percentages provided.

Table J21. C-ADR vs. ACDF (1-level) non-randomized study data: Function and pain scores

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
NDI (0-50/100) higher score = greater disability†				
Kim 2009	0 mos.	25.3 ± 1.8 (n = 39)	25.5 ± 1.5 (n = 26)	NS‡
Hou 2014	0 mos.	49.8 ± 19.7 (n = 117)	51.2 ± 17.3 (n = 108)	NS
Kim 2009	Mean 18 (12-40) mos.	7.6 ± 0.9 (n = 39)	7.2 ± 1.6 (n = 26)	NS‡
Hou 2014	Mean 22 (12-26) mos.§	17.2 ± 13.4 (n = 117)	18.3 ± 11.4 (n = 108)	
Pain VAS (0-10) higher score = greater pain				
Kim 2009	0 mos.	8.3 ± 1.0 (n = 39)	8.3 ± 0.9 (n = 26)	NS‡
Hou 2014	0 mos.	8.1 ± 1.1 (n = 117)	8.2 ± 1.4 (n = 108)	NS
Kim 2009	Mean 18 (12-40) mos.	3.7 ± 0.9 (n = 39)	3.8 ± 1.1 (n = 26)	NS‡
Hou 2014	Mean 22 (12-26) mos.§	2.6 ± 1.0 (n = 117)	3.1 ± 0.8 (n = 108)	NS
Arm pain GRS (0-10) higher score = greater pain				
Staub 2016 (matching sub-study)	16.8 ± 8 mos.	Δ from baseline: -4.0 ± 0.3** (n = 190)	Δ from baseline: -3.3 ± 0.3** (n = 190)	0.06
Staub 2016 (atypical patients sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡‡	Δ from baseline: -3.4 ± 0.7** (n = 27)	Δ from baseline: -3.1 ± 0.3** (n = 221)	NS
Staub 2016 (long-term sub-study)	24 mos.	Δ from baseline: -3.7 ± 0.5** (n = 55)	Δ from baseline: -3.0 ± 0.4** (n = 94)	NS
Staub 2016 (long-term sub-study)	60 mos.	Δ from baseline: -3.8 ± 0.5** (n = 55)	Δ from baseline: -3.1 ± 0.4** (n = 94)	NS
Neck pain GRS (0-10) higher score = greater pain				
Staub 2016 (matching sub-study)	16.8 ± 8 mos.	Δ from baseline: -2.7 ± 0.2** (n = 190)	Δ from baseline: -2.3 ± 0.2** (n = 190)	NS
Staub 2016 (atypical patients sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡‡	Δ from baseline: -2.7 ± 0.7** (n = 27)	Δ from baseline: -2.6 ± 0.2** (n = 221)	NS
Staub 2016 (long-term sub-study)	24 mos.	Δ from baseline: -3.0 ± 0.4** (n = 55)	Δ from baseline: -2.2 ± 0.3** (n = 94)	NS
Staub 2016 (long-term sub-study)	60 mos.	Δ from baseline: -2.7 ± 0.4** (n = 55)	Δ from baseline: -2.4 ± 0.4** (n = 94)	NS
COMI (0-10) higher score = greater global distress				
Staub 2016 (matching sub-study)	16.8 ± 8 mos.	Δ from baseline: -4.7 ± 0.2** (n = 190)	Δ from baseline: -3.7 ± 0.2** (n = 190)	<0.01
Staub 2016 (atypical patients sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡‡	Δ from baseline: -3.9 ± 0.6** (n = 27)	Δ from baseline: -3.6 ± 0.2** (n = 221)	NS
Staub 2016 (long-term sub-study)	24 mos.	Δ from baseline: -5.2 ± 0.4** (n = 55)	Δ from baseline: -3.7 ± 0.3** (n = 94)	<0.01
Staub 2016 (long-term sub-study)	60 mos.	Δ from baseline: -4.8 ± 0.5** (n = 55)	Δ from baseline: -3.8 ± 0.3** (n = 94)	0.08

COMI: Core Outcome Measures Index; GRS: graphic rating scale (part of the COMI questionnaire); NS: p>0.05

* As reported by the study unless otherwise indicated.

† For Kim 2009, it is unclear which scale was used.

‡ Calculated by SRI.

§ Last available follow-up data reported rather than 24-month data (for those 89% of patients with 24 month follow-up).

** Standard error

†† For C-ADR vs. ACDF (p=0.04)

‡‡ Based on the adjusted mean difference to control for significant between-group baseline differences (Adj. MD -0.1 (95% CI -1.5 to 1.2)).

Table J22. C-ADR vs. ACDF (1-level) non-randomized study data: Responder outcomes

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Arm pain responders† (≥2-point improvement)	Staub 2016 (matching sub-study)	16.8 ± 8 mos.	78.4% (149/190)	67.4% (128/190)	0.02
	Staub 2016 (atypical sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡	63.0% (17/27)	66.5% (147/221)	NS
	Staub 2016 (long-term sub-study)	≥24 mos.	80.0% (44/55)	64.9% (61/94)	0.05
Neck pain responders† (≥2-point improvement)	Staub 2016 (matching sub-study)	16.8 ± 8 mos.	62.1% (118/190)	57.9% (110/190)	NS
	Staub 2016 (atypical sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡	59.3% (16/27)	61.5% (136/221)	NS
	Staub 2016 (long-term sub-study)	≥24 mos.	63.6% (35/55)	64.9% (61/94)	NS (adj.)§
COMI responders† (≥2-point improvement)	Staub 2016 (matching sub-study)	16.8 ± 8 mos.	81.6% (155/190)	67.9% (129/190)	<0.01
	Staub 2016 (atypical sub-study)	17.5 ± 7.5 vs. 14.2 ± 8.0‡	66.7% (18/27)	67.4% (149/221)	NS
	Staub 2016 (long-term sub-study)	≥24 mos.	76.4% (42/55)	68.1% (64/94)	NS

ADR: artificial disc replacement; CI: Confidence interval; F/U: Follow-up; COMI: Core Outcome Measures Index; NS: p>0.05

* Calculated by the study.

† A responder is defined as achieving minimum clinically important change (MCIC) of 2 points for neck pain relief, arm pain relief, or COMI score.

‡ For ADR vs. Fusion, Follow-up time (mean ± SD): 16.8 ± 8.1 vs. 16.7 ± 7.8 mos.

§ Adj. OR, 1.02 (0.50, 2.11); adjusted for patient age, operated segment, and follow-up time.

C-ADR vs. ACDF (2-level)**Table J23. C-ADR vs. ACDF (2-level) RCT data: Overall success***Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p- value*
Overall success: 1) NDI improvement of at least 15 points (out of 50) from baseline; 2) no subsequent surgical intervention at the index level or levels; 3) no potentially (possibly or probably) device-related adverse event; 4) maintenance or improvement in all components of neurological status; and 5) no Mobi-C intraoperative changes in treatment.					
Mobi-C trial (2-level) (Radcliff 2016)	24 mos.	65.6% (145/221)	42.4% (42/99)	23.2% (11.6%, 34.8%)	<0.01
	48 mos.	61.6% (125/203)	32.6% (29/89)	29.0% (17.2%, 40.8%)	<0.01
	60 mos.	60.8% (124/204)	31.2% (29/93)	29.6% (18.1%, 41.2%)	<0.01
Overall success (alternate NDI requirement, radiographic success): 1) ≥ 30 -point improvement for patients with baseline NDI ≥ 60 or 50% improvement for patients with baseline NDI < 60 ; 2) no subsequent surgical intervention at either treated level; 3) no adverse events assessed by the Clinical Events Committee as major complications; 4) maintenance or improvement in neurological function; and 5) radiographic success (i.e., ADR group: $\geq 2^\circ$ angular motion in flexion/extension or no evidence of bridging trabecular bone across the disc space; ACDF group: fusion of both treated levels— $\leq 2^\circ$ of angular motion in flexion/extension and evidence of bridging bone across the disc space and radiolucent lines at no more than 50% of the graft vertebral interfaces).					
Mobi-C trial (2-level) (Davis 2013)	24 mos.	69.7% (154/221)	37.4% (37/99)	32.3% (21.0%, 43.6%)	<0.01
Mobi-C trial (2-level) (Davis 2015)	48 mos.	66.0% (132/200)	36.0% (31/85)	29.5% (17.4%, 41.7%)	<0.01

* Calculated by SRI

Table J24. C-ADR vs. ACDF (2-level) RCT data: NDI success*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p- value*
NDI success: postoperative ≥ 30 -point improvement on the NDI if the baseline score was ≥ 60 , or $\geq 50\%$ improvement if the baseline score was < 60					
Mobi-C trial (2-level) (Davis 2013)†	24 mos.	78.2% (173/221)	61.8% (61/99)	16.7% (5.7%, 27.7%)	<0.01
Mobi-C trial (2-level) (Davis 2015)†	48 mos.	79.3% (159/200)	53.4% (45/85)	26.6% (14.6%, 38.6%)	<0.01

* Calculated by SRI

† Numerators were back-calculated using the percentage reported.

Table J25. C-ADR vs. ACDF (2-level) RCT data: NDI scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
NDI (0-100) higher score = greater disability†					
Mobi-C trial (2-levels) (Radcliff 2016)	0 mos.	53.9 ± 15.6 (n=225)	55.4 ± 15.3 (n=105)	NA	NS
Cheng 2009	0 mos.	50 (n=31)	51 (n=34)	NA	NS
Mobi-C trial (2-levels) (Radcliff 2016)	24 mos.	16.5 ± 16.9 (n=208)	24.0 ± 19.3 (n=83)	-7.5 (-12.0, -3.0)	<0.01
Cheng 2009	24 mos.	11 (n=30)	19 (n=32)	-8 (NC)	0.02†
Mobi-C trial (2-levels) (Radcliff 2016)	60 mos.	16.8 ± 17.4 (n=186)	26.4 ± 20.4 (n=72)	-9.6 (-14.6, -4.6)	<0.01

* Calculated by SRI.

† Reported by the study

Table J26. C-ADR vs. ACDF (2-level) RCT data: Neurological success*Completer analysis*

Risk of bias	Study	F/U	C-ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Neurological success: maintenance or improvement (compared with preoperative status) in all 3 of the following clinical findings: motor function, sensory function and deep tendon reflexes.						
Moderately Low RoB	Mobi-C trial (2-levels) (Davis 2013)†	24 mos.	94.4% (209/221)	93.3% (92/99)	1.6% (-4.2%, 7.5%)	0.57
Moderately Low RoB	Mobi-C trial (2-levels) (Radcliff 2016)	60 mos.	92.0% (186/204)	94.3% (87/93)	-2.4% (-8.7%, 4.0%)	0.49

RoB: risk of bias

* Calculated by SRI.

† Numerators back-calculated based on denominator and percentage given.

Table J27. C-ADR vs. ACDF (2-level) RCT data: Arm pain VAS scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
VAS (0-100) higher score = greater pain					
Mobi-C trial (2-levels) (Radcliff 2016)	0 mos.	68.7 ± 25.0 (n=225)	72.7 ± 21.6 (n=105)	NA	NS
Cheng 2009†	0 mos.	71 (n=31)	72 (n=34)	NA	NS
Mobi-C trial (2-levels)‡ (Radcliff 2016)	24 mos.	11.9 ± 19.5 (n=208)	16.2 ± 21.9 (n=83)	-4.3 (-9.5, 0.9)	0.10
Cheng 2009†	24 mos.	14 (n=30)	27 (n=32)	-13 (NC)	0.01§
Mobi-C trial (2-levels)‡ (Davis 2015)	48 mos.	Δ score: -56 ± 31 (n=186)	Δ score: -53 ± 31 (n=69)	-3.0 (-11.6, 5.6)	0.49
Mobi-C trial (2-levels)‡,** (Radcliff 2016)	60 mos.	Δ score: -56.8	Δ score: -50.5	-6.3 (NC)	0.15§

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
		(n=186)	(n=72)		

*Calculated by SRI

† Score was reported on 0-10 scale; SRI converted the score to a 0-100 scale

‡For the Mobi-C trial, the arm with the worst pain at baseline was followed at each subsequent time-point.

§As reported by the study

** Study reported follow-up scores (ADR: 11.9 ± 21.2; ACDF: 22.2 ± 27.4) but reported that the difference between groups in change scores was not statistically significant (p=0.15). SRI reported change scores here, as it was the more conservative estimate.

Table J28. C-ADR vs. ACDF (2-level) RCT data: Neck pain VAS scores

Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
VAS (0-100) higher score = greater pain					
Mobi-C trial (2-levels) (Radcliff 2016)	0 mos.	71.2 ± 20.5 (n=225)	74.6 ± 18.9 (n=105)	NA	NS
Cheng 2009†	0 mos.	73† (n=31)	71† (n=34)	NA	NS
Mobi-C trial (2-levels) (Radcliff 2016)	24 mos.	16.6 ± 24.2 (n=208)	20.5 ± 24.0 (n=83)	-3.9 (-10.1, 2.3)	0.21
Cheng 2009†	24 mos.	15 (n=30)	26 (n=32)	-11 (NC)	0.01‡
Mobi-C trial (2-levels) (Davis 2015)	48 mos.	Δ score: -53 ± 30 (n=186)	Δ score: -48 ± 29 (n=69)	-5.0 (-13.3, 3.3)	0.23
Mobi-C trial (2-levels)§ (Radcliff 2016)	60 mos.	Δ score: -52.5 (n=186)	Δ score: -45.8 (n=72)	-6.7 (NC)	0.07‡

*Calculated by SRI

† Score was reported on 0-10 scale; SRI converted the score to a 0-100 scale

‡As reported by the study

§§ Study reported follow-up scores (ADR: 18.7 ± 26.1; ACDF: 28.5 ± 28.8) but reported that the difference between groups in change scores was not statistically significant (p=0.15). SRI reported change scores here, as it was the more conservative estimate.

Table J29. C-ADR vs. ACDF (2-level) RCT data: SF-36 PCS scores

Completer analysis

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
SF-36 PCS (0-100) higher score = less disability					
Mobi-C trial (2-levels) (Radcliff 2016)†	0 mos.	33.4 ± 6.7 (n=225)	32.5 ± 7.7 (n=105)	NA	NS
Cheng 2009	0 mos.	35 (n=31)	34 (n=34)	NA	NS
Mobi-C trial (2-levels) (Radcliff 2016)†	24 mos.	46.9 ± 10.7 (n=208)	43.4 ± 12.6 (n=83)	3.5 (0.6, 6.4)	0.02
Cheng 2009	24 mos.	50	45	5 (NC)	0.01‡

Study	F/U	C-ADR Mean \pm SD (n=30)	ACDF Mean \pm SD (n=32)	MD (95% CI)*	p-value*
Mobi-C trial (2-levels) (Radcliff 2016)†	60 mos.	46.8 \pm 11.3 (n=186)	42.2 \pm 12.3 (n=72)	4.6 (1.4, 7.8)	<0.01
SF-36 MCS (0-100) higher score = less disability					
Mobi-C trial (2-levels) (Radcliff 2016)†	0 mos.	41.9 \pm 11.3 (n=225)	42.01 \pm 11.9 (n=105)	NA	NS
Mobi-C trial (2-levels) (Davis 2013)†	24 mos.	Δ score: 9.5 (n=221)	Δ score: 7.2 (n=99)	2.3 (NC)	0.03‡
Mobi-C trial (2-levels) (Davis 2015)†	48 mos.	11 \pm 12 (n=200)	10 \pm 12 (n=85)	1.0 (-2.1, 4.1)	0.52

* Calculated by SRI.

† Reported the SF-12 PCS.

‡ As reported by the study.

Table J30. C-ADR vs. ACDF (2-level) RCT data: Patient Satisfaction*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Very or somewhat satisfied					
Mobi-C trial (2-level) (Davis 2013)†	24 mos.	95.8% (212/221)	92.0% (91/99)	4.0% (-2.0%, 10.0%)	0.14
Mobi-C trial (2-level) (Radcliff 2016)†	60 mos.	96.4% (179/186)	89.5% (64/72)	7.4% (-0.4%, 15.1%)	0.02
Would definitely or probably recommend surgery to a friend					
Mobi-C trial (2-level) (Davis 2013)†	24 mos.	95.8% (212/221)	88.5% (88/99)	7.0% (0.3%, 13.8%)	0.02
Mobi-C trial (2-level) (Radcliff 2016)†	60 mos.	94.8% (176/186)	84.2% (61/72)	9.9% (1.0%, 18.8%)	0.01

* Calculated by SRI.

† Numerators back-calculated based on denominator and percentage provided.

Table J31. C-ADR vs. ACDF (2-level) RCT data: Odom's Criteria*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Odom's criteria: Excellent or Good					
Cheng 2009	24 mos.	80% (24/30)	68.8% (22/32)	11% (-10%, 33%)	0.32
Odom's criteria: Good					
Cheng 2009	24 mos.	16.7% (5/30)	15.6% (5/32)	1% (-17%, 19%)	0.91
Odom's criteria: Fair					
Cheng 2009	24 mos.	3.3% (1/30)	12.5% (4/32)	-9% (-22%, 4%)	0.19
Odom's criteria: Poor					
Cheng 2009	24 mos.	0% (0/30)	3.1% (1/32)	-3% (-9%, 3%)	0.33

* Calculated by SRI.

Table J32. C-ADR vs. ACDF (2-level) RCT data: Time to Return to Work*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
Time to return to work (mean days after surgery)					
Mobi-C trial (two- levels) (Davis 2015)	48 mos.	46 ± 101 (n=191)†	67 ± 113 (n=86)†	-21 (-48, 6)	0.12

* Calculated by SRI unless otherwise reported.

† Calculated in working patients only.

Table J33. C-ADR vs. ACDF (2-level) non-randomized study data: Function and pain scores

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
NDI (0-50/100) higher score = greater disability†				
Kim 2009	0 mos.	26.4 ± 1.5 (n = 12)	26.2 ± 1.9 (n = 28)	NS‡
Hou 2014	0 mos.	48.6 ± 18.4 (n = 32)	50.2 ± 17.8 (n = 88)	NS
Kim 2009	Mean 18 (13-37) mos. vs. mean 21 (14-38) mos.**	7.8 ± 1.3 (n = 12)	8.0 ± 0.9 (n = 28)	NS
Hou 2014	Mean 24 (12-27) mos.§	19.5 ± 12.7 (n = 29)	18.7 ± 12.3 (n = 82)	NS
Pain VAS (0-10) higher score = greater pain				
Kim 2009	0 mos.	8.8 ± 0.9 (n = 12)	8.1 ± 1.0 (n = 28)	0.04‡, ††
Hou 2014	0 mos.	8.3 ± 1.0 (n = 32)	8.0 ± 0.9 (n = 88)	NS‡
Kim 2009	Mean 18 (13-37) mos. vs. mean 21 (14-38) mos.**	3.3 ± 0.8 (n = 12)	3.4 ± 1.1 (n = 28)	NS
Hou 2014	Mean 24 (12-27) mos.§	2.8 ± 0.9 (n = 29)	3.0 ± 1.0 (n = 82)	NS

NS: p>0.05

* As reported by the study unless otherwise indicated.

† For Kim 2009, it is unclear which scale was used.

‡ Calculated by SRI.

§ Last available follow-up data reported rather than 24-month data (for those 93% of patients with 24 month follow-up).

** For C-ADR vs. ACDF.

†† This difference is not likely to be clinically meaningful.

C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3-levels))**Table J34. C-ADR vs. ACDF (Mixed levels) RCT data: NDI scores***Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
NDI (0-100) higher score = greater disability†					
Skeppholm 2015	0 mos.	64.6 ± 16.2 (n=81)	61.4 ± 14.2 (n=70)	NA	NS
Cheng 2011	0 mos.	50.6 ± 6.0 (n=41)	50.1 ± 5.8 (n=42)	NA	NS
Skeppholm 2015	24 mos.	39.1 ± 20.2 (n=76)	40.1 ± 18.5 (n=67)	-1.0 (-7.4, 5.4)	0.76
Cheng 2011§	24 mos.	13 (n=41)	16 (n=40)	-3 (NC)	<0.01‡
Cheng 2011§	36 mos.	12 (n=41)	17 (n=40)	-5 (NC)	<0.01‡

* Calculated by SRI.

† NDI scale not clearly reported by the majority of studies; the raw score (0-50) should be converted to a final score (0-100), and we assumed this was done (because the baseline scores were commonly >50) except for Qizhi, which reported mean baseline NDI scores of 13.

‡ Reported by the study

§ Data estimated from graph

Table J35. C-ADR vs. ACDF (Mixed levels) RCT data: Arm pain VAS scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
VAS (0-100) higher score = greater pain					
Skeppholm 2015	0 mos.	57.1 ± 27.5 (n=81)	56.9 ± 23.0 (n=70)	NA	NS
	24 mos.	20.7 ± 23.1 (n=76)	20.3 ± 25.7 (n=67)	0.4 (-7.7, 8.5)	0.40

* Calculated by SRI.

Table J36. C-ADR vs. ACDF (Mixed levels) RCT data: Neck pain VAS scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
VAS (0-100) higher score = greater pain					
Skeppholm 2015	0 mos.	57.6 ± 26.4 (n=81)	58.2 ± 23.1 (n=70)	NA	NS
	24 mos.	27.4 ± 27.3 (n=76)	28.6 ± 24.8 (n=67)	-1.2 (-9.9, 7.5)	0.78

* Calculated by SRI.

Table J37. C-ADR vs. ACDF (Mixed levels) RCT data: Quality of Life Scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
SF-36 PCS (0-100) higher score = less disability					
Cheng 2011	0 mos.	35.7 ± 4.3 (n=41)	35.3 ± 4.3 (n=42)	NA	NS
Cheng 2011†	24 mos.	50 (n=41)	45.5 (n=40)	4.5 (NC)	<0.05‡
Cheng 2011†	36 mos.	50.5 (n=41)	44.5 (n=40)	6 (NC)	<0.05‡
EQ-12 (-0.109 - 1) higher score = less disability					
Skeppholm 2015	0 mos.	0.36 ± 0.32 (n=81)	0.47 ± 0.30 (n=70)	NA	0.03
Skeppholm 2015	24 mos.	0.70 ± 0.30 (n=76)	0.71 ± 0.26 (n=67)	-0.01 (-0.10, 0.08)	0.83

* Calculated by SRI.

† Data estimated from graph

‡ As reported by the study

Table J38. C-ADR vs. ACDF (Mixed levels) RCT data: Odom's Criteria*Completer analysis*

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Odom's criteria: Excellent or Good					
Cheng 2011†	36 mos.	58.5% (24/41)	58.5% (23/40)	1% (-20%, 23%)	0.93
Odom's criteria: Good					
Cheng 2011†	36 mos.	34.1% (14/41)	25.0% (10/40)	9% (-11%, 29%)	0.37
Odom's criteria: Fair					
Cheng 2011†	36 mos.	7.3% (3/41)	15.0% (6/40)	7% (-21%, 6%)	0.27
Odom's criteria: Poor					
Cheng 2011†	36 mos.	0% (0/41)	5% (2/40)	-13% (-23%, 3%)	0.02

* Calculated by SRI.

† Numerators back-calculated using estimated percentage.

Table J39. C-ADR vs. ACDF (Mixed levels) RCT data: Time to Return to Work*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
Time to return to work (median days after surgery)					
Cheng 2011	36 mos.	Median 20 (n=41)	Median 84 (n=42)	NR	<0.01

* As reported by the study.

Table J40. C-ADR vs. ACDF (Mixed levels) RCT data: JOA Scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
JOA (0-17) higher score = better outcome					
Cheng 2011	0 mos.	9.0 ± 1.4 (n=41)	8.9 ± 1.4 (n=42)	NA	NS
Cheng 2011	24 mos.	15.3† (n=41)	14.8† (n=40)	NR	0.02
Cheng 2011	36 mos.	15.4† (n=41)	14.7† (n=40)	NR	0.02

* As reported by the study.

† Estimated from graph in article.

Table J41. C-ADR vs. ACDF (Mixed levels) non-randomized study data: Outcome scores

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
NDI (0-50/100) higher score = greater disability‡				
Capelletto 2013	0 mos.	22.5 (n = 84)§	17.0 (n = 92)§	NR
Peng 2011	0 mos.	42.2 ± 12.0 (n = 40)	38.5 ± 12.1 (n = 75)	NS†
Capelletto 2013	12 mos.	3.1 (n = 84)§	6.0 (n = 92)§	<0.043
Peng 2011	24 mos.	15.2 ± 6.8 (n = 40)	15.5 ± 6.6 (n = 75)	NS
Pain VAS (0-10) higher score = greater pain				
Capelletto 2013	0 mos.	7.0 (n = 84)§	1.0 (n = 92)§	NR
Capelletto 2013	12 mos.	5.0 (n = 84)§	1.5 (n = 92)§	NR
Neck pain VAS (0-10) higher score = greater pain				
Peng 2011	0 mos.	5.1 ± 1.6 (n = 40)	4.3 ± 1.2 (n = 75)	<0.01†
Peng 2011	24 mos.	1.8 ± 0.6 (n = 40)	2.0 ± 1.0 (n = 75)	NS
Arm pain VAS (0-10) higher score = greater pain				
Peng 2011	0 mos.	5.4 ± 1.7 (n = 40)	4.0 ± 1.3 (n = 75)	<0.01†
Peng 2011	24 mos.	1.9 ± 0.8 (n = 40)	1.8 ± 0.6 (n = 75)	NS
AAOS Neck Disability Score (0-6) higher score = greater disability				
Peng 2011	0 mos.	3.5 ± 1.7 (n = 40)	4.0 ± 1.8 (n = 75)	NS†
Peng 2011	24 mos.	1.9 ± 0.8 (n = 40)	1.8 ± 0.7 (n = 75)	NS
AAOS Neurogenic Symptom Score (0-6) higher score = greater disability				
Peng 2011	0 mos.	5.5 ± 1.8 (n = 40)	5.6 ± 2.1 (n = 75)	NS†
Peng 2011	24 mos.	2.3 ± 1.2 (n = 40)	2.5 ± 1.1 (n = 75)	NS
JOA (0-17) higher score = better outcome				
Peng 2011	0 mos.	14.7 ± 2.5 (n = 40)	11.6 ± 2.6 (n = 75)	<0.01†
Peng 2011	24 mos.	15.6 ± 3.0 (n = 40)	14.5 ± 2.7 (n = 75)	NS
SF-36 Physical functioning (0-100) higher score = better outcome				
Peng 2011	0 mos.	63.5 ± 20.3 (n = 40)	60.3 ± 19.3 (n = 75)	NS†
Peng 2011	24 mos.	75.0 ± 23.5 (n = 40)	71.0 ± 23.9 (n = 75)	NS†
SF-36 Physical role functioning (0-100) higher score = better outcome				
Peng 2011	0 mos.	41.5 ± 18.2 (n = 40)	33.2 ± 15.2 (n = 75)	0.01†
Peng 2011	24 mos.	57.9 ± 14.2 (n = 40)	64.8 ± 20.2 (n = 75)	0.06†
SF-36 Bodily pain (0-100) higher score = better outcome				

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p- value*
Peng 2011	0 mos.	39.5 ± 15.8 (n = 40)	37.2 ± 14.3 (n = 75)	NR
Peng 2011	24 mos.	60.4 ± 21.2 (n = 40)	57.2 ± 18.9 (n = 75)	NS†
SF-36 General health (0-100) higher score = better outcome				
Peng 2011	0 mos.	64.2 ± 22.8 (n = 40)	66.6 ± 22.1 (n = 75)	NR
Peng 2011	24 mos.	66.4 ± 21.2 (n = 40)	62.0 ± 20.2 (n = 75)	NS†
SF-36 Vitality (0-100) higher score = better outcome				
Peng 2011	0 mos.	46.9 ± 16.3 (n = 40)	50.5 ± 15.3 (n = 75)	NS†
Peng 2011	24 mos.	57.1 ± 13.4 (n = 40)	61.6 ± 21.2 (n = 75)	NS†
SF-36 Social functioning (0-100) higher score = better outcome				
Peng 2011	0 mos.	58.3 ± 18.9 (n = 40)	51.2 ± 16.4 (n = 75)	0.04†
Peng 2011	24 mos.	85.0 ± 24.8 (n = 40)	83.4 ± 28.9 (n = 75)	NS
SF-36 Emotional role functioning (0-100) higher score = better outcome				
Peng 2011	0 mos.	44.4 ± 16.3 (n = 40)	50.3 ± 15.8 (n = 75)	0.06†
Peng 2011	24 mos.	75.4 ± 23.2 (n = 40)	83.3 ± 25.5 (n = 75)	NS†
SF-36 Mental health (0-100) higher score = better outcome				
Peng 2011	0 mos.	65.0 ± 21.2 (n = 40)	66.3 ± 20.3 (n = 75)	NR
Peng 2011	24 mos.	72.4 ± 24.1 (n = 40)	78.3 ± 26.3 (n = 75)	NS
Patient satisfaction (1-6) higher score = better outcome				
Peng 2011	24 mos.	4.5 ± 1.2 (n = 40)	4.4 ± 1.2 (n = 75)	NS†
COMI (0-10) higher score = greater global distress				
Grob 2010	0 mos.	7.2 ± 2.0 (n=73)	6.9 ± 2.1 (n=269)	NS
Grob 2010	12 mos.	Δ from baseline: -4.8 ± 3.0 (n = 58)	Δ from baseline: -3.7 ± 2.9 (n = 208)	<0.01
Grob 2010	24 mos.	Δ from baseline: -5.1 ± 2.8 (n = 30)	Δ from baseline: -3.8 ± 2.9 (n = 139)	0.03

COMI: Core Outcome Measures Index; NS: p>0.05

* As reported by the study unless otherwise indicated.

† Calculated by SRI.

‡ For Cappelletto 2013, it is unclear which scale was used.

§ Estimated from figure.

Table J42. C-ADR vs. ACDF (Mixed levels) non-randomized study data: Responder outcomes

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Complete resolution of radicular pain‡	Capelletto 2013	12 mos.	89% (66/74)	86% (49/57)	NS†
Complete disappearance of myelopathy signs‡	Capelletto 2013	12 mos.	80% (8/10)	51% (20/39)	NS†
Good global outcome (operation helped or helped a lot)§	Grob 2010	12 mos.	89.7% (52/58)	80.3% (167/208)	NS
		24 mos.	93.3% (28/30)	82.0% (114/139)	NS
Good patient satisfaction**	Grob 2010	12 mos.	89.7% (52/58)	80.3% (167/208)	NS†
		24 mos.	93.3% (28/30)	82.0% (114/139)	NS†

ADR: artificial disc replacement; CI: Confidence interval; F/U: Follow-up; COMI: Core Outcome Measures Index; NS: p>0.05

* Calculated by the study.

† Calculated by SRI.

‡ Of those patients who had radicular (with or without myelopathy) at baseline.

§ As opposed to “poor global outcome”, in which the operation only helped a little, did not help, or made things worse.

** Not defined, but dichotomized 5-point Likert scale scores into good vs. poor patient satisfaction.

C-ADR vs. ACDF with a Zero-Profile Device (2 non-contiguous levels)**Table J43. C-ADR vs. ACDF with a zero-profile device (2-level) RCT data: NDI Scores***Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
NDI (assumed 0-50 scale); higher score = greater disability†					
Qizhi 2016	0 mos.	12.9 ± 2.3 (n=14)	13.1 ± 2.3.6 (n=16)	NA	NS
Qizhi 2016	Mean 32.4 mos. (24-46)	3.6 ± 0.9 (n=14)	3.3 ± 0.9 (n=16)	0.3 (-0.4, 1.0)	0.30

* Calculated by SRI.

† NDI scale not clearly reported by the majority of studies; the raw score (0-50) should be converted to a final score (0-100), and we assumed this was done (because the baseline scores were commonly >50) unless otherwise indicated.

Table J44. C-ADR vs. ACDF with a zero-profile device (2-level) RCT data: JOA Scores*Completer analysis*

Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	MD (95% CI)*	p-value*
JOA (0-17) higher score = better outcome					
Qizhi 2016	0 mos.	8.57 ± 1.65 (n=14)	8.44 ± 1.36 (n=16)	NA	NS
Qizhi 2016	Mean 32.4 mos. (24-46)	13.79 ± 1.05 (n=14)	13.69 ± 1.49 (n=16)	0.1 (-0.9, 1.1)	0.84

* As reported by the study.

APPENDIX K. L-ADR SUMMARY SAFETY TABLES.

L-ADR vs. Fusion (1-level)

Table K1. L-ADR vs. Fusion (1 level) RCTs Safety data: Major, device-related, and any adverse events

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Major adverse events						
Major complications‡	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	1.0% (1/99)	0.03% (-2.4, 2.4) 1.0 (0.9, 10.5)	0.9773
	ProDisc-L IDE trial (Zigler 2007)	24 mos.	0% (0/161)	0% (0/75)	0% (NC) NC	NS
	Charite IDE trial (Guyer 2009)	60 mos.	0% (0/90)	0% (0/43)	0% (NC) NC	NS
Severe or life-threatening adverse events	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	0.58 per patient (n=161)	0.38 per patient (n=75)	NR	0.036
Death						
Death (related to treatment)	Charite IDE trial (Blumenthal 2005, FDA SSED 2004)	24 mos.	0.5% (1/205)§	0% (0/99)	0.5% (NC) NC	0.4871
	ProDisc IDE trial (Zigler 2007, FDA SSED 2006)	24 mos.	0% (0/161)	0% (0/75)	0% (NC) NC	NS
Death (unrelated to surgery or implants)	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	2.5% (4/161)	1.3% (1/75)	1.2% (-2.4, 4.7) 1.9 (0.2, 16.4)	0.5683
Device-related major adverse events						
Catastrophic device failure resulting in death or injury	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	0% (0/99)	0% (NC) NC	NS
Device related adverse events** (any/all; including index-level reoperation)	Charite IDE trial (FDA SSED 2004)	24 mos.	7.8% (16/205)	4.0% (4/99)	3.8% (-1.6, 9.1) 1.9 (0.7, 5.6)	0.2155
	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	18.0% (29/161)	21.3% (16/75)	-3.3% (-14.3, 7.7) 0.8 (0.5, 1.5)	0.5462

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Device related adverse events** (any/all; excluding index-level reoperation)	Charite IDE trial (FDA SSED 2004)	24 mos.	7.3% (15/205)	4.0% (4/99)	3.3% (-2.0, 8.5) 1.8 (0.6, 5.3)	0.2695
	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	16.8% (27/161)	16.0% (12/75)	0.8% (-9.3, 10.9) 1.0 (0.6, 2.0)	0.8823
All adverse events (irrespective of relationship to treatment)						
All adverse events/ complications	Charite IDE trial (FDA SSED 2004)	24 mos.	75.6% (155/205)	77.8% (77/99)	-2.2% (-12.3, 7.9) 1.0 (0.9, 1.1)	0.6774
	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	84.5% (136/161)	93.3% (70/75)	-8.9% (-16.8, -0.9) 0.9 (0.8, 1.0)	0.0576
Adverse events (per patient)	ProDisc-L IDE trial (Zigler 2012 Five year)	≤60 mos.	5.1 per patient (n=161)	5.4 per patient (n=75)	NR	0.5072

ADR: artificial disc replacement; CI: confidence interval; DDD: degenerative disc disease; F/U: follow-up; NR: not reported; NS: not significant; RD: risk difference; RR: relative risk.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

‡Defined as major vessel injury, neurological damage, nerve root injury, and death.

§Narcotics-related death.

**Defined as adverse events considered by the investigators to be device-related, including back and lower extremities pain, nerve root injury, implant displacement, and subsidence.

Table K2. L-ADR vs. Fusion (1 level) RCTs Safety Data: Subsequent surgery at the index level

Outcome	F/U	Study	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value‡
Subsequent surgery index level (any)	≤24 mos.	Charite IDE trial (Blumenthal 2005)	5.4% (11/205)	9.1% (9/99)	-3.7% (-10.2, 2.7) 0.6 (0.3, 1.4)	0.2203
		ProDisc-L IDE trial (Zigler 2012 Five-year)	4.3% (7/161)	5.3% (4/75)	-1.0% (-7.0, 5.0) 0.8 (0.3, 2.7)	0.7386
Revision	≤24 mos.	Charite IDE trial (Blumenthal 2005)	2.4% (5/205)	0% (0/99)	NR	NR
		ProDisc-L IDE trial (Zigler 2012 Five-year)	1.2% (2/161)‡	0% (0/75)	NR	NR
Reoperation	≤24 mos.	Charite IDE trial (Blumenthal 2005)	2.0% (4/205)	8.1% (8/99)	NR	NR
		ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)§	2.7% (2/75)	NR	NR
Device/ hardware removal	≤24 mos.	Charite IDE trial (Blumenthal 2005)	1.0% (2/205)	1.0% (1/99)	NR	NR
		ProDisc-L IDE trial (Zigler 2012 Five-year)	0% (0/161)	2.7% (2/75)	NR	NR
Supplemental fixation	≤24 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	0% (0/75)	NR	NR
Hemi-laminotomy and discectomy with nerve root de-compression	≤24 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	0% (0/75)	NR	NR
Surgery not specified	≤24 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	1.2% (2/161)**	0% (0/75)	NR	NR
Subsequent surgery at index level	>24-60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	3.7% (6/161)	6.7% (5/75)	-2.9% (-9.3, 3.4) 0.6 (0.2, 1.8)	0.3195
Supplemental fixation	>24-60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	3.1% (5/161)	0% (0/75)	NR	NR
Reoperation	>24-60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0% (0/161)	4.0% (3/75)	NR	NR
Hardware removal	>24-60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0% (0/161)	2.7% (2/75)	NR	NR
Hemi-laminectomy nerve de-compression + removal of small disc fragment	>24-60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	0% (0/75)	NR	NR
Subsequent surgery at index	≤60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-	8.1% (13/161)	12.0% (9/75)	-3.9% (-12.4, 4.6)	0.3352

Outcome	F/U	Study	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
level		year)			0.7 (0.3, 1.5)	
Revision surgery	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	1.2% (2/161)	0% (0/75)	NR	NR
Reoperation	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	6.7% (5/75)	NR	NR
Device removal	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0% (0/161)	5.3% (4/75)	NR	NR
Supplemental fixation	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0% (6/161)	0% (0/75)	NR	NR
Hem-ilaminotomy + discectomy with nerve root de-compression	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	0% (0/75)	NR	NR
Hemi-laminectomy nerve de-compression + removal of small disc fragment	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	0.6% (1/161)	0% (0/75)	NR	NR
Not specified	60 mos.	ProDisc-L IDE trial (Zigler 2012 Five-year)	1.2% (2/161)	0% (0/75)	NR	NR

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; RD: risk difference; RR: risk ratio.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

‡2 cases of polyethylene migration due to extreme trauma: 1 case (injured while power lifting) sustained an iliac vein laceration during revision surgery and a postoperative compartment syndrome with complications; 1 case (motor vehicle accident 23 mos. post implantation + fall in the shower): patient did not show significant clinical improvement from his preoperative status.

§case of technical error in which the inlay was inserted backward requiring reoperation and reinsertion of the inlay

**1 polyethylene inlay migration within 48 hours that was not locked correctly at the time of implantation and 1 case of implant migration as a result of oversizing.

Table K3. L-ADR vs. Fusion (1 level) RCTs Safety Data: Approach-related adverse events

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
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Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI) [†] RR (95% CI) [†]	p-value [†]
Any approach-related adverse event	Charite IDE trial (Blumenthal 2005, FDA SSED 2004)	Peri-op	9.8% (20/205)	10.1% (10/99)	NR	NR
Dural tear	Charite IDE trial (Blumenthal 2005)	Peri-op	0.5% (1/205)	0% (0/99)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year, FDA SSED 2006)	Peri-op	0% (0/161)	2.7% (2/75)‡	NR	NR
Deep vein thrombosis	Charite IDE trial (Blumenthal 2005)	Peri-op.	0% (0/205)	0% (0/99)	NR	NR
	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	1.2% (2/161)	1.3% (1/75)	NR	NR
Blood loss >1500 cc	Charite IDE trial (Blumenthal 2005)	Peri-op	0.5% (1/205)	2.0% (2/99)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year, FDA SSED 2006)	Peri-op	0% (0/161)	2.7% (2/75)‡	NR	NR
Retrograde ejaculation	Charite IDE trial (Blumenthal 2005)	Peri-op	3.3% (3/99 men)	5.5% (3/55 men)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year, FDA SSED 2006)	Peri-op	1.2% (2/161)	1.3% (1/75)	NR	NR
Venous injury	Charite IDE trial (Blumenthal 2005)	Peri-op	4.4% (9/205)	2.0% (2/99)	NR	NR
Vessel damage/ bleeding (major)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	0.6% (1/161)	1.3% (1/75)		
Vessel damage/ bleeding (minor)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	2.5% (4/161)	6.7% (5/75)		
Ileus	Charite IDE trial (Blumenthal 2005)	Peri-op	1.0% (2/205)	1.0% (1/99)	NR	NR
Vein thrombosis	Charite IDE trial (Blumenthal 2005)	Peri-op	1.0% (2/205)	0% (0/99)	NR	NR
Arterial thrombosis	Charite IDE trial (Blumenthal 2005)	Peri-op	0% (0/205)	0% (0/99)	NR	NR
Thrombosis (NOS)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	0% (0/161)	0% (0/75)		
Incisional hernia	Charite IDE trial (Blumenthal 2005)	Peri-op	0.5% (1/205)	2.0% (2/99)	NR	NR
Epidural hematoma	Charite IDE trial (Blumenthal 2005)	Peri-op.	0.5% (1/205)	0% (0/99)	NR	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
	2005)					
During revision surgery						
Iliac vein laceration	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos.	0.7% (1/134)	0% (0/52)	NR	NR
Blood loss >1500 cc	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos	0.7% (1/134)	0% (0/52)	NR	NR
Compartment syndrome with complications	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos	0.7% (1/134)	0% (0/52)	NR	NR

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; RD: risk difference; RR: risk ratio.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

‡No clinical sequelae.

Table K4. L-ADR vs. Fusion (1 level) RCTs Safety data: Infection

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Any infection	Charite IDE trial (Blumenthal 2005)	≤24 mos.	12.7% (26/205)	8.1% (8/99)	NR	NR
Superficial wound infection with incision site pain	Charite IDE trial (Blumenthal 2005)	≤24 mos.	6.3% (13/205)	2.0% (2/99)	NR	NR
	ProDisc-L IDE trial (Zigler 2007, FDA SSED 2006)	≤24 mos.	0% (0/161)	2.7% (2/75)	NR	NR
Other non-wound-related infection	Charite IDE trial (Blumenthal 2005)	≤24 mos.	2.4% (5/205)	1.0% (2/99)	NR	NR
	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	3.1% (5/161)	6.7% (5/75)	NR	NR
Urinary tract infection	Charite IDE trial (Blumenthal 2005)	≤24 mos.	2.4% (5/205)	1.0% (2/99)	NR	NR
	ProDisc-L IDE trial (FDA	≤24 mos.	0% (0/161)	1.3% (1/75)	NR	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
	SSED 2006)					
Pulmonary infection	Charite IDE trial (Blumenthal 2005)	≤24 mos.	0.5% (1/205)	0% (0/99)	NR	NR
	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	0% (0/161)	1.3% (1/75)	NR	NR
Graft site infection	Charite IDE trial (Blumenthal 2005)	≤24 mos.	0% (0/205)	3.0% (3/99)	NR	NR
	ProDisc IDE trial (Zigler 2012 Five-year)	≤24 mos.	0% (0/161)	0% (0/75)	0% (NC) NC	NS
Wound swelling	Charite IDE trial (Blumenthal 2005)	≤24 mos.	1.0% (2/205)	0% (0/99)	NR	NR
Peritonitis	Charite IDE trial (Blumenthal 2005)	≤24 mos.	0% (0/205)	1.0% (1/99)	NR	NR

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; RD: risk difference; RR: risk ratio.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

Table K5. L-ADR vs. Fusion (1 level) RCTs Safety data: Treatment-Specific Adverse events

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI) [†] RR (95% CI) [†]	p-value [†]
Fusion treatment-related adverse events						
Any fusion treatment-related adverse events	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	27.3% (27/99)	NR	NR
Pseudarthrosis	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	9.1% (9/99)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	0% (0/143)	2.9% (2/69)	NR	NR
	Charite IDE trial (Guyer 2009)	60 mos.	0% (0/90)	11.6% (5/43)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	0% (0/124)‡	4.2% (2/48)‡	NR	0.077
Bone graft donor site pain	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	18.2% (18/99)	NR	NR
Prosthesis-related adverse event						
Any prosthesis-related adverse event	Charite IDE trial (Blumenthal 2005)	24 mos.	3.9% (8/205)	1.0% (1/99)	2.9% (-0.4, 6.2) 3.9 (0.5, 30.5)	0.1639
Collapse or subsidence of implant into adjacent vertebrae	Charite IDE trial (Blumenthal 2005)	24 mos.	3.4% (7/205)	1.0% (1/99)	NR	NR
Implant displacement	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR	NR
Device subsidence	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	1.2% (2/161)	1.3% (1/75)		
	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	0% (0/43)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	1.6% (2/124)‡	0% (0/48)‡	NR	1.0
Implant displacement	Charite IDE trial (Guyer 2009)	60 mos.	2.2% (2/90)	0% (0/43)	NR	NR
Polyethylene inlay migration	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	1.9% (3/161)§	NA	NR	NR
Device migration (radiographic)	ProDisc-L IDE trial (Zigler 2007)	24 mos.	2.1% (3/143)	1.4% (1/69)	NR	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	2.4% (3/124)‡	0% (0/48)‡	NR	0.561

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Device migration (requiring surgery)	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	2.5% (4/161)	0% (0/75)	NR	NR
Device migration (not requiring surgery)	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	1.9% (3/161)	1.3% (1/75)	NR	NR

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; RD: risk difference; RR: risk ratio.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

‡Only patients with complete radiographic data.

§Of the 3 cases of polyethylene migration, 2 were due to extreme trauma (underwent revision surgery, also counted in that outcome) and 1 occurred within 48 hours that was not locked correctly at the time of implantation (underwent a secondary surgery but not type specified; also counted in that outcome).

Table K6. L-ADR vs. Fusion (1 level) RCTs Safety data: Other adverse events and adjacent level surgery

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Annulus ossification	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR	NR
Calcification resulting in bridging trabecular bone	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR	NR
Undefined persistent back pain (requiring supplemental fixation)‡	Charite IDE trial (Guyer 2009)	60 mos.	0% (0/90)	2.3% (1/43)	NR	NR
Symptomatic spondylolisthesis at L5 pars interarticularis (requiring supplemental fixation)‡	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	0% (0/43)	NR	NR
Facet degeneration (requiring supplemental fixation)‡	Charite IDE trial (Guyer 2009)	60 mos.	2.2% (2/90)	2.3% (1/43)	NR	NR
Additional nonsurgical treatment for DDD (pain management)	Charite IDE trial (Guyer 2009)	60 mos.	4.4% (4/90)	13.9% (6/43)	NR	NR
Spinal cord stimulator implantation	ProDisc-L IDE trial (Zigler 2012 Five-year adjacent-level)	60 mos.	0.8% (1/119)§	0% (0/42)	NR	NR
Adjacent level surgery						

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Adjacent level surgery for ASD	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	4.7% (2/43)	NR	NR
Any adjacent level surgery	ProDisc-L IDE trial (Zigler 2012 Five-year adjacent- level)	60 mos.	2.5% (3/119)	7.1% (3/42)	NR	0.682

CI: confidence interval; DDD: degenerative disc disease; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; NS: not significant; RD: risk difference; RR: risk ratio.

*All analyses are based on the baseline, as-treated population:

- For the ProDisc-L IDE trial (Zigler 2007/2012), of a total of 242 patients treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.
- For the Charite IDE trial, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†Calculated.

‡Included under subsequent surgery above.

§While not considered adjacent-level surgery, a spinal cord stimulator was implanted in a fourth L4–5 TDR patient 3 years after the index surgery to address persistent pain at the L5–S1 segment. The index level was not disturbed, with the TDR device left intact.

Table K7. L-ADR vs. Fusion (1-level) Adverse events data from the Charite IDE trial randomized patients plus additional training cases – Cohort analysis

Risk of Bias	Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)
Prospective cohort†					
Moderately High RoB	Charite IDE trial + 71 training cases (Guyer 2008)†	Approach-related event (any)	Peri-op	10.1% (28/276)	NR
		Venous injuries	Peri-op	6.9% (19/276)	NR
		Retrograde ejaculation	Peri-op	2.2% (6/276)	NR
		Ileum	Peri-op	1.8% (5/276)	NR
		Thrombosis	Peri-op	0.7% (2/276)	NR
		Blood loss >1500 cc	Peri-op	0.4% (1/276)	NR
		Hernia	Peri-op	1.1% (3/276)	NR
		Epidural hematoma	Peri-op	0.4% (1/276)	NR
		Dural tear	Peri-op	0.4% (1/276)	NR
		Major neurological event (any)	24 mos.	4.7% (13/276)	NR
		Burning/leg pain	24 mos.	2.9% (8/276)	NR
Motor deficit	24 mos.	1.4% (4/276)	NR		

Risk of Bias	Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)
		Nerve root injury	24 mos.	0.4% (1/276)	NR
		Technique-related event (any)	24 mos.	4.3% (12/276)	NR
		Implant subsidence	24 mos.	2.5% (7/276)	NR
		Implant migration	24 mos.	1.8% (5/276)	NR
		Adjacent level disease	24 mos.	0.7% (2/276)	NR
		Reoperation	24 mos.	5.8% (16/276)	NR

CI: Confidence interval; F/U: Follow-up; L-ADR: Artificial disc replacement NR: Not reported; RD: risk difference; RR: Risk ratio
 NS: p>0.05

*As reported by the study unless otherwise indicated.

†This study includes 71 ADR training cases in addition to the 205 patients randomized to ADR in the Charite IDE trial for the FDA and reported adverse events only. We considered this study a cohort given the nonrandomized nature of the training cases.

Table K8. L-ADR vs. Fusion (1-level) Non-randomized Study Data: Adverse Events

Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)*	RR/OR/HR (95% CI)†	p-value†
Retrospective cohort						
Lee 2015	Surgical-approach-related complications (any)	Peri-op	16.7% (9/54)	5.0% (1/20)	NR	0.192
	Peritoneal injuries	Peri-op	9.3% (5/54)	0% (0/20)	NR	0.1616‡
	Superficial abdominal infection	Peri-op	5.6% (3/54)	0% (0/20)	NR	0.2851‡
	Retrograde ejaculation	Peri-op	1.9% (1/54)	0% (0/20)	NR	0.5428‡
	Dura tear	Peri-op	0% (0/54)	5.0% (1/20)	NR	0.1003‡
	Revision surgery§	≥24 mos.§	10.5% (4/38)**	12.5% (2/16)**	NR	0.833
Administrative database						
Eliasberg 2016	All-cause readmissions following index procedure	3 mos.	4.76% (115/2415)	6.04% (3048/50,462)	NR Adj. OR 0.93 (0.77, 1.13)††	0.009 Adj. 0.456††
		Subsequent lumbar surgery	3 mos.	2.94% (71/2415)	4.01% (2024/50,462)	NR Adj. OR 0.78 (0.61, 0.99)††
		12 mos.	3.46% (84/2415)	4.78% (2412/50,462)	NR	0.009
		36 mos.	4.35% (105/2415)	5.3% (2674/50,462)	NR	0.223

Study	Outcome	F/U	ADR % (n/N)*	Fusion % (n/N)*	RR/OR/HR (95% CI)†	p-value‡
		60 mos.	6.12% (148/2415)	5.54% (2796/50,462)	NR Time to event analysis: HR 0.79 (0.63, 1.0)‡‡	0.858 0.058
	Wound infection	3 mos.	0.25% (6/2415)	1.03% (520/50,462)	NR Adj. OR 0.29 (0.13, 0.66)††	<0.001 Adj. 0.003††
	Mechanical complication	3 mos.	0.87% (21/2415)	0.69% (348/50,462)	NR	0.315
	Pulmonary embolism	3 mos.	0.21% (5/2415)	0.20% (101/50,462)	NR	0.819
	Septicemia	3 mos.	0.12% (3/2415)	0.20% (101/50,462)	NR	0.633
	Surgical site bleeding	3 mos.	0.12% (3/2415)	0.13% (66/50,462)	NR	1.0
	Death	3 mos.	0% (0/2415)	0.14% (72/50,462)	NR	0.08
	Pneumonia	3 mos.	0.04% (1/2415)	0.09% (45/50,462)	NR	0.723
	Myocardial infarction	3 mos.	0.04% (1/2415)	0% (0/50,462)	NR	0.131
	Periprosthetic joint infection	3 mos.	0.04% (1/2415)	0% (0/50,462)	NR	0.131

ADR: Artificial disc replacement; CI: Confidence interval; F/U: Follow-up; NR: Not reported; RR: Risk ratio

NS: p>0.05

*For Lee 2005 and Eliasberg 2016, numerators were back-calculated based on denominators and percentages provided.

†As reported by the study unless otherwise indicated.

‡Calculated by SRI.

§Only patients with at least two years of follow-up (n = 54/74) were included in this analysis; for ADR vs. Fusion, mean follow-up time (range): 4.92 (2.1-9.3) vs. 7.43 (3.7-10.2) months.

**In the ADR group, 1 revision occurred at 2 weeks, 2 at 6 months, and 1 at 12 months; in the fusion group, 1 revision occurred at 48 months, and 1 at 60 months.

††Logistic regression analysis to determine the effects of independent variables on various complications.

‡‡Time-to-event analysis was conducted using a Cox proportional hazards model examining each covariate (i.e., age, sex, race/ethnicity, comorbidities, and insurance type) for potential associations with subsequent lumbar surgery.

L-ADR vs. Fusion (2-level)**Table K9. L-ADR vs. Fusion (2 levels) RCTs safety data: Subsequent surgery at the index level**

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
Secondary surgical procedure at the index level(s) [†]						
<i>ITT analysis</i> [‡]	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	2.4% (4/165)	8.3% (6/72)	-5.9% (-12.7, 0.09) 0.3 (0.1, 0.9)	0.0378
<i>Completers analysis</i> [§]	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	2.8% (4/143)	10.0% (6/60)	-7.2% (-15.3, 0.09) 0.3 (0.1, 0.9)	0.0309
Revision procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	1.4% (1/72)	-0.8% (-3.7, 2.2) 0.4 (0.03, 6.9)	0.5454
Secondary decompression procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	1.8% (3/165)	1.4% (1/72)	0.4% (-3.0, 3.8) 1.3 (0.1, 12.4)	0.8139
Device/implant removal procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0% (0/165)	8.3% (6/72)**	-8.3% (-14.7, -2.0) NC	0.0002

CI: confidence interval; F/U: follow-up; L-ADR: artificial disc replacement; NC: not calculable; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio.

* Calculated by SRI.

[†] The average number of days from the index procedure to secondary surgery was 567.7 (range, 480 to 736) in the ADR group and 255.5 (range, 21 to 560) in the fusion group.

[‡] ITT analyses are based on the baseline, as-treated population: 10 Fusion patients and 9 ADR patients did not received the treatment they were randomized to and they are not accounted for in any analysis.

[§] A total of 203 patients (including 143 in the total disc replacement group and 60 in the fusion group) had complete data sets at twenty-four months; this is the denominator that was used for safety after loss-to-follow-up.

** One of the fusion patients underwent implant removal, decompression (bilateral medial facetectomy and hemilaminectomy), and revision of the bone fusion sites because of a pseudarthrosis at L5-S1; this patients is included in all three secondary surgery categories but only included once for the total risk of any subsequent surgery.

Table K10. L-ADR vs. Fusion (2 levels) RCTs safety data: Major adverse events

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
Death (unrelated to treatment)						
<i>ITT analysis†</i>	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	0% (0/72)	0.6% (NC) NC	0.5089
<i>Completers analysis‡</i>	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.7% (1/143)	0% (0/60)	0.7% (NC) NC	0.5171
Major-surgery-related complications (any)	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.7% (5/165)	4.9% (7/72)	-6.7% (-14.0, 0.6%) 0.3 (0.1, 0.9)	0.0311
Dural tear§	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.6% (1/165)	4.2% (3/72)	-3.6% (-8.3, 1.2) 0.1 (0.02, 1.4)	0.0508
Blood loss of >1500 mL**	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	1.2% (2/165)	2.8% (2/72)	-1.6% (-5.7, 2.6) 0.4 (0.06, 3.0)	0.3905
Iliac artery tear	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.6% (1/165)	0% (0/72)	0.6% (NC) NC	0.5089
Deep vein thrombosis	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Postop	1.2% (2/165)	2.8% (2/72)	-1.6% (-5.7, 2.6) 0.4 (0.06, 3.0)	0.3905

CI: confidence interval; F/U: follow-up; L-ADR: artificial disc replacement; NC: not calculable; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio.

* Calculated by SRI.

† ITT analyses are based on the baseline, as-treated population: 10 Fusion patients and 9 ADR patients did not received the treatment they were randomized to and they are not accounted for in any analysis.

‡ A total of 203 patients (including 143 in the total disc replacement group and 60 in the fusion group) had complete data sets at twenty-four months; this is the denominator that was used for safety after loss-to-follow-up.

§ All successfully repaired.

** Of the patients who had clinically significant blood loss, 1 of the 2 ADR patients sustained an iliac artery tear, while the other ADR patient and all fusion patients had excessive oozing from the decompression, decorticated bone, and graft sites.

Table K11. L-ADR vs. Fusion (2 levels) RCTs safety data: Other reported complications

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Implant migration (anterior)‡	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	NR	NC	NC
Pseudarthrosis	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	NR	1.4% (1/72)§	NC	NC
Radiolucency or halos around implant	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0% (0/165)	4.2% (3/72)	-4.2 (-8.8, 0.5) NC	0.0085
Implant subsidence (>3 mm)**	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	1.8% (3/165)	NR	NC	NC
Implant migration or subsidence (>3 mm)	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	NR	1.4% (1/72)	NC	NC

CI: confidence interval; F/U: follow-up; L-ADR: artificial disc replacement; NC: not calculable; NR: not reported; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio.

* All analyses are based on the baseline, as-treated population: 10 Fusion patients and 9 ADR patients did not received the treatment they were randomized to and they are not accounted for in any analysis.

† Calculated by SRI.

‡ Migration of the superior implant resulting in revision arthrodesis (same patient as included in “revision” under subsequent surgeries at the index level.

§ Same patient with who underwent device removal, decompression, and revision procedures (also counted under those outcomes).

** Not clinically relevant in any patient.

†† All successfully repaired.

‡‡Of the patients who had clinically significant blood loss, 1 of the 2 ADR patients sustained an iliac artery tear, while the other ADR patient and all fusion patients had excessive oozing from the decompression, decorticated bone, and graft sites.

L-ADR vs. Fusion (1- to 2-level)**Table K12. L-ADR vs. Fusion (1- or 2- levels) RCTs safety data: Complications**

Outcome	Study	F/U*	ADR % (n/N)	Control % (n/N)	RD (95% CI) [†] RR (95% CI) [†]	p-value [†]
Total complications‡	Berg trial (Berg 2009 Total disc)	24 mos.	17.5% (14/80)	20.8% (15/72)	-3.3% (-15.9, 9.2) 0.8 (0.4, 1.6)	0.6027
	Berg trial (Skold 2013)	60 mos.	16.3% (13/80)	12.7% (9/71)	3.6% (-7.6, 14.7) 1.3 (0.6, 2.8)	0.5357
Total major complications‡	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	8.3% (6/72)	-5.8% (-13.1, 1.4) 0.3 (0.6, 1.4)	0.1090
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	8.5% (6/71)	-6.0% (-13.3, 1.4) 0.3 (0.6, 1.4)	0.1044
Infection (major)	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	5.6% (4/72)	-5.6% (-10.9, -0.03) NC	0.0332
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	5.6% (4/71)	-5.6% (-11.0, -0.03) NC	0.0320
Pseudarthrosis	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	2.8% (2/72)	-2.8% (-6.6, -1.0) NC	0.1347
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	2.8% (2/71)	-2.8% (-6.7, -1.0) NC	0.1320
Nerve entrapment	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	1.3% (NC) NC	0.3428
Subsidence/ reoperation	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	1.3% (NC) NC	0.3428
Total minor complications‡	Berg trial (Berg 2009 Total disc)	24 mos.	15.0% (12/80)	12.5% (9/72)	2.5% (-8.4, 13.4) 1.2 (0.5, 2.7)	0.6567
	Berg trial (Skold 2013)	60 mos.	13.8% (11/80)	4.2% (3/71)	9.5% (0.7, 18.4) 1.2 (0.5, 2.7)	0.0447
Hematoma	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	1.4% (1/72)	1.1% (-3.3, 5.5) 1.8 (0.2, 19.4)	0.6240
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	1.4% (1/71)	1.1% (-3.3, 5.5) 1.8 (0.2, 19.2)	0.6325

Outcome	Study	F/U*	ADR % (n/N)	Control % (n/N)	RD (95% CI)† RR (95% CI)†	p-value‡
Suspected facet joint pain	Berg trial (Berg 2009 Total disc)	24 mos.	7.5% (6/80)	0% (0/72)	7.5% (NC) NC	0.0181
	Berg trial (Skold 2013)	60 mos.	7.5% (6/80)	0% (0/71)	7.5% (NC) NC	0.0189
Wound hernia	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	0% (0/71)	2.5% (NC) NC	0.1783
Donor site pain	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	-1.4% (-4.1, 1.3) NC	0.2918
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1.4% (1/71)	-1.4% (-4.1, 1.3) NC	0.2918
Adjacent	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	8.3% (6/72)	-7.1% (-13.9, -0.3)	0.0381
Dural tear	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	1.4% (1/72)	-0.1% (-3.8, 3.5) 0.9 (0.06, 14.1)	0.9404
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1.4% (1/71)	-1.4% (-4.1, 1.3) NC	0.2918
Meralgia paresthetica	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	1.3% (NC) NC	0.3428

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NC: not calculable; NR: not reported; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio.

*No events were specifically stated as being “peri-procedural”. Some, by their very nature, most likely were, however (e.g., dural tear).

†Calculated by SRI.

‡The grading of complications into major and minor used in “The Swedish Spine Study” was applied here. Major complications were defined as potentially life threatening or cause of considerable suffering and minor as reversible relevant minor event/cause of minor suffering.

Table K13. L-ADR vs. Fusion (1- or 2- levels) RCTs safety data: Subsequent surgery at the index and adjacent level and additional interventions

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
Reoperation at index level (device- related)	Berg trial (Berg 2009 total disc)	24 mos.	5.0% (4/80)	27.8% (20/72)	-22.8% (-34.2, -11.4) 0.2 (0.06, 0.5)	0.0001
	Berg trial (Skold 2013)	60 mos.	11.3% (9/80)	28.2% (20/71)	-16.9% (-29.5, -4.4) 0.4 (0.2, 0.8)	0.01
Extraction of pedicle screws (due to pain)	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	27.8% (20/72)	-27.8% (-38.1, -17.4) NC	<0.0001
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	28.2% (20/71)	-26.9% (-37.7, -16.2)	<0.0001
Fusion at ADR level	Berg trial (Berg 2009 Total disc)	24 mos.	5.0% (4/80)	0% (0/72)	5.0% (NC) NC	0.0553
	Berg trial (Skold 2013)	60 mos.	10.0% (8/80)	0% (0/71)	10.0% (NC) NC	0.0064
Reoperation at index level (non-device related)†	Berg trial (Berg 2009 total disc)	24 mos.	5.0% (4/80)	2.8% (2/72)	2.2% (-3.9, 8.3) 1.8 (0.3, 9.5)	0.4838
	Berg trial (Skold 2013)	60 mos.	6.3% (5/80)	8.5% (6/71)	-2.2% (-10.6, 6.2) 0.7 (0.2, 2.3)	0.6047
Decompression	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	1 procedure	0% (0/71)	NC	NR
Extraction of pedicle screws + decompression	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	-1.4% (-4.1, 1.3) NC	0.2918
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1 procedure	NC	NR
Re-fusion	Berg trial (Skold 2013)	60 mos.	1 procedure	5 procedures	NC	NR
Hematoma removal	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	0% (0/72)	2.5% (NC) NC	0.1783
	Berg trial (Skold 2013)	60 mos.	2 procedures	1 procedure	NC	NR
Hernia repair	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	1.3% (NC) NC	0.3428
	Berg trial (Skold 2013)	60 mos.	4 procedures	0% (0/71)	NR	NR

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	RD (95% CI)* RR (95% CI)*	p-value*
	2013)					
Dural tear repair	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	-1.4% (-4.1, 1.3) NC	0.2918
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1 procedure	NC	NR
New operation at new level‡	Berg trial (Skold 2013)	60 mos.	7 procedures	11 procedures	NC	NR
ADR above fusion	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	6.9% (5/72)	-6.9 (-12.8, -1.1)	0.0169
ADR	Berg trial (Skold 2013)	60 mos.	2 procedures	8 procedures	NC	NR
PLF	Berg trial (Skold 2013)	60 mos.	3 procedures	0% (0/71)	NC	NR
Decompression + PLF	Berg trial (Skold 2013)	60 mos.	0% (0/80)	2 procedures	NC	NR
Decompression	Berg trial (Skold 2013)	60 mos.	1 procedure	1 procedure	NC	NR
Disc hernia	Berg trial (Skold 2013)	60 mos.	1 procedure	0% (0/71)	NC	NR
Reoperation, new operation, or both	Berg trial (Skold 2013)	60 mos.	20.0% (16/80)	42.3% (30/71)	-22.3% (-36.7, -7.8) 0.5 (0.3, 0.8)	0.0031
Additional interventions						
Facet block	Berg trial (Berg 2009 Total disc)	Post-op	27.5% (22/80)	1.4% (1/72)	26.1% (-16.0, -36.3) 19.8 (2.7, 143.2)	<0.0001
Discography	Berg trial (Berg 2009 Total disc)	Post-op	2.5% (2/80)	12.5% (9/72)	-10.0% (-18.4, -1.6) 0.2 (0.4, 0.9)	0.0179

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NC: not calculable; NR: not reported; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio.

*Calculated by SRI.

†For non-device related reoperation the total number of patients with any (1+) such reoperation was provided; however, only the number of procedures were given for each individual operation type and patients could have more than one operation.

‡ For new operation at new level, the total number of patients with any (1+) such reoperation was not provided and since patients could have more than one procedure, only the number of procedures is reported.

Table K14. L-ADR vs. Fusion (2 levels) Nonrandomized safety data: Reoperations

Study	Outcome	F/U	L-ADR % (n/N)	Anterior Fusion % (n/N)	Posterior Fusion % (n/N)	p-value*
Retrospective cohort (multi-level; number of levels treated NR)						
Lindley 2012	Retrograde ejaculation†	NR	9.8% (4/41)	7.4% (4/54) (w/ BMP)	NA	0.7226
Registry (1- or 2-levels)						
Berg 2010	Reoperation	12 mos.	8% (11/132)	10% (15/147)	NR	NR
		24 mos.	0% (0/53)	10% (8/84)	NR	NR
Administrative database (multi-level; number of levels treated NR)						
Kurtz 2010‡	Routinely discharged to home	24 mos.	89.0% (5669/6370 procedures)	76.3% (45,086/59,090 procedures)	68.8% (196,114/285,050 procedures)	NR
	In-hospital mortality	24 mos.	0.1% (6/6370 procedures)	0.3% (177/59,090 procedures)	0.2% (570/285,050 procedures)	NR
	Device-related infections	24 mos.	0% (0/6370 procedures)	0.5% (295/59,090 procedures)	0.2% (570/285,050 procedures)	NR
	Device-related mechanical complications	24 mos.	0.7% (45/6370 procedures)	4.9% (2895/59,090 procedures)	2.5% (7126/285,050 procedures)	NR
	Average revision burden	24 mos.	11.2% (800/7170 procedures)	5.8% (3650/62,740 procedures)	7.4% (22,700/307,750 procedures)	<0.0001 vs ALIF and PLIF

ALIF: anterior lumbar interbody fusion; CI: Confidence interval; F/U: Follow-up; L-ADR: lumbar artificial disc replacement; NR: Not reported; PLIF: posterior lumbar interbody fusion

*As calculated by the study.

†Of the 8 patients who experienced RE, 2 reported resolution of their symptoms (1 ADR and 1 ALIF). In addition, 2 patients (2.1%) who received ALIF with BMP were found to have sexual dysfunction other than RE, including difficulty obtaining an erection, painful erection, and a decrease in sexual desire.

‡For all outcomes except revision, only data for patients who underwent primary L-ADR or Fusion (anterior or posterior) were included in this report.

L-ADR vs. Multidisciplinary Rehabilitation**Table K15. L-ADR vs. Multidisciplinary Rehabilitation RCTs safety data: Major and any complication**

Outcome	Study	F/U	ADR* % (n/N)	Rehab % (n/N)	RD (95% CI)† RR (95% CI)†	p-value‡
Total with any complication						
<i>ITT analysis*</i>	Hellum 2011	≤24 mos.	33.8% (26/77)	NA	NA	NA
<i>Completer analysis</i>	Hellum 2011	24 mos.	36.6% (26/71)	NA	NA	NA
Dural tear	Hellum 2011	Peri-op	1.4% (0/77)	NA	NA	NA
Blood loss of >1500 mL	Hellum 2011	Peri-op	5.2% (4/77)	NA	NA	NA
Abdominal hernia	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA	NA
Superficial haematoma	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA	NA
Ileus	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA	NA
Temporary warm left foot	Hellum 2011	Peri-op	2.6% (2/77)	NA	NA	NA
Superficial wound infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA	NA
Deep wound infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA	NA
Urinary tract infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA	NA
Intimal lesion in left common iliac artery‡,§	Hellum 2011	3 mos.	1.3% (1/77)	NA	NA	NA
Retrograde ejaculation§	Hellum 2011	12 mos.	1.3% (1/77)	NA	NA	NA
Temporary nausea	Hellum 2011	12 mos.	1.3% (1/77)	NA	NA	NA
Motor deficit	Hellum 2011	24 mos.	0% (0/71)	NA	NA	NA
Temporary motor deficit	Hellum 2011	24 mos.	0% (0/71)	NA	NA	NA
Sensory loss (thigh)§	Hellum 2011	24 mos.	2.6% (2/77)	NA	NA	NA
Temporary sensory loss	Hellum 2011	24 mos.	5.2% (4/77)	NA	NA	NA
Radicular pain (new)§	Hellum 2011	24 mos.	2.6% (2/77)	NA	NA	NA
Temporary radicular pain	Hellum 2011	24 mos.	5.2% (4/77)	NA	NA	NA
Arterial thrombosis of dorsalis pedis artery (temporarily slightly colder foot)§	Hellum 2011	24 mos.	1.3% (1/77)	NA	NA	NA
Major complication resulting in impairment§						
<i>ITT analysis*</i>	Hellum 2011	24 mos.	7.8% (6/77)	NA	NA	NA

Outcome	Study	F/U	ADR* % (n/N)	Rehab % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
<i>Completer analysis</i>	Hellum 2011	24 mos.	8.5% (6/71)	NA	NA	NA
Worsening of low back pain	Hellum 2011	24 mos.	11% (8/73)**	9% (6/67)**	2.0% (-7.9, 11.9) 1.2 (0.4, 3.3)	0.6941

F/U: follow-up; L-ADR: artificial disc replacement; NA: not applicable; NR: not reported; RCT: randomized controlled trial; Rehab: rehabilitation; RD: risk difference; RR: risk ratio.

* ITT analyses are based on the baseline, as-treated population: Six patients (3 in each group) were excluded shortly after randomization and not accounted for in the studies analyses.

†Calculated by SRI.

‡ At the 3 month follow-up, the polyethylene inlay was found to be dislodged. During revision surgery, injury to the left common iliac artery led to compartment syndrome resulting in a lower leg amputation.

§ These adverse events were classified as “Major complications resulting in impairment” (see outcome); a total of 7 events in 6 patients were reported at the 24 month follow-up.

**Denominators back-calculated based on % and numerators provided.

Table K16. L-ADR vs. Multidisciplinary Rehabilitation RCTs safety data: Subsequent surgery at the index level.

Outcome	Study	F/U	ADR* % (n/N)	Rehab % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Total reoperation/operation						
<i>ITT analysis*</i>	Hellum 2011	24 mos.	6.5% (5/77)	NA	NA	NA
<i>Completer analysis</i>	Hellum 2011	24 mos.	7.0% (5/71)	NA	NA	NA
Subsequent fusion surgery at index level§	Hellum 2011	24 mos.	2.8% (2/71)	NA	NA	NA
Reoperation at index level**	Hellum 2011	24 mos.	1.4% (1/71)	NA	NA	NA
Subsequent surgery – resection of spinous process††	Hellum 2011	24 mos.	2.8% (2/71)	NA	NA	NA

F/U: follow-up; L-ADR: artificial disc replacement; NA: not applicable; NR: not reported; RCT: randomized controlled trial; Rehab: rehabilitation; RD: risk difference; RR: risk ratio.

* ITT analyses are based on the baseline, as-treated population: Six patients (3 in each group) were excluded shortly after randomization and not accounted for in the studies analyses.

† Calculated by SRI.

‡ Five patients underwent ADR and one patient received fusion; one patient crossed over between 6 and 12 months and five patients between 12 and 24 months.

§ At level with disc prosthesis and level above.

** Insertion of new polyethylene inlay (same patient with intimal lesion in left common iliac artery).

†† Partial resection of spinous process because of possible painful contact between adjacent levels; both patients were experiencing persistent back pain.

APPENDIX L. L-ADR SAFETY DATA ABSTRACTION TABLES.**L-ADR vs. Fusion (1-level)****Table L1. L-ADR vs. Fusion (1 level) RCT data: Safety data abstraction – Charite IDE trial**

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
Major complications‡	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	1.0% (1/99)	NR
Subsequent surgery at index level	Charite IDE trial (Blumenthal 2005)	24 mos.	5.4% (11/205)	9.1% (9/99)	NR
Revision	Charite IDE trial (Blumenthal 2005)	24 mos.	2.4% (5/205)	0% (0/99)	NR
Reoperation	Charite IDE trial (Blumenthal 2005)	24 mos.	2.0% (4/205)	8.1% (8/99)	NR
Device/hardware removal	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	1.0% (1/99)	NR
Death	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)§	0% (0/99)	NR
Any approach-related adverse event	Charite IDE trial (Blumenthal 2005)	24 mos.	9.8% (20/205)	10.1% (10/99)	NR
Venous injury	Charite IDE trial (Blumenthal 2005)	24 mos.	4.4% (9/205)	2.0% (2/99)	NR
Retrograde ejaculation	Charite IDE trial (Blumenthal 2005)	24 mos.	3.3% (3/99 men)	5.5% (3/55 men)	NR
Ileus	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	1.0% (1/99)	NR
Perioperative vein thrombosis,	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	0% (0/99)	NR
Blood loss >1500 cc	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	2.0% (2/99)	NR
Incisional hernia	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	2.0% (2/99)	NR
Epidural hematoma	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
Dural tear	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
DVT	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	0% (0/99)	NR
Arterial thrombosis	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	0% (0/99)	NR
Any infection	Charite IDE trial (Blumenthal 2005)	24 mos.	12.7% (26/205)	8.1% (8/99)	NR
Superficial wound infection with incision site pain	Charite IDE trial (Blumenthal 2005)	24 mos.	6.3% (13/205)	2.0% (2/99)	NR
Other non-wound-related infection	Charite IDE trial (Blumenthal 2005)	24 mos.	2.4% (5/205)	1.0% (2/99)	NR
Urinary tract infection	Charite IDE trial (Blumenthal 2005)	24 mos.	2.4% (5/205)	1.0% (2/99)	NR
Wound swelling	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	0% (0/99)	NR
Pulmonary infection	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
Peritonitis	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	1.0% (1/99)	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
Graft site infection	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	3.0% (3/99)	NR
Any fusion treatment-related adverse events	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	27.3% (27/99)	NR
Nonunion/pseudarthrosis	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	9.1% (9/99)	NR
Bone graft donor site pain	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	18.2% (18/99)	NR
Any prosthesis-related adverse event	Charite IDE trial (Blumenthal 2005)	24 mos.	3.9% (8/205)	1.0% (1/99)	NR
Collapse or subsidence of implant into adjacent vertebrae	Charite IDE trial (Blumenthal 2005)	24 mos.	3.4% (7/205)	1.0% (1/99)	NR
Implant displacement	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
Device related adverse events** (any/all; including index-level reoperation)	Charite IDE trial (FDA SSED 2004)	24 mos.	7.8% (16/205)	4.0% (4/99)	NR
Device related adverse events** (any/all; excluding index-level reoperation)	Charite IDE trial (FDA SSED 2004)	24 mos.	7.3% (15/205)	4.0% (4/99)	NR
Catastrophic device failure resulting in death or injury	Charite IDE trial (Blumenthal 2005)	24 mos.	0% (0/205)	0% (0/99)	NR
Any other adverse events	Charite IDE trial (Blumenthal 2005)	24 mos.	1.0% (2/205)	0% (0/99)	NR
Annulus ossification	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
Calcification resulting in bridging trabecular bone	Charite IDE trial (Blumenthal 2005)	24 mos.	0.5% (1/205)	0% (0/99)	NR
All adverse events and complications (irrespective of relationship to treatment)	Charite IDE trial (FDA SSED 2004)	24 mos.	75.6% (155/205)	77.8% (77/99)	NR
Guyer 2009 includes only patients with both 24 and 60 months data from 8 of the original 14 study sites					
Major complications‡	Charite IDE trial (Guyer 2009)	60 mos.	0% (0/90)	0% (0/43)	NS
Subsequent surgery at index level	Charite IDE trial (Guyer 2009)	≤24 mos.	5.5% (5/90)	16.3% (7/43)	NR
Supplemental fixation	Charite IDE trial (Guyer 2009)	≤24 mos.	5.5% (5/90)	14.0% (6/43)	NR
Reoperation	Charite IDE trial (Guyer 2009)	≤24 mos.	0% (0/90)	2.3% (1/43)	NR
Subsequent surgery at index level	Charite IDE trial (Guyer 2009)	>24-60 mos.	2.2% (2/90)	0% (0/43)	NR
Supplemental fixation	Charite IDE trial (Guyer 2009)	>24-60 mos.	1.1% (1/90)	0% (0/43)	NR
Reoperation	Charite IDE trial (Guyer 2009)	>24-60 mos.	1.1% (1/90)	0% (0/43)	NR
Subsequent surgery at index level	Charite IDE trial (Guyer 2009)	≤60 mos.	7.7% (7/90)	16.3% (7/43)	0.144
Supplemental fixation	Charite IDE trial (Guyer 2009)	≤60 mos.	6.7% (6/90)	14.0% (6/43)	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
Reoperation	Charite IDE trial (Guyer 2009)	≤60 mos.	1.1% (1/90)	2.3% (1/43)	NR
Pseudarthrosis	Charite IDE trial (Guyer 2009)	60 mos.	NA	11.6% (5/43)	NR
Undefined persistent back pain	Charite IDE trial (Guyer 2009)	60 mos.	0% (0/90)	2.3% (1/43)	NR
Symptomatic spondylolisthesis at L5 pars interarticularis	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	0% (0/43)	NR
Device subsidence (resulting in low back pain)	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	0% (0/43)	NR
Facet degeneration	Charite IDE trial (Guyer 2009)	60 mos.	2.2% (2/90)	2.3% (1/43)	NR
Implant displacement (early displacement resulting in low back pain at 12 mos.)	Charite IDE trial (Guyer 2009)	60 mos.	2.2% (2/90)	0% (0/43)	NR
Adjacent level surgery for ASD	Charite IDE trial (Guyer 2009)	60 mos.	1.1% (1/90)	4.7% (2/43)	NR
Additional nonsurgical tx for DDD (pain management)	Charite IDE trial (Guyer 2009)	60 mos.	4.4% (4/90)	13.9% (6/43)	NR

ADR: artificial disc replacement; ASD: adjacent segment disease; CI: confidence interval; DDD: degenerative disc disease; DVT: deep vein thrombosis; F/U: follow-up; NR: not reported; NS: not significant; RD: risk difference; RR: relative risk; UTI: urinary tract infection.

*All analyses are based on the baseline, as-treated population. Regarding Guyer 2009, of the 14 initial sites, 6 declined participation in the 60-month continuation study, which eliminated 64 randomized patients. Furthermore, the patient numbers reported at 60 months include only those patients with both 24- AND 60-month follow-up and therefore may not accurately represent the number of patients with 60 month data.

†As reported by the study unless otherwise indicated.

‡Defined as major vessel injury, neurological damage, nerve root injury, and death.

§Classified as a treatment-related death, due to narcotics use.

Table L2. L-ADR vs. Fusion (1 level) RCT data: Safety data abstraction – ProDisc-L IDE trial

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
Polyethylene inlay migration‡	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	1.9% (3/161)	NA	NR
Device migration (radiographic)	ProDisc-L IDE trial (Zigler 2007)	24 mos.	2.1% (3/143)§	1.4% (1/69)§	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	2.4% (3/124)§	0% (0/48)§	0.561
Device subsidence (radiographic)	ProDisc-L IDE trial (Zigler 2007)	24 mos.	0.7% (1/143)§	0% (0/69)§	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	1.6% (2/124)§	0% (0/48)§	1.0
Pseudarthrosis	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	0% (0/143)§	2.9% (2/69)§	NR
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	0% (0/124)§	4.2% (2/48)§	0.077
Radiolucency around implant	ProDisc-L IDE trial (Zigler 2012 Five-year)	24 mos.	0% (0/143)§	1.4% (1/69)§	1.0
	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	0% (0/124)§	0% (0/48)§	1.0
Any secondary surgery index level	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	4.3% (7/161)	5.3% (4/75)	NR
Revision surgery	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	1.2% (2/161)**	0% (0/75)	NR
Reoperation	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	0.6% (1/161)††	2.7% (2/75)	NR
Supplemental fixation	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	0.6% (1/161)	0% (0/75)	NR
Hemilaminotomy and discectomy with nerve root decompression	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	0.6% (1/161)	0% (0/75)	NR
Hardware removal	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	0% (0/161)	2.7% (2/75)	NR
Not specified	ProDisc-L IDE trial (Zigler 2012 Five-year)	<24 mos.	1.2% (2/161)	0% (0/75)	NR
Any secondary surgery index level	ProDisc-L IDE trial (Zigler 2012 Five-year)	>24-60 mos.	3.7% (6/161)	6.7% (5/75)	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
Reoperation	ProDisc-L IDE trial (Zigler 2012 Five-year)	>24-60 mos.	0% (0/161)	4.0% (3/75)	NR
Supplemental fixation	ProDisc-L IDE trial (Zigler 2012 Five-year)	>24-60 mos.	3.1% (5/161)	0% (0/75)	NR
Hemi-laminectomy nerve decompression + removal of small disc fragment	ProDisc-L IDE trial (Zigler 2012 Five-year)	>24-60 mos.	0.6% (1/161)	0% (0/75)	NR
Hardware removal	ProDisc-L IDE trial (Zigler 2012 Five-year)	>24-60 mos.	0% (0/161)	2.7% (2/75)	NR
Any secondary surgery index level	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos.	8.1% (13/161)	12.0% (9/75)	NR
Blood loss >1500 cc	ProDisc-L IDE trial (Zigler 2012 Five-year)	Intra-op	0% (0/161)	2.7% (2/75)‡‡	NR
Blood loss >1500 cc (during revision surgery)	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos.	0.6% (1/161)	0% (0/75)	NR
Dural tear	ProDisc-L IDE trial (Zigler 2012 Five-year)	Intra-op	0% (0/161)	2.7% (2/75)‡‡	NR
Vessel damage/bleeding (major)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	0.6% (1/161)	1.3% (1/75)	NR
Vessel damage/bleeding (minor)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	2.5% (4/161)	6.7% (5/75)	NR
Retrograde ejaculation	ProDisc-L IDE trial (Zigler 2012 Five-year)	Peri-op	1.2% (2/161)	1.3% (1/75)	NR
Superficial wound infection with incision site pain	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	0% (0/161)	2.7% (2/75)	NR
Other non-wound-related infection	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	3.1% (5/161)	6.3% (5/75)	NR
Deep vein thrombosis	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	1.2% (2/161)	1.3% (1/75)	NR
Thrombosis (NOS)	ProDisc-L IDE trial (FDA SSED 2006)	Peri-op	0% (0/161)	0% (0/75)	NR
Urinary tract infection	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	0% (0/161)	1.3% (1/75)	NR
Pulmonary infection	ProDisc-L IDE trial (FDA SSED 2006)	≤24 mos.	0% (0/161)	1.3% (1/75)	NR
Graft site infection	ProDisc-L IDE trial (Zigler)	≤24 mos.	0% (0/161)	0% (0/75)	NR

Outcome	Study	F/U	L-ADR* % (n/N)	Fusion* % (n/N)	p-value†
	2012 Five-year)				
Iliac vein laceration (during revision surgery)	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos.	0.6% (1/161)	0% (0/75)	NR
Compartment syndrome with complications (post-op revision surgery)	ProDisc-L IDE trial (Zigler 2012 Five-year)	≤60 mos.	0.6% (1/161)§§	0% (0/75)	NR
Death (related to treatment)	ProDisc IDE trial (Zigler 2007, FDA SSED 2006)	24 mos.	0% (0/161)	0% (0/75)	NR
Death (unrelated to surgery or implants)	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	2.5% (4/161)	1.3% (1/75)	NR
Severe or life-threatening adverse events (per patient)	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	0.58 per patient	0.38 per patient	0.036
Any adjacent level surgery	ProDisc-L IDE trial (Zigler 2012 Five-year adjacent-level)	60 mos.	2.5% (3/119)	7.1% (3/42)	0.682
Spinal cord stimulator implantation	ProDisc-L IDE trial (Zigler 2012 Five-year adjacent-level)	60 mos.	0.8% (1/119)***	0% (0/42)	NR
Device related adverse events††† (any/all; including index-level reoperation)	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	18.0% (29/161)	21.3% (16/75)	NR
Device related adverse events††† (any/all; excluding index-level reoperation)	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	16.8% (27/161)	16.0% (12/75)	NR
Major adverse events‡‡‡	ProDisc-L IDE trial (Zigler 2007)	24 mos.	0% (0/161)	0% (0/75)	NR
All adverse events and complications (irrespective of relationship to treatment)	ProDisc-L IDE trial (FDA SSED 2006)	24 mos.	84.5% (136/161)	93.3% (70/75)	NR
Any adverse event (per patient)	ProDisc-L IDE trial (Zigler 2012 Five-year)	60 mos.	5.1 per patient	5.4 per patient	0.507

ADR: artificial disc replacement; ASD: adjacent segment disease; CI: confidence interval; DDD: degenerative disc disease; DVT: deep vein thrombosis; F/U: follow-up; NR: not reported; NS: not significant; RD: risk difference; RR: relative risk; UTI: urinary tract infection;

*All analyses are based on the baseline, as-treated population: a total of 242 patients were treated (162 ADR and 80 fusion), 6 patients (1 ADR and 5 fusion) were treated off-protocol and were excluded from the analyses.

†As reported by the study unless otherwise indicated.

‡Of the 3 cases of polyethylene migration, 2 were due to extreme trauma (underwent revision surgery, received fusion) and 1 case occurred within 48 hours because the inlay was not locked correctly at the time of implantation (underwent a secondary surgery but type not specified); all 3 cases also counted under subsequent surgery at the index level.

§Only in patients with complete radiographic data sets.

**2 cases of polyethylene migration due to extreme trauma; 1 case (injured while power lifting) sustained an iliac vein laceration during revision surgery and a postoperative compartment syndrome with complications and 1 case (motor vehicle accident 23 mos. post implantation + fall in the shower) did not show significant clinical improvement from his preoperative status.

††Case of technical error in which the inlay was inserted backward requiring reoperation and reinsertion of the inlay.

‡‡No clinical sequelae.

§§Same patient listed under revision surgery and polyethylene inlay migration due to trauma (injured while power lifting).

***While not considered adjacent-level surgery, a spinal cord stimulator was implanted in a fourth L4–5 TDR patient 3 years after the index surgery to address persistent pain at the L5–S1 segment. The index level was not disturbed, with the TDR device left intact.

†††Defined as adverse events considered by the investigators to be device-related, including back and lower extremities pain, nerve root injury, implant displacement, and subsidence.

‡‡‡Defined as major vessel injury, neurological damage, nerve root injury, and death.

L-ADR vs. Fusion (2-level)

Table K3. L-ADR vs. Fusion (2 levels) RCTs safety data: ProDisc-L (2 level) IDE trial

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Secondary surgical procedure at the index level(s)‡	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	2.4% (4/165)	8.3% (6/72)	NR	0.0465
Revision procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	1.4% (1/72)	NR	NR
Secondary decompression procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	1.8% (3/165)	1.4% (1/72)	NR	NR
Device/implant removal procedure	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0% (0/165)	8.3% (6/72)§	NR	NR
Death (unrelated to treatment)	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	0% (0/72)	NR	NR
Major-surgery-related complications (any)	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.7% (5/165)	4.9% (7/72)	NR	NR
Dural tear**	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.6% (1/165)	4.2% (3/72)	NR	NR
Blood loss of >1500 mL††	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	1.2% (2/165)	2.8% (2/72)	NR	NR
Iliac artery tear	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Intra-op	0.6% (1/165)	0% (0/72)	NR	NR

Outcome	Study	F/U	ADR* % (n/N)	Control* % (n/N)	RD (95% CI)† RR (95% CI)†	p-value†
Deep vein thrombosis	ProDisc-L IDE trial–2 levels (Delamarter 2011)	Postop	1.2% (2/165)	2.8% (2/72)	NR	NR
Implant migration (anterior)‡‡	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0.6% (1/165)	NR	NC	NC
Pseudarthrosis	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	NA	1.4% (1/72)	NC	NC
Radiolucency or halos around implant	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	0% (0/165)	4.2% (3/72)	NR	NR
Implant subsidence (>3 mm)§§	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	1.8% (3/165)	NR	NC	NC
Implant migration or subsidence (>3 mm)	ProDisc-L IDE trial–2 levels (Delamarter 2011)	24 mos.	NR	1.4% (1/72)	NC	NC

ADR: artificial disc replacement; CI: confidence interval; DVT: deep vein thrombosis; F/U: follow-up; NR: not reported; RCT: randomized controlled trial; RD: risk difference.

* All analyses are based on the baseline, as-treated population: 10 Fusion patients and 9 ADR patients did not received the treatment they were randomized to and they are not accounted for in any analysis.

† As reported by the authors.

‡ The average number of days from the index procedure to secondary surgery was 567.7 (range, 480 to 736) in the ADR group and 255.5 (range, 21 to 560) in the fusion group.

§ One of the fusion patients underwent implant removal, decompression (bilateral medial facetectomy and hemilaminectomy), and revision of the bone fusion sites because of a pseudarthrosis at L5-S1 (also included under “pseudarthrosis” outcome; this patients is included in all three secondary surgery categories but only included once for the total risk of any subsequent surgery.

**All successfully repaired.

†† Of the patients who had clinically significant blood loss, 1 of the 2 ADR patients sustained an iliac artery tear, while the other ADR patient and all fusion patients had excessive oozing from the decompression, decorticated bone, and graft sites.

‡‡ Migration of the superior implant resulting in revision arthrodesis (same patient as included in “revision” under subsequent surgeries at the index level.

§§ Not clinically important in any patient.

L-ADR vs. Fusion (1- or 2-level)**Table L4. L-ADR vs. Fusion (1 or 2 levels): Safety data abstraction – Berg 2009 RCT**

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	p-value*
Infection (major)	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	5.6% (4/72)	0.03†
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	5.6% (4/71)	0.03†
Hematoma	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	1.4% (1/72)	NR
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	1.4% (1/71)	NR
Suspected facet joint pain	Berg trial (Berg 2009 Total disc)	24 mos.	7.5% (6/80)	0% (0/72)	0.02†
	Berg trial (Skold 2013)	60 mos.	7.5% (6/80)	0% (0/71)	0.02†
Pseudarthrosis	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	2.8% (2/72)	NR
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	2.8% (2/71)	NR
Wound hernia	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	0% (0/71)	NR
Nerve entrapment	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	NR
Donor site pain	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	NR
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1.4% (1/71)	NR
Adjacent	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	8.3% (6/72)	0.04†
Dural tear	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	1.4% (1/72)	NR
	Berg trial (Skold 2013)	60 mos.	0% (0/80)	1.4% (1/71)	NR
Meralgia paresthetica	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	NR
Subsidence	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	0% (0/71)	NR
Total complications	Berg trial (Berg 2009 Total disc)	24 mos.	17.5% (14/80)	20.8% (15/72)	NR
	Berg trial (Skold 2013)	60 mos.	16.3% (13/80)	12.7% (9/71)	NR
Total major complications	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	8.3% (6/72)	NS†
	Berg trial (Skold 2013)	60 mos.	2.5% (2/80)	8.5% (6/71)	NS†
Total minor complications	Berg trial (Berg 2009 Total disc)	24 mos.	15.0% (12/80)	12.5% (9/72)	NS†
	Berg trial (Skold 2013)	60 mos.	13.8% (11/80)	4.2% (3/71)	0.04†
Reoperation at index level (non-device related)	Berg trial (Berg 2009 total disc)	24 mos.	5.0% (4/80)	2.8% (2/72)	NR
	Berg trial (Skold 2013)	60 mos.	6.3% (5/80)	8.3% (6/71)	NR
Decompression	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR

Outcome	Study	F/U	ADR % (n/N)	Control % (n/N)	p-value*
	Berg trial (Skold 2013)	60 mos.	1 procedure	0 procedures	NR
Extraction of pedicle screws + decompression	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	NR
	Berg trial (Skold 2013)	60 mos.	0 procedures	1 procedure	NR
Refusion	Berg trial (Skold 2013)	60 mos.	1 procedure	5 procedures	NR
Hematoma removal	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	2 procedures	1 procedure	NR
Hernia repair	Berg trial (Berg 2009 Total disc)	24 mos.	1.3% (1/80)	0% (0/72)	NR
	Berg trial (Skold 2013)	60 mos.	4 procedures	0 procedures	NR
Dural tear repair	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	1.4% (1/72)	NR
	Berg trial (Skold 2013)	60 mos.	0 procedures	1 procedure	NR
Reoperation at index level (device- related)	Berg trial (Berg 2009 total disc)	24 mos.	5.0% (4/80)	27.8% (20/72)	0.01 [†]
	Berg trial (Skold 2013)	60 mos.	11.3% (9/80)	28.2% (20/71)	NR
Extraction of pedicle screws (due to pain)	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	27.8% (20/72)	<0.0001 [†]
	Berg trial (Skold 2013)	60 mos.	1.3% (1/80)	28.2% (20/71)	<0.0001 [†]
Fusion at ADR level	Berg trial (Berg 2009 Total disc)	24 mos.	5.0% (4/80)	0% (0/72)	NS [†]
	Berg trial (Skold 2013)	60 mos.	10.0% (8/80)	0% (0/71)	0.006 [†]
New operation at new level	Berg trial (Skold 2013)	60 mos.	7 procedures	11 procedures	NR
ADR above fusion	Berg trial (Berg 2009 Total disc)	24 mos.	0% (0/80)	6.9% (5/72)	0.02 [†]
ADR	Berg trial (Skold 2013)	60 mos.	2 procedures	8 procedures	NR
PLF	Berg trial (Skold 2013)	60 mos.	3 procedures	0 procedures	NR
Decompression + PLF	Berg trial (Skold 2013)	60 mos.	0 procedures	2 procedures	NR
Decompression	Berg trial (Skold 2013)	60 mos.	1 procedure	1 procedure	NR
Disc hernia	Berg trial (Skold 2013)	60 mos.	1 procedure	0 procedures	NR
Reoperation, new operation, or both	Berg trial (Skold 2013)	60 mos.	20.0% (16/80)	42.3% (30/71)	0.003 [†]
Facet block (postop)	Berg trial (Berg 2009 Total disc)	24 mos.	27.5% (22/80)	1.4% (1/72)	<0.0001 [†]
Discography (postop)	Berg trial (Berg 2009 Total disc)	24 mos.	2.5% (2/80)	12.5% (9/72)	0.02 [†]

CI: confidence interval; F/U: follow-up; L-ADR: lumbar artificial disc replacement; NR: not reported; RCT: randomized controlled trial.

*As reported by the trial unless otherwise indicated.

[†]Calculated by SRI.

L-ADR vs. Multidisciplinary Rehabilitation**Table L5. L-ADR vs. Multidisciplinary Rehabilitation (1 to 2 levels) RCTs safety data: Hellum 2011**

Outcome	Study	F/U	L-ADR* % (n/N)	Rehab % (n/N)	p-value†
Total with any complication	Hellum 2011	≤24 mos.	33.8% (26/77)	NA	NA
Intimal lesion in left common iliac artery‡,§	Hellum 2011	3 mos.	1.3% (1/77)	NA	NA
Arterial thrombosis of dorsalis pedis artery (temporarily slightly colder foot)§	Hellum 2011	24 mos.	1.3% (1/77)	NA	NA
Dural tear	Hellum 2011	Peri-op	1.4% (0/77)	NA	NA
Blood loss of >1500 mL	Hellum 2011	Peri-op	5.2% (4/77)	NA	NA
Retrograde ejaculation§	Hellum 2011	12 mos.	1.3% (1/77)	NA	NA
Abdominal hernia	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA
Superficial haematoma	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA
Ileus	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA
Temporary nausea	Hellum 2011	Peri-op	1.3% (1/77)	NA	NA
Temporary warm left foot	Hellum 2011	Peri-op	2.6% (2/77)	NA	NA
Motor deficit	Hellum 2011	24 mos.	0% (0/71)	NA	NA
Temporary motor deficit	Hellum 2011	Peri-op	0% (0/71)	NA	NA
Sensory loss (thigh)§	Hellum 2011	24 mos.	2.6% (2/77)	NA	NA
Temporary sensory loss	Hellum 2011	Peri-op	5.2% (4/77)	NA	NA
Radicular pain (new)§	Hellum 2011	24 mos.	2.6% (2/77)	NA	NA
Temporary radicular pain	Hellum 2011	Peri-op	5.2% (4/77)	NA	NA
Superficial wound infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA
Deep wound infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA
Urinary tract infection	Hellum 2011	Peri-op	0% (0/77)	NA	NA
Major complication resulting in impairment§	Hellum 2011	24 mos.	7.8% (6/77)	NS	NA
Total reoperation/operation rate	Hellum 2011	24 mos.	6.5% (5/77)	7.5% (6/80)**	NR
Subsequent fusion surgery at index level††	Hellum 2011	24 mos.	2.8% (2/71)	NA	NA
Reoperation at index level‡‡	Hellum 2011	24 mos.	1.4% (1/71)	NA	NA
Subsequent surgery – resection of spinous process§§	Hellum 2011	24 mos.	2.8% (2/71)	NA	NA
ADR (crossed over)	Hellum 2011	24 mos.	NA	6.3% (5/80)	NA
Fusion (crossed over)	Hellum 2011	24 mos.	NA	1.3% (1/80)	NA

Outcome	Study	F/U	L-ADR* % (n/N)	Rehab % (n/N)	p-value†
Worsening of low back pain	Hellum 2011	24 mos.	11% (8/73)***	9% (6/67)***	NR

F/U: follow-up; L-ADR: artificial disc replacement; NA: not applicable; NR: not reported; RCT: randomized controlled trial; Rehab: rehabilitation.

* All analyses are based on the baseline, as-treated population: Six patients (3 in each group) were excluded shortly after randomization and not accounted for in the studies ITT analysis

† As reported by the authors.

‡ At the 3 month follow-up, the polyethylene inlay was found to be dislodged. During revision surgery, injury to the left common iliac artery led to compartment syndrome resulting in a lower leg amputation.

§ These adverse events were classified as “Major complications resulting in impairment” (see outcome); a total of 7 events in 6 patients were reported at the 24 month follow-up.

**Five patients underwent ADR and one patient received fusion; one patient crossed over between 6 and 12 months and five patients between 12 and 24 months.

††At level with disc prosthesis and level above.

‡‡Insertion of new polyethylene inlay (same patient with intimal lesion in left common iliac artery).

§§Because of possible painful contact between adjacent levels.

***Denominators back-calculated based on % and numerators provided.

APPENDIX M. C-ADR SUMMARY SAFETY TABLES.**C-ADR vs. ACDF (1-level)****Table M1. C-ADR vs. ACDF (1-level) RCT data: Secondary Surgery Involving the Index Level***

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)††	p-value††
Revision surgery at index level	Nabhan 2011	0-12 mos.	0% (0/10)	0% (0/10)	0% (NC)	1.0
Any secondary surgery at index level*	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	3.3% (9/276)	7.2% (19/265)	-3.9% (-7.7%, -0.2%)	0.04
Revision	Prestige ST IDE trial (FDA SSED)†	0-24 mos.	0% (0/276)	1.9% (5/265)	-1.9% (-3.5%, -0.3%)	0.02
Removal	Prestige ST IDE trial (FDA SSED)†	0-24 mos.	1.8% (5/276)	3.4% (9/265)	-1.6% (-4.3%, 1.1%)	0.25
Supplemental fixation	Prestige ST IDE trial (Burkus 2014)*	0-24 mos.	0% (0/276)	1.1% (3/265)	-1.1% (-2.4%, 0.1%)	0.08
Reoperation	Prestige ST IDE trial (FDA SSED)†	0-24 mos.	1.4% (4/276)	0.8% (2/265)	0.7% (-1.1%, 2.3%)	0.44
Any secondary surgery at index level*	Bryan IDE trial (Sasso 2011)	0-24 mos.	2.4% (6/253)	3.8% (8/210)	-1.4% (-4.6%, 1.8%)	0.37
Revision	Bryan IDE trial (Sasso 2011)	0-24 mos.	0.4% (1/253)	0% (0/210)	0.4% (NC)	0.36
Removal	Bryan IDE trial (Sasso 2011)	0-24 mos.	1.2% (3/253)	1.4% (3/210)	-0.2% (-2.3%, 1.8%)	0.82
Supplemental fixation	Bryan IDE trial (Sasso 2011)	0-24 mos.	0% (0/253)	1.9% (4/210)	-1.9% (-3.8%, -0.1%)	0.03
Reoperation	Bryan IDE trial (Sasso 2011)	0-24 mos.	0.8% (2/253)	0.5% (1/210)	0.3% (-1.1%, 1.8%)	0.68
Any secondary surgery at index level*	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	1.2% (2/164)	6.2% (5/81)	-5.0% (-10.5%, 0.6%)	0.03
Revision	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0% (0/164)	0% (0/81)	0% (NC)	1.0
Removal	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0.6% (1/164)	3.7% (3/81)	-3.1% (-7.4%, 1.2%)	0.07
Supplemental fixation	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0% (0/164)	2.5% (2/81)	-2.5% (-5.9%, 0.9%)	0.04

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)††	p-value††
Reoperation	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0.6% (1/164)	0% (0/81)	0.6% (NC)	0.48
Any secondary surgery at index level*	PCM IDE trial (FDA SSED for device)‡	0-24 mos.	5.5% (12/218)	5.4% (10/185)	0.1% (-4.4%, 4.6%)	0.97
Revision	PCM IDE trial (Phillips 2015)	0-24 mos.	NR	NR	NR	NR
Removal	PCM IDE trial (Phillips 2015)	0-24 mos.	3.7% (8/218)	2.2% (4/185)	1.5% (-1.8%, 4.8%)	0.38
Supplemental fixation	PCM IDE trial (Phillips 2015)	0-24 mos.	0% (0/218)	0% (0/185)	0% (NC)	1.0
Reoperation	PCM IDE trial (Phillips 2015)	0-24 mos.	1.4% (3/218)	0% (0/185)	1.4% (NC)	0.11
Any secondary surgery at index level*	ProDisc-C IDE trial (Murrey 2009)§	0-24 mos.	1.9% (2/103)	7.5% (9/106)	-6.6% (-12.5%, -0.6%)	0.03
Revision	ProDisc-C IDE trial (Murrey 2009, Delamarter 2013)	0-24 mos.	0% (0/103)	4.7% (5/106)	-4.7% (-8.8%, -0.7%)	0.03
Removal	ProDisc-C IDE trial (Murrey 2009, Delamarter 2013)	0-24 mos.	1.9% (2/103)	0% (0/106)	1.9% (NC)	0.15
Supplemental fixation	ProDisc-C IDE trial (Murrey 2009, Delamarter 2013)	0-24 mos.	0% (0/103)	2.8% (3/106)	-2.8% (-5.6%, 0.3%)	0.09
Reoperation	ProDisc-C IDE trial (Murrey 2009, Delamarter 2013)	0-24 mos.	0% (0/103)	0.9% (1/106)	-0.9% (-2.8%, 0.9%)	0.32
Any secondary surgery at index level*	Secure-C IDE trial (Vaccaro 2013, FDA SSED)**	0-24 mos.	2.6% (4/151)	10.0% (14/140)	-7.4% (-12.9%, -1.8%)	0.01
Revision	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0% (0/236)	4.3% (6/140)	-4.3% (-7.6%, -0.9%)	<0.01
Removal	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	1.7% (4/236)	5.0% (7/140)	-3.3% (-7.3%, 0.7%)	0.07
Supplemental fixation	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0.9% (2/236)	0.7% (1/140)	0.1% (-1.7%, 2.0%)	0.89

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)††	p-value††
Reoperation	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0% (0/236)	0% (0/140)	0% (NC)	1.0
Reoperation at index level	Karabag 2014	0-24 mos.	5.3% (1/19)	0% (0/23)	5.3% (NC)	0.27
Reoperation at the index level	Rozankovic 2014	0-24 mos.	0% (0/54)	2.0% (1/51)	-2.0% (-5.8%, 1.8%)	0.30
Any secondary surgery at index level*	Bryan IDE trial (Sasso 2011)	0-48 mos.	3.6% (9/253)	4.8% (10/210)	-1.2% (-4.9%, 2.5%)	0.52
Revision	Bryan IDE trial (Sasso 2011)	0-48 mos.	0.4% (1/253)	0% (0/210)	0.4% (NC)	0.36
Removal	Bryan IDE trial (Sasso 2011)	0-48 mos.	1.6% (4/253)	1.9% (4/210)	-0.3% (-2.7%, 2.1%)	0.79
Supplemental fixation	Bryan IDE trial (Sasso 2011)	0-48 mos.	0% (0/253)	2.4% (5/210)	-2.4% (-4.4%, -0.3%)	0.01
Reoperation	Bryan IDE trial (Sasso 2011)	0-48 mos.	1.6% (4/253)	0.5% (1/210)	1.1% (-0.7%, 2.9%)	0.25
Any secondary surgery at index level*	Prestige ST IDE trial (Burkus 2010)	0-60 mos.	NR	NR	NR	NR
Revision	Prestige ST IDE trial (Burkus 2010)	0-60 mos.	0% (0/276)	1.9% (5/265)	-1.9% (-3.5%, -0.3%)	0.02
Removal	Prestige ST IDE trial (Burkus 2010)†	0-60 mos.	2.5% (7/276)	4.9% (13/265)	-2.4% (-5.6%, 0.8%)	0.14
Supplemental fixation	Prestige ST IDE trial (Burkus 2010)	0-60 mos.	0% (0/276)	1.9% (5/265)	-1.9% (-3.5%, -0.3%)	0.02
Reoperation	Prestige ST IDE trial (Burkus 2010)	0-60 mos.	1.4% (4/276)	0.8% (2/265)	0.7% (-1.1%, 2.5%)	0.44
Any secondary surgery at index level*	Mobi-C IDE trial (Jackson 2016)††	0-60 mos.	3.4% (6/179)	12.3% (10/81)	-9.0% (-16.6%, -1.4%)	0.01
Any secondary surgery at index level*	PCM IDE trial (Phillips 2015)	0-60 mos.	7.8% (17/218)	11.9% (22/185)	-4.1% (-10.0%, 1.8%)	0.17
Revision	PCM IDE trial (Phillips 2015)	0-60 mos.	NR	NR	NR	NR
Removal	PCM IDE trial (Phillips 2015)	0-60 mos.	6.4% (14/218)	2.7% (5/185)	NR	NR
Supplemental fixation	PCM IDE trial (Phillips 2015)	0-60 mos.	0% (0/218)	0% (0/185)	0% (NC)	1.0

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)††	p-value††
	2015)					
Reoperation	PCM IDE trial (Phillips 2015)	0-60 mos.	1.4% (3/218)	0% (0/185)	1.4% (NC)	0.11
Any secondary surgery at index level*	ProDisc-C IDE trial (Murrey 2009)	0-60 mos.	2.9% (3/103)	7.5% (8/106)	-4.6% (-10.6%, 1.4%)	0.13
Any secondary surgery at index level*	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	4.8% (11/276)	13.7% (29/265)	-7.0% (-11.4%, -2.6%)	<0.01
Revision	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0% (0/276)	1.9% (5/265)	-1.9% (-3.5%, -0.3%)	0.02
Removal	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	2.9% (8/276)	7.9% (21/265)	-5.0% (-8.8%, -1.2%)	<0.01
Supplemental fixation	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0% (0/276)	1.9% (5/265)	-1.9% (-3.5%, -0.3%)	0.02
Reoperation	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	1.4% (4/276)	1.5% (4/265)	-0.1% (-2.1%, 2.0%)	0.95
Any secondary surgery at index level*	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	5.8% (6/103)	15.1% (16/106)	-9.3% (-17.5%, -1.1%)	0.03
Revision	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	0% (0/103)	3.8% (4/106)	-3.8% (-7.4%, -0.2%)	0.047
Removal	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	4.9% (5/103)	0.9% (1/106)	3.9% (-0.6%, 8.5%)	0.09
Supplemental fixation	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	1.0% (1/103)	12.3% (13/106)	-11.3% (-17.8%, -4.8%)	<0.01
Reoperation	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	0% (0/103)	0.9% (1/106)	-0.9% (-2.8%, 0.9%)	0.32

* All data may include procedures at index level alone or that involved both the index and adjacent levels:

- Prestige ST IDE trial (84 months): 3 C-ADR and 14 ACDF patients underwent secondary procedures that involved both the index and adjacent levels.
- Bryan IDE trial: data not stratified by the number of procedures performed at index level alone or that involved both the index and adjacent levels.
- Mobi-C IDE trial (1-level) (60 months): 2 C-ADR and 2 ACDF patients underwent secondary procedures that involved both the index and adjacent levels; totals do not include 3 patients in the ACDF group who underwent plate removal as a result of adjacent-level indications only.
- PCM IDE trial: data not stratified by the number of procedures performed at index level alone or that involved both the index and adjacent levels.
- ProDisc-C IDE trial (60/84 months): 2/NR C-ADR and NR/11 ACDF patients underwent secondary procedures that involved both the index and adjacent levels

† Prestige ST IDE trial: C-ADR: Index trial doesn't report the total number of second surgeries at the index level, but reported 5 hardware removals, 0 revisions, and 0 supplemental fixations. The IDE trial additionally reported 4 reoperations; Burkus 2014 reports 6 removals and 4 reoperations in 9 patients total at the index level. ACDF: Index trial doesn't report the total number of second surgeries at the index level, but reported hardware removal in 9 patients, revisions in 5 patients, and supplemental

fixations in 8 patients (9 procedures) (at the index level). The IDE trial additionally reported 2 reoperations; Burkus 2014 reported 12 removals and 4 revisions, 3 supplemental fixations, and 2 reoperations in 19 patients total (at the index level).

‡ PCM IDE trial: C-ADR: index trial reported 11 patients (8 removals, 2 reoperations, 0 revisions, 0 supplemental fixations); the SSED reported 12 patients using the modified ITT analysis (includes all treated patients) & 11 patients using per protocol (pts who received treatment and adhered to protocol); Phillips 2015 reported 11 procedures total.

ACDF: index trial reported 10 patients but gave no details other than that all were removals “which were predominately nonunions and adjacent-level procedures;” however the SSED reported 10 patients underwent subsequent secondary surgical interventions at the index level (see Table 20 and preceding paragraph) for both mITT and per protocol populations; Phillips 2015 reports 10 procedures total but that 6 were for ASD (Table 2).

§ ProDisc-C IDE trial: ACDF: Delamarter 2013 reports this to be 8 patients, but both the index trial and the FDA SSED reported that 9 patients underwent secondary surgery at the index level (Table 6 in SSED).

** Secure-C IDE trial: ACDF: SSED reported 17/144 (Table 14) but then only accounted for 14 patients in the detailed table (Table 16); index study reported 17 events in 14 patients (Table 5).

†† Mobi-C trial, 60 months: denominator used by Jackson 2016 included 15 non-randomized training cases in the ADR group. (179 vs. 164); SRI was unable to obtain the number of procedures for the randomized patients only.

‡‡ Calculated by SRI.

§§ Secure-C IDE trial: C-ADR denominator for revision, reoperation, removal, and supplemental fixation includes both randomized (n=148) and non-randomized (n=88) patients.

Table M2. C-ADR vs. ACDF (1-level) RCT data: Serious Adverse Events

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Serious/major adverse events as classified by the trial†						
Serious/major adverse events	Prestige ST IDE trial (Mummaneni 2007)	Any	NR	NR	NR	>0.05
Any serious adverse event†	Bryan IDE trial (Anderson 2008)	0-24 mos.	28.9% (73/253)	38.1% (80/210)	See meta-analysis for calculations	
Any serious adverse event†	Mobi-C IDE trial (1-level) (FDA SSED)	0-24 mos.	18.3% (30/164)	25.9% (21/81)		
Serious adverse events†**	PCM IDE trial (FDA SSED)	0-24 mos.	31.2% (68/218)	30.8% (57/185)		
Severe or life-threatening adverse event†	ProDisc-C IDE trial (FDA SSED)	0-24 mos.	15.5% (16/103)	30.2% (32/106)		
Severe or life-threatening adverse event†	Secure-C IDE trial (Secure-C FDA SSED)	0-24 mos.	19.2% (29/151)	24.3% (34/140)		
Any serious adverse event†	Bryan IDE trial (Sasso 2011)	24-48 mos.	17.4% (44/253)	17.1% (36/210)	See meta-analysis for calculations	
Any serious adverse event†‡§	Mobi-C IDE trial (1-level) (Hisey 2015)	0-48 mos.	9.8% (18/179)	9.9% (8/81)	See meta-analysis for calculations	
Serious adverse events†**	PCM IDE trial (Phillips 2015)	24–84 mos.‡	21.0% (45/214)	17.4% (33/190)	See meta-analysis for calculations	

* Calculated by SRI.

† Defined as:

- Bryan IDE trial: Most serious adverse events were related to medical conditions and not to the procedure, implant, or cervical spine disease. Classified as WHO grade 3 or 4 (taken from Anderson 2008) (grade 3 events required medical treatment or may have had a long-term health effect; grade 4 events required an operation, were life threatening, permanent disability, or caused death).
- PCM IDE trial: any event that results in death, serious injury, permanent impairment; or that prolongs hospitalization or requires surgical intervention to prevent death or serious injury; classified by the Clinical Events Committee.
- Mobi-C IDE trial: any event that results in death, serious injury, permanent impairment; or that prolongs hospitalization or requires surgical intervention to prevent death or serious injury; or that was a congenital anomaly or birth defect; classified by the Clinical Events Committee.
- ProDisc-C IDE trial: “Severe or life-threatening adverse event”: defined as any event requiring hospitalization or surgery (see SSED Table 18).
- Secure-C IDE trial: “Severe or life-threatening adverse event”: a severe event was defined as any event that significantly limits the patient’s ability to perform routine activities despite symptomatic therapy; a life-threatening event was defined as any event that required removal of the implant or put the patient at immediate risk of death (including death) (see SSED Table 19).

‡ Numerators back-calculated.

§ Mobi-C trial: denominator used included 15 non-randomized training cases in the ADR group. (179 vs. 164); SRI was unable to obtain the number of events for the randomized patients only.

** Majority were systemic or medical in nature and not related to device or surgery. For 24 months, the index trial (Phillips 2013) reported serious adverse events occurred in 46 ADR and 41 ACDF patients but this was calculated in an as-treated population. For 24-84 months, the denominators represent as-treated patients include crossover between treatment groups.

Table M3. C-ADR vs. ACDF (1-level) RCT data: Death

Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Death†					
Prestige ST IDE trial (FDA SSED, Burkus 2014)	0-24 mos.	0% (0/276)	1.3% (3/265)	-1.1% (-2.4%, 0.1%)	0.08
Mobi-C IDE trial (1-level) (Hisey 2014)	0-24 mos.	0% (0/179)‡	0% (0/81)	0% (NC)	1.0
Secure-C IDE trial (Vaccaro 2013, FDA SSED)†	0-24 mos.	0.4% (1/236)§	0.7% (1/144)§	-0.3% (-1.9%, 1.3%)	0.73
Bryan IDE trial (Anderson 2008)	0-36 mos.	0% (0/242)**	0.5% (1/221)**	-0.5% (-1.3%, 0.4%)	0.30
Nabhan 2007	0-36 mos.	5% (1/20)†	0% (0/21)	5% (NC)	0.31
Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0.9% (2/276)	2.2% (5/265)	-1.2% (-3.1%, 0.8%)	0.23

* Calculated by SRI

† Cause of death:

- Prestige IDE trial:
 - 0-24 months: 3 deaths in the ACDF group attributed to myocardial infarction or cardiac arrest.
 - 0-84 months: cause of death not reported
- Bryan IDE trial:
 - 0-36 months: 1 death attributed to a motor vehicle crash, considered unrelated to cervical spine
- Secure-C IDE trial: cause of death not reported
- Nabhan 2007: 1 C-ADR patient died of severe subarachnoid hemorrhage at 6 weeks; relationship to procedure not stated

‡ Data includes that from 15 non-randomized C-ADR patients.

§ As treated; data includes that from 89 non-randomized C-ADR patients.

** As treated

Table M4. C-ADR vs. ACDF (1-level) RCT data: Device-Related Adverse Events

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Device-related adverse events as classified by the trial†						
Device-related or device/surgical procedure-related†	Prestige ST IDE trial (FDA SSED)	0-24 mos.	3.3% (9/276)	9.8% (26/265)	See meta-analysis for calculations	
Device-related or device/surgical procedure-related†	Bryan IDE trial (FDA SSED)	0-24 mos.	2.8% (7/253)	5.7% (12/210)		
Implant-related adverse events†	PCM IDE trial (FDA SSED)	0-24 mos.	13.3% (29/218)	23.8% (44/185)		
Device-related adverse events†§	Mobi-C IDE trial (1-level) (Hisey 2015)	0-24 mos.	3.9% (7/179)	7.4% (6/81)		
Implant-related adverse events†	ProDisc-C IDE trial (FDA SSED)	0-24 mos.	1.9% (2/103)	4.7% (5/106)		
Device-related adverse events†	Secure-C IDE trial (Secure-C FDA SSED)	0-24 mos.	2.6% (4/151)	10.0% (14/140)		
Device-related adverse events†‡§	Mobi-C IDE trial (1-level) (Hisey 2016)	0-60 mos.	5.5% (10/179)	3.7% (3/81)	See meta-analysis for calculations	
Implant-related adverse events**	ProDisc-C IDE trial (Zigler 2013)	0-60 mos.	1.0% (1/103)	2.8% (3/106)		
Any device-related adverse event†	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	27% (28/103)	28% (30/106)	See meta-analysis for calculations	

* Calculated by SRI.

† Defined as:

- Prestige ST IDE trial: events included anatomical/technical difficulty, implant displacement/loosening, infection, neck and/or arm pain, neurological, non-union, pending non-union, and subsidence.
- Bryan IDE trial: events included malpositioned implant, neck and/or arm pain, non-union, other, pending non-union, spinal event, and trauma.
- Mobi-C IDE trial: events included spinal ligament ossification, neck pain, muscle spasms, radiculopathy, subsidence, medical device complication, misplaced screw coded as device complication.
- ProDisc-C IDE trial (0-24 months): events included dysphagia, superficial wound infection, musculoskeletal, neck pain, and index-level surgery.
- ProDisc-C IDE trial (0-84 months): adjacent-level degenerative disc disease or degenerative joint changes, cardiovascular, dysphagia, headache, musculoskeletal, musculoskeletal neck spasms, neurologic, numbness, ossification, other, back and lower extremity pain, incision site pain, neck pain, neck and other pain, neck and shoulder pain, neck and upper extremity pain, neck and upper extremity pain with numbness, surgery for device related events (index or other level), wound issues.
- Secure-C IDE trial: device-related adverse events were classified by the Clinical Events Committee and included those events that were linked to the device (revision, removal, reoperation, or supplemental fixation at the index level; fracture or mechanical failure of the device, pseudarthrosis, radiolucency around the device, migration, subsidence, loosening, etc. Neck and arm pain were excluded from this category of adverse events.

‡ Numerators back-calculated.

§ Mobi-C trial: denominator used included 15 non-randomized training cases in the ADR group. (179 vs. 164); SRI was unable to obtain the number of events for the randomized patients only.

** ProDisc-C (60 months): it is unclear why the number of implant-related adverse events at 60 months was lower than that reported through 24 months.

Table M5. C-ADR vs. ACDF (1-level) RCT data: Secondary Surgery Involving an Adjacent Level

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)**	p-value**		
Secondary surgery at adjacent level ONLY (procedures at both index and adjacent not included)	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	2.9% (8/276)	3.8% (10/265)	See meta-analysis for calculations			
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	ProDisc-C ST IDE trial (ProDisc-C FDA SSED)	0-24 mos.	0% (0/103)	2.8% (3/106)				
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	Mobi-C (1-level) (FDA SSED)	0-24 mos.	0.6% (1/164)	3.7% (3/81)				
Secondary surgery at an adjacent level (details NR)	Bryan IDE trial (Bryan FDA SSED)	0-24 mos.	2.8% (7/253)	1.9% (4/210)				
Secondary surgery at an adjacent level (details NR)	PCM IDE trial (PCM FDA SSED)*	0-24 mos.	2.3% (5/218)	3.2% (6/185)				
Secondary surgery at an adjacent level (details NR)	Secure-C IDE trial (Vaccaro 2013)§	0-24 mos.	1.7% (4/236)	1.4% (2/140)				
Second surgical procedure for ASD	Karabag 2014	0-24 mos.	0% (0/19)	0% (0/23)				
Reoperation at adjacent segments	Zhang 2012	24 mos.	1.8% (1/56)	5.7% (3/53)				
Secondary surgery at adjacent level only	Nabhan 2007	0-36 mos.	0% (0/20)	5% (1/21)			-4.8% (-13.9%, 4.4%)	0.33
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	ProDisc-C IDE trial (Delamarter 2013)	0-60 mos.	1.9% (2/103)	5.7% (6/106)			See meta-analysis for calculations	
Secondary surgery at an adjacent level (at adjacent levels only or	Mobi-C IDE trial (1-level) (Jackson)	0-60 mos.	2.2% (4/179)	11.1% (9/81)				

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)**	p-value**
that involved <u>both</u> adjacent and index levels)	2016)‡					
Secondary surgery at adjacent level ONLY (procedures at both index and adjacent not included)	Bryan IDE trial (Sasso 2011)	0-48 mos.	4.0% (10/253)	4.3% (9/210)		
Secondary surgery at an adjacent level (details NR)	PCM IDE trial (PCM FDA SSED)†	0-48 mos.	2.8% (6/218)	5.9% (11/185)		
Adjacent-segment reoperation	Zhang 2014	0-48 mos.	0% (0/55)	7.1% (4/56)		
Secondary surgical procedures involving adjacent level	ProDisc-C IDE trial (Janssen 2015)	0-84 mos.	5.8% (6/103)	12.3% (13/106)	See meta-analysis for calculations	
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	4.0% (11/276)	9.1% (24/265)		

* PCM IDE trial: there is a discrepancy in the number of adjacent level surgeries reported between the FDA SSED report (5 vs. 7 for PCM vs. ACDF, see Table 43) and Phillips 2015 (which doesn't clearly report the number of surgeries at the adjacent level, but indicates 0 vs. 6 for PCM vs. ACDF were performed for adjacent segment disease (Table 2)). Because of this discrepancy and because the latter did not clearly report the number of surgeries at the adjacent level, data from this report were not used for 24 months or for 60 months.

† PCM IDE trial, 48 month cumulative data: the SSED report indicated not all patients had completed 48 month follow-up, but no details were reported. The cumulative 36-month incidence of surgery at the adjacent level was 6 ADR patients and 7 ACDF patients.

‡ Mobi-C trial, 60 months: denominator used by Jackson 2016 included 15 non-randomized training cases in the ADR group. (179 vs. 164); SRI was unable to obtain the number of procedures for the randomized patients only.

§ Secure-C IDE trial: C-ADR group included 151 randomized patients plus 89 nonrandomized patients; SRI was unable to obtain the number of procedures for the randomized patients only.

** Calculated by SRI.

Table M6. C-ADR vs. ACDF (1-level) RCT data: Any Adverse Event

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
“Any adverse event” as reported by the trial†						
Any adverse event	Nabhan 2011	0-12 mos.	0% (0/10)	0% (0/10)	0% (NC)	1.0
Any adverse event†‡**	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	85.1% (235/276)	82.6% (219/265)	See meta-analysis for calculations	
Any adverse event†	ProDisc-C IDE trial (ProDisc-C FDA SSED)	0-24 mos.	81.6% (84/103)	81.1% (86/106)		
Any adverse event†§	Mobi-C IDE trial (1-level) (Hisey 2014)	0-24 mos.	95.0% (170/179)	92.6% (75/81)		
Any adverse event†	PCM IDE trial (PCM FDA SSED)	0-24 mos.	82.6% (180/218)	88.1% (163/185)		
Any adverse event†	Bryan IDE trial (Bryan FDA SSED)	0-24 mos.	73.2% (202/276)	73.2% (174/265)		
Any adverse event†	Secure-C IDE trial (Secure-C FDA SSED)	0-24 mos.	70.9% (107/151)	81.4% (114/140)		
Any adverse event†‡**	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	93.8% (259/276)	87.5% (232/265)	See meta-analysis for calculations	

* Calculated by SRI.

† Cumulative number of events reported by the study

‡ Prestige ST IDE trial: Burkus 2014 reported the cumulative rate of adverse events based on the life-table method for ADR vs. ACDF to be 86.4% vs. 87.5% (0-24 months) and 97.7% vs. 94.5% (0-84 months).

§ Mobi-C trial: denominator used included 15 non-randomized training cases in the ADR group. (179 vs. 164); SRI was unable to obtain the number of events for the randomized patients only.

** Prestige ST IDE trial: events included anatomical/technical difficulty, cancer, cardiovascular, carpal tunnel syndrome, death, dysphagia/dysphonia, gastrointestinal, implant displacement/loosening, infection, neck and/or arm pain, neurological, non-union, other, other pain, pending non-union, respiratory, spinal event, subsidence, trauma, urogenital, and vascular intra-op.

Table M7. C-ADR vs. ACDF (1-level): Adverse events reported by one or more RCTs to be significantly more common with C-ADR

See tables in Appendix N for full reporting of all adverse events from cervical RCTs.

Adverse event	Study	F/U	ADR % (n/N)*	ACDF % (n/N)*	p-value†
Cardiovascular	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	2.5% (6/242)	0% (0/221)	0.02
Carpal tunnel syndrome	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	6.8% (18/276)	2.9% (7/265)	0.03
Compressive peripheral neuropathy (non-CTS)	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	3.0% (7/236)	0% (0/144)	0.04
Dysphagia incidence (based on Bazaz scale mild, moderate, or severe)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	44.6% (62/139)	57.8% (48/83)	<0.01
Infection‡	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	27.0% (62/276)	20.5% (41/265)	0.04
Infection (local)	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	11.2% (20/179)	22.2% (18/81)	0.02
Musculoskeletal	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	12.7% (30/236)	6.3% (9/144)	0.04
Neck or arm pain	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	70.2% (178/276)	64.8% (148/265)	0.04
Pain, neck and upper extremities	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	11.0% (26/236)	19.4% (28/144)	0.02
Other pain	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	58.7% (137/276)	50.1% (107/265)	0.03
Superficial wound infection	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	2.9% (7/242)	0.5% (1/221)	0.04
Trauma§	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	27.2% (72/276)	20.8% (50/265)	0.04
Urogenital	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	7.7% (20/276)	3.3% (8/265)	0.03
Urogenital	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	20.1% (44/276)	12.2% (23/265)	0.01
Procedure-related adverse events (all rated WHO grade 1 or 2, “non-serious”)	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	33.9% (82/242)	29.0% (64/221)	0.02

* Denominators as reported by the study.

† Calculated by SRI.

‡ No difference at 0-24 months (11.9% vs. 10.0%)

§ No difference at 0-84 months (44.9% vs. 44.9%)

Table M8. C-ADR vs. ACDF (1-level): Adverse events reported by one or more RCTs to be significantly more common with C-ADR

See tables in Appendix N for full reporting of all adverse events from cervical RCTs.

Adverse event	Study	F/U	ADR % (n/N)*	ACDF % (n/N)*	p-value†
Spinal event	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	8.6% (23/276)	20.6% (50/265)	<0.01
Spinal event	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	20.9% (45/276)	38.9% (82/265)	<0.01
Spinal disorder	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	12.3% (10/81)	<0.01
Spinal disorder: Non cervical	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	6.2% (5/81)	<0.01
Dysphagia incidence, (based on Bazaz scale mild, moderate, or severe)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	15.0% (10/67)	27.6% (8/29)	0.04
Dsyphagia (some degree of ongoing dysphagia)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	15.8% (6/38)	42.1% (16/38)	0.01
Dsyphagia – mild (Bazzaz scale)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	5.3% (2/38)	23.7% (9/38)	0.03
Dsyphagia – moderate (Bazzaz scale)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	5.3% (2/38)	15.8% (6/38)	0.03
Dysphagia severity – Moderate (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	18.7% (26/139)	32.5% (27/83)	0.02
Dysphagia severity – Moderate (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	2.9% (2/67)	13.8% (4/29)	0.46

* Denominators as reported by the study.

† Calculated by SRI.

C-ADR vs. ACDF (2-level)**Table M9. C-ADR vs. ACDF (2-level) RCT data: Secondary Surgery Involving the Index Level***

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)‡	p-value‡
Any secondary surgery at index level	Mobi-C IDE trial (2-level) (Davis 2013)	0-24 mos.	3.1% (7/225)	11.4% (12/105)	-8.3% (-14.8%, -1.8%)	<0.01
Device removal	Mobi-C IDE trial (2-level) (Davis 2013)	0-24 mos.	1.8% (4/225)	5.7% (6/105)	-3.9% (-8.7%, 0.8%)	0.052
Revision	Mobi-C IDE trial (2-level) (Davis 2013)	0-24 mos.	0.4% (1/225)	1.0% (1/105)	-0.5% (-2.6%, 1.5%)	0.58
Supplemental fixation	Mobi-C IDE trial (2-level) (Davis 2013)	0-24 mos.	0% (0/225)	2.9% (3/105)	-2.9% (-6.0%, 0.3%)	0.01
Reoperation	Mobi-C IDE trial (2-level) (Davis 2013)	0-24 mos.	0.9% (2/225)	1.9% (2/105)	-1.0% (-3.9%, 1.9%)	0.43
Device failure or removal	Cheng 2009	0-24 mos.	0% (0/31)	NR	NC	NC
Any secondary surgery at index level†	Mobi-C IDE trial (2-level) (Jackson 2016)	0-60 mos.	4.7% (11/234)	12.4% (13/105)	-7.7% (-14.5%, -0.8%)	0.01

* Numbers include patients who had surgery at the index level alone or at the index AND adjacent levels

† Data includes procedures at index level alone or that involved both the index and adjacent levels: 2 C-ADR and 9 ACDF patients underwent secondary procedures that involved both the index and adjacent levels; totals do not include 6 patients in the ACDF group who underwent plate removal as a result of adjacent-level indications only.

Denominator used by Jackson 2016 included 9 non-randomized training cases in the ADR group. (225 vs. 234); SRI was unable to obtain the number of procedures for the randomized patients only.

‡ Calculated by SRI.

Table M10. C-ADR vs. ACDF (2-level) RCT data: Serious Adverse Events

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Serious/major adverse events as classified by the trial†						
Serious adverse event†	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	24.4% (55/225)	32.4% (34/105)	-7.9% (-18.5%, 2.6%)	0.13

* Calculated by SRI.

† Serious adverse events met one or more of the following criteria: 1) resulted in death; 2) was life-threatening (immediate risk of death); 3) required inpatient hospitalization or prolonged hospitalization; 4) resulted in persistent or significant disability or incapacity; 5) necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or 6) was a congenital anomaly or birth defect. Reported events included: anatomy/technical difficulty, cancer, cardiovascular, death, dysphagia/dysphonia, gastrointestinal, infection (systemic or local), malpositioned implant, migration of implant, neck and/or arm pain, neurological, non-union, other, other pain, respiratory, spinal disorder, trauma, upper extremity nerve entrapment, urogenital, non-infectious wound issue (hematoma, CSF leakage)

Table M11. C-ADR vs. ACDF (2-level) RCT data: Device-Related Adverse Events

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Device-related adverse events as classified by the trial†						
Device-related adverse event†	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	16.0% (36/225)	34.3% (36/105)	-18.3% (-28.6%, -8.0%)	<0.01
Definitely related to the device†	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	4.0% (9/225)	4.8% (5/105)	-0.8% (-5.6%, 4.1%)	0.75
Possibly related to the device†	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	15.1% (34/225)	32.4% (34/105)	-17.3% (-27.4%, -7.2%)	<0.01

* Calculated by SRI.

† Classified by the Clinical Events Committee as possibly or definitely related to the device, and included anatomy/technical difficulty, dysphagia/dysphonia, gastrointestinal, heterotopic ossification, malpositioned implant, neck and/or arm pain, neurological, non-union, other, other pain, respiratory, spinal disorder, trauma.

Table M12. C-ADR vs. ACDF (2-level) RCT data: Secondary Surgery Involving an Adjacent Level

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	Mobi-C (2-level) (FDA SSED)	0-24 mos.	0.9% (2/225)	3.8% (4/105)	-2.9% (-6.8%, 0.9%)	0.065
Secondary surgery at an adjacent level (at adjacent levels only or that involved <u>both</u> adjacent and index levels)	Mobi-C IDE trial (2-level) (Jackson 2016)†	0-60 mos.	3.4% (8/234)	11.4% (12/105)	-8.0% (-14.5%, -1.5%)	<0.01

* Calculated by SRI.

† Mobi-C trial, 60 months: denominator used by Jackson 2016 included 9 non-randomized training cases in the ADR group. (225 vs. 234); SRI was unable to obtain the number of procedures for the randomized patients only.

Table M13. C-ADR vs. ACDF (2-level) RCT data: Any Adverse Event

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
“Any adverse event” as reported by the trial						
Any adverse event	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	89.3% (201/225)	95.2% (100/105)	-5.9% (-11.6%, -0.2%)	0.08

* Calculated by SRI.

† Trial-reported totals only.

C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3 level))**Table M14. C-ADR vs. ACDF (Mixed levels) RCT data: Secondary Surgery Involving the Index Level**

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Reoperation at index level	Skeppholm 2015	0-24 mos.	6.2% (5/81)	1.4% (1/70)	4.7% (-1.2%, 10.7%)	0.14
Second surgical procedure at the index level	Cheng 2011	0-36 mos.	0% (0/41)	0% (0/42)	0% (NC)	1.0

* Calculated by SRI.

Table M15. C-ADR vs. ACDF (Mixed levels) RCT data: Secondary Surgery Involving an Adjacent Level

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	RD (95% CI)*	p-value*
Secondary surgery at an adjacent level	Skeppholm 2015	0-24 mos.	2.5% (2/81)	2.9% (2/70)	-0.4% (-5.6%, 4.8%)	0.88

* Calculated by SRI.

APPENDIX N. C-ADR SAFETY DATA ABSTRACTION TABLES.**C-ADR vs. ACDF (1-level)****Table N1. ADR vs. ACDF (1-level): Safety data abstraction- Prestige ST IDE trial**

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Any secondary surgery at index level	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	3.4% (9/276)	7.9% (19/265)	NR
Any secondary surgery at index level	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	4.8% (11/276)	13.7% (29/265)	<0.001
Revision (index level)	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	0% (0/276)	1.6% (4/265)	NR
Revision (index level)	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	0% (0/276)	2.1% (5/265)	0.019
Removal (index level)	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	2.3% (6/276)	3.3% (8/265)	NR
Removal (index level)	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	3.6% (8/276)	3.3% (8/265)	0.808
Elective removal (index level)	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	0% (0/276)	1.7% (4/265)	NR
Elective removal (index level)	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	0% (0/276)	7.0% (13/265)	<0.001
Supplemental fixation (index level)	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	0% (0/276)	1.3% (3/265)	0.017
Supplemental fixation (index level)	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	0% (0/276)	2.3% (5/265)	0.017
Reoperation (at index level)	Prestige ST IDE trial (Burkus 2014)†	0-24 mos.	1.5% (4/276)	0.8% (2/265)	NR
Reoperation (at index level)	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	1.5% (4/276)	3.0% (4/265)	0.894
Secondary surgery at adjacent level only	Prestige ST IDE trial (Burkus 2014)†‡	0-24 mos.	3.9% (8/205)	5.4% (10/185)	0.451
Secondary surgery that involved adjacent levels	Prestige ST IDE trial (Burkus 2014)†	0-84 mos.	4.6% (11/239)	11.9% (24/202)	0.008

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
(i.e., those at adjacent levels only or involved both adjacent and index levels)	2014)†‡				
Device-related or device/surgical procedure-related adverse events	Prestige ST IDE trial (FDA SSED)	0-24 mos.	3.3% (9/276)	9.8% (26/265)	<0.01**
Bridging bone (radiographic analysis)	Prestige ST IDE trial (Burkus 2014)†§	0-24 mos.	0.8% (2/250)	NR	NR
Bridging bone (radiographic analysis)	Prestige ST IDE trial (Burkus 2014)†§	0-60 mos.	6.2% (13/209)	NR	NR
Bridging bone (radiographic analysis)	Prestige ST IDE trial (Burkus 2014)†§	0-84 mos.	10.0% (20/201)	NR	NR
Disc/graft implant migration (radiographic analysis)	Prestige ST IDE trial (Burkus 2014)†§	84 mos.	0.5% (1/204)	0% (n=NR)	NR
Broken/fractured screw (radiographic analysis)	Prestige ST IDE trial (Burkus 2014)†§	84 mos.	2.4% (5/204)	0% (n=NR)	NR
Any peri-operative adverse event	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	6.2% (17/276)	4.2% (11/265)	0.29**
Neurological**	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	1.4% (4/276)	0.4% (1/265)	NR
Vascular/vessel injury	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.7% (2/276)	0.4% (1/265)	NR
Respiratory	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.4% (1/276)	0% (0/265)	NR
Neck and/or arm pain	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.4% (1/276)	0% (0/265)	NR
Other pain	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.7% (2/276)	0.8% (2/265)	NR
Gastrointestinal	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0% (0/276)	0.8% (2/265)	NR
Anatomical/technical difficulty	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.4% (1/276)	0% (0/265)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Dysphagia/ dysphonia	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.7% (2/276)	1.1% (3/265)	NR
Infection	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.7% (2/276)	0% (0/265)	NR
Other	Prestige ST IDE trial (Mummaneni 2007)	Peri-op	0.7% (2/276)	0.8% (2/265)	NR
Any adverse event	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	86.4% (235/276)	87.5% (219/265)	NR
Any adverse event	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	97.7% (259/276)	94.5% (232/265)	NR
Anatomical technical difficulty	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0.4% (1/276)	0% (0/265)	NR
Anatomical technical difficulty	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0.4% (1/276)	0% (0/265)	NR
Cancer	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	1.9% (5/276)	0.8% (2/265)	NR
Cancer	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	5.2% (12/276)	2.4% (5/265)	0.10**
Cardiovascular	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	6.8% (18/276)	5.5% (13/265)	NR
Cardiovascular	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	17.8% (39/276)	15.5% (31/265)	NR
Carpal tunnel syndrome	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	6.8% (18/276)	2.9% (7/265)	0.03**
Carpal tunnel syndrome	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	10.6% (24/276)	6.0% (12/265)	0.052**
Death	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0% (0/276)	1.3% (3/265)	NR
Death	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0.9% (2/276)	2.2% (5/265)	NR
Dysphagia/dysphonia	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	8.7% (24/276)	8.4% (22/265)	NR
Dysphagia/dysphonia	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	11.5% (29/276)	10.5% (26/265)	NR
Gastrointestinal	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	11.2% (30/276)	12.5% (30/265)	NR
Gastrointestinal	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	24.7% (56/276)	24.9% (51/265)	NR
Implant displacement/ loosening	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0.8% (2/276)	2.1% (5/265)	NR
Implant displacement/ loosening	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	3.1% (6/276)	3.1% (7/265)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Infection	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	11.9% (32/276)	10.0% (24/265)	NR
Infection	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	27.0% (62/276)	20.5% (41/265)	0.04**
Neck or arm pain	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	53.8% (145/276)	48.8% (121/265)	0.11
Neck or arm pain	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	70.2% (178/276)	64.8% (148/265)	0.04**
Neurological	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	25.2% (68/276)	24.6% (60/265)	NR
Neurological	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	42.5% (99/276)	41.5% (87/265)	NR
Nonunion	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0% (0/276)	3.6% (9/265)	NR
Nonunion	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0% (0/276)	3.6% (9/265)	NR
Nonunion (outcome pending)	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0% (0/276)	8.9% (21/265)	NR
Nonunion (outcome pending)	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	0% (0/276)	10.0% (22/265)	NR
Other	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	30.2% (81/276)	35.0% (85/265)	NR
Other	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	57.2% (137/276)	57.1% (127/265)	NR
Other pain	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	31.1% (82/276)	26.3% (64/265)	0.15**
Other pain	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	58.7% (137/276)	50.1% (107/265)	0.03**
Respiratory	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	3.8% (10/276)	3.4% (8/265)	NR
Respiratory	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	9.7% (22/276)	10.1% (19/265)	NR
Spinal event	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	8.6% (23/276)	20.6% (50/265)	<0.01**
Spinal event	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	20.9% (45/276)	38.9% (82/265)	<0.01**
Subsidence	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	0.4% (1/276)	0% (0/265)	NR
Subsidence	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	2.3% (3/276)	0% (0/265)	NR
Trauma	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	27.2% (72/276)	20.8% (50/265)	0.04**
Trauma	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	44.9% (107/276)	44.9% (93/265)	NR
Urogenital	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	7.7% (21/276)	3.3% (8/265)	0.03**

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	trial (Burkus 2014)	mos.	(20/276)		
Urogenital	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	20.1% (44/276)	12.2% (23/265)	0.01**
Intraoperative vascular injury	Prestige ST IDE trial (Burkus 2014)	0-24 mos.	1.8% (5/276)	0.8% (2/265)	NR
Intraoperative vascular injury	Prestige ST IDE trial (Burkus 2014)	0-84 mos.	2.2% (6/276)	1.3% (3/265)	NR

* As reported by the study unless otherwise indicated.

† Cumulative adverse event rates reported using the life-table method.

‡ Denominators calculated based on patients and percentages provided.

§ Patients with complete radiographic follow-up.

** Calculated by SRI.

Table N2. ADR vs. ACDF (1-level): Safety data abstraction- Bryan ST IDE trial

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Any secondary procedure at the index level	Bryan IDE trial (Sasso 2011)	0-24 mos.	2.5% (6/242)	3.6% (8/221)	NR
Any secondary procedure at the index level	Bryan IDE trial (Sasso 2011)	24-48 mos.	1.2% (3/242)	0.9% (2/221)	NR
Any secondary procedure at the index level	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	3.7% (9/242)	4.5% (10/221)	0.816
Revision (at index level)	Bryan IDE trial (Sasso 2011)	0-24 mos.	0.4% (1/242)	0% (0/221)	NR
Revision (at index level)	Bryan IDE trial (Sasso 2011)	24-48 mos.	0% (0/242)	0% (0/221)	NR
Revision (at index level)	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	0.4% (1/242)	0% (0/221)	NR
Removals (at index level)	Bryan IDE trial (Sasso 2011)	0-24 mos.	1.2% (3/242)	1.4% (3/221)	NR
Removals (at index level)	Bryan IDE trial (Sasso 2011)	24-48 mos.	0.4% (1/242)	0.5% (1/221)	NR
Removals (at index level)	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	1.7% (4/242)	1.8% (4/221)	NR
Supplemental fixation (at index level)	Bryan IDE trial (Sasso 2011)	0-24 mos.	0% (0/242)	1.8% (4/221)	NR
Supplemental fixation (at index level)	Bryan IDE trial (Sasso 2011)	24-48 mos.	0% (0/242)	0.5% (1/221)	NR
Supplemental fixation (at index level)	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	0% (0/242)	2.3% (5/221)	NR
Reoperation (at index level)	Bryan IDE trial (Sasso 2011)	0-24 mos.	0.8% (2/242)	0.5% (1/221)	NR
Reoperation (at index level)	Bryan IDE trial (Sasso 2011)	24-48 mos.	0.8% (2/242)	0% (0/221)	NR
Reoperation (at index level)	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	1.7% (4/242)	0.5% (1/221)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Secondary procedure at an adjacent level	Bryan IDE trial (Sasso 2011)	0-24 mos.	2.5% (6/242)	2.3% (5/221)	NR
Secondary procedure at an adjacent level	Bryan IDE trial (Sasso 2011)	24-48 mos.	1.7% (4/242)	1.8% (4/221)	NR
Secondary procedure at an adjacent level	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	4.1% (10/242)	4.1% (9/221)	1.000
Secondary procedure at other cervical levels	Bryan IDE trial (Sasso 2011)	0-24 mos.	0.4% (1/242)	1.4% (3/221)	NR
Secondary procedure at other cervical levels	Bryan IDE trial (Sasso 2011)	24-48 mos.	0% (0/242)	0% (0/221)	NR
Secondary procedure at other cervical levels	Bryan IDE trial (Sasso 2011)	48 mos. cumulative	0.4% (1/242)	1.4% (3/221)	0.352
Any severe adverse event (WHO grade 3 or 4) [†] (Most related to medical conditions and not to the procedure, implant, or cervical spine disease.)	Bryan IDE trial (Anderson 2008)	0-24 mos.	28.9% (73/253)	38.1% (80/210)	0.012
Any severe adverse event (WHO grade 3 or 4) ^{†‡} (Most related to medical conditions and not to the procedure, implant, or cervical spine disease.)	Bryan IDE trial (Sasso 2011)	24-48 mos.	n=44 (63 events)	n=36 (64 events)	NS
Any implant-related or implant/surgical-procedure related adverse event	Bryan IDE trial (Heller 2009)	0-24 mos.	2.9%	5.4%	NS
Serious implant-related or implant/surgical-procedure related adverse event	Bryan IDE trial (Heller 2009)	0-24 mos.	1.7%	3.2%	NS
Severe episodes of neck and arm pain [‡]	Bryan IDE trial (Sasso 2011)	24-48 mos.	n=3	n=5	NR
New neurological deficits [‡]	Bryan IDE trial (Sasso 2011)	24-48 mos.	n=0	n=2	NR
Procedure-related adverse events (all rated WHO grade 1 or 2, “non-serious”)	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	33.9% (82/242)	29.0% (64/221)	0.023
Anesthesia-related adverse events	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	3.3% (8/242)	2.3% (5/221)	0.15
Allergic reaction	Bryan IDE trial	Intra-/	2.5%	0.5% (1/221)	0.07 ^{‡‡}

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
(routine, not attributed to implant)§	(Anderson 2008)	Peri-op	(6/242)		
Cardiovascular	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	2.5% (6/242)	0% (0/221)	0.02‡‡
Central nervous system	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.8% (2/242)	0.9% (2/221)	NR
Endocrine	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.4% (1/242)	0.9% (2/221)	NR
Gastrointestinal	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	1.7% (4/242)	1.8% (4/221)	NR
Genitourinary	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Infection	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	1.2% (3/242)	0.5% (1/221)	NR
Musculoskeletal	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Psychiatric	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.9% (2/221)	NR
Pulmonary	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	1.2% (3/242)	2.7% (6/221)	0.25‡‡
Drill failure	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.4% (1/242)	0% (0/221)	NR
Malposition	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.4% (1/242)	0% (0/221)	NR
Technical problems	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Wound contamination	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
CSF leak	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.8% (2/242)	1.4% (3/221)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Superficial wound infection	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	2.9% (7/242)	0.5% (1/221)	0.04##
Deep wound infection	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0% (0/221)	NR
Intraoperative bleeding	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.8% (2/242)	0.9% (2/221)	NR
Hematoma	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.8% (2/242)	1.4% (3/221)	NR
Hematoma evacuation	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Dysphagia/ dysphonia	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	10.7% (26/242)	7.2% (16/221)	0.19##
Sensory change in upper extremities	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	2.1% (5/242)	1.8% (4/221)	NR
Motor change in upper extremities	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.4% (1/242)	0.5% (1/221)	NR
Myelopathy	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Spinal cord injury	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0% (0/242)	0.5% (1/221)	NR
Sensory change in lower extremities	Bryan IDE trial (Anderson 2008)	Intra-/ Peri-op	0.8% (2/242)	0% (0/221)	NR
General medical events – possibly or directly related to procedure (any, WHO grades 1-4)**	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	14.9% (36/242)	15.4% (34/221)	0.07
Cancer	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0% (0/242)	0% (0/221)	NR
Cardiovascular	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	2.1% (5/242)	0% (0/221)	0.03##
Gastrointestinal	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	2.5% (6/242)	2.3% (5/221)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2008)				
Infection	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	1.7% (4/242)	1.4% (3/221)	NR
Dermatologic/ allergy	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	2.5% (6/242)	1.8% (4/221)	NR
Psychiatric	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0% (0/242)	1.8% (4/221)	NR
Pulmonary	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	2.5% (6/242)	3.2% (7/221)	NR
Genitourinary	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0% (0/242)	0% (0/221)	NR
Musculoskeletal	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0.4% (1/242)	1.8% (4/221)	NR
Endocrine	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0.4% (1/242)	1.4% (3/221)	0.15††
Central nervous system	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	2.9% (7/242)	1.8% (4/221)	NR
Death (procedure- related)	Bryan IDE trial (Anderson 2008)	Peri-op to 1.5 mos.	0% (0/242)	0% (0/221)	NR
General medical events – unrelated to procedure (any, WHO grades 1-4)††	Bryan IDE trial (Anderson 2008)	1.5-36 mos.	35.1% (85/242)	31.2% (69/221)	0.049
Death (unrelated to procedure)	Bryan IDE trial (Anderson 2008)	1.5-36 mos.	0% (0/242)	0.5% (1/221)	NR
Sensory change in upper extremities	Bryan IDE trial (Anderson 2008)	36 mos. cumulative	15.3% (37/242)	16.3% (36/221)	NR
Upper extremity motor loss	Bryan IDE trial (Anderson 2008)	36 mos. cumulative	2.5% (7/242)	3.6% (8/221)	NR
Myelopathy	Bryan IDE trial (Anderson 2008)	36 mos. cumulative	0.4% (1/242)	1.8% (4/221)	NR
Sensory change in lower extremities	Bryan IDE trial (Anderson 2008)	36 mos. cumulative	2.5% (6/242)	0.5% (1/221)	0.07††

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2008)				

* As reported by the study unless indicated otherwise.

† WHO grades (taken from Anderson 2008): Adverse events graded as a “3” or “4” were considered “serious” whereas grades “1” or “2” were considered “non-serious.”

- Grade 1: events did not require treatment and had no effect on outcome
- Grade 2: events may have required non-operative treatment, but had no effect on outcome or health of patient
- Grade 3: events required medical treatment or may have had a long-term health effect.
- Grade 4 events required an operation, were life threatening, permanent disability, or caused death.

‡ Sasso 2011 only provides the number of patients who had an adverse event but and does not provide % and/or denominator.

§ Discrepancy b/w table and text. Text says all allergic reactions occurred in the investigational group.

** It is unclear if these events also those listed in the intra-/peri-operative event category.

†† For ADR vs. Fusion, events included: cardiovascular (8 vs. 9), central nervous system (14 vs. 11), dermatologic/allergy (1 vs. 0), endocrine (8 vs. 7), gastrointestinal (14 vs. 4), genitourinary (7 vs. 3), hematologic (0 vs. 0), infection (7 vs. 9), musculoskeletal (18 vs. 16), psychiatric (6 vs. 3), pulmonary (0 vs. 6), cancer (2 vs. 0), and death (0 vs. 1).

‡‡ Calculated by SRI.

Table N3. ADR vs. ACDF (1-level): Safety data abstraction- PCM IDE trial

Outcome	Study	F/U	ADR % (n/N)†	ACDF % (n/N)	p-value*
Serious adverse events (any) (majority were systemic or medical in nature and not related to device or surgery)†	PCM IDE trial (Phillips 2013)	0-24 mos.	21.5% (46/214)	21.6% (41/190)	NR
Serious adverse events (any) (majority were systemic or medical in nature and not related to device or surgery)†	PCM IDE trial (Phillips 2015)	24–84 mos.‡	21.0% (45/214)	17.4% (33/190)	NR
Serious device-related adverse events †	PCM IDE trial (Phillips 2013)	0-24 mos.	5.6% (12/214)	7.4% (14/190)	NR
Serious device-related adverse events †	PCM IDE trial (Phillips 2015)	24–84 mos.‡	0.5% (1/214)	1.1% (2/190)	NR
Any secondary surgical intervention	PCM IDE trial (Phillips 2015)	24 mos. cumulative	5.2% (11/211)	5.4% (10/184)	NR
Any secondary surgical intervention	PCM IDE trial (Phillips 2015)	60 mos. cumulative	8.1% (17/211)	12.0% (22/184)	0.237
Any secondary surgical intervention	PCM IDE trial (Phillips 2015)	24-60 mos.	2.8% (6/211)	6.5% (12/184)	NR
Device removal	PCM IDE trial (Phillips 2015)	0-24 mos.	3.8% (8/211)	5.4% (10/184)	NR
Device removal	PCM IDE trial (Phillips 2015)	24-60 mos.	2.8% (6/211)	6.5% (12/184)	NR
Reoperation (additional decompression)	PCM IDE trial (Phillips 2015)	0-24 mos.	1.4% (3/211)	0% (0/184)	NR
Reoperation (additional decompression)	PCM IDE trial (Phillips 2015)	24-60 mos.	0% (0/211)	0% (0/184)	NR
Supplemental fixation (adjacent ACDF)	PCM IDE trial (Phillips 2015)	0-24 mos.	0% (0/211)	0% (0/184)	NR
Supplemental fixation (adjacent ACDF)	PCM IDE trial (Phillips 2015)	24-60 mos.	0% (0/211)	0% (0/184)	NR
Persistent pain (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	0-24 mos.	1.4% (3/211)	0.5% (1/184)	NR
Persistent pain (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	24-60 mos.	0.9% (2/211)	0% (0/184)	NR
Device migration/subsidence (requiring device removal; included in subsequent	PCM IDE trial (Phillips 2015)	0-24 mos.	1.9% (4/211)	0% (0/184)	NR

Outcome	Study	F/U	ADR % (n/N)†	ACDF % (n/N)	p- value*
operations above)					
Device migration/subsidence (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	24-60 mos.	1.9% (4/211)	0% (0/184)	NR
ASD (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	0-24 mos.	0% (0/211)	3.3% (6/184)	NR
ASD (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	24-60 mos.	0% (0/211)	6.0% (11/184)	NR
Nonunion (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	0-24 mos.	NA	1.6% (3/184)	NR
Nonunion (requiring device removal; included in subsequent operations above)	PCM IDE trial (Phillips 2015)	24-60 mos.	NA	0.5% (1/184)	NR
ASD, at either segment	PCM IDE trial (Phillips 2013)	24 mos.	39.1% (59/151)	49.2% (60/122)	0.111
ASD, superior segment	PCM IDE trial (Phillips 2013)	24 mos.	17.1% (30/175)	25.6% (35/137)	0.091
ASD, superior segment	PCM IDE trial (Phillips 2015)	60 mos.	33.1% (48/145)	50.9% (54/106)	0.006
ASD, inferior segment	PCM IDE trial (Phillips 2013)	24 mos.	23.1% (34/147)	29.4% (35/119)	0.263
ASD, inferior segment	PCM IDE trial (Phillips 2015)	60 mos.	49.2% (58/118)	51.7% (46/89)	0.779
Heterotopic ossification (grade III)	PCM IDE trial (Phillips 2013)	24 mos.	3.3% (6/182)	NA	NA
Heterotopic ossification (grade III)	PCM IDE trial (Phillips 2015)	60 mos.	6.7% (10/149)	NA	NA
Heterotopic ossification (grade IV)	PCM IDE trial (Phillips 2013)	24 mos.	1.1% (2/182)	NA	NA
Heterotopic ossification (grade IV)	PCM IDE trial (Phillips 2015)	60 mos.	6.0% (9/149)	NA	NA
Pseudoarthrosis	PCM IDE trial (Phillips 2013)	24 mos.	NA	7.9% (12/151)	NA
Pseudoarthrosis	PCM IDE trial (Phillips 2015)	60 mos.	NA	5.6% (7/126)	NA
Fusion	PCM IDE trial	24 mos.	1.1% (2/182)	NA	NA

Outcome	Study	F/U	ADR % (n/N)†	ACDF % (n/N)	p-value*
	(Phillips 2013)				
Fusion	PCM IDE trial (Phillips 2015)	60 mos.	6.0% (9/150)	NA	NA
Dysphagia incidence, (based on Bazaz scale mild, moderate, or severe)	PCM IDE trial (McAfee 2010 subgroup)	0 mos.	17.2% (26/151)	18.0% (18/100)	0.848
Dysphagia incidence (based on Bazaz scale mild, moderate, or severe)§	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	44.6% (62/139)	57.8% (48/83)	0.007
Dysphagia incidence, (based on Bazaz scale mild, moderate, or severe)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	15.0% (10/67)	27.6% (8/29)	0.040
Dysphagia severity – None (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	0 mos.	82.8% (125/151)	82.0% (82/100)	NS
Dysphagia severity – None (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	55.4% (77/139)	42.2% (35/83)	<0.05
Dysphagia severity – None (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	85.0% (57/67)	72.4% (21/29)	<0.05
Dysphagia severity – Mild (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	0 mos.	10.6% (16/151)	11.0% (11/100)	NS
Dysphagia severity – Mild (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	25.9% (36/139)	20.5% (17/83)	NS
Dysphagia severity – Mild (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	11.9% (8/67)	13.8% (4/29)	NS
Dysphagia severity – Moderate (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	0 mos.	6.0% (9/151)	4.0% (4/100)	NS
Dysphagia severity – Moderate (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	18.7% (26/139)	32.5% (27/83)	<0.05
Dysphagia severity – Moderate (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	2.9% (2/67)	13.8% (4/29)	<0.05
Dysphagia severity – Severe (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	0 mos.	0.7% (1/151)	3.0% (3/100)	NS
Dysphagia severity – Severe (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	1.5 mos.	0% (0/139)	4.8% (4/83)	NS

Outcome	Study	F/U	ADR % (n/N)†	ACDF % (n/N)	p-value*
Dysphagia severity – Severe (Bazaz Dysphagia Score)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	0% (0/67)	0% (0/29)	NS
Dysphonia (moderate to severe; 40/100)	PCM IDE trial (McAfee 2010 subgroup)	24 mos.	4.7% (16/338 visits)	8.9% (16/180 visits)	0.097

* As reported by the study unless indicated otherwise

† As treated patients; denominators include crossover between treatment groups

‡ Complete follow-up was not available at 84 months.

§ A significantly larger percentage of patients who were complaining of dysphagia 6-weeks after PCM (72%) resolved their symptoms by 1 year postoperatively compared with only 41% of patients with ACDF (P = 0.015).

Table N4. ADR vs. ACDF (1-level): Safety data abstraction- Mobi-C IDE trial

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Any secondary surgery at index level	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	1.2% (2/169)	5.7% (5/87)	NR
Revision (at index level)	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0% (0/169)	0% (0/87)	NR
Removals (at index level)	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0.6% (1/169)	3.4% (3/87)	NR
Supplemental fixation (at index level)	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0% (0/169)	2.3% (2/87)	NR
Reoperation (at index level)	Mobi-C IDE trial (Hisey 2014)	0-24 mos.	0.6% (1/169)	0% (0/87)	NR
Subsequent surgery (considered to be any operation that occurred at the initial treatment level or at adjacent levels after the primary operation)‡	Mobi-C IDE trial (1-level) (Jackson 2016)	60 mos.	4.5% (8/179)	17.3% (14/81)	0.0012
Subsequent surgery at the index level‡	Mobi-C IDE trial (1-level) (Jackson 2016)	60 mos.	2.2% (4/179)	6.2% (5/81)	NR
Subsequent surgery at an adjacent level‡	Mobi-C IDE trial (1-level) (Jackson 2016)	60 mos.	1.1% (2/179)	4.9% (4/81)	NR
Subsequent surgery at the index and adjacent level‡	Mobi-C IDE trial (1-level) (Jackson 2016)	60 mos.	1.1% (2/179)	6.2% (5/81)	NR
Device-related adverse events‡**	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.9% (7/179)	7.4% (6/81)	0.23††
Major complications (overall)	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	9.8%	9.9%	NR
Neurological deterioration (major complication)	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	1.2%	2.5%	NR
Radiographic determination (major complication)	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	4.9%	3.7%	NR
Adverse events deemed a major complication per CEC	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	4.3%	3.7%	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
Device migration	Mobi-C IDE trial (1-level) (Hisey 2016)	60 mos.	0%	0%	NR
Radiolucency around implant	Mobi-C IDE trial (1-level) (Hisey 2016)	60 mos.	4.8%	1.9%	NR
Heterotopic Ossification (Grade III or IV, index level)	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	23.8%		NR
Heterotopic Ossification (Grade IV, index level)	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	7.9%		NR
Heterotopic Ossification (Grade IV, index level)§	Mobi-C IDE trial (1-level) (Hisey 2016)	60 mos.	8.5%		NR
ASD (overall)§	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	44.3%	60.7%	<0.05
ASD (Kellgren-Lawrence score ≥1), superior segment§	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	14.6%	25.0%	NS
ASD, superior segment§	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	34%	53%	<0.025
ASD, superior segment§	Mobi-C IDE trial (1-level) (Hisey 2016)	60 mos.	37%	55%	<0.05
ASD (Kellgren-Lawrence score ≥1), inferior segment	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	7.7%	21.0%	<0.05
ASD, inferior segment	Mobi-C IDE trial (1-level) (Hisey 2015)	48 mos.	30%	50%	NR
ASD, inferior segment§	Mobi-C IDE trial (1-level) (Hisey 2016)	60 mos.	37%	55%	<0.05
Any adverse event‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	95.0% (170/179)	92.6% (75/81)	NR
Anatomical/technical difficulty – any‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	6.1% (11/179)	2.5% (2/81)	0.21††
Cervical – study surgery‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.2% (4/179)	2.5% (2/81)	NR
Cervical – non study surgery‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.8% (5/179)	1.2% (1/81)	NR
Non Cervical	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	1.1% (2/179)	0% (0/81)	NR
Cancer‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.2% (4/179)	1.2% (1/81)	NR
Cardiovascular‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	11.2% (20/179)	12.3% (10/81)	NR
Death‡	Mobi-C IDE trial (1-	24 mos.	0% (0/179)	0% (0/81)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
	level) (Hisey 2014)				
Dysphagia‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	10.6% (19/179)	18.5% (15/81)	0.08††
Dysphonia‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	1.7% (3/179)	3.7% (3/81)	NR
Gastrointestinal‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	21.8% (39/179)	18.5% (15/81)	NR
Heterotopic ossification – any‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	5.0% (9/179)	4.9% (4/81)	NR
Heterotopic ossification – index level‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.8% (5/179)	0% (0/81)	NR
Heterotopic ossification – adjacent level‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	1.2% (1/81)	NR
Heterotopic ossification – non cervical‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.2% (4/179)	3.7% (3/81)	NR
Infection – any‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	18.4% (33/179)	24.7% (20/81)	0.25††
Superficial wound infection‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	1.2% (1/81)	NR
Deep wound infection‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR
Other wound infection – no study surgery‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	3.7% (3/81)	NR
Systemic infection‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	4.5% (8/179)	2.5% (2/81)	0.44††
Local infection‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	11.2% (20/179)	22.2% (18/81)	0.02††
Malpositioned implant‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	1.1% (2/179)	1.2% (1/81)	NR
Neck and/or arm pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	57.0% (102/179)	58.0% (47/81)	NR
Neck pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	41.3% (74/179)	45.7% (37/81)	NR
Arm pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	25.7% (46/179)	24.7% (20/81)	NR
Neck and arm pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	5.0% (9/179)	8.6% (7/81)	NR
Neurological ‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	57.0% (102/179)	58.0% (47/81)	NR
Sensory – upper	Mobi-C IDE trial (1-	24 mos.	37.4%	39.5%	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
extremity‡	level) (Hisey 2014)		(67/179)	(32/81)	
Sensory – lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	6.1% (11/179)	2.5% (2/81)	0.21††
Sensory – upper and lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	1.2% (1/81)	NR
Motor – upper extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	14.5% (26/179)	18.5% (15/81)	NR
Motor – lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	4.9% (4/81)	NR
Motor – upper and lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR
Reflex – upper extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	10.1% (18/179)	8.6% (7/81)	NR
Reflex – lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	1.2% (1/81)	NR
Reflex – upper and lower extremity‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR
Neck‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	22.9% (41/179)	25.9% (21/81)	NR
Back‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.9% (7/179)	2.5% (2/81)	NR
Spinal cord disturbance‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR
Gait disturbance‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	1.2% (1/81)	NR
Non-specific‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	1.2% (1/81)	NR
Other‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	19.6% (35/179)	9.9% (8/81)	NR
Nonunion‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	4.9% (4/81)	NR
Other‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	43.0% (77/179)	40.7% (33/81)	NR
Other pain – any‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	57.0% (102/179)	58.0% (47/81)	NR
Shoulder pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	21.8% (39/179)	25.9% (21/81)	NR
Back pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	24.6% (44/179)	22.2% (18/81)	NR
Torso pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.8% (5/179)	3.7% (3/81)	NR
Lower extremity	Mobi-C IDE trial (1-	24 mos.	14.5%	14.8%	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
pain‡	level) (Hisey 2014)		(26/179)	(12/81)	
Headache‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	25.1% (45/179)	32.1% (26/81)	0.24††
Other pain‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	8.4% (15/179)	9.9% (8/81)	NR
Respiratory‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	7.4% (6/81)	0.15††
Spinal disorder‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	3.4% (6/179)	12.3% (10/81)	<0.01††
Cervical – study surgery‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	2.5% (2/81)	NR
Cervical – non study surgery‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	2.8% (5/179)	3.7% (3/81)	NR
Non cervical‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	6.2% (5/81)	<0.01††
Trauma‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	26.3% (47/179)	24.7% (20/81)	NR
Urogenital ‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	5.0% (9/179)	11.1% (9/81)	0.07††
Upper Extremity Nerve Entrapment‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	4.5% (8/179)	4.9% (4/81)	NR
Vascular Intraop‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	0% (0/81)	NR
Hematoma‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0.6% (1/179)	3.7% (3/81)	0.06††
Hematoma evacuation‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR
CSF leak ‡	Mobi-C IDE trial (1-level) (Hisey 2014)	24 mos.	0% (0/179)	0% (0/81)	NR

* As reported by the study unless indicated otherwise.

† Denominators back-calculated based on percentages and numerators provided

‡ Includes 15 non-randomized training cases in the ADR group. (179 vs. 164)

§ Estimated from graph in article

** Events included spinal ligament ossification, neck pain, muscle spasms, radiculopathy, subsidence, medical device complication, misplaced screw coded as device complication.

†† Calculated by SRI.

Table N5. ADR vs. ACDF (1-level): Safety data abstraction- ProDisc-C IDE trial

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Secondary surgical procedures	ProDisc-C IDE trial (Murrey 2009)	24 mos.	1.9% (2/103)	8.5% (9/106)	0.029
Secondary surgical procedures	ProDisc-C IDE trial (Delamarter 2010)	48 mos.	2.9% (3/103)	11.3% (12/106)	0.029
Secondary surgical procedures	ProDisc-C IDE trial (Zigler 2013)	60 mos.	2.9% (3/103)	11.3% (12/106)	0.029
Secondary surgical procedures	ProDisc-C IDE trial (Janssen 2015)	84 mos.	6.8% (7/103)	17.9% (19/106)	0.020
Secondary surgical procedures – index level	ProDisc-C IDE trial (Delamarter 2010)	48 mos.	2.9% (3/103)	11.3% (12/106)	0.02††
Secondary surgical procedures – index level	ProDisc-C IDE trial (Zigler 2013)	60 mos.	2.9% (3/103)	7.5% (8/106)	0.13††
Secondary surgical procedures – index level	ProDisc-C IDE trial (Janssen 2015)	84 mos.	5.8% (6/103)	15.1% (16/106)	0.041
Secondary surgical procedures – involving adjacent level	ProDisc-C IDE trial (Delamarter 2010)	48 mos.	0% (0/103)	5.7% (6/106)	0.01††
Secondary surgical procedures – involving adjacent level	ProDisc-C IDE trial (Zigler 2013)	60 mos.	1.9% (2/103)	5.7% (6/106)	0.16††
Secondary surgical procedures – involving adjacent level	ProDisc-C IDE trial (Janssen 2015)	84 mos.	5.8% (6/103)	12.3% (13/106)	0.11††
Bridging bone on radiograph with loss of motion	ProDisc-C IDE trial (Murrey 2009)	24 mos.	2.9% (3/103)	NR	NC
Bridging bone on radiograph with loss of motion	ProDisc-C IDE trial (Delamarter 2010)	48 mos.	(5/NR)	NR	NC
Bridging bone on radiograph with loss of motion	ProDisc-C IDE trial (Zigler 2013)	60 mos.	(6/NR)	NR	NC
Bridging bone on radiograph with loss of motion	ProDisc-C IDE trial (Janssen 2015)	84 mos.	11.3% (8/71)	NR	NC
Pseudarthrosis	ProDisc-C IDE trial (Zigler 2013)	60 mos.	NR	(22/NR)	NC
Implant-or implantation related adverse events†	ProDisc-C IDE trial (Murrey 2009)	24 mos.	2.9% (3/103)	6.6% (7/106)	0.21††

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2009)				
Implant-related adverse events‡	ProDisc-C IDE trial (Zigler 2013)	60 mos.	1.0% (1/103)	2.8% (3/106)	NS
Surgery-related adverse events§	ProDisc-C IDE trial (Zigler 2013)	60 mos.	11.7% (12/103)	20.8% (22/106)	0.09
Severe or life-threatening adverse event††	ProDisc-C IDE trial (FDA SSED)	24 mos.	15.5% (16/103)	30.2% (32/106)	0.01
Any device-related adverse event	ProDisc-C IDE trial (Janssen 2015)	84 mos.	27% (28/103)	28% (30/106)	0.878
Adjacent-level degenerative disc disease or degenerative joint disease changes	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	1.9% (2/106)	1.00
Cardiovascular	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Dysphagia	ProDisc-C IDE trial (Janssen 2015)	84 mos.	0% (0/103)	1.9% (2/106)	0.498
Headache	ProDisc-C IDE trial (Janssen 2015)	84 mos.	5.8% (6/103)	0.9% (1/106)	0.063
Musculoskeletal	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	5.7% (6/106)	0.280
Musculoskeletal: neck spasms	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Neurologic	ProDisc-C IDE trial (Janssen 2015)	84 mos.	0% (0/103)	0.9% (1/106)	1.00
Numbness – index level related	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	1.9% (2/106)	1.00
Numbness – non index level related	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	0.9% (1/106)	0.618
Ossification	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Other	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	1.9% (2/106)	1.00
Pain – back and lower	ProDisc-C IDE	84 mos.	1.0% (1/103)	0.9% (1/106)	1.00

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
extremities	trial (Janssen 2015)				
Pain – incision site	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Pain – neck	ProDisc-C IDE trial (Janssen 2015)	84 mos.	4.9% (5/103)	6.6% (7/106)	0.768
Pain – neck and other	ProDisc-C IDE trial (Janssen 2015)	84 mos.	0% (0/103)	0.9% (1/106)	1.00
Pain – neck and shoulder	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	1.9% (2/106)	1.00
Pain – neck and upper extremities	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	2.8% (3/106)	1.00
Pain – neck and upper extremities with numbness	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	1.9% (2/106)	1.00
Pain – shoulder	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	1.9% (2/106)	1.00
Pain –upper extremities	ProDisc-C IDE trial (Janssen 2015)	84 mos.	0% (0/103)	1.9% (2/106)	0.498
Pain –upper extremities with numbness	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Surgery for device-related events – index level	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.9% (2/103)	4.7% (5/106)	0.446
Surgery for device-related events – other	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	5.7% (6/106)	0.119
Other wound issues	ProDisc-C IDE trial (Janssen 2015)	84 mos.	1.0% (1/103)	0% (0/106)	0.493
Migration (> 3 mm)	ProDisc-C IDE trial (Murrey 2009)	24 mos.	0% (0/NR)	0% (0/92)	NS
Migration (> 3 mm)	ProDisc-C IDE trial (Zigler 2013)	60 mos.	0% (0/NR)	0% (0/NR)	NS
Subsidence (> 3 mm)	ProDisc-C IDE trial (Murrey 2009)	24 mos.	0% (0/NR)	0% (0/92)	NS

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2009)				
Subsidence (> 3 mm)	ProDisc-C IDE trial (Zigler 2013)	60 mos.	% (1/NR)	0% (0/NR)	NR
Pseudarthrosis**	ProDisc-C IDE trial (Murrey 2009)	24 mos.	0% (0/NR)	8.7% (8/92)	NR
Radiolucency**	ProDisc-C IDE trial (Murrey 2009)	24 mos.	0% (0/NR)	1.1% (1/92)	NR
Dysphagia (some degree of ongoing dysphagia)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	15.8% (6/38)	42.1% (16/38)	0.01
Dysphagia – mild (Bazzaz scale)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	5.3% (2/38)	23.7% (9/38)	0.03
Dysphagia – moderate (Bazzaz scale)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	5.3% (2/38)	15.8% (6/38)	0.03
Dysphagia – severe (Bazzaz scale)	ProDisc-C IDE trial (Segebarth 2010 subgroup from 2 centers)	12 mos.	5.3% (2/38)	2.6% (1/38)	0.55††

* Reported by the study unless indicated otherwise.

† The three ProDisc-C patients who did not achieve AE success had two implant-related and one implantation-related events: two patients reported continued pain and one patient elected removal of the device and conversion to a fusion and the other did not, and one patient who sustained a dural tear. The seven Fusion patients did not achieve AE success from implant-related (6) and implantation-related (1) events because of painful pseudoarthrosis requiring revision (2); plate subsidence/migration requiring revision (2); dysphagia (1); superficial wound infection (1); and foraminotomy as a result of persistent radicular pain (1).

‡ For the 3 patients with ACDF, 5 events were reported, including dysphagia, musculoskeletal pain, neck pain, and surgery at both index and adjacent levels. (Details not reported for the 1 ADR pt).

§ Events included dysphagia, edema, gastrointestinal symptoms, genitourinary symptoms, dural tear (1 ProDisc-C), infection (1 ACDF), and pain.

** ACDF denominator back-calculated using n and % given. This denominator was used for the other radiographic outcomes above at 24 months.

†† Defined as any event requiring hospitalization or surgery; events included cardiovascular, dermatological, dural tear, gastrointestinal, infection (non-wound), infection (superficial wound), other, index level surgery, other surgery (see SSED Table 18).

Table N6. ADR vs. ACDF (1-level): Safety data abstraction- Secure-C IDE trial

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Cancer§	Secure-C IDE trial (Vacarro 2013)†	24 mos.	1.7% (4/236)	0% (0/144)	0.12‡
Cardiovascular	Secure-C IDE trial (Vacarro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NS
Cardiovascular	Secure-C IDE trial (Vacarro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Cardiovascular	Secure-C IDE trial (Vacarro 2013)†	>6 wks to >24 mos.	3.0% (7/236)	0.7% (1/144)	0.14‡
Cardiovascular	Secure-C IDE trial (Vacarro 2013)†	>24 mos. cumul.	3.4% (8/236)	0.7% (1/144)	0.14‡
Carpal tunnel syndrome	Secure-C IDE trial (Vacarro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NS
Carpal tunnel syndrome	Secure-C IDE trial (Vacarro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Carpal tunnel syndrome	Secure-C IDE trial (Vacarro 2013)†	>6 wks to >24 mos.	4.7% (11/236)	5.6% (8/144)	NR
Carpal tunnel syndrome	Secure-C IDE trial (Vacarro 2013)†	>24 mos. cumul.	5.1% (12/236)	5.6% (8/144)	NR
Cerebrovascular	Secure-C IDE trial (Vacarro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Cerebrovascular	Secure-C IDE trial (Vacarro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Cerebrovascular	Secure-C IDE trial (Vacarro 2013)†	>6 wks to >24 mos.	0.8% (2/236)	1.4% (2/144)	NR
Cerebrovascular	Secure-C IDE trial (Vacarro 2013)†	>24 mos. cumul.	1.3% (3/236)	1.4% (2/144)	NR
Compressive peripheral neuropathy (non-CTS)	Secure-C IDE trial (Vacarro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Compressive peripheral neuropathy (non-CTS)	Secure-C IDE trial (Vacarro 2013)†	Peri-op (>2 days)	0.8% (2/236)	0% (0/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2013)†	to 6 wks)			
Compressive peripheral neuropathy (non-CTS)	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	2.1% (5/236)	0% (0/144)	0.08‡
Compressive peripheral neuropathy (non-CTS)	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	3.0% (7/236)	0% (0/144)	0.04‡
Death	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Death	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Death	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.4% (1/236)	0.7% (1/144)	NR
Death	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.4% (1/236)	0.7% (1/144)	NR
Dysesthesia, lower extremities	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Dysesthesia, lower extremities	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Dysesthesia, lower extremities	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.8% (2/236)	0.7% (1/144)	NR
Dysesthesia, lower extremities	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.8% (2/236)	0.7% (1/144)	NR
Dysesthesia, other	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Dysesthesia, other	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0.8% (2/236)	0.7% (1/144)	NR
Dysesthesia, other	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0% (0/236)	1.4% (2/144)	NR
Dysesthesia, other	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.8% (2/236)	2.1% (3/144)	NR
Dysesthesia, upper extremity	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0.4% (1/236)	0% (0/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2013)†				
Dysesthesia, upper extremity	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	8.5% (20/236)	10.4% (15/144)	NR
Dysphagia	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	2.8% (4/144)	NR
Dysphagia	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	1.7% (4/236)	2.1% (3/144)	NR
Dysphagia	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.8% (2/236)	0.7% (1/144)	NR
Dysphagia	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	2.5% (6/236)	5.6% (8/144)	0.13‡
Dysphonia	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0.7% (1/144)	NR
Dysphonia	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0.7% (1/144)	NR
Dysphonia	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.4% (1/236)	0% (0/144)	NR
Dysphonia	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.4% (1/236)	1.4% (2/144)	NR
Gastrointestinal	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Gastrointestinal	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0.7% (1/144)	NR
Gastrointestinal	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	2.5% (6/236)	0% (0/144)	0.054‡
Gastrointestinal	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	2.5% (6/236)	0.7% (1/144)	NR
Headache	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Headache	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days)	0.4% (1/236)	1.4% (2/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2013)†	to 6 wks)			
Headache	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	3.0% (7/236)	6.3% (9/144)	0.12‡
Headache	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	3.4% (8/236)	7.6% (11/144)	0.07‡
Infection, other	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Infection, other	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0.7% (1/144)	NR
Infection, other	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	1.3% (3/236)	1.4% (2/144)	NR
Infection, other	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	1.3% (3/236)	2.1% (3/144)	NR
Infection, superficial wound	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Infection, superficial wound	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	1.4% (2/144)	NR
Infection, superficial wound	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0% (0/236)	0% (0/144)	NR
Infection, superficial wound	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0% (0/236)	1.4% (2/144)	NR
Muscle spasms	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Muscle spasms	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Muscle spasms	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0% (0/236)	0.7% (1/144)	NR
Muscle spasms	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0% (0/236)	0.7% (1/144)	NR
Musculoskeletal**	Secure-C IDE trial (Vaccaro	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2013)†				
Musculoskeletal**	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	12.7% (30/236)	6.3% (9/144)	0.04‡
Neurological	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Neurological	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0.7% (1/144)	NR
Neurological	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.8% (2/236)	2.1% (3/144)	NR
Neurological	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	1.3% (3/236)	2.8% (4/144)	NR
Other††	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	4.7% (11/236)	2.8% (4/144)	NR
Pain, back and/or lower extremities	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Pain, back and/or lower extremities	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	15.3% (36/236)	16.0% (23/144)	NR
Pain, neck	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0.4% (1/236)	0% (0/144)	NR
Pain, neck	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	21.2% (50/236)	28.5% (41/144)	0.11‡
Pain, neck and upper extremities	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Pain, neck and upper extremities	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	11.0% (26/236)	19.4% (28/144)	0.02‡
Pain, neck and upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Pain, neck and upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Pain, neck and upper extremities with	Secure-C IDE trial (Vaccaro	>6 wks to >24 mos.	0% (0/236)	2.1% (3/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
dysesthesia	2013)†				
Pain, neck and upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.4% (1/236)	2.1% (3/144)	NR
Pain, neck with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Pain, neck with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0.7% (1/144)	NR
Pain, neck with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.8% (2/236)	2.1% (3/144)	NR
Pain, neck with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.8% (2/236)	2.8% (4/144)	NR
Pain, other	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0.4% (1/236)	0% (0/144)	NR
Pain, other	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Pain, other	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0.4% (1/236)	0.7% (1/144)	NR
Pain, other	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.8% (2/236)	0.7% (1/144)	NR
Pain, upper extremities	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	13.6% (32/236)	16.7% (24/144)	NR
Pain, upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Pain, upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Pain, upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	1.7% (4/236)	1.4% (2/144)	NR
Pain, upper extremities with dysesthesia	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	2.1% (5/236)	1.4% (2/144)	NR
Psychological	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	2013)†				
Psychological	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0.4% (1/236)	0% (0/144)	NR
Psychological	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0% (0/236)	0.7% (1/144)	NR
Psychological	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0.4% (1/236)	0.7% (1/144)	NR
Surgery, adjacent level	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Surgery, adjacent level	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Surgery, adjacent level	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	1.7% (4/236)	1.4% (2/144)	NR
Surgery, adjacent level	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	1.7% (4/236)	1.4% (2/144)	NR
Any secondary surgery at index level*	Secure-C IDE trial (Vaccaro 2013, FDA SSED)**	0-24 mos.	2.6% (4/151)	10.0% (14/140)	0.01‡
Revision	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0% (0/236)	4.3% (6/140)	<0.01‡
Removal	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	1.7% (4/236)	5.0% (7/140)	0.07‡
Supplemental fixation	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0.9% (2/236)	0.7% (1/140)	0.89‡
Reoperation	Secure-C IDE trial (FDA SSED)§§	0-24 mos.	0% (0/236)	0% (0/140)	1.0‡
Surgery, lumbar level	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Surgery, lumbar level	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	1.4% (2/144)	NR
Surgery, lumbar level	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	2.5% (6/236)	2.1% (3/144)	NR
Surgery, lumbar level	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	2.5% (6/236)	3.5% (5/144)	NR
Surgery, other cervical	Secure-C IDE	Intra-op	0% (0/236)	0% (0/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	trial (Vacarro 2013) [†]	(0-2 days)			
Surgery, other cervical	Secure-C IDE trial (Vacarro 2013) [†]	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Surgery, other cervical	Secure-C IDE trial (Vacarro 2013) [†]	>6 wks to >24 mos.	0% (0/236)	0% (0/144)	NR
Surgery, other cervical	Secure-C IDE trial (Vacarro 2013) [†]	>24 mos. cumul.	0% (0/236)	0.7% (1/144)	NR
Surgery, thoracic level	Secure-C IDE trial (Vacarro 2013) [†]	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Surgery, thoracic level	Secure-C IDE trial (Vacarro 2013) [†]	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Surgery, thoracic level	Secure-C IDE trial (Vacarro 2013) [†]	>6 wks to >24 mos.	0.4% (1/236)	0% (0/144)	NR
Surgery, thoracic level	Secure-C IDE trial (Vacarro 2013) [†]	>24 mos. cumul.	0.4% (1/236)	0% (0/144)	NR
Trauma	Secure-C IDE trial (Vacarro 2013) [†]	>24 mos. cumul.	12.7% (30/236)	11.8% (17/144)	NR
Urogenital	Secure-C IDE trial (Vacarro 2013) [†]	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Urogenital	Secure-C IDE trial (Vacarro 2013) [†]	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Urogenital	Secure-C IDE trial (Vacarro 2013) [†]	>6 wks to >24 mos.	0.4% (1/236)	0% (0/144)	NR
Urogenital	Secure-C IDE trial (Vacarro 2013) [†]	>24 mos. cumul.	0.4% (1/236)	0% (0/144)	NR
Weakness	Secure-C IDE trial (Vacarro 2013) [†]	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Weakness	Secure-C IDE trial (Vacarro 2013) [†]	Peri-op (>2 days to 6 wks)	0% (0/236)	0% (0/144)	NR
Weakness	Secure-C IDE	>6 wks to	1.3% (3/236)	0.7% (1/144)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
	trial (Vaccaro 2013)†	>24 mos.			
Weakness	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	1.3% (3/236)	0.7% (1/144)	NR
Wound issue	Secure-C IDE trial (Vaccaro 2013)†	Intra-op (0-2 days)	0% (0/236)	0% (0/144)	NR
Wound issue	Secure-C IDE trial (Vaccaro 2013)†	Peri-op (>2 days to 6 wks)	0% (0/236)	2.8% (4/144)	NR
Wound issue	Secure-C IDE trial (Vaccaro 2013)†	>6 wks to >24 mos.	0% (0/236)	0% (0/144)	NR
Wound issue	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	0% (0/236)	2.8% (4/144)	NR
Any surgery-related adverse event††	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	5.5% (13/236)	12.5% (18/144)	NS
Any severe or life-threatening adverse event (details NR)††	Secure-C IDE trial (Vaccaro 2013)†	>24 mos. cumul.	19.5% (46/236)	23.6% (34/144)	NS
Radiolucency on radiograph††	Secure-C IDE trial (Vaccaro 2013)†	24 mos.	0% (0/236)	3.8% (5/144)	NR
Device migration (>3 mm)	Secure-C IDE trial (Vaccaro 2013)†	24 mos.	0% (0/236)	NR	NC
Device displacement (>3 mm)	Secure-C IDE trial (Vaccaro 2013)†	24 mos.	0% (0/236)	NR	NC
Prosthesis subsidence (superior-inferior)	Secure-C IDE trial (Vaccaro 2013)†	24 mos.	0% (0/236)	NR	NC

* As reported by the study unless indicated otherwise.

† The “as-treated” population (88 nonrandomized SECURE-C, 148 randomized SECURE-C, 144 ACDF) was used for safety analyses, which includes 88 nonrandomized patients in the ADR group and 4 patients intended to be treated with SECURE-C (1 nonrandomized and 3 randomized) were intraoperatively treated with ACDF (one of these crossovers was due to a randomization error by the site, one was due to an inability to visualize the disc space because of the patient’s large shoulders, and 2 were due to small patient anatomy).

‡ Calculated by SRI.

§ 3 non-randomized SEC: prostate cancer at 692 days, metastatic colon cancer at 959 days, metastatic esophageal cancer at 979 days; 1 randomized SEC: lymphoma at 358 days.

** Including non-spinal arthritis, shoulder injury, epicondylitis, extremity fractures, knee ligament tears

†† Numerators were back-calculated using % in text

Table N7. ADR vs. ACDF (1-level): Safety data abstraction- RCTs other than IDE trials

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
Esophageal perforation (intraoperative)	Karabag 2014	Intra-op	0% (0/19)	0% (0/23)	NR
Vascular complications (intraoperative)	Karabag 2014	Intra-op	0% (0/19)	0% (0/23)	NR
Neurological complications (intraoperative)	Karabag 2014	Intra-op	0% (0/19)	0% (0/23)	NR
Reoperation at index level	Karabag 2014	24 mos.	5.3% (1/19)	0% (0/23)	0.27§
Second surgical procedure for ASD	Karabag 2014	24 mos.	0% (0/19)	0% (0/23)	NR
Any perioperative complication	Nabhan 2011	Peri-op	0% (0/10)	0% (0/10%)	NR
Any postoperative complication	Nabhan 2011	12 mos.	0% (0/10)	0% (0/10%)	NR
Revision surgery at index level	Nabhan 2011	12 mos.	0% (0/10)	0% (0/10%)	NR
Secondary surgery at adjacent level only	Nabhan 2007	36 mos.	0% (0/20)	5% (1/21)	0.33§
Aseptic loosening	Nabhan 2007	36 mos.	0% (0/19)	0% (0/20)	NR
Mechanical failure	Nabhan 2007	36 mos.	0% (0/19)	0% (0/20)	NR
Bony fusion	Nabhan 2007	36 mos.	0% (0/19)	NA	NA
Death	Nabhan 2007	36 mos.	5% (1/20) [†]	0% (0/21)	0.31§
Neurological	Peng-Fei 2008	Mean 17 mos.	0% (0/12)	0% (0/12)	NR
Vascular	Peng-Fei 2008	Mean 17 mos.	0% (0/12)	0% (0/12)	NR
Subsidence	Peng-Fei 2008	Mean 17 mos.	0% (0/12)	0% (0/12)	NR
Extrusion	Peng-Fei 2008	Mean 17 mos.	0% (0/12)	0% (0/12)	NR
Intraoperative prosthesis related complications	Rozankovic 2014	Intra-op	0% (0/51)	NR	NR
Reoperation at the index level	Rozankovic 2014	3 mos. (24 mos. total)	0% (0/51)	2.0% (1/50)	0.31§
Prosthesis migration	Rozankovic 2014	24 mos.	0% (0/51)	NA	NA
Heterotopic ossification	Rozankovic 2014	24 mos.	7.8% (4/51)	NR	NA
Dural tear	Rozankovic 2014	24 mos.	1.9% (1/51)	2.0% (1/50)	NR
Reoperation at adjacent segments	Zhang 2012	24 mos.	1.8% (1/56)	5.7% (3/53)	0.28§
Reoperation, other	Zhang 2012	24 mos.	0% (0/56)	1.9% (1/53)	NR
Heterotopic ossification	Zhang 2012	24 mos.	12.5% (7/56)	NR	NA

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
Vascular complications	Zhang 2012	24 mos.	0% (0/56)	0% (0/53)	NR
Neurological complications	Zhang 2012	24 mos.	0% (0/56)	0% (0/53)	NR
Kyphosis	Zhang 2012	24 mos.	0% (0/56)	NR	NA
Blood transfusion	Zhang 2014	Intra-op	0% (0/55)	0% (0/56)	NR
Pharyngeal discomfort or hoarseness (ranging in severity)‡	Zhang 2014	Peri-op	27.3% (15/55)	23.2% (13/56)	NR
Heterotopic ossification	Zhang 2014	48 mos.	32.7% (18/55)	NR	NA
Device migration (2-3 mm) (i.e., forward movement)	Zhang 2014	48 mos.	5.5% (3/55)	NR	NA
Prosthesis subsidence (obvious)	Zhang 2014	48 mos.	0% (0/55)	NR	NA
Prosthesis excursion (obvious)	Zhang 2014	48 mos.	0% (0/55)	NR	NA
Exacerbated symptoms	Zhang 2014	48 mos.	0% (0/55)	NR	NA
Recompression of the spinal cord or nerve root	Zhang 2014	48 mos.	0% (0/55)	NR	NA
Spontaneous fusion	Zhang 2014	48 mos.	0% (0/55)	NR	NA
Pseudarthrosis	Zhang 2014	48 mos.	NR	12.5% (7/56)	NA
Adjacent-segment reoperation	Zhang 2014	48 mos.	0% (0/55)	7.1% (4/56)	0.04§
Wound/donor site infection (resolved following antibiotics)	Zhang 2014	48 mos.	NR	3.6% (2/56)	NA

* As reported by the study unless indicated otherwise.

† Patient died 6 weeks after surgery due to severe subarachnoid hemorrhage

‡ All patients recovered in 2 weeks w/o special treatment.

§ Calculated by SRI.

Table N8. C-ADR vs. ACDF (1-level) Non-randomized Study Data: Adverse Events

Outcome	Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
Adverse events (any)	Kim 2009	Mean 18 (12-40) mos.	NR	NR	NA
Any adverse event	Hou 2014	Mean 22 (12-26) mos.	15.4% (18/117)	21.3% (23/108)	NS
Dysphagia	Hou 2014	Mean 22 (12-26) mos.	6.8% (8/117)	8.9% (9/108)	NS†
Prosthesis migration	Hou 2014	Mean 22 (12-26) mos.	1.7% (2/117)	0.9% (1/108)	NR
Prosthesis subsidence	Hou 2014	Mean 22 (12-26) mos.	0% (0/117)	0.9% (1/108)	NR
Prevertebral hematoma	Hou 2014	Mean 22 (12-26) mos.	0.9% (1/117)	1.9% (2/108)	NR
Cerebrospinal fluid leak	Hou 2014	Mean 22 (12-26) mos.	1.7% (2/117)	0.9% (1/108)	NR
Epidural hematoma	Hou 2014	Mean 22 (12-26) mos.	0.9% (1/117)	1.9% (2/108)	NR
Vertebral artery injury	Hou 2014	Mean 22 (12-26) mos.	0% (0/117)	0% (0/108)	NR
Hoarseness	Hou 2014	Mean 22 (12-26) mos.	1.7% (2/117)	2.8% (3/108)	NR
C5 Radiculopathy	Hou 2014	Mean 22 (12-26) mos.	1.7% (2/117)	2.8% (3/108)	NR
Wound infections	Hou 2014	Mean 22 (12-26) mos.	0% (0/117)	0.9% (1/108)	NR
Any adverse event	Radcliff 2015	0-1.5 mos.	0% (0/327)	0.44% (29/6635)	NS†
		1.5-3 mos.	0% (0/317)	0.70% (45/6416)	NS†
		3-6 mos.	0% (0/317)	1.33% (83/6260)	0.04†
		6-12 mos.	0.69% (2/291)	1.70% (99/5825)	NS†
		12-18 mos.	0.38% (1/266)	2.17% (112/5163)	0.046†
		18-24 mos.	0.85% (2/236)	1.92% (88/4576)	NS†
		24-36 mos.	0% (0/212)	2.16% (89/4124)	0.03†
36-48 mos.	0% (0/76)	0.51% (8/1576)	NS†		
Reoperation (cumulative)	Radcliff 2015	Mean 26 mos. (through last f/u)	5.7% (12/212)	10.5% (433/4124)	0.02
Reoperation	Radcliff 2015	0-1.5 mos.	0.00% (0/327)	0.68% (45/6635)	NS†
		1.5-3 mos.	0.00% (0/317)	0.15% (10/6416)	NS†
		3-6 mos.	0.32% (1/317)	0.67% (43/6260)	NS†
		6-12 mos.	1.01% (3/291)	1.78% (106/5825)	NS†
		12-18 mos.	0.75% (2/266)	1.56% (82/5163)	NS†
		18-24 mos.	0.82% (2/236)	1.05% (49/4576)	NS†
		24-36 mos.	0.46% (1/212)	1.60% (67/4124)	NS†
36-48 mos.	1.14% (1/76)	1.09% (19/1576)	NS†		
Dysphagia	Radcliff 2015	0-1.5 mos.	0% (0/327)	0.03% (2/6635)	NS†
		1.5-3 mos.	0% (0/317)	0.016% (1/6416)	NS†
		3-6 mos.	0% (0/317)	0% (0/6260)	NS†
		6-12 mos.	0% (0/291)	0.052% (3/5825)	NS†
		12-18 mos.	0% (0/266)	0.039% (2/5163)	NS†

Outcome	Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
		18-24 mos.	0% (0/236)	0.044% (2/4576)	NS†
		24-36 mos.	0% (0/212)	0% (0/4124)	NS†
		36-48 mos.	0% (0/76)	0% (0/1576)	NS†
Pain-related adverse event (cumulative)	Radcliff 2015	Mean 26 mos. (through last f/u)	3.84% (13/327)	3.47% (143/4124)	NS†
Any pain-related adverse event	Radcliff 2015	0-1.5 mos.	0% (0/327)	0.17% (11/6635)	NS†
		1.5-3 mos.	0% (0/317)	0.20% (13/6416)	NS†
		3-6 mos.	0.32% (1/317)	0.45% (28/6260)	NS†
		6-12 mos.	1.03% (3/291)	0.7% (41/5825)	NS†
		12-18 mos.	0.75% (2/266)	0.68% (35/5163)	NS†
		18-24 mos.	1.27% (3/236)	0.59% (27/4576)	NS†
		24-36 mos.	0.47% (1/212)	0.68% (28/4124)	NS†
Any device-related (“mechanical”) complication	Radcliff 2015	0-1.5 mos.	0% (0/327)	0.06% (0/6635)	NS†
		1.5-3 mos.	0% (0/317)	0.06% (4/6416)	NS†
		3-6 mos.	0% (0/317)	0.10% (6/6260)	NS†
		6-12 mos.	0% (0/291)	0.15% (9/5825)	NS†
		12-18 mos.	0% (0/266)	0.21% (11/5163)	NS†
		18-24 mos.	0% (0/236)	0.17% (8/4576)	NS†
		24-36 mos.	0% (0/212)	0.10% (4/4124)	NS†

NS: p>0.05

* As reported by the study unless otherwise indicated.

† Calculated by SRI.

C-ADR vs. ACDF (2-level)**Table N9. ADR vs. ACDF (2-level): Safety data abstraction- Mobi-C (2-level) IDE trial**

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Nonunion‡	Mobi-C trial (2-level) (Davis 2013)	24 mos.	NA	20.2% (20/99)	NA
Nonunion‡§	Mobi-C trial (2-level) (Davis 2015)	48 mos.	NA	14.3% (12/81 with available radiographs)	NA
Nonunion	Mobi-C trial (2-level) (Radcliff 2016)	60 mos.	NA	14.3% (15/105)	NA
Symptomatic nonunion requiring subsequent surgical interventions (subset of above 15 nonunions)	Mobi-C trial (2-level) (Radcliff 2016)	60 mos.	NA	8.6% (9/105)	NA
Secondary surgery (revision, removal, reoperation, or supplemental fixation at the index level)	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	3.1% (7/225)	11.4% (12/105)	<0.01‡‡
Device removal	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	1.8% (4/225)	5.7% (6/105)	0.05‡‡
Revision	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/225)	1.0% (1/105)	NR
Supplemental fixation	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0% (0/225)	2.9% (3/105)	NR
Reoperation	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/225)	1.9% (2/105)	0.01‡‡
Reoperation (adjacent-level)	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/225)	0% (0/105)	<0.05
Reoperation (adjacent-level)†	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	3.1% (7/225)	11.4% (12/105)	<0.05
Subsequent surgery (considered to be any operation that occurred at the initial treatment level or at adjacent levels after	Mobi-C IDE trial (2-level) (Jackson 2016)	60 mos.	7.3% (17/234)	21.0% (22/105)	0.0007

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
the primary operation)**					
Subsequent surgery at the index level**	Mobi-C IDE trial (2-level) (Jackson 2016)	60 mos.	3.8% (9/234)	9.5% (10/105)	0.04‡‡
Subsequent surgery at an adjacent level**	Mobi-C IDE trial (2-level) (Jackson 2016)	60 mos.	2.6% (6/234)	2.9% (3/105)	NR
Subsequent surgery at the index and adjacent level**	Mobi-C IDE trial (2-level) (Jackson 2016)	60 mos.	0.9% (2/234)	8.6% (9/105)	<0.01‡‡
Any device-related adverse event (CEC defined as definitely or possibly device related)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	16.7% (39/225)	34.3% (36/105)	<0.01‡‡
Anatomical/technical difficulty**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/234)	1.9% (2/105)	NR
Dysphagia**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	3.8% (9/234)	7.6% (8/105)	0.14‡‡
Dysphonia**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	1.0% (1/105)	NR
Gastrointestinal**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	0% (0/105)	NR
Heterotopic ossification (index level)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/234)	0% (0/105)	NR
Heterotopic ossification (adjacent level)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	0% (0/105)	NR
Malpositioned implant**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	1.7% (4/234)	0% (0/105)	NR
Neck pain**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	6.0% (14/234)	10.5% (11/105)	0.14‡‡
Arm pain**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	2.2% (5/234)	4.8% (5/105)	NR
Neck and arm pain**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	1.9% (2/105)	NR
Sensory, upper	Mobi-C IDE trial	24 mos.	2.6% (6/234)	3.8% (4/105)	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
extremity (neurological)**	(2-level) (Davis 2013)				
Reflex, upper extremity (neurological)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	1.0% (1/105)	NR
Motor, upper extremity (neurological)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	1.9% (2/105)	NR
Neck (neurological)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/234)	5.7% (6/105)	<0.01‡‡
Back (neurological)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	1.0% (1/105)	NR
Other (neurological)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0% (0/234)	1.0% (1/105)	NR
Nonunion**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0% (0/234)	7.6% (8/105)	NR
Other**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0% (0/234)	1.9% (2/105)	NR
Headache (pain)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (2/234)	1.9% (2/105)	NR
Shoulder (pain)**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	1.7% (4/234)	1.0% (1/105)	NR
Respiratory**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	0% (0/105)	NR
Spinal event**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	1.3% (3/234)	4.8% (5/105)	0.05‡‡
Trauma**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.4% (1/234)	0% (0/105)	NR
Serious adverse event (CEC- adjudicated AEs)§§	Mobi-C (2-level) IDE trial (FDA SSED)	0-24 mos.	24.4% (55/225)	32.4% (34/105)	<0.01‡‡
Potentially device-related serious adverse events (CEC-adjudicated AEs)†	Mobi-C IDE trial (2-level) (Radcliff 2016)	24 mos.	3.6% (8/225)	6.7% (7/105)	0.21‡‡
Potentially device-related	Mobi-C IDE trial	36 mos.	4.0%	6.7%	NR

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
serious adverse events (CEC-adjudicated AEs)†	(2-level) (Radcliff 2016)		(9/225)	(7/105)	
Potentially device-related serious adverse events (CEC-adjudicated AEs)†	Mobi-C IDE trial (2-level) (Radcliff 2016)	48 mos.	4.0% (9/225)	7.6% (8/105)	NR
Potentially device-related serious adverse events (CEC-adjudicated AEs)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	4.4% (10/225)	8.6% (9/105)	0.13‡‡
Dysphagia/dysphonia†	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	16% (36/225)	21% (22/105)	0.27‡‡
Implant malposition (suboptimal or undesired location)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	1.7% (4/225)	NR	NR
Heterotopic ossification**	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	1.3% (1/234)	NA	NA
Heterotopic ossification, superior segment (Grade III/IV, clinically relevant)	Mobi-C IDE trial (2-level) (Davis 2013)	24mos.	11.5% (n=NR)	NA	NA
Heterotopic ossification, inferior segment (Grade III/IV, clinically relevant)	Mobi-C IDE trial (2-level) (Davis 2013)	24mos.	10.1% (n=NR)	NA	NA
Heterotopic ossification (Grade III/IV, clinically relevant)†	Mobi-C IDE trial (2-level) (Davis 2015)	48 mos.	25.6% (48/187 with available radiographs)	NA	NA
Heterotopic ossification (Grade III/IV, clinically relevant)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	29.7% (n=pts with available radiographs, NR)	NA	NA
Heterotopic ossification (Grade IV, in at least 1- level)†	Mobi-C IDE trial (2-level) (Davis 2015)	48 mos.	10.2% (19/187 with available radiographs)	NA	NA
Heterotopic ossification (Grade IV, in at least 1- level)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	9.7% (n=pts with available radiographs, NR)	NA	NA
ASD, superior segment (≥1 point increase of the Kellegren-Lawrence grading scale in the superior	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	13.1% (N=NR)	33.3% (N=NR)	<0.03

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
segment compared with baseline)					
ASD, inferior segment (≥1 point increase of the Kellegren-Lawrence grading scale in the inferior segment compared with baseline)	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	2.9% (N=NR)	18.1% (N=NR)	<0.03
ASD (≥1 point increase of the Kellegren-Lawrence grading scale in either segment compared with baseline)†	Mobi-C IDE trial (2-level) (Davis 2015)	48 mos.	41.5% (78/187 with available radiographs)	85.9% (70/81 with available radiographs)	<0.0001
ASD (≥1 point increase of the Kellegren-Lawrence grading scale in either segment compared with baseline)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	50.7% (n=pts with available radiographs, NR)	90.5% (n=pts with available radiographs, NR)	<0.0001
Worsened muscle weakness (vs. baseline)	Mobi-C IDE trial (2-level) (Radcliff 2016)	60 mos.	8.0% (18/225)	11.4% (12/105)	0.31‡
Migration (significant posterior device migration: 3mm posterior motion of the device parallel to the vertebral endplates)††	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0.9% (1/225)	0% (0/105)	NR
Migration (significant posterior device migration: 3mm posterior motion of the device parallel to the vertebral endplates)	Mobi-C IDE trial (2-level) (Davis 2015)	48 mos.	0% (0/225)	0% (0/105)	NR
Subsidence (significant: 3mm of cranial or caudal motion of the device perpendicular to the vertebral endplates)	Mobi-C IDE trial (2-level) (Davis 2013)	24 mos.	0% (0/225)	0% (0/105)	NR
Subsidence (significant: 3mm of cranial or caudal motion of the device perpendicular to the vertebral endplates)	Mobi-C IDE trial (2-level) (Davis 2015)	48 mos.	0% (0/225)	0% (0/105)	NR

* As reported by the study unless indicated otherwise.

† Numerator back-calculated based on denominator and % given.

‡ Denominator back-calculated based on n and % given.

§ Does not included patients who had corrective surgery for failed fusion at earlier timepoints

** The denominator includes 9 nonrandomized training cases in the ADR group (234 vs. 225).

†† Required device removal. Included in the count for that outcome as well.

‡‡ Calculated by SRI.

§§ Serious adverse events met one or more of the following criteria: 1) resulted in death; 2) was life-threatening (immediate risk of death); 3) required inpatient hospitalization or prolonged hospitalization; 4) resulted in persistent or significant disability or incapacity; 5) necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or 6) was a congenital anomaly or birth defect. Reported events included: anatomy/technical difficulty, cancer, cardiovascular, death, dysphagia/dysphonia, gastrointestinal, infection (systemic or local), malpositioned implant, migration of implant, neck and/or arm pain, neurological, non-union, other, other pain, respiratory, spinal disorder, trauma, upper extremity nerve entrapment, urogenital, non-infection wound issue (hematoma, CSF leakage)

Table N10. ADR vs. ACDF (2-level): Safety data abstraction- RCTs other than IDE trials

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p-value*
Prosthesis subsidence	Cheng 2009	24 mos.	0% (0/30)	NR	NA
Prosthesis subsidence	Cheng 2009	24 mos.	0% (0/30)	NR	NA
CSF leak	Cheng 2009	24 mos.	0% (0/30)	0% (0/32)	NR
Wound hematomas	Cheng 2009	24 mos.	0% (0/30)	0% (0/32)	NR
Vascular complications (intraoperative)	Cheng 2009	Intra-op	0% (0/30)	0% (0/32)	NR
Neurological complications (intraoperative)	Cheng 2009	Intra-op	0% (0/30)	0% (0/32)	NR
Spontaneous fusion	Cheng 2009	24 mos.	0% (0/30)	NR	NA
Device failure	Cheng 2009	24 mos.	0% (0/30)	NR	NA
Device explantation	Cheng 2009	24 mos.	0% (0/30)	NR	NA
DVT	Cheng 2009	24 mos.	3.3% (1/30)	0% (0/32)	NR
Dysphagia	Cheng 2009	24 mos.	0% (0/30)	3.1% (1/32)	NR

* As reported by the study unless otherwise indicated

Table N11. C-ADR vs. ACDF (1-level) Non-randomized Study Data: Adverse Events

Outcome	Study	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
Adverse events (any)	Kim 2009	Mean 18 (12-40) mos.	NR	NR	NA
Any adverse event	Hou 2014	Mean 24 (12-27) mos.	21.9% (7/32)	29.5% (26/88)	NS
Dysphagia	Hou 2014	Mean 24 (12-27) mos.	9.4% (3/32)	11.4% (10/88)	NS†
Prosthesis migration	Hou 2014	Mean 24 (12-27) mos.	0% (0/32)	1.1% (1/88)	NS†
Prosthesis subsidence	Hou 2014	Mean 24 (12-27) mos.	0% (0/32)	2.3% (2/88)	NS†
Prevertebral hematoma	Hou 2014	Mean 24 (12-27) mos.	0% (0/32)	1.1% (1/88)	NS†
Cerebrospinal fluid leak	Hou 2014	Mean 24 (12-27) mos.	0% (0/32)	2.3% (2/88)	NS†
Epidural hematoma	Hou 2014	Mean 24 (12-27) mos.	3.1% (1/32)	2.3% (2/88)	NS†
Vertebral artery injury	Hou 2014	Mean 24 (12-27) mos.	0% (0/32)	0% (0/88)	NS†
Hoarseness	Hou 2014	Mean 24 (12-27) mos.	3.1% (1/32)	3.4% (3/88)	NS†
C5 Radiculopathy	Hou 2014	Mean 24 (12-27) mos.	3.1% (1/32)	3.4% (3/88)	NS†
Wound infections	Hou 2014	Mean 24 (12-27) mos.	3.1% (1/32)	2.3% (2/88)	NS†

NS: p>0.05

* As reported by the study unless otherwise indicated.

† Calculated by SRI.

C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3-level))**Table N12. ADR vs. ACDF (Mixed levels (1-, 2-, or 3- level): Safety data abstraction- RCTs**

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
Neurological complications (intraoperative)	Cheng 2011	Intra-op	0% (0/41)	0% (0/42)	NS
Vascular complications (intraoperative)	Cheng 2011	Intra-op	0% (0/41)	0% (0/42)	NS
Prosthesis subsidence	Cheng 2011	36 mos.	0% (0/41)	NR	NA
Dysphagia	Cheng 2011	36 mos.	2.4% (1/41)	16.7% (7/42)	<0.001
Pseudarthrosis	Cheng 2011	36 mos.	NR	7.1% (3/42)	NA
Spontaneous fusion	Cheng 2011	36 mos.	2.4% (1/41)	NR	NA
DVT	Cheng 2011	36 mos.	2.4% (1/41)	0% (0/42)	NR
Heterotropic ossification	Cheng 2011	36 mos.	2.4% (1/41)	NR	NA
Device failure	Cheng 2011	36 mos.	0% (0/41)	NR	NA
Device explantation	Cheng 2011	36 mos.	0% (0/41)	NR	NA
CSF leak	Cheng 2011	36 mos.	0% (0/41)	0% (0/42)	NS
Wound hematomas	Cheng 2011	36 mos.	0% (0/41)	0% (0/42)	NS
Second surgical procedure	Cheng 2011	36 mos.	0% (0/41)	0% (0/42)	NS
Hematoma (leading to reoperation- level NR) (ITT population)	Skeppholm 2015	Peri-op	1.2% (1/81)	0% (0/70)	NR
Hematoma (leading to reoperation- level NR) (PP population)	Skeppholm 2015	Peri-op	1.4% (1/72)	0% (0/67)	NR
Donor site infection (ITT population)	Skeppholm 2015	Peri-op	N/A	4.3% (3/70)	NA
Donor site infection (PP population)	Skeppholm 2015	Peri-op	N/A	4.5% (3/67)	NA
Horner syndrome (ITT population)	Skeppholm 2015	Peri-op	1.2% (1/81)	0% (0/70)	NR
Horner syndrome (PP population)	Skeppholm 2015	Peri-op	1.4% (1/72)	0% (0/67)	NR
Donor site pain (i.e. VAS ≥ 4) (ITT population)	Skeppholm 2015	24 mos.	N/A	7.5% (5/67)	NA
Donor site pain (i.e. VAS ≥ 4) (PP population)	Skeppholm 2015	24 mos.	N/A	8.6% (5/58)	NA
Dysphagia (i.e. Dysphagia Short Questionnaire ≥ 4) (ITT population)	Skeppholm 2015	24 mos.	11.8% (9/76)	17.9% (12/67)	0.31 [†]
Dysphagia (i.e. Dysphagia Short Questionnaire ≥ 4) (PP population)	Skeppholm 2015	24 mos.	13.4% (9/67)	20.7% (12/58)	0.28 [†]
Implant failure (i.e. material insufficiency with breakage or loosening) (ITT population)	Skeppholm 2015	24 mos.	0% (0/76)	0% (0/67)	NS
Implant failure (i.e. material insufficiency with breakage or loosening) (PP population)	Skeppholm 2015	24 mos.	0% (0/67)	0% (0/58)	NS

Outcome	Study	F/U	ADR % (n/N)	ACDF % (n/N)	p- value*
population)					
C7 palsy (ITT population)	Skeppholm 2015	Unclear:peri- op 24 mos.	1.2% (1/81) 1.3% (1/76)	0% (0/67)	NR
C7 palsy (PP population)	Skeppholm 2015	Unclear:peri- op 24 mos.	1.4% (1/72) 1.5% (1/67)	0% (0/58)	NR
Wound infection (ITT population)	Skeppholm 2015	Unclear:peri- op 24 mos.	1.2% (1/81) 1.3% (1/76)	0% (0/67)	NR
Wound infection (PP population)	Skeppholm 2015	Unclear:peri- op 24 mos.	1.4% (1/72) 1.5% (1/67)	0% (0/58)	NR
Pseudarthrosis (leading to reoperation) (ITT population)	Skeppholm 2015	24 mos.	N/A	1.5% (1/67)	NA
Pseudarthrosis (leading to reoperation) (PP population)	Skeppholm 2015	24 mos.	N/A	1.7% (1/58)	NA
Dural tear (ITT population)	Skeppholm 2015	Intra-op	0% (1/81)	0% (0/70)	NS
Dural tear (PP population)	Skeppholm 2015	Intra-op	0% (1/72)	0% (0/67)	NS
Hoarseness (ITT population)	Skeppholm 2015	Peri-op	3.7% (3/81)	5.7% (4/70)	NR
Hoarseness (PP population)	Skeppholm 2015	Peri-op	4.2% (3/72)	6.0% (4/67)	NR
Reoperation at index level (ITT population)	Skeppholm 2015	24 mos.	6.6% (5/76)	1.5% (1/67)	0.13†
Reoperation at index level (PP population)	Skeppholm 2015	24 mos.	7.5% (5/67)	1.7% (1/58)	0.14†
Secondary surgery (ITT population)	Skeppholm 2015	24 mos.	2.6% (2/76)	0% (0/67)	NR
Secondary surgery (PP population)	Skeppholm 2015	24 mos.	3.0% (2/67)	0% (0/58)	0.19†
Secondary surgery for symptomatic ASD (ITT population)	Skeppholm 2015	24 mos.	2.6% (2/76)	3.0% (2/67)	NR
Secondary surgery for symptomatic ASD (PP population)	Skeppholm 2015	24 mos.	3.0% (2/67)	3.4% (2/58)	NR

* Reported by the study unless indicated otherwise.

† Calculated by SRI.

Table N13. C-ADR vs. ACDF (Mixed levels (1-, 2-, or 3- level) Non-randomized Study Data: Adverse Events

Outcome	F/U	C-ADR Mean ± SD	ACDF Mean ± SD	p-value*
Cappelletto 2013				
Second operation‡	12 mos.	2.4% (2/84)	5.4% (5/92)	NS
Dysphagia	12 mos.	2.4% (2/84)	4.3% (4/92)	NS†
Peng 2011				
Implant failures, migrations/ dislocations, subsidence	24 mos.	0% (0/40)	0% (0/75)	NS†
Approach- or device-related complications	24 mos.	0% (0/40)	0% (0/75)	NS†
Neurologic deterioration or complications	24 mos.	0% (0/40)	NR	NA
Grob 2010				
General peri- operative complications	Peri-op	0.0%	2.2%	NS
Surgical peri- operative complications	Peri-op	1.4%	2.2%	NS
Complications from index procedure§	12 mos.	19.0% (11/58)	26.1% (54/208)	NS
	24 mos.	7.0% (2/30)	23.0% (32/139)	0.045
Reoperation at the index level	12 mos.	1.7% (1/58)	2.4% (5/208)	NS†
	24 mos.	0% (0/30)	3.6% (5/139)	NS†
Reoperation at a different spine segment	12 mos.	1.7% (1/58)	2.4% (5/208)	NS†
	24 mos.	3.3% (1/30)	5.1% (9/139)	NS†
Nandyala 2014				
Overall complication rate per 1000 cases †	In-hospital	31.9 per 1000 cases	40.0 per 1000 cases	0.058
Dysphagia	In-hospital	19.2% (351/1830)	23.2% (32765/141230)	NS (adj.**)
Pulmonary embolism	In-hospital	0.5% (9/1830)	0.8% (1130/141230)	NS (adj.**)
Deep venous thrombosis	In-hospital	2.2% (40/1830)	2.4% (3390/141230)	NS (adj.**)
Infection	In-hospital	2.2% (40/1830)	3.6% (5084/141230)	NS (adj.**)
Cardiac	In-hospital	3.3% (60/1830)	3.1% (4378/141230)	NS (adj.**)
Hematoma	In-hospital	2.2% (40/1830)	5.0% (7061/141230)	NS (adj.**)
CSF leak	In-hospital	0.5% (9/1830)	0.2% (282/141230)	NS (adj.**)
Neurological complications	In-hospital	1.6% (29/1830)	1.7% (2401/141230)	NS (adj.**)

Outcome	F/U	C-ADR Mean \pm SD	ACDF Mean \pm SD	p-value*
Mortality per 1000 cases	In-hospital	0.5 per 1000 cases	2.2 per 1000 cases	NS (adj.**)

NS: $p > 0.05$

* As reported by the study unless otherwise indicated.

† Calculated by SRI.

‡ Patients receiving ADR who underwent a second operation did so due to the pull-out of the prosthesis. Patients receiving fusion who underwent a second operation did so due to the pull-out of the screws or nonfusion.

§ Most commonly reported complications included sensory disturbances, general neurological complications, continued/new pain, and problems with wound healing.

** Adjusted for baseline differences between groups in age, sex, race, Charlson Comorbidity Index, and hospital characteristics.

C-ADR vs. ACDF with a Zero-Profile Device (2 non-contiguous levels)**Table N14. ADR vs. ACDF with zero-profile device (2 non-contiguous levels): Safety data abstraction-RCTs**

Outcome	Study	F/U	ADR % (n/N)	Zero-profile device % (n/N)	p-value*
Blood transfusion	Qizhi 2016	Intra-op	0% (0/14)	0% (0/16)	1.0
CSF leak (due to dura tear)	Qizhi 2016	Intra-op	7.1% (1/14)	12.5% (2/16)	0.62
Hoarseness	Qizhi 2016	Peri-op	7.1% (1/14)	6.3% (1/16)	0.92
Dysphagia (mild)	Qizhi 2016	Peri-op	7.1% (1/14)	6.3% (1/16)	0.92
ASD (radiographic; non-symptomatic)	Qizhi 2016	Mean 32.4 mos. (24-46)	0% (0/14)	18.7% (3/16)	0.04
Heterotopic ossification	Qizhi 2016	Mean 32.4 mos. (24-46)	0% (0/14)	NR	NA
Pseudarthrosis	Qizhi 2016	12 mos.	NA	0% (0/16)	NA
Instrument dislodgement	Qizhi 2016	Mean 32.4 mos. (24-46)	0% (0/14)	0% (0/16)	1.0
Instrument breakage	Qizhi 2016	Mean 32.4 mos. (24-46)	0% (0/14)	0% (0/16)	1.0
Instrument subsidence	Qizhi 2016	Mean 32.4 mos. (24-46)	0% (0/14)	0% (0/16)	1.0

NA: not applicable; NR: not reported

APPENDIX O. Ongoing Clinical Trials**Table O1. Ongoing Clinical Trials**

Trial Number, Condition (Estimated N)	Population	Intervention(s)	Trial Name	Country	Primary outcomes	Status (Estimated Completion)
L-ADR						
NCT00589797 Degenerative Disc Disease (N = 414)	Adults	Single-level L-ADR (Activ-L) vs. L-ADR (ProDisc or Charité)	Clinical Study to Evaluate the Safety and Effectiveness of the Aesculap Activ-L™ Artificial Disc in the Treatment of Degenerative Disc Disease	United States	Overall success relative to baseline at 24 months after surgery, defined by absence of treatment failure; absence or serious device-related adverse events; maintenance or improvement of range of motion at index level; maintenance or improvement in neurological status; and improvement in ODI score.	Active, not recruiting (07/2017)
NCT02381574 Lumbar total disc replacement (N = 600)	Child, adult, seniors	L-ADR (device NR)*	French Lumbar Total Disk Replacement Observational Study (FLTDR Observational Study)	France	Rate of re-intervention during the first five years after T-ADR.	Recruiting (12/2020)
NCT00484458 Low back pain (N = 340)	Adult	L-ADR (device NR)* vs. Interspinous stabilization (Wallis stabilization system)	A Prospective, Multi-center, Randomized, Active-Controlled Study of the Wallis System for the Treatment of Mild to Moderate Degenerative Disc Disease of the Lumbar Spine	United States	Non-inferiority to commercially available L-ADR after 24 months.	Unknown (Last verified 10/2011, estimated completion: 11/2014)
C-ADR						
NCT02417272 Cervical degenerative disc disease (N = 110)	Adults	Single-level C-ADR (CP ESP®) vs. ACDF (Axelle®)	Comparison of 2 Surgical Approaches in the Treatment of Cervical Degenerative Disc Disease: Total Disc Replacement Versus Anterior Cervical Decompression and Fusion	France	Success rate, defined as absence of radiological degenerative disease at adjacent levels 24 months after surgery	Recruiting (05/2019)

Trial Number, Condition (Estimated N)	Population	Intervention(s)	Trial Name	Country	Primary outcomes	Status (Estimated Completion)
NCT02498028 Cervical disc disorders (N = 80)	Adults, Senior (>60 years)	C-ADR (Freedom® or Active® C)* vs. ACDF (titanium cage + plating system)	Clinical Outcome After Anterior Cervical Decompression and Fusion and Cervical Total Disc Replacement	France	Change in pain as assessed by VAS at 24 months after surgery	Recruiting (06/2016)
NCT00432159 Cervical Degenerative Disc Disease (N = 500)	Adults, Senior (21-70 years)	Single-level C-ADR (Discover) vs. ACDF† 2-level C-ADR (Discover) vs. ACDF	A Multi-Center, Prospective, Randomized Controlled Trial Comparing Cervical Arthroplasty to Anterior Cervical Discectomy and Fusion for the Treatment of Cervical Degenerative Disc Disease	United States	Overall success at 24 months after surgery, defined as a 15-point improvement in the NDI from baseline, as well as have had no device-related serious adverse events, secondary surgical interventions at the index level, nor any new permanent neurological deterioration.	Active, not recruiting (05/2016)
NCT01609374 Cervical radiculopathy, degenerative disc disease (N = 243)	Adults, Seniors (18-75 years)	Single-Level C-ADR (M6-C) vs. ACDF (plate system with allograft)	Prospective, Concurrently Controlled, Multi-Center Study to Evaluate the Safety and Effectiveness of the Spinal Kinetics™ M6-C Artificial Cervical Disc Compared to Anterior Cervical Discectomy and Fusion (ACDF) for the Treatment of Symptomatic Cervical Radiculopathy	United States	Safety as assessed through adverse events and neurological function through 24 months.	Active, not recruiting (05/2017)
NCT00735176 Cervical radiculopathy (N = 146)	Adult (25-60 years)	Single-level C-ADR (Discover) vs. ACDF	Treatment of Cervical Radiculopathy With Arthroplasty Compared With Discectomy With Fusion and Cage (ACDF). Clinical, Radiological and Biomechanical Aspects. A Randomized Multicenter Study.	Norway	Clinical effect as measured by use of the NDI at 6 weeks, 3 months, 6 months, 1 year, 2 years, and 5 years postoperatively	Active, not recruiting (07/2018)
NCT00637156	Adults, Seniors	2-level C-ADR (Prestige LP	A Prospective, Randomized, Controlled, Multicenter Pivotal	United States	Overall success 24 months after surgery, as determined by: a	Ongoing, not recruiting

Trial Number, Condition (Estimated N)	Population	Intervention(s)	Trial Name	Country	Primary outcomes	Status (Estimated Completion)
Cervical degenerative disc disease, radiculopathy, myelopathy (N = 397)		device) vs. 2-level ACDF (Atlantis cervical plate system)	Clinical Trial of the Artificial Cervical Disc-LP at Two Levels for Symptomatic Cervical Disc Disease		postoperative NDI score improvement ≥ 15 points; maintenance or improvement in neurological status; no serious adverse event classified as implant-associated or implant/surgical procedure associated; and no additional surgical procedure classified as a “failure”.	(03/2018)
NCT00389597 Degenerative disc disease (N = 599)	Adults, Seniors	Single-level C-ADR (Mobi-C) vs. ACDF 2-level C-ADR (Mobi-C) vs. ACDF	LDR Spine USA Mobi-C(R) Cervical Disc Prosthesis IDE	United States	Composite definition of study success at 2 years, defined as improvement of NDI of at least 15/50 points in subjects with NDI scores of $\geq 30/50$ points, or a 50% improvement in subjects with a baseline NDI of $< 30/50$ where the NDI is a measure designed to enable the physician to understand how much a subject’s neck pain has affected his ability to manage everyday activities; no study failures due to secondary surgical interventions at the index level; absence of major complications defined as radiographic failure, neurologic failure, or failure by adverse event.	Unknown (Last verified 04/2014, estimated completion: 03/2015)

ACDF: Anterior cervical discectomy and fusion; C-ADR: Cervical Artificial Disc Replacement; IDE: Investigational Device Exemption; L-ADR: Lumbar Artificial Disc Replacement; NCT: National Clinical Trial; NDI: Neck Disability Index; NR: Not reported; ODI: Oswestry Disability Index; VAS: Visual Analog Scale

* Number of levels not indicated.

† Also includes an experimental training group/training cohort comprised of patients undergoing 1- or 2-level C-ADR (Discover).

APPENDIX P. Clinical Experts

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