Mobi-C® Cervical Disc Value Analysis Brief

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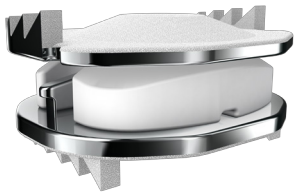

There is strong evidence through 7 years supporting the clinical and economic value of Mobi-C® Cervical Disc for both one- and two-level cervical disc replacement.

Extensive supporting data in this brief is intended to be used for consideration when validating Mobi-C® Cervical Disc against technology evaluation criteria.

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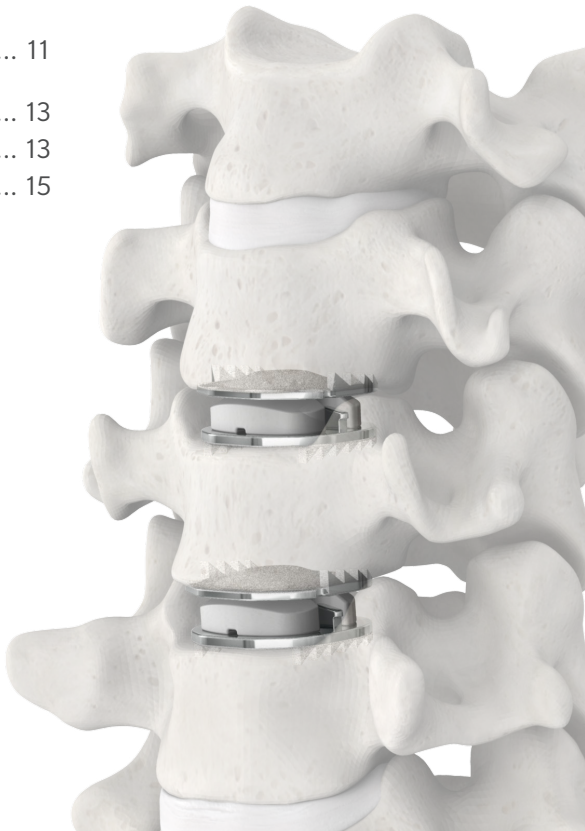

CERVICAL DISC PATHOLOGY AND ANTERIOR INSTRUMENTATION

Degenerative disc disease, typically from repetitive stresses experienced during the normal aging process, accounts for the large majority of operative conditions affecting the spine. The disease progression involves gradual weakening and thinning of the shock absorbing intervertebral discs. The progressive changes in the discs can lead to a host of conditions, including osteoarthritis, herniated disc, and spinal stenosis.

Typical cervical symptoms include neck pain, pain radiating in the arm, numbness, loss of motor and reflex functions, and lack of flexibility. Over time, the progression of these conditions can be compounded because damage to one vertebral segment can place additional stress on the adjacent vertebral levels, leading to multilevel disc disease. Once conservative care fails or in cases where the pathology is more advanced, instrumented cervical surgery is often the next option.

Anterior Cervical Discectomy and Fusion

Anterior cervical discectomy and fusion (ACDF) was historically the instrumented standard of care for the treatment of cervical disc disease. ACDF surgery decompresses the spinal nerves by removing the diseased cervical disc material, and then stabilizes the vertebral segment by inserting bone grafts, interbody devices, and/or fixation systems including screws and plates.

Generally, ACDF achieves successful outcomes with acceptable complication rates.[1-2] However, as the ACDF process eliminates the natural motion of treated segments, it is widely accepted to induce hypermobility and heightened intradiscal pressures at adjacent levels after surgery.[3-6] It is also accepted that treatment with ACDF accelerates degeneration of adjacent spinal levels post-surgery.[7-9]

Cervical Total Disc Replacement – the Non Fusion Alternative to ACDF

Like fusion, cervical total disc replacement (cTDR) removes the diseased cervical disc and restores the natural disc height, decompressing the nerves causing pain. However, cTDR devices are designed to maintain normal spinal motion at the operated vertebral segments. By preserving segmental motion as well as overall cervical spine biomechanics, cTDR has been shown to maintain preoperative intradiscal pressures in adjacent segments.[4]

cTDR Indicated Patient Population

Market reports* estimate approximately 300,000 anterior cervical procedures are performed annually in the U.S. These are adults that have failed conservative care, present with radiculopathy (with or without neck pain) or myelopathy, and have radiographically confirmed disc degeneration and/or loss of disc height.

* Source: iDATA 2015 U.S. Markets for Spinal Implants, MRG 2015 Spinal Implants US Market Analysis

MOBI-C CERVICAL DISC: HISTORY AND DESIGN

The Mobi-C Cervical Disc (Mobi-C) was first introduced outside the United States (US) in November 2004 by LDR Spine, now part of Zimmer Biomet, and has been implanted over 40,000 times in 25 countries. In 2006, LDR Spine initiated an Investigational Device Exemption (IDE) trial to obtain Food and Drug Administration (FDA) approval for use of Mobi-C in the US. In 2013, Mobi-C earned the distinction of being the first cTDR device to be FDA approved for both one and two-level implantation. In 2015, FDA approved an update to the Mobi-C labeling to include five year clinical results. Of note, Mobi-C demonstrated superiority at all time points to five years on overall trial success as compared to two-level ACDF.

The Mobi-C consists of two cobalt chromium (CoCr) endplates that are plasma sprayed with titanium and coated with hydroxyapatite and an ultra-high molecular weight polyethylene insert. CoCr-on-polyethylene is the material used in more than half of the cTDR devices on the market today. In addition, CoCr and polyethylene are proven general orthopedic materials that have been used in hip and knee applications for over 60 years.

MOBI-C IN PEER-REVIEWED MEDICAL JOURNALS

Comparative data from the US Mobi-C IDE trial have been reviewed, accepted, and published in multiple peer-reviewed medical journals.

PMID #	One-Level IDE	Journal	Year
Overall Trial Success			
25694918	24M Follow-up	Hisey, et al., International Journal of Spine Surgery[10]	2014
25310394	48M Follow-up	Hisey, et al., Journal of Spinal Disorders & Techniques[11]	2015
27162712	60M Follow-up	Hisey, et al., International Journal of Spine Surgery[44]	2016
PMID #	**Two-Level IDE**	**Journal**	**Year**
Cost Effectiveness			
25321869	24M Follow-up	Ament, et al., JAMA Surgery[12]	2014
26855020	60M Follow-up	Ament, et al., Neurosurgery[45]	2016
Overall Trial Success			
24010901	24M Follow-up	Davis, et al., Journal of Neurosurgery: Spine[13]	2013
25380538	48M Follow-up	Davis, et al., Journal of Neurosurgery: Spine[14]	2015
25785955	48M Follow-up*	Bae, et al., Spine Journal[15]	2015
26966971	60M Follow-up*	Zigler, et al., Spine Journal[46]	2015
27015130	60M Follow-up	Radcliff et al., Journal of Neurosurgery: Spine[47]	2016
Subsequent Surgery			
26799118	60M Follow-up*	Jackson, et al., Journal of Neurosurgery: Spine[48]	2016
Cervicogenic Headache			
	60M Follow-up*	Liu, et al., Global Spine Journal[49]	2015

*One and two-level results

Highlights from Radcliff et al., Journal of Neurosurgery: Spine 2016

Replacement Compared with Anterior Discectomy and Fusion for Treatment of 2-Level Symptomatic Degenerative Disc Disease: A Prospective, Randomized, Controlled, Multicenter Investigational Device Exemption Clinical Trial

This paper represents the first report of long-term outcomes of two-level cTDR from a U.S. FDA IDE study.[47] Based on the FDA composite outcome measure for success, the overall success rates at five years were 61% and 31% for the cTDR and ACDF groups, respectively ($p<0.0001$). The significantly higher overall success rate for the cTDR group meets superiority criteria. Mobi-C also provided a lower incidence of index level and adjacent level reoperation with cTDR. The Mobi-C patients had a statistically significant greater improvement than ACDF patients in Neck Disability Index (NDI) score, Short Form Health Survey — Physical Component Score (SF-12 PCS), and overall satisfaction with treatment at five years. All of the authors are independent without any institutional or financial bias. They had no prior involvement in the Mobi-C cTDR study or any other consulting or financial relationship with LDR Spine at the time the study was conducted.

The advantages and safety of Mobi-C have been demonstrated to the FDA and recognized in multiple peer-reviewed medical journals.

Highlights from Jackson, et al., Neurosurgery 2016

Subsequent Surgery Rates After Cervical Total Disc Replacement Using a Mobi-C Cervical Disc Prosthesis Versus Anterior Cervical Discectomy and Fusion: A Prospective Randomized Clinical Trial With 5-Year Follow-Up

At 5 years, the occurrence of subsequent surgical intervention was significantly higher among ACDF patients for one- and two-level treatment.[48] The cTDR group demonstrated significantly fewer index- and adjacent-level subsequent surgeries in both the one- and two-level cohorts at five-years.

Subsequent Surgeries at the Treated Levels at 5 Years (Jackson)

One-level		Two-level	
Mobi-C®	ACDF	Mobi-C®	ACDF
4.5%	17.3%	7.3%	21.0%

MOBI-C IN PEER-REVIEWED MEDICAL JOURNALS (cont.)

Highlights from Hisey, et al., International Journal of Spine Surgery 2016
Prospective, Randomized Comparison of One-level Mobi-C Cervical Total Disc Replacement vs. Anterior Cervical Discectomy and Fusion: Results at 5-year Follow-up

Five-year results demonstrate the safety and efficacy of Mobi-C as a viable alternative to ACDF with the potential advantage of lower rates of reoperation and adjacent segment degeneration, in the treatment of one-level symptomatic cervical degenerative disc disease.[44] This prospective, randomized study with 5-year follow-up adds to the existing literature indicating that cervical TDR is a viable alternative to ACDF in appropriately selected patients.

SPECIALTY SOCIETY COVERAGE POLICY RECOMMENDATIONS FOR CERVICAL DISC

North American Spine Society (NASS)
NASS coverage policy recommendations are intended to assist payers and providers in determining whether medical procedures should be covered for payment based on review of the best available clinical evidence and the expert opinion of committee members. In November 2015, NASS updated their important coverage recommendations eBook on cervical arthroplasty to include both one and two-level indications with qualifying criteria. The NASS two-level patients recommendations may be found at: https://www.spine.org/PolicyPractice/CoverageRecommendations/AboutCoverageRecommendations

In 2015, NASS updated their coverage policy recommendations on cervical disc replacement to include both one and two-level indications.

The rationale for coverage of one and two-level disc replacement by NASS is based on the indications and results of many randomized controlled trials, supporting at least equivalency to cervical fusion following adequate decompression.

International Society for the Advancement of Spine Surgery (ISASS)
ISASS published a position statement in 2009 in favor of cervical disc arthroplasty when performed according to the indications outlined in FDA labeling. More recently, ISASS published a policy statement in 2014 supporting the safety and efficacy of cervical disc arthroplasty, based on a growing body of Level 1 evidence from multiple devices, at multiple sites, with long-term follow-up. ISASS stated cervical disc arthroplasty, "is a viable alternative to ACDF in select patients with symptomatic 1- and 2-level cervical radiculopathy or myelopathy."

MOBI-C FDA APPROVAL

Mobi-C FDA Approval at Two Years
In 2013, Mobi-C received approval from the US FDA for one and two-level use.
- P110002 – Mobi-C one-level use Summary of Safety and Effectiveness Data (SSED) – FDA Approved August 7, 2013[16]
- P110009 – Mobi-C two-level use SSED – FDA Approved August 23, 2013[17]

In conjunction with market approval, the FDA drew the following conclusions: "The valid scientific evidence presented in the preceding sections of the SSEDs provides reasonable assurance that the Mobi-C® Cervical Disc is a safe and effective disc replacement for C3 to C7 in skeletally mature patients."[16-17]

Mobi-C FDA Approval at Five Years
In 2015, the FDA approved an update to Mobi-C labeling to include five year clinical results. The updated data remains consistent with the previous findings at 24 months, namely, that at 60 months of follow-up, Mobi-C is statistically non-inferior in terms of overall study success for one-level use and statistically superior in terms of overall study success for two-level use.

FDA approved an update to Mobi-C labeling to include five year clinical results

IDE DESIGN AND FOLLOW-UP: ONE AND TWO-LEVEL ARMS

The Mobi-C IDE trial was multi-centered, prospective, randomized, and controlled. The trial tested Mobi-C for non-inferiority to the current standard of care, ACDF. The trial planned for the testing of superiority in the event that non-inferiority was established. The primary trial endpoint analysis was based upon 24 month results. The IDE trial consisted of one-level and two-level treatment arms conducted simultaneously under the same FDA-approved protocol.

- Investigational treatment: anterior discectomy followed by insertion of Mobi-C
- Control treatment: anterior discectomy followed by insertion of allograft bone and an anterior cervical plate (DePuy Spine Slim-Loc® or the Medtronic Atlantis® or Atlantis Vision®)
- Randomization scheme: 2 to 1 ratio, Mobi-C to ACDF respectively

	Two-Level Arm	One-Level Arm
Total Randomized Patients	330	245
Mobi-C®	225	164
ACDF	105	81

- The trial allowed for 1 non-randomized training case per site and resulted in 9 non-randomized Mobi-C subjects in the two-level arm and 15 in the one-level arm
- 24 investigative sites
- Post-operative follow-up: 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months

Follow-up Rates

The Mobi-C IDE maintains excellent patient follow-up rates and has one of the highest follow-up rates of any cervical disc on the market.

	One-Level			Two-Level		
	2 Years	5 Years	7 Years	2 Years	5 Years	7 Years
Mobi-C® | ACDF	94.3% | 92.0%	85.5% | 78.9%	80.1% | 74.3%	98.1% | 93.3%	90.7% | 86.7%	84.4% | 75.0%
ProDisc® | ACDF[18-20]	98.1% | 94.8%	72.7% | 63.5%	91.9% | 92.4%	Not studied		
Prestige ST | ACDF[21-23]	93.4% | 82.4%	79.7% | 71.7%	76.8% | 69.1%	Not studied		
Prestige LP | ACDF[24-26]	96.8% | 83.7%	Not available	75.9% | 70.0%	Not available		73.7% | 67.0%
Secure®-C | ACDF[27]	93.2% | 75.4%	Not available	Not available	Not studied		
PCM | ACDF[28-29]	89.6% | 82.1%	74.8% | 70.3%	Not available	Not studied		

Post Approval Studies

There are FDA requirements for all Premarket Approval (PMA), commercially available implants like Mobi-C.

- The Post Approval Study (PAS) gathers data for seven years on the original study patients to help assure continued safety and effectiveness of the approved device. All seven year PAS patient follow-up visits were completed by July of 2015. The final PAS data set will be submitted to the FDA in Q2 of 2016. Once approved by the FDA, the PAS will be closed.
- Under the FDA's Enhanced Surveillance Study (ESS), Zimmer Biomet surveys all Mobi-C surgeons annually and solicits user feedback. Any data collected regarding actual conditions of use, including patient outcomes, are reported to FDA in an annual report. The FDA utilizes the ESS to monitor real world usage of PMA devices and requires companies to actively collect and report data for ten years following the date of approval.
- The PAS and ESS are standard FDA requirements for this type of product; there are no additional or extraneous FDA requirements for Mobi-C.

IDE OVERALL RESULTS: ONE AND TWO-LEVEL PRIMARY ENDPOINT

Success Criteria for Primary Endpoint

Mobi-C trial success was based on a composite endpoint. A patient was considered a success if all of the following criteria were met:

- Sufficient Neck Disability Index (NDI) improvement
- No subsequent surgery at the treated level
- No radiographic failure
- No neurologic deterioration
- No adverse event determined to be a major complication

Two-level Mobi-C demonstrated SUPERIORITY in overall trial success compared to ACDF at ALL measured endpoints through 60 months.

Between IDE cervical disc trials, the success criteria for the composite primary endpoints are not equivalent. The success criteria for Mobi-C's primary endpoint is among the most stringent.

Zimmer Biomet Mobi-C[16-17]	DePuy Synthes ProDisc-C[18]	Globus Secure-C[27]	Medtronic Prestige LP[24]	Nuvasive PCM[28]
NDI Success				
If baseline ≥30 points, then NDI score improvement must be ≥ 15 points	>20% improvement	≥ 25% improvement	>15% improvement	>20% improvement
If baseline <30 points, then NDI score improvement must be 50% improvement	*All studies did not require varying levels of NDI improvement based on the patient's baseline score.*			
No Radiographic Failure				
For Mobi-C: ≥2°segmental movement in F/E or the absence of continuous bridging bone	Not part of the analysis	Not part of the analysis	Not part of the analysis	Absence of failures
	Patient could have no movement in flexion-extension and still be a study success.			
No Neurologic Deterioration				
Neurologic status maintained or improved	Same as Mobi-C®	Not part of the analysis	Same as Mobi-C®	Same as Mobi-C®
No Adverse Event (AE) Determined to be a Major Complication				
Determined by an Independent Clinical Events Committee to be device related	**AE determined by treating physician to be device related**	**Absence of major vessel injury, neurologic damage or nerve injury**	**Similar as Mobi-C®**	**Similar as Mobi-C®**
	AEs were evaluated by the surgeon or were less stringent.			

Mobi-C Two-Level IDE: Overall Trial Success

Mobi-C established superiority in overall trial success compared to ACDF at two contiguous levels at all measured endpoints through 84 months.

Overall Trial Success (Two-Level) (p<0.0001)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
69.7%	37.4%	62.8%	34.1%	60.8%	34.6%

Mobi-C One-Level IDE: Overall Trial Success

Mobi-C established non-inferiority in overall trial success compared to ACDF at one level. At 12, 18, and 36 months, Mobi-C was statistically superior to ACDF in overall trial success.

Overall Trial Success (One-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
73.7%	65.3%	65.9%	60.7%	55.2%	50.0%

SUMMARY OF CLINICAL RESULTS

Primary Endpoint Component Results

- ***Mobi-C patients had fewer subsequent surgeries at the treated level(s)***
- ***Mobi-C patients demonstrated greater improvement in NDI scores***
- ***In most cases, Mobi-C patients had fewer complications determined to be device-related adverse events***

Mobi-C Demonstrated Fewer Subsequent Surgeries at the Treated Level(s)

Mobi-C patients had fewer subsequent surgeries at the treated levels compared to ACDF at 24, 36, 48, 60, and 84 months

Subsequent Surgeries at the Treated Levels (Two-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
3.0%	11.4%	3.8%	16.2%	4.4%	16.2%

Subsequent Surgeries at the Treated Levels (One-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
1.1%	6.2%	2.8%	11.1%	3.0%	12.3%

Mobi-C Demonstrated Greater Improvement in Mean Neck Disability Index (NDI) Scores

Mobi-C Two-Level

For NDI, Mobi-C patients had statistically more improvement than ACDF patients at all measured time points through 60 months.

Mobi-C One-Level

Both groups showed significant improvement in mean NDI scores through 60 months.

Mean NDI Scores (Two-Level)					
24 Months (p<0.05)		60 Months (p<0.05)		84 Months (p<0.05)	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
16.5%	24.0%	16.8%	26.4%	18.0%	26.5%

Mean NDI Scores (One-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
16.6%	18.9%	16.4%	17.2%	18.2%	18.2%

Mobi-C Had Fewer Complications Determined to Be Related Adverse Events

Adverse Events (AEs) were determined by an independent Clinical Events Committee (CEC), as events possibly or definitely related to the study device, but not necessarily deemed severe or live threatening.

Mobi-C at two-levels is safe and effective with a lower rate of device-related major complications compared to ACDF.

Major complications determined to be related AEs (Two-Level)			
24 Months		60 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF
4.0% (9 out of 225 pts.)	6.7% (7 out of 105 pts.)	4.4% (10 out of 225 pts.)	8.6% (9 out of 105 pts.)

AEs by Subject	
ACDF	Mobi-C®
• Pseudoarthosis C5-7 • Possible pseudoarthrosis • Numbness in hands bilaterally radiating up to elbow of right side • Pseudoarthrosis C5-6, C6-7 • Pseudoarthrosis C5-6 • Pseudoarthrosis • Right arm radiculopathy • Removal of ADR/Corpectomy/ACF • C5-6 Pseudoarthrosis	• Autofusion C5-6 • Osteophyte bridge anteriorly from C5-6, C6-7 • C7 Radiculopathy • Autofusion C5-6, C6-7 • Mild heterotopic ossification • Decreased ROM across the device with some moderate HO noted • Fusion of vertebral bodies and anterior bridging • Autofusion C5-6 • Dislodged device at C5-C6 (migration of >3mm) • Poor function of device and poor attachment to bone

SUMMARY OF CLINICAL RESULTS (cont.)

Mobi-C at one-level is safe and effective with a lower rate of device-related major complications at 24 months compared to ACDF, as determined by the CEC. At 60 months, Mobi-C had more complications determined to be AEs compared to ACDF, a difference of 1.8% which was not significantly different. Of note, 4 of the 9 Mobi-C AEs were due to bone growth or fusion at the operated level. These patients may have benefited from motion for a period of time, but then progressed to restricted motion or fusion similar to the ACDF patient results.

Major complications determined to be related AEs (One-Level)			
24 Months		60 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF
3.0% (5 out of 164 pts.)	3.7% (3 out of 81 pts.)	5.5% (9 out of 164 pts.)	3.7% (3 out of 81 pts.)

AEs by Subject	
Mobi-C®	ACDF
• Fused at C5-6 • Left arm pain • Temporary paralysis-bilateral LE • Anterior ossification at C5-6 • Worsening dysphagia • Postop hoarseness from removal of the device • Heterotopic bone formation anterior to the device • Device malposition • Anterior and posterior bone bridging/fusion	• Worsening arm pain • Failure of fusion, C5-6 • Pseudoarthrosis

No Radiographic Failure and No Neurologic Deterioration

Results for the remaining two components of the primary endpoint, no radiographic failure and no neurologic deterioration, can be found in the Instructions for Use. Mobi-C results for both these components were non-inferior to the control ACDF.

Secondary EndPoint Results

- ***Mobi-C patients had fewer subsequent surgeries at adjacent levels***
- ***Mobi-C patients returned to work sooner***
- ***Mobi-C patients reported higher treatment satisfaction***
- ***Mobi-C patients had less adjacent level degeneration***

Mobi-C Demonstrated Fewer Subsequent Surgeries at Adjacent Levels

Mobi-C patients had fewer subsequent surgeries at the adjacent levels compared to ACDF at 24, 36, 48, 60, and 84 months.

Subsequent Surgeries at the Adjacent Levels (Two-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
2.1%	3.8%	3.4%	11.4%	4.4%	11.4%

Subsequent Surgeries at the Adjacent Levels (One-Level)					
24 Months		60 Months		84 Months	
Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
0.5%	3.7%	2.2%	11.1%	3.7%	13.6%

Mobi-C Patients Returned to Work in Less Time

Mobi-C Two-Level

Mobi-C patients returned to work on average 20.9 days sooner than ACDF patients (45.9 days for Mobi-C versus 66.8 days for ACDF).

Mobi-C One-Level

Mobi-C patients returned to work on average 7.5 days sooner than ACDF patients (29.3 days for Mobi-C versus 36.8 days for ACDF).

SUMMARY OF CLINICAL RESULTS (cont.)

Mobi-C Gave Patients More Treatment Satisfaction

Mobi-C Two-Level

There was higher reported patient satisfaction with Mobi-C versus ACDF. At 3, 6, 12, 48, and 60 months the number of patients that were "very satisfied" or "somewhat satisfied" was statistically significant in favor of Mobi-C.

Mobi-C One-Level

There was higher reported patient satisfaction with Mobi-C versus ACDF. At 60 months the number of patients that were "very satisfied" or "somewhat satisfied" was statistically significant in favor of Mobi-C.

Patient Satisfaction (Two-Level)			
24 Months		60 Months	
"very satisfied" or "somewhat satisfied" with their treatment			
Mobi-C®	ACDF	Mobi-C®	ACDF
95.8%	92.1%	96.4%	89.5%

Patient Satisfaction (One-Level)			
24 Months		60 Months	
"very satisfied" or "somewhat satisfied" with their treatment			
Mobi-C®	ACDF	Mobi-C®	ACDF
98.1%	94.3%	97.1%	96.4%

Mobi-C Demonstrated Significantly Less Adjacent Level Degeneration

Mobi-C Two-Level

At both the superior and inferior adjacent segments, statistically fewer Mobi-C patients experienced radiographically identified degeneration of the adjacent segment through 60 months compared to ACDF patients. The incidence between groups was significant at 24, 36, 48, and 60 months for both superior and inferior segments ($p<0.0001$).

	Two-Level					
	24 Months		60 Months		84 Months	
Degeneration at:	Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
Superior Adjacent Level	13.1%	33.9%	32.6%	70.8%	37.5%	73.7%
Inferior Adjacent Level	2.9%	17.9%	22.5%	55.1%	30.3%	66.7%

Mobi-C One-Level

Statistically fewer Mobi-C patients experienced radiographically identified degeneration of the adjacent segment at 24, 48, and 60 months compared to ACDF patients ($p<0.05$) at the superior adjacent segment. At the inferior adjacent segment, statistically fewer Mobi-C patients experienced radiographically identified degeneration of the adjacent segment at 24 months compared to ACDF patients ($p<0.05$).

	One-Level					
	24 Months		60 Months		84 Months	
Degeneration at:	Mobi-C®	ACDF	Mobi-C®	ACDF	Mobi-C®	ACDF
Superior Adjacent Level	15.0%	26.1%	37.1%	54.7%	40.4%	65.1%
Inferior Adjacent Level**	7.7%	21.0%	37.1%	55.3%	43.8%	63.0%

**Only the 24 month results are statistically significant.

Other Secondary Endpoints

Results for other secondary endpoints can be found in the Instructions for Use.

SUMMARY OF CLINICAL RESULTS (cont.)

Mobi-C: Level 1 evidence for both one and two-level procedures
The scientific evidence for the Mobi-C meets the Oxford Center for Evidence Based Medicine's criteria and the North American Spine Society's criteria for Level 1 evidence, including proper follow-up and randomization criteria.[30-31] In May 2014, the International Society for the Advancement of Spine Surgery (ISASS) published a position statement that stated, "The safety and efficacy of cervical arthroplasty has been established with a growing body of Level 1 evidence that is compelling enough to no longer consider cTDR investigational."

Mobi-C: Supported by Level 1, five year data

Given that the Mobi-C IDE trial meets the criteria of the highest standard of evidence according to these influential medical societies, Zimmer Biomet maintains that evidence from the Mobi-C trial:

- Is sufficient to draw conclusions concerning the effect of Mobi-C on positive health outcomes; and
- Supports the FDA decision that Mobi-C is a safe and effective treatment option for indicated patients.

Mobi-C and ACDF: Five year data for both one and two-level procedures
While the benefit of fusion in indicated patients is not contested, cervical fusion displaces stress onto adjacent levels and has been shown to cause accelerated rates of disc degeneration at adjacent levels. Additionally, data from multiple clinical trials, including the Mobi-C IDE trial, demonstrate that treatment with fusion results in high rates of subsequent surgical intervention. Therefore, it is relevant to ask if cervical fusion, as a treatment for degenerative disc disease, can deliver the same results as cervical disc replacement with the Mobi-C.

The results of the Mobi-C trial, approved and published through 60 months, consistently demonstrate a greater benefit for Mobi-C patients versus ACDF. Mobi-C demonstrated:

- ***Significantly more improvement in pain and functional outcomes***
- ***Significantly lower subsequent surgery rates***
- ***Significantly lower prevalence of adjacent segment degeneration***
- ***Statistically superior rate of overall success for the Mobi-C two-level patients.***

SUMMARY OF ECONOMIC VALUE

Ament et al. 2014

In December 2014, a peer-reviewed manuscript by Ament et al., on the cost effectiveness of two-level cTDR with Mobi-C versus ACDF based on two-year outcomes was published in JAMA Surgery.[12] This paper utilized the clinical outcomes from the two-level Mobi-C IDE trial, as well as the resource use associated with each procedure to compare the incremental cost effectiveness of the procedures.

Methods

Using the NDI and Visual Analog Scale (VAS) data collected in the two-level IDE study, patients were assigned to different health states in order of pain severity and disability (mild disability, moderate disability, severe disability, crippled, bedbound, and death). Using the clinical outcomes data, the model determined how likely a patient was to transition from one health state to another over time. Resource use data, derived from the codes utilized by the IDE sites, were translated into costs (US$) by applying 2012 national average Medicare rates and adjusted for inflation. Both direct medical costs (surgery, medications, ancillary services, revisions) and indirect medical costs (productivity loss) were included. A standard measurement used in this type of research, the quality adjusted life year (QALY), was calculated using these study data.

Results

The paper concludes that Mobi-C appears to be a cost-effective surgical modality when compared with ACDF for two-level cervical disc disease. The incremental cost-effectiveness ratio (ICER) is calculated as the difference in the expected cost of two interventions divided by the difference in the expected outcomes produced by the two interventions. In this case, the ICER of Mobi-C over ACDF is $24,594 per QALY. The standard threshold used in the field of cost-effectiveness research is $50,000 per QALY. As $24,594 is well below the threshold of $50,000, the authors concluded that Mobi-C appears to be cost effective when compared with ACDF.

Mobi-C as compared to ACDF for two-level use, appears to be cost effective relative to ACDF over the two-year time period evaluated in the IDE (and continues to be cost effective according to the model/sensitivity analysis after that time period).

Ament et al. 2016

In February 2016, a peer-reviewed manuscript by Ament et al., re-evaluating the cost effectiveness of two-level cTDR with Mobi-C versus ACDF based on five-year outcomes data, was published online in Neurosurgery with print publication to follow.[45] Similar to the Ament et al. 2014 paper, the 2016 analysis utilized clinical outcomes from the two-level Mobi-C IDE trial, as well as the resource use associated with each procedure to compare the incremental cost effectiveness of the procedures.

Methods

Like the 2014 Ament et al. study, using the NDI and VAS IDE data, two-level patients were assigned to six different health states. Using the clinical outcomes data at 5 years, the model determined how likely a patient was to transition from one health state to another over time. Resource use data, derived from the codes utilized by the IDE sites, were translated into costs (US$) by applying 2014 national average Medicare rates and adjusted for inflation. The same direct and indirect medical costs were included for both Ament studies.

Results

The paper concludes that Mobi-C appears to be a cost-effective surgical modality when compared with ACDF for two-level cervical disc disease at five years. The ICER of Mobi-C over ACDF at 5 years was $8,518 per QALY, well below the standard threshold of $50,000 per QALY.

When comparing the Ament study from 2016 to the 2014 study, one notable takeaway emerged. The ICER for the five-year data far exceeded that of the two-year data, suggesting that Mobi-C becomes more cost-effective over time. This is not surprising because the QALY improvement between Mobi-C and ACDF increased from 0.087 at 2 years to 0.198 at 5 years, respectively. Similarly, Mobi-C was $2,139 more costly than ACDF at 2 years compared with a cost savings of $32,690 at 5 years. The dramatic difference in the 2- and 5-year data was believed to be secondary to a more comprehensive return to work analysis than was previously conducted.

For patients with two-level degenerative disc disease over the 5 year time period, Mobi-C appears to be a "highly cost-effective surgical modality compared with ACDF" and that "from a societal perspective, Mobi-C imparts greater quality of life at less cost than ACDF."

SUMMARY OF ECONOMIC VALUE (cont.)

Radcliff et al.

In 2015, a peer-reviewed manuscript by Radcliff et al., on the reoperation rates, adverse event rates, and the direct and follow-on costs of one-level cTDR (ProDisc-C, Bryan, and Prestige) compared to ACDF was published in Spine.[32] This was a retrospective, matched cohort analysis of claims from the Blue Health Intelligence (BHI) database of costs and outcomes for patients aged 18 to 60 years, who were continuously enrolled in a Blue Cross/Blue Shield Plan contributing to the BHI claims database. The Radcliff paper showed:

- Patients who underwent cTDR for single-level degenerative disease had lower readmission rates, fewer mechanical complications, and most importantly, lower reoperation rates than ACDF patients.
- The cost of care (payer perspective) is reduced in cTDR compared to ACDF patients:
  - At the time of the index procedure;
  - During the 90-day postoperative period; and
  - Monthly, up to three years postoperatively.

A growing body of clinical and economic evidence positively supports coverage of cervical disc replacement with Mobi-C.

The authors conclude that cTDR is a safe and less costly operation than ACDF and is more likely to reduce the rate of reoperation in patients with single-level disease. Cervical disc replacement provides a cost-conscious alternative for appropriately selected patients.

APPENDIX

Instructions for Use: Indications / Contraindications / Warnings / Precautions

Indications for Use

The Mobi-C® Cervical Disc Prosthesis is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following discectomy at one or two contiguous levels for intractable radiculopathy (arm pain and/or neurological deficit) with or without neck pain, or myelopathy due to abnormality localized to the level of the disc space and at least one of the following conditions confirmed by radiographic imaging (CT, MRI, or X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height compared to adjacent levels. The Mobi-C® Cervical Disc Prosthesis is implanted using an anterior approach. Patients should have failed at least 6 weeks of conservative treatment or demonstrated progressive signs or symptoms despite nonoperative treatment prior to implantation of the Mobi-C® Cervical Disc Prosthesis.

Contraindications

The Mobi-C® Cervical Disc Prosthesis should not be implanted in patients with the following conditions:

- Acute or chronic infection, systemic or at the operative site;
- Known allergy or sensitivity to the implant materials (cobalt, chromium, molybdenum, titanium, hydroxyapatite, or polyethylene);
- Compromised vertebral bodies at the index level due to previous trauma to the cervical spine or to significant cervical anatomical deformity or disease (e.g., ankylosing spondylitis, rheumatoid arthritis);
- Marked cervical instability on resting lateral or flexion/extension radiographs demonstrated by translation greater than 3.5mm, and/or > 11° angular difference to that of either adjacent level;
- Osteoporosis or osteopenia defined as DEXA bone mineral density T-score < -1.5;
- Severe facet joint disease or degeneration

Warnings

The Mobi-C should only be used by surgeons who are experienced with anterior cervical spinal procedures and have undergone hands-on training in the use of this device. Only surgeons who are familiar with the implant components, instruments, procedure, clinical applications, biomechanics, adverse events, and risks associated with the Mobi-C should use this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, including neurological complications.

Correct selection of the appropriate implant size is extremely important to assure the placement and function of the device. Information regarding proper implant size selection, implant site preparation, and the use of the instrumentation before, during, and after Mobi-C® surgery is provided in the Mobi-C® Surgical Technique Manual and the Mobi-C® Instrument System Instructions for Use. Users are advised to read and understand the surgical technique manual and instructions for use prior to surgery.

Due to the proximity of vascular and neurological structures to the implantation site, there are risks of serious or fatal hemorrhage and risks of neurological damage with the use of the device. Care must be taken to identify and protect these structures.

Heterotopic Ossification (HO) is a potential complication associated with artificial cervical discs and could lead to reduced cervical motion. However, the presence of HO has not been correlated with adverse clinical outcomes involving the Mobi-C® Cervical Disc Prosthesis in the G050212 clinical trial.

APPENDIX (cont.)

Precautions

The safety and effectiveness of this device has not been established in patients with the following conditions:

- Skeletally immature patients, pediatric or adolescent children (<21 years old), or those over the age of 67;
- Prior cervical spine surgery, including prior surgery at the index level;
- More than two diseased or immobile cervical spine levels requiring surgical intervention;
- Disc height less than 3mm measured from the center of the disc in a neutral position and disc height less than 20% of the anterior-posterior width of the inferior vertebral body;
- Significant kyphotic deformity or significant reversal of lordosis;
- Active malignancy
- Paget's disease, osteomalacia, or other metabolic bone disease;
- Taking medications known to potentially interfere with bone/soft tissue healing (e.g. steroids);
- Pregnancy;
- Diabetes mellitus requiring daily insulin management;
- Clinical extreme obesity (class III) as defined by the NIH Clinical Guidelines Body Mass Index (i.e. BMI 40);
- Neck or arm pain of unknown etiology;
- Systemic disease including AIDS, HIV, and Hepatitis;
- Intractable radiculopathy or myelopathy due to pathology at more than two levels and/or pathology not localized to the level of the disc space;
- Prior fusion at an adjacent vertebral level;
- Neck pain alone;
- Rheumatoid arthritis or other autoimmune disease;
- Neuromuscular disorders such as muscular dystrophy, spinal muscular atrophy, or amyotrophic lateral sclerosis;
- Acute mental illness or substance abuse.

Complete Instructions for Use Text can be found at https://us.ldr.com/Products/Cervical/MobiC®CervicalDisc.

Heterotopic Ossification

Heterotopic Ossification (HO) is a known complication of cTDR, appearing as abnormal bone formation originating from the vertebral body.[33-34] However, no association has been established between the presence of clinically relevant HO and clinical outcomes following cTDR.[33-37]

Rates for HO following both one-level and two-level cTDR have been reported from the Mobi-C FDA IDE clinical trial. Using a classification system adapted from McAfee and Mehren, HO was classified on a scale from Grade 0 HO with no evident osteophyte formation to Grade 4 HO with bridging bone and little or no motion.[38-39]

The majority of Mobi-C patients were assessed as having non-clinically relevant HO (Grades 0-2). The rates of clinically relevant HO (Grades 3-4) in Mobi-C subjects were low and are similar to that of available data from other cTDR IDE clinical trials at two years.[21, 27-28, 40-41]

The protocol from the Mobi-C IDE trial stated, "Because of the potential to delay bony healing, non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited between one week prior to surgery until 3 months following surgery in both the Mobi-C and fusion groups unless intended to treat HO."

NSAID use has been shown to delay and reduce the formation of HO and is now typically prescribed postoperatively in a prophylactic manner for cTDR patients to prevent or mitigate HO formation.[42] Postoperative NSAID use was not restricted in the Prestige ST, Prestige LP, or PCM clinical trials, and therefore the HO rates from these studies may reflect lower observed rates.

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