INSTRUCTIONS FOR USE

Important Information – Please Read Prior to Use

Rx Only

Orthofix Inc.
3451 Plano Parkway
Lewisville, Texas 75056-9453 U.S.A.
1-214-937-3199
1-888-298-5700
www.orthofix.com
OSI-CustomerService@Orthofix.com

Spinal Kinetics LLC, an Orthofix Company
501 Mercury Drive
Sunnyvale, CA 94085 USA
1-888-298-5700

Device System Name:

M6-C™ Artificial Cervical Disc

English EN **2-42**

PK 0255 Rev 01

Caution: Federal (United States) law restricts this device to sale by or on the order of a Physician.

HOW SUPPLIED:
M6-C™ Artificial Cervical Disc – Sterile
M6-C™ Surgical Instruments – Non-sterile

DEVICE DESCRIPTION

The M6-C™ Artificial Cervical Disc is an intervertebral disc prosthesis designed to permit motion of a functional spinal unit in the cervical spine when replacing a degenerated native disc. The device is comprised of ultra-high molecular weight polyethylene (UHMWPE) fiber wound in a specific pattern, with multiple redundant layers, creating a fiber matrix (artificial annulus). The fiber is wound around a polycarbonate urethane polymer (PCU) core (artificial nucleus) and through the slots in two Ti6Al4V titanium alloy inner endplates (see **Figure 1**). The core is situated between and in contact with the two inner endplates, but not affixed to them. A PCU sheath surrounds the fiber matrix and is retained by two Ti6Al4V weld bands that are welded to the inner endplates. Two Ti6Al4V outer endplates are also welded to the inner endplates. The exterior surfaces of the outer endplates include low profile fins and are coated with titanium plasma spray (TPS).

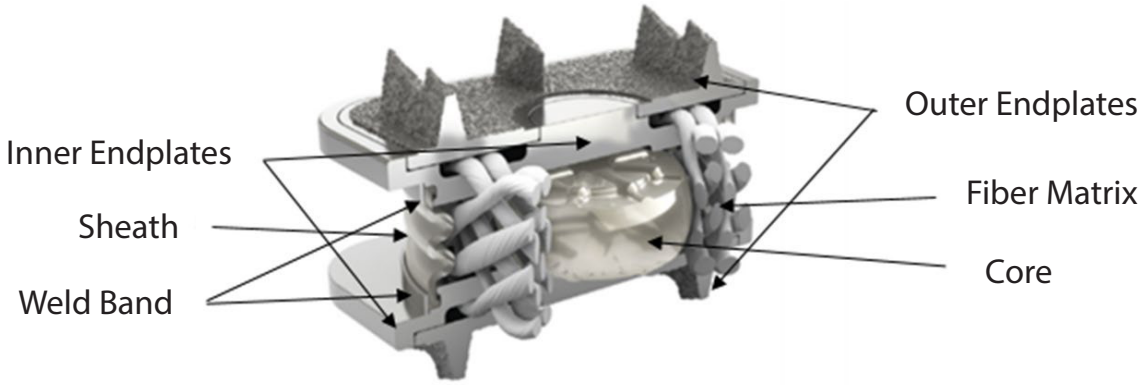
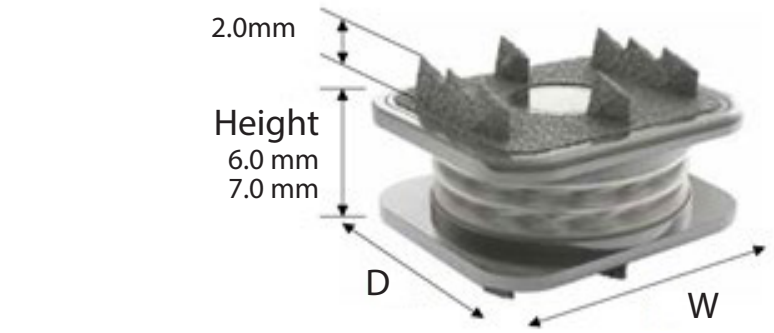


Figure 1: Cross-Section View of the M6-C™ Artificial Cervical Disc

The M6-C™ Artificial Cervical Disc is designed to maintain the natural behavior of a functional spinal unit by replicating the biomechanical characteristics of the native disc. This design enables the M6-C™ Artificial Cervical Disc to move in all six degrees of freedom, with independent angular rotations (flexion-extension, lateral bending and axial rotation) along with independent translational motions (anterior-posterior and lateral translations as well as axial compression). The device is intended to replicate the physiological phenomenon of progressive resistance to motion in all six degrees of freedom. The sheath is designed to minimize any tissue ingrowth as well as the migration of wear debris. The serrated fins provide acute fixation to the superior and inferior vertebral bodies. The TPS coating increases the bone contact surface area.

The M6-C™ Artificial Cervical Disc is currently offered in four different footprint sizes and two heights, as shown below in **Figure 2** and **Table 1**.



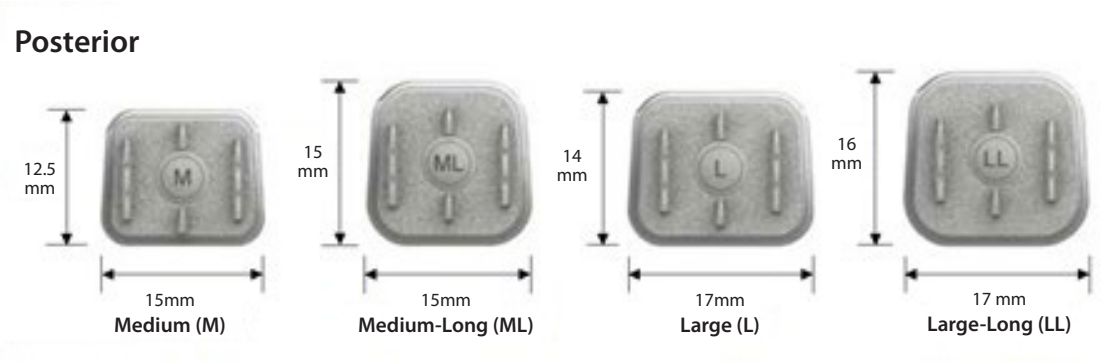


Figure 2: M6-C™ Artificial Cervical Disc Heights and Footprint Sizes

Table 1: M6-C™ Artificial Cervical Disc Catalog Number and Size

REF	Description	Provided Sterile
CDM-625	Cervical Disc – 6 Medium (15mm W x 12.5mm D x 6mm H)	Yes
CDM-725	Cervical Disc – 7 Medium (15mm W x 12.5mm D x 7mm H)	Yes
CDL-627	Cervical Disc – 6 Large (17mm W x 14mm D x 6mm H)	Yes
CDL-727	Cervical Disc – 7 Large (17mm W x 14mm D x 7mm H)	Yes
CDM-635L	Cervical Disc – 6 Medium-Long (15mm W x 15mm D x 6mm H)	Yes
CDM-735L	Cervical Disc – 7 Medium-Long (15mm W x 15mm D x 7mm H)	Yes
CDL-637L	Cervical Disc – 6 Large-Long (17mm W x 16mm D x 6mm H)	Yes
CDL-737L	Cervical Disc – 7 Large-Long (17mm W x 16mm D x 7mm H)	Yes

INDICATIONS FOR USE

The M6-C™ Artificial Cervical Disc is indicated for reconstruction of the disc following single level discectomy in skeletally mature patients with intractable degenerative cervical radiculopathy with or without spinal cord compression at one level from C3 – C7. Degenerative cervical radiculopathy is defined as arm pain and/or a neurological deficit (numbness, weakness, deep tendon reflexes changes) with or without neck pain due to disc herniation and/or osteophyte formation and confirmed by radiographic imaging (CT, MRI, x-rays). The M6-C™ Artificial Cervical Disc is implanted via an anterior approach. Patients should have failed at least 6 weeks of conservative treatment or exhibit progressive neurological symptoms which could lead to permanent impairment prior to implantation of the M6-C™ Artificial Cervical Disc.

CONTRAINDICATIONS

The M6-C™ Artificial Cervical Disc should not be implanted in patients with the following conditions:

- Advanced cervical anatomical deformity (e.g., ankylosing spondylitis, scoliosis) at the operative or adjacen levels
- Symptomatic facet arthrosis defined as pain in the neck that is worse when in extension and/or rotation and/or stiffness or the inability to move part of the neck attributable to the facets as confirmed by imaging (x-ray, CT, MRI, bone scan)
- Advanced degenerative changes (e.g., spondylosis) at the index vertebral level as evidenced by bridging osteophytes, excessive translation or kyphotic deformity > 11º on neutral x-rays
- Active systemic infection or infection at the operative site
- Osteoporosis defined as DEXA bone mineral density T-score ≤ -2.5
- Known allergy to titanium, stainless steel, polyurethane, polyethylene, or ethylene oxide residuals

WARNINGS

Correct placement of the M6-C™ Artificial Cervical Disc is essential to optimal performance.

- The M6-C™ Artificial Cervical Disc should only be used by surgeons who are experienced in the surgical procedure and have undergone adequate training with this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, such as vascular or neurological complications.
- During implantation, the surgeon should ensure that none of the surgical instruments or the M6-C™ Artificial Cervical Disc progress beyond the posterior border of the vertebral bodies. 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 this device and allowing the instruments or the M6-C™ Artificial Cervical Disc to progress beyond the posterior border of the vertebrae may result in injury to these structures.
- Fluoroscopic confirmation of positioning of certain instruments and the implant should be performed during the surgical procedure. Failure to confirm position of instruments and the implant during the surgical implantation procedure may result in patient injury.

PRECAUTIONS

The safety and effectiveness of the M6-C™ Artificial Cervical Disc has not been established in patients with the following conditions:

- Those over 68 years of age
- More than one cervical level requiring surgery
- Previous anterior cervical spine surgery at the index level
- Axial neck pain as the solitary symptom

- Previous posterior cervical spine surgery (e.g., posterior element decompression) that destabilizes the cervical spine at the index level
- Less than 4° of motion in flexion/extension at the index level
- Instability as evidenced by subluxation > 3 mm at the index or adjacent levels as indicated on flexion/extension x-rays
- History of an osteoporotic fracture of the spine, hip or wrist
- History of an endocrine or metabolic disorder (e.g., Paget's disease) known to affect bone and mineral metabolism
- Taking medications that may interfere with bony/soft tissue healing including chronic steroid use
- Insulin-dependent diabetes
- Severe obesity (Body Mass Index > 40)

Pre-operative:

- Patient selection is extremely important. In selecting patients for a total disc replacement, the following factors can be of extreme importance to the success of the procedure: the patient's occupation or activity level; a condition of senility, mental illness, alcoholism or drug abuse; certain degenerative diseases that may be so advanced at the time of implantation that the expected useful life of the device is substantially decreased, and medical conditions that may affect postoperative management, such as Alzheimer's disease and emphysema.
- In order to minimize the risk of periprosthetic vertebral fractures, surgeons must consider all co-morbidities, past and present medications, previous treatments, etc. A screening questionnaire for osteopenia or osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), may be used to screen patients to determine if a DEXA scan to measure bone mineral density is necessary. If a DEXA scan is performed, the patient should be excluded from receiving the device if osteoporosis is present as defined by a T score ≤ -2.5.
- The patient should be informed of the potential adverse effects (risks/complications) contained in this insert (see Safety Results / Adverse Events).
- Information on the proper implant site preparation, implant size selection, and the use of surgical instrumentation for the M6-C™ Artificial Cervical Disc is provided in the *M6-C™ Artificial Cervical Disc Operative Technique Manual* and the *Care and Handling Instructions for M6-C™ Surgical Instruments* and should be reviewed prior to surgery.
- Preoperative planning may be used to estimate the required implant size and to assure that the appropriate range of sizes is available for surgery. Correct selection of the appropriate implant size is extremely important to assure the placement and function of the disc. The procedure should not take place if the appropriate range of sizes are not available.
- The M6-C™ Artificial Cervical Disc is intended to be used with the M6-C™ Surgical Instruments. The M6-C™ Surgical Instruments are reusable, supplied non-sterile and must be sterilized in accordance with the recommended cleaning and sterilization procedures prior to use.
- The M6-C™ Artificial Cervical Disc is supplied sterile. It is not intended to be re-sterilized. Do not use if sterility is compromised.
- Examine all instruments prior to surgery for wear or damage. Instruments which have been used excessively may be more likely to break. Replace any worn or damaged instruments.

Intra-operative:

- Use aseptic technique when removing the M6-C™ Artificial Cervical Disc from the innermost packaging. Carefully inspect each device and its packaging for any signs of damage, including damage to the sterile

barrier. Do not use the M6-C™ Artificial Cervical Disc if the packaging is damaged or the implant shows signs of damage.

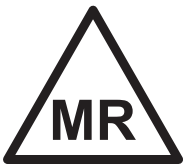
- Use care when handling the M6-C™ Artificial Cervical Disc to ensure that it does not come into contact with objects that could damage the implant. Damaged implants are no longer functionally reliable. Visual inspection of the prosthesis is recommended prior to implanting the device. If any part of the device appears damaged or not fully assembled, do not use.
- The M6-C™ Artificial Cervical Disc should not be used with instruments of spinal systems from other manufacturers. See the Operative Technique Manual for step-by-step instructions.
- Take care not to over-distract the disc space.
- Perform a complete discectomy of the disc space between the uncinates and up to the posterior ligament. Take care to release / decompress the foramen bilaterally.
- Excessive removal of endplate cortical bone may result in sub-optimal outcomes.
- It is important to remove all anterior and posterior osteophytes on the superior and inferior vertebral endplates. Liberally cover bleeding with bone wax. To prevent weakening of the endplates, use of a burr/drill is discouraged during endplate preparation. Use the Cervical Retainer as needed to maintain distraction. Ensure proper alignment and placement of the device as misalignment may cause excessive wear and/or early failure of the device.
- The M6-C™ Artificial Cervical Disc is designed to be implanted with the endplates parallel to each other. Excessive endplate lordosis or kyphosis can lead to less than optimal M6-C™ Artificial Cervical Disc performance.
- Surgical implants must never be re-used or re-implanted. Even though the device appears undamaged, it may have small defects and internal stress patterns that can lead to early breakage.

Post-operative:

- Patients should be instructed in postoperative care procedures and should be advised of the importance of adhering to these procedures for successful treatment with the device including the avoidance of heavy lifting, repetitive bending, and prolonged or strenuous acti vity initially and for a period of weeks to months depending on the individual patient's progress and the stability and functioning of the implant.

Note to Physician: Although the physician is the learned intermediary between the company and the patient, the important medical information given in this document should be conveyed to the patient.

MRI SAFETY INFORMATION



Non-clinical testing has demonstrated that the M6-C™ Artificial Cervical Disc is MR Conditional. A patient with the M6-C™ Artificial Cervical Disc can be scanned safely in an MR system under the following conditions:

- Static magnetic field of 1.5-T or 3.0-T, only
- Maximum spatial gradient magnetic field of 4,000-Gauss/cm (40-T/m)
- Maximum MR system reported whole body averaged specific absorption rate (SAR) of 2-W/kg for 15 minutes of scanning (i.e., per pulse sequence) in the Normal Operating Mode.

Under the scan conditions defined, the M6-C™ Artificial Cervical Disc is expected to produce a maximum temperature rise of 2.2°C after 15-minutes of continuous scanning (i.e., per pulse sequence).

In non-clinical testing, the image artifact caused by the M6-C™ Artificial Cervical Disc extends approximately 10-mm from this device when imaged using a gradient echo pulse sequence and a 3.0-Tesla MR system.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) identified from the M6-C™ Artificial Cervical Disc clinical study results, approved device labeling for other cervical total disc replacement devices, and published scientific literature including: (1) those associated with any general surgical procedure; (2) those associated with anterior cervical spine surgery; and (3) those associated with a cervical artificial disc device, including the M6-C™ Artificial Cervical Disc. In addition to the risks listed below, there is also the risk that surgery may not be effective in relieving symptoms or may cause worsening of symptoms. Additional surgery may be required to correct some of the adverse effects.

General Surgery Risks

General surgical risks are, but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Blood clots, including pulmonary emboli
- Medication and anesthesia reactions
- Phlebitis
- Pneumonia
- Atelectasis
- Soft tissue damage
- Septicemia
- Hemorrhage possibly requiring a blood transfusion, with possible transfusion reaction
- Myocardial infarction
- Paralysis
- Poor tissue healing
- Cerebrovascular accident (CVA)
- Death

Anterior Cervical Surgery Risks

Anterior cervical surgical risks are, but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Injury or damage to the trachea, esophagus, nerves or blood vessels
- Dysphagia
- Hoarseness
- Vocal cord paralysis
- Paresis
- Recurrent laryngeal nerve palsy
- Soft tissue damage
- Spinal cord damage
- Dural tear with cerebrospinal fluid leakage
- Arm weakness or numbness
- Death
- Bowel, bladder or sexual dysfunction
- Nerve root injury
- Airway obstruction
- Epidural hematoma or bleeding
- Epidural fibrosis
- Vertebral body fracture
- Dysesthesia or numbness
- Paresthesia
- Unresolved pain
- Surgical intervention at incorrect level
- Need for supplemental fixation
- Spinal instability

Cervical Artificial Disc Risks

Risks specific to cervical artificial discs, including the M6-C™ Artificial Cervical Disc, are but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Allergic reaction to the implant materials
- Implant failure
- Device migration
- Device subsidence
- Device fatigue or fracture or breakage
- Device instability
- Separation of device components
- Placement difficulties, device malposition
- Improper device sizing
- Excessive device height loss
- Wear debris
- Disc space collapse
- Material degradation
- Excessive facet loading
- Kyphosis or hyper-extension

- Loss of flexibility
- Asymmetric range of motion
- Vertebral body fracture
- Spinal cord damage
- Dural tear with cerebrospinal fluid leakage
- Soft tissue damage
- Epidural fibrosis
- Nerve injury, paralysis or weakness that is temporary or permanent
- Injury or damage to the trachea, esophagus, or blood vessels
- Epidural hematoma or bleeding
- Dysesthesia or numbness
- Paresthesia
- Failure to relieve symptoms including unresolved pain
- Additional surgery due to loss of fixation, infection or injury
- Spontaneous fusion due to heterotopic ossification, development of bridging bone or osteophytes
- Periarticular calcification and fusion
- Development of spinal conditions, including but not limited to spinal stenosis, spondylolisthesis, or retrolisthesis
- Removal, revision, reoperation or supplemental fixation of the disc
- Osteolysis, bone loss, or bone resorption
- Death

These conditions do not include all potential adverse events that may occur, but are important considerations in relation to the use of the M6-C™ Artificial Cervical Disc. For the specific adverse events that occurred in the clinical study of the M6-C™ Artificial Cervical Disc, please see the Safety Results in the SUMMARY OF CLINICAL STUDIES section below.

SUMMARY OF CLINICAL STUDIES

The pivotal clinical study was performed to establish a reasonable assurance of safety and effectiveness of replacement of the disc with the M6-C™ Artificial Cervical Disc following single level discectomy in skeletally mature patients with intractable degenerative cervical radiculopathy with or without spinal cord compression at one level from C3 – C7. Degenerative cervical radiculopathy is defined as discogenic neck and/or arm pain and is demonstrated by signs and/or symptoms (e.g., numbness, weakness, pathologic reflexes, etc.) of disc herniation and/or osteophyte formation and is confirmed by subject history and radiographic imaging (CT, MRI, x-rays). A summary of the clinical study is presented below.

Study Design

Subjects in the M6-C™ pivotal study were treated between May 2014 and June 2016. The database for this PMA reflected data collected through May 2018 and included 160 M6-C™ subjects at 12 sites and 72 ACDF subjects treated at 11 sites. An additional 192 ACDF treated subjects were available from a previously conducted cervical disc IDE study, with subjects treated between November 2005 and October 2007.

The prospective, non-randomized, concurrently controlled study was performed in the United States under IDE #G050254 combined with additional control ACDF data from a previous multi-center, prospective, randomized concurrently-controlled cervical disc IDE study performed in the United States. This previous study incorporated a similar study design, indication for use, study entry criteria, study endpoints, and data collected. The two studies were not identical, and differences were identified in some categories and are discussed below.

A statistical plan utilizing propensity score (PS) modeling was developed to incorporate both the concurrent control and historical control and to match the baseline covariates to the M6-C™ group. The PS method was used to address selection bias in the observational study design when pooling data from the concurrent and historical controls. The objective of the observational design was to select from the candidate pool of concurrent and historical controls those subjects whose baseline covariate distribution was approximately the same as M6-C™ subjects within five PS subclasses. The final ITT (PS Selected) analysis set included all 160 M6-C™ subjects, 46 of 72 available concurrent control subjects and 143 of 192 historical control subjects for a

total control sample size of 189 subjects. Rigorous statistical criteria and graphical analyses demonstrated that within PS subclasses, M6-C™ subjects and selected controls had approximately the same multivariate baseline covariate distribution. Consequently, controlling for PS subclass, selection bias was eliminated for a rich set of observed demographic and baseline covariates.

The resultant PS Selected study cohort used for the primary analysis population thus included all investigational M6-C™ subjects and the pooled concurrent and historical control subjects and is termed the "**ITT (PS Selected) Cohort**."

Clinical Inclusion/Exclusion Criteria

To be eligible for the M6-C™ IDE study, subjects had to be eligible for a fusion procedure and meet all of the inclusion criteria and none of the exclusion criteria (**Table 2**):

Table 2: Study Inclusion/Exclusion Criteria

Study Inclusion Criteria	Study Exclusion Criteria
1. Diagnosis of degenerative cervical radiculopathy with or without spinal cord compression requiring surgical treatment at one level from C3 to C7 demonstrated by signs and/or symptoms of disc herniation and/or osteophyte formation (e.g. neck and/or arm pain, radiculopathy, etc.) and is confirmed by patient history and radiographic studies (e.g. MRI, CT, x-rays, etc.) 2. Inadequate response to conservative medical care over a period of at least 6 weeks 3. Neck Disability Index score of ≥ 30% (raw score of ≥ 15/50) 4. Neck or arm pain VAS ≥ 4 on a scale of 0 to 10 5. Willing and able to comply with the requirements of the protocol including follow-up requirements 6. Willing and able to sign a study specific informed consent 7. Skeletally mature and ≥ 18 years old and ≤ 75 years old	1. More than one cervical level requiring surgery 2. Previous anterior cervical spine surgery 3. Axial neck pain as the solitary symptom 4. Previous posterior cervical spine surgery (e.g., posterior element decompression) that destabilizes the cervical spine 5. Advanced cervical anatomical deformity (e.g., ankylosing spondylitis, scoliosis) at the operative or adjacent levels 6. Symptomatic facet arthrosis 7. Less than 4° of motion in flexion/extension at the index level 8. Instability as evidenced by subluxation > 3 mm at the index or adjacent levels as indicated on flexion/extension x-rays 9. Advanced degenerative changes (e.g., spondylosis) at the index vertebral level as evidenced by bridging osteophytes, central disc height < 4mm and/or < 50% of the adjacent normal intervertebral disc, or kyphotic deformity > 11° on neutral x-rays 10. Severe cervical myelopathy (i.e., Nurick's Classification > 2) 11. Active systemic infection or infection at the operative site 12. Co-morbid medical conditions of the spine or upper extremities that may affect the cervical spine neurological and/or pain assessment 13. Metabolic bone disease such as osteoporosis that contradicts spinal surgery (for females over 50 and males over 55 years old, or if the score on the Osteoporosis Self-Assessment Test is < 2, a dual energy x-ray absorptiometry [DEXA scan] of the spine is required; if the bone mineral density T-score in the spine is = -2.5 the patient must be excluded) 14. History of an osteoporotic fracture of the spine, hip or wrist 15. History of an endocrine or metabolic disorder (e.g., Paget's disease) known to affect bone and mineral metabolism 16. Taking medications that may interfere with bony/soft tissue healing including chronic steroid use

Study Inclusion Criteria	Study Exclusion Criteria
	17. Known allergy to titanium, stainless steels, polyurethane, polyethylene, or ethylene oxide residuals 18. Rheumatoid arthritis or other autoimmune disease or a systemic disorder such as HIV, active hepatitis B or C or fibromyalgia 19. Insulin-dependent type 1 or type 2 diabetes 20. Medical condition (e.g., unstable cardiac disease, cancer) that may result in patient death or have an effect on outcomes prior to study completion 21. Pregnant, or intend to become pregnant, during the course of the study 22. Severe obesity (Body Mass Index > 40) 23. Physical or mental condition (e.g., psychiatric disorder, senile dementia, Alzheimer's disease, alcohol or drug addiction) that would interfere with patient self-assessment of function, pain or quality of life. 24. Involved in current or pending spinal litigation where permanent disability benefits are being sought 25. Incarcerated at the time of study enrollment 26. Current participation in other investigational study that may impact study outcomes

Postoperative Care

The recommended postoperative care was according to the individual surgeon's discretion and consisted of a physician-managed individual post-operative rehabilitation program which may have included the optional use of a cervical collar.

Subjects were instructed to return to normal activity at the discretion of the surgeon with the following restrictions for at least the initial two weeks:

- No heavy physical activity
- Use of a soft collar (at the discretion of the surgeon)
- Limit the frequency of extended automobile rides, working, lifting, bending and twisting
- Discourage sexual activity
- Encourage short walks

Follow-up Schedule

All subjects were evaluated preoperatively (within 30 days prior to surgery), postoperatively (prior to discharge) and postoperatively at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 1 year (±2 months), 2 years (±2 months), and annually thereafter (±2 months). The following parameters were measured throughout the study (**Table 3**):

Table 3: M6-C™ Artificial Cervical Disc Study Assessment Schedule

Evaluation	Pre-op	Operative/ Discharge	6 Week	3 Month	6 Month	1 Year	2+ Years
Demographics	X						
Work Status	X		X	X	X	X	X
Medications	X		X	X	X	X	X
Neurological Examination	X	X	X	X	X	X	X
Neck Disability Index (NDI)	X		X	X	X	X	X
Neck and Arm Pain (VAS)	X		X	X	X	X	X
SF-36	X				X	X	X
Patient Satisfaction							X
Odom's Criteria							X
Surgery Data		X					
Adverse Event Assessment		X	X	X	X	X	X
AP & Lateral X-rays	X	X	X	X	X	X	X
Flexion/Extension X-rays	X			X	X	X	X
L & R Lateral Bending X-rays	M6-C™			M6-C™	M6-C™	M6-C™	M6-C™
MRI within 3 Months	X						

Clinical Endpoints

The effectiveness of the M6-C™ Artificial Cervical Disc was assessed using a composite primary endpoint. Effectiveness was further evaluated by secondary endpoints including improvements in the Neck Disability Index (NDI), neck and arm pain based on a Visual Analog Scale (VAS), and quality of life using the short-form 36 questionnaire (SF-36) as well as patient satisfaction of the investigational group compared to the ACDF control group. Similar criteria were used to measure success in both groups.

The safety of the M6-C™ Artificial Cervical Disc was assessed by comparison to the ACDF control group with respect to the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the implant), additional index level surgical procedures and maintenance or improvement in neurological status.

Primary Endpoint (Overall Subject Success)

All subjects were assessed for overall success using the parameters defined in the M6-C™ IDE study protocol including the safety components. A subject was considered a study success at two years follow-up if he/she met all of the following criteria:

- No serious adverse event(s) classified as device or device procedure related (as determined by the Clinical Events Committee),
- No supplemental surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation),
- Maintenance or improvement in neurological function compared to baseline, and
- Improvement of the NDI of at least 15 points (on a 100-point scale).

Secondary Endpoints and Assessments

Secondary objectives, measured in both groups, included:

- Neck Pain and Arm Pain as assessed using a 10-cm Visual Analog Scale (VAS)

- Health-Related Quality of Life (SF-12 or SF-36v2)
- Radiographic assessment including assessment of fusion status
- Pain Medication Use
- Surgery Time
- Length of Hospital Stay
- Return to Work
- Patient Satisfaction
- Odom's Criteria
- Adverse Events

In addition, quantitative and qualitative radiographic measurements were performed by an independent core laboratory and included range of motion, center of rotation, disc angle, disc height, device condition, device subsidence, device migration, radiolucency, spinal fusion status, heterotopic ossification, neural impingement, and soft tissue impingement.

Accountability of PMA Cohort

Two hundred fifty-eight (258) subjects were consented under the M6-C™ IDE study. Twenty-six (26) subjects were withdrawn prior to surgery resulting in 232 subjects treated, comprising 160 M6-C™ and 72 ACDF subjects. The historical control population resulted in an additional 192 available control subjects.

The 424 available subjects (160 M6-C™, 72 concurrent ACDF, and 192 historical ACDF) were assessed via the Propensity Score (PS) sub-classification process. After applying an established heuristic for 9 iterations (18 models), a total of 160 M6-C™ investigational subjects and 189 pooled control subjects (46 concurrent ACDF and 143 historical ACDF) were retained in the final PS designed sample. Inclusion into a PS subclass is the observational study analogue to randomized treatment allocation. For subjects at 24 months, the follow-up rates are 95.0% for the M6-C™ subjects and 87.7% for the PS Selected ACDF subjects (**Table 4**).

Table 4: Subject Accounting and Follow-up Compliance of the M6-C™ and PS Selected Pooled Control (ACDF) Subjects – ITT (PS Selected) Cohort

	Pre-Op		Month 12		Month 24	
	M6-C™	ACDF	M6-C™	ACDF	M6-C™	ACDF
[1] Theoretical Due	160	189	160	189	160	189
[2] Cumulative Deaths	0	0	1	0	1	0
[3] Cumulative Terminal Failures[1]	0	0	4	6	5	10
[4] Not Yet Overdue	0	0	0	0	0	2
[5] Expected[2]	160	189	156	183	155	177
[6] Expected + Terminal Failures among Theoretical Due	160	189	160	189	160	187
[7] Actual % Follow-Up for Overall Success[3]	160 (100%)	189 (100%)	153 (95.6%)	175 (92.6%)	152 (95.0%)	164 (87.7 %)
[8] Actual % Within Window[4]	160 (100%)	189 (100%)	140 (87.5%)	167 (88.4%)	136 (85.0%)	151 (80.7%)

[1] Subsequent surgical intervention and definitely device- or procedure- related SAEs
[2] Expected = [1] – [4] – ([2] + [3])
[3] The number of subjects with overall success (denominator = [6])
[4] The number of subjects with overall success within window (denominator = [6])

The subject accountability for Month 12 and Month 24 clinical evaluations is presented in **Table 5**.

Table 5: Subject Accounting and Follow-up Compliance for Month 12 and Month 24 Outcomes - ITT (PS Selected) Cohort

	Month 12				Month 24			
	M6-C™		ACDF		M6-C™		ACDF	
	n	%	n	%	n	%	n	%
ITT (PS Selected Cohort)	**160**	**--**	**189**	**--**	**160**	**--**	**189**	**--**
Deaths (not surgery-related)	*0*	*--*	*0*	*--*	*0*	*--*	*0*	*--*
Not Yet Overdue/Not Yet Due	*0*	*--*	*0*	*--*	*1*	*--*	*2*	*--*
Expected Due	**160**	**--**	**189**	**--**	**160**	**--**	**187**	**--**
• Overall Success Evaluation	153	95.6	175	92.6	152	95.6%	164	87.7%
• Neurological Evaluation	152	95.0	175	92.6	150	93.8%	164	87.7%
Terminal Failures[1]	*4*	*--*	*6*	*--*	*5*	*--*	*10*	*--*
Expected for Clinical Evaluation	**156**	**--**	**183**	**--**	**155**	**--**	**177**	**--**
• NDI Evaluation	149	95.5	168	92.8	147	94.8%	154	87.0%
• VAS Neck Pain Evaluation	148	94.9	168	92.8	147	94.8%	154	87.0%
• VAS Arm Pain Evaluation	148	94.9	168	92.8	147	94.8%	154	87.0%
• SF-12/36 Evaluation	148	94.9	164	89.6	147	94.8%	150[2]	84.7%
• Radiographic Evaluation	143	91.7	162	88.5	141	91.0%	140	79.1%
• Odom's Criteria	--	--	--	--	150	93.8%	164	86.8%
• Patient Satisfaction	--	--	--	--	150	93.8%	162	85.7%

[1] Subsequent surgical intervention and definitely device- or procedure- related SAEs

[2] Two subjects did not have baseline SF-12/36 measurement. Change from baseline scores in PMA Results section use 148 subjects.

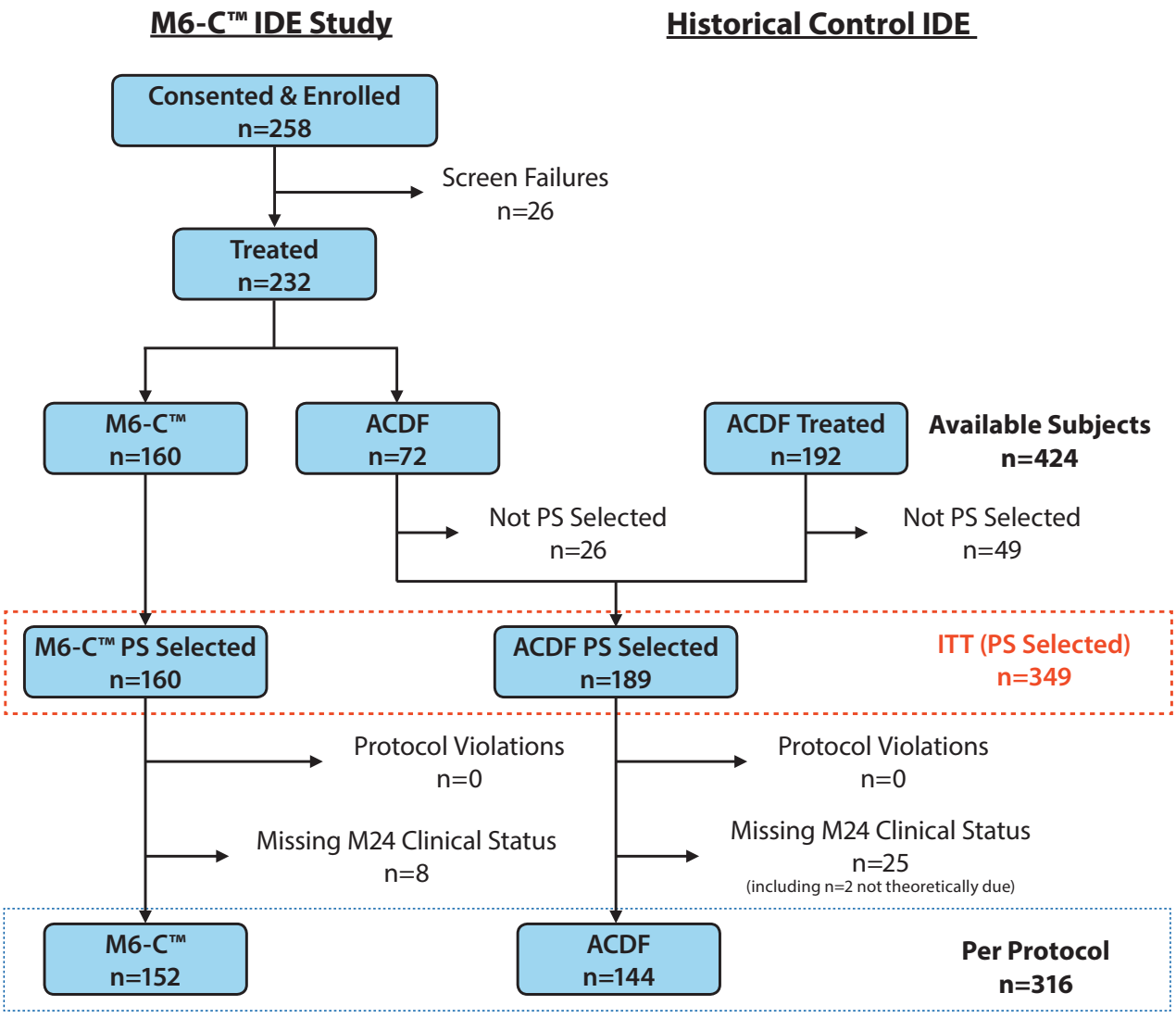


Figure 3: Subject Accountability Tree

Study Population Demographics and Baseline Parameters

The demographics of the study population are consistent with demographics reported for prior cervical artificial disc studies conducted in the US. Demographic data showed that the treatment groups were well-balanced and no statistically significant differences were noted in the demographic characteristics and categorical values (**Table 6** and **Table 7**). The mean baseline pre-operative assessments for NDI, VAS neck pain, VAS arm pain, the MCS component of SF-12/SF-36, and baseline radiographic parameters were also similar between treatment groups. The Short Form Physical Function scores were slightly higher in the M6-C™ group; however, when adjusting for PS subclass, there was no significant difference between groups in baseline NDI, indicating similar neck pain and function.

Table 6: Summary of Demographic and Baseline Continuous Variables (Clinical) with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]			Unadj[2]
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	160	43.64	9.10	42.35	21.8	68.4	189	44.74	7.87	44.60	24.0	65.4	-0.22	-2.18	1.74	-1.10
Height (inches)	160	67.86	3.98	68.00	58.0	83.0	189	67.93	3.85	68.00	59.0	77.0	-0.04	-0.95	0.86	-0.07
Weight (lbs)	160	178.93	38.03	183.00	85.0	283.0	189	183.67	39.33	183.00	104.0	315.0	-0.94	-9.91	8.03	-4.75
BMI (k/m^2)	160	27.18	4.77	26.85	17.8	39.6	189	27.84	4.86	27.30	19.1	47.8	-0.05	-1.16	1.07	-0.66
Osteo Self Assessment Test	160	80.73	18.84	81.46	34.4	132.1	189	82.89	19.42	82.00	43.4	146.3	-0.43	-4.86	4.01	-2.15
Duration of Symptoms	153	18.21	36.77	8.00	0.5	360.0	178	21.32	32.17	9.00	0.9	253.0	0.02	-8.21	8.25	-3.11
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	82	45.47	8.89	43.75	28.2	68.4	93	45.07	7.51	45.00	26.0	65.4	0.12	-2.47	2.72	0.41
Height (inches)	82	70.43	3.06	70.00	61.0	83.0	93	70.80	2.63	71.00	63.0	77.0	-0.12	-1.02	0.78	-0.37
Weight (lbs)	82	199.68	28.95	195.00	140.0	283.0	93	202.82	33.31	200.00	130.0	315.0	-1.68	-11.63	8.26	-3.14
BMI (k/m^2)	82	28.35	4.08	28.00	20.9	38.4	93	28.38	3.97	28.10	20.4	42.3	-0.04	-1.32	1.25	-0.03
Osteo Self Assessment Test	82	90.75	14.57	89.26	62.9	132.1	93	92.40	16.31	91.60	57.2	146.3	-0.87	-5.78	4.04	-1.65
Duration of Symptoms	78	13.05	16.55	7.00	1.0	107.0	85	18.31	23.75	9.00	1.0	119.0	-1.89	-8.48	4.71	-5.26
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	78	41.71	8.96	41.00	21.8	60.5	96	44.42	8.23	44.25	24.0	63.0	-0.02	-2.85	2.81	-2.71
Height (inches)	78	65.17	2.92	66.00	58.0	71.0	96	65.15	2.59	66.00	59.0	71.0	0.00	-0.95	0.96	0.02
Weight (lbs)	78	157.10	34.12	152.50	85.0	246.0	96	165.13	35.78	155.00	104.0	270.0	0.02	-11.92	11.97	-8.02
BMI (k/m^2)	78	25.96	5.14	24.70	17.8	39.6	96	27.32	5.56	26.40	19.1	47.8	0.02	-1.80	1.84	-1.36
Osteo Self Assessment Test	78	70.21	17.04	67.84	34.4	112.2	96	73.68	17.73	69.37	43.4	128.2	0.02	-5.96	5.99	-3.47
Duration of Symptoms	75	23.58	49.34	8.00	0.5	360.0	93	24.08	38.20	9.00	0.9	253.0	2.30	-13.15	17.76	-0.50
Baseline Functional Status[3]	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Neck Disability Index (NDI)	160	54.83	14.08	54.00	26.0	96.0	189	51.86	14.47	50.00	30.0	90.0	-0.09	-3.31	3.13	2.96
VAS Neck Pain	160	7.25	1.86	7.60	0.00	10.0	189	7.05	1.95	7.40	0.40	10.0	-0.01	-0.46	0.43	0.20
VAS Left Arm/Shoulder Pain	160	4.63	3.74	5.57	0.00	10.0	189	4.48	3.56	5.10	0.00	10.0	0.46	-0.38	1.31	0.16
VAS Right Arm/Shoulder Pain	160	4.19	3.61	4.51	0.00	10.0	189	4.63	3.65	5.00	0.00	10.0	-0.55	-1.39	0.29	-0.44
VAS Worst Arm Pain	160	7.26	2.19	7.60	0.15	10.0	189	7.46	1.91	7.70	0.10	10.0	-0.07	-0.54	0.40	-0.21
PCS (SK SF-36v2 / CC SF-12v2)[4]	160	34.88	7.71	34.56	16.1	55.0	187	32.66	8.04	32.37	10.8	56.9	2.84	1.01	4.67	2.22
MCS (SK SF-36v2 / CC SF-12v2)[4]	160	41.38	13.88	42.08	7.7	66.6	187	42.47	12.77	42.04	16.0	73.6	0.47	-2.58	3.53	-1.09

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worst arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

[2] Comparison of the PS adjusted group differences to the unadjusted group differences in this column demonstrate the covariate balance obtained using the PS model. The adjusted mean differences are always smaller than unadjusted values for variables in the PS model, and for some variables, the difference is very large.

[3] VAS Worst Arm/Shoulder Pain was included in PS modeling but not individual Left and Right VAS scores.

[4] PCS and MCS were not included in PS model due to uncertainty concerning comparability between SF-36 and SF-12 versions.

Table 7: Summary of Demographic and Baseline Categorical Variables – ITT (PS Selected) Cohort

	M6-C™		ACDF		M6-C™ - ACDF[1]		
	n	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	160		189				
Males	82	51.3	93	49.2	-0.2	-11.6	11.1
Females	78	48.8	96	50.8			
Use of Nicotine Products	**n**	**%**	**n**	**%**	**p[2]**		
No, never smoked	103	64.4	107	56.6			
No, but prior history	40	25.0	56	29.6	0.789		
Current smoker	17	10.6	26	13.8			
Narcotics Use[3,4]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	88	55.0	117	62.2	-2.3	-13.7	9.2
No	72	45.0	71	37.8			
Prior Cervical Surgery[5]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	3	1.9	1	0.5	1.4	-10.6	13.4
No	157	98.1	188	99.5			

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

[2] P-values are from Mantel-Haenszel PS subclass stratified comparisons between device groups.

[3] For M6-C™ and concurrent controls based on yes/no narcotics use variables. For supplemental controls based on collapsing "INTERMITTENT SHORT-ACTING NARCOTICS", "CHRONIC DAILY SHORT-ACTING NARCOTICS", "CHRONIC DAILY LONG-ACTING NARCOTICS", and "IV OR INJECTED NARCOTICS".

[4] One supplemental control value missing was set to "Yes" in in PS modeling.

[5] Variable not included as covariate in PS modeling due to insufficient sample size.

Operative Data

Statistically significant differences were observed in both surgery time and length of hospital stay. The mean surgery time for the M6-C™ subjects was 74.5 minutes compared to 120.2 minutes for the ACDF group. Length of stay was significantly shorter in the M6-C™ group (0.61 days) compared to the ACDF group (1.10 days). Similar trends were observed when these operative details were evaluated by gender. There was no statistically significant difference between the two groups in operative blood loss or level treated (**Table 8** and **Table 9**).

Table 8: Summary of Operative Continuous Variables with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery in mins	160	74.5	23.2	75.0	28.0	146.0	188	120.2	39.4	116.5	27.0	275.0	-45.7	-53.3	-38.1
Length of Hospital Stay in days	160	0.61	0.62	1.00	0.00	5.00	189	1.10	0.58	1.00	0.00	4.00	-0.53	-0.66	-0.39
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Time in Surgery in mins	82	77.2	24.7	77.5	28.0	146.0	93	125.0	41.2	119.0	39.0	275.0	-46.7	-57.6	-35.7
Length of Hospital Stay in days	82	0.67	0.72	1.00	0.00	5.00	93	1.11	0.50	1.00	0.00	3.00	-0.47	-0.66	-0.27
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Time in Surgery in mins	78	71.7	21.4	72.5	28.0	127.0	95	115.5	37.1	113.0	27.0	216.0	-44.7	-55.4	-34.1
Length of Hospital Stay in days	78	0.55	0.50	1.00	0.00	1.00	96	1.08	0.64	1.00	0.00	4.00	-0.58	-0.78	-0.38

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

Table 9: Summary of Operative Categorical Variables – ITT (PS Selected) Cohort

	M6-C™		ACDF		
	n	**%**	**n**	**%**	
Number of Subjects	160		187		
Operative Blood Loss	**n**	**%**	**n**	**%**	**p[1]**
<25 cc	72	45.0	85	45.5	0.490
25-<50 cc	46	28.8	61	32.6	
50-<100 cc	40	25.0	38	20.3	
>=100 cc	2	1.3	3	1.6	
Treated Levels	**n**	**%**	**n**	**%**	**p[1]**
C3-C4	4	2.5	4	2.1	0.887
C4-C5	10	6.3	10	5.3	
C5-C6	82	51.3	102	54.0	
C6-C7	64	40.0	73	38.6	

Note:

[1] P-value is from Mantel-Haenszel PS subclass stratified comparisons between device groups. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

Safety and Effectiveness Results

Safety Results

At the 24-month time-point, higher rates of any adverse event, any serious adverse event, and device related adverse events occurred in the ACDF group. At the same time-point, a higher rate of procedure-related adverse events occurred in the M6-C™ group. The combined device and procedure-related adverse event rate for each study arm is also higher in the control arm, although this difference is small. Adverse events rates were comparable in the two study arms. These data should be viewed in the context of the different classification categories and definitions used in the two studies.

Specifically, adverse events were not classified as procedure related in the historical study. To harmonize the data, patient level adverse event data were reviewed by the sponsor, at which time 49 adverse events in 32 subjects were identified as procedure related. These events were adjudicated by the CEC and subsequently classified for procedure-relatedness.

In summary, there were 358 adverse events in 108 M6-C™ subjects and 594 adverse events in 157 control subjects (**Table 10**).

Table 10: Comparisons of Summary Adverse Event Rates between M6-C™ and ACDF Groups with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)		ACDF (C) (N=189)		I vs. C[1]		
	n	%	n	%	Diff (%)	LB	UB
Any adverse event (per patient)[4]	108	67.5	157	83.1	-13.7	-23.3	-4.2
Any device related AE[2]	4	2.5	26	13.8	-11.9	-17.6	-6.1
Any procedure related AE[2]	59	36.9	51	27.0	11.6	1.2	21.9
Any AE related to device or procedure[2]	60	37.5	69	36.5	1.9	-8.8	12.6
Any serious AE	15	9.4	28	14.8	-6.3	-13.3	0.8
Serious AE that is either device or procedure related[2]	6	3.8	12	6.3	-2.7	-7.3	1.9
Deaths[3]	1	0.6	0	0.0	0.7	-0.7	2.1

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

[2] Includes possible, probable, or definite.

[3] The very low event rates for these variables required that PS subclass be included in the generalized linear model as a continuous variable (df=1) rather than as a stratification variables (df=4).

[4] Historical control follow-up exceed two-years in many cases. Therefore, in order to provide meaningful comparisons between groups, AEs with onset dates more than 790 days (24 months + 60 days) post index surgery were excluded from primary safety tables for all subjects.

Table 11: Counts of Specific Adverse Events by Time of Occurrence – ITT (PS Selected) Cohort through 24 Months

	Day or Surgery		Immed. Post-Op to Month 3 (Day 1-90)		>Mo. 3 to Mo. 6 (Day 91-180)		>Mo. 6 to Mo. 12 (Day 181-365)		>Mo. 12 to Mo. 24 (Day 365-730)		Post Month 24 (Day >730)		Totals	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
ANATOMY\TECHNICAL DIFRCULTY	0	0	0	1	0	0	0	1	0	0	0	0	0	2
Cervical – Non-Study Surgery	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Cervical – Study Surgery	0	0	0	1	0	0	0	0	0	0	0	0	0	1
CANCER	0	0	0	0	1	0	2	1	4	0	1	2	8	3
CARDIOVASCULAR	0	0	1	3	0	1	0	1	2	2	0	2	3	9
DEATH	0	0	1	0	0	0	0	0	0	0	0	0	1	0
DYSPHAGIA/DYSPHONIA	0	0	14	9	1	0	2	2	0	1	0	0	17	12
Dysphagia	0	0	13	8	1	0	2	2	0	0	0	0	16	10
Dysphonia	0	0	1	1	0	0	0	0	0	1	0	0	1	2
GASTROINTESTINAL	0	0	6	12	2	1	0	3	2	8	0	2	10	26
INFECTION	0	0	4	9	1	1	1	5	2	11	0	0	8	26
Local	0	0	1	2	1	1	1	4	1	8	0	0	4	15
Superficial Wound - Cervical	0	0	3	5	0	0	0	0	0	0	0	0	3	5
Deep Wound - Cervical	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Systemic	0	0	0	2	0	0	0	1	0	2	0	0	0	5
Other Wound - Non Study Surgery	0	0	0	0	0	0	0	0	0	1	0	0	0	1
NECK AND/OR ARM PAIN	0	0	17	22	14	11	12	15	16	27	3	5	62	80
Arm Pain	0	0	6	7	3	3	4	4	4	7	1	3	18	26
Neck Pain	0	0	9	14	10	8	5	8	10	19	1	2	35	51
Neck and Arm Pain	0	0	2	1	1	0	3	1	2	1	1	0	9	3
NEUROLOGICAL	0	0	17	35	10	16	16	26	21	34	4	4	68	115
Neck	0	0	4	11	3	2	5	1	3	2	0	0	15	16
Back	0	0	0	3	1	0	0	3	3	0	0	1	4	7
Gait Disturbance	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Spinal Gord Disturbance	0	0	2	0	0	0	0	0	0	0	0	0	2	0
Upper Extremity	0	0	9	19	4	9	8	15	10	21	3	3	34	67
Lower Extremity	0	0	1	1	2	5	1	6	3	7	1	0	8	19
Non - Specific	0	0	1	0	0	0	1	0	2	0	0	0	4	0
Other	0	0	0	0	0	0	0	1	0	4	0	0	0	5
NON-UNION	0	0	0	0	0	1	0	5	0	5	0	0	0	11
OTHER PAIN	0	0	27	42	20	20	20	28	19	33	5	4	91	127
Back	0	0	2	14	7	5	4	10	9	8	1	3	23	40
Headache	0	0	5	7	5	3	7	4	3	3	3	1	23	18
Lower Extremity	0	0	2	5	3	3	3	4	4	10	1	0	13	22
Shoulder	0	0	11	12	5	7	5	9	2	10	0	0	23	38
Torso	0	0	1	1	0	0	0	1	0	0	0	0	1	2
Other	0	0	6	3	0	2	1	0	1	1	0	0	8	6
RESPIRATORY	0	0	2	1	0	1	1	3	1	3	0	0	4	8
SPINAL DISORDER	0	0	1	2	0	3	1	5	5	16	0	2	7	28
'No subcategory for CerviCore"	0	0	0	1	0	1	0	0	0	3	0	2	0	7
Cerical - Non-StudySurgery	0	0	0	1	0	1	0	1	3	5	0	0	3	8
Cervical - Studysurgery	0	0	0	0	0	1	0	0	1	0	0	0	1	1
Non cervical	0	0	1	0	0	0	1	4	1	8	0	0	3	12
TRAUMA	0	0	3	7	2	7	4	13	7	16	0	2	16	45
UPPER EXTREMITY NERVEENTRAPMENT	0	0	5	4	1	0	0	5	1	6	0	0	7	15
UROGENITAL	0	0	1	3	0	2	0	2	2	2	1	0	4	9
WOUND ISSUE NON - INFECTION	0	0	21	6	0	0	0	3	0	1	0	0	21	10
OTHER	0	0	10	23	9	6	8	10	4	19	0	10	31	68
Total AE Categories	0	0	130	179	61	70	67	128	86	184	14	33	358	594

At 24 months, the nature and incidence of specific adverse events were comparable in the two study arms. In both study arms, the highest counts of adverse events were dysphagia/dysphonia, neck and arm pain, neurological events and wound complications. In each of these categories, the counts were numerically higher for the control group, with the exception of dysphagia and dysphonia and wound complications, which were higher for the M6-C™ group.

Definitely Device Related Adverse Events

There was 1 event in the M6-C™ group (in 1 subject, 0.6% rate) and 13 events in the ACDF group (in 7 subjects, 3.7% rate) that were considered definitely related to the device (**Table 12**). The event categories where the ACDF rate is higher than the M6-C™ rate are neurological (upper extremity). The non-union adverse event rate for the ACDF group was 2.6%. Adverse events related to non-union were not expected in the M6-C™ group since it is a motion-sparing technology. These data should be interpreted in the context of different adverse event categorizations and definitions for device-related adverse events between the two studies.

Table 12: Counts and Percentages of Subjects with Specific Definitely Device Related Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	**No. of Evemts**	**No. of Pts.**	**% of Pts.**	**No. of Evemts**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DYSPHAGIA\DYSPHONIA	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Dysphagia	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
INFECTION	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Deep Wound - Cervical	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
NECK AND\OR ARM PAIN	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Arm Pain	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
NEUROLOGICAL	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
Upper Extremity	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
NON-UNION	0	0	0.0	5	5	2.6	-2.6	-13.1	7.9
RESPIRATORY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Subjects with at least 1 adverse event		1			7				

Notes:
[1] Exact 95% binomial confidence interval without PS adjustment.

Serious Adverse Events (SAEs)

There were a total of 25 SAEs in the M6-C™ group in 15 subjects and 62 SAEs in 28 subjects in the control group (**Table 13**). Categories where the rates were higher in the ACDF control included gastrointestinal (2.6%) and other pain (4.2%). The non-union adverse event rate for the ACDF control was 3.2%. Adverse events related to non-union were not expected in the M6-C™ group since it is a motion-sparing technology. There was one category where the M6-C™ group had a higher rate than the ACDF group (Infection, deep wound – cervical; 0.6%).

Table 13: Counts and Percentages of Subjects with Specific Serious Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	**No. of Evemts**	**No. of Pts.**	**% of Pts.**	**No. of Evemts**	**No. of Pts.**	**% of ts.**	**Diff**	**LB**	**UB**
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
CANCER	7	3	1.9	1	1	0.5	1.3	-9.2	11.8
CARDIOVASCULAR	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DEATH	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
DYSPHAGIA\DYSPHONIA	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Dysphagia	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
GASTROINTESTINAL	1	1	0.6	6	5	2.6	-2.0	-12.5	8.5
INFECTION	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Local	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
NECK AND\OR ARM PAIN	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Arm Pain	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Neck Pain	0	0	0.0	3	3	1.6	-1.6	-12.1	8.9
NEUROLOGICAL	5	4	2.5	8	8	4.2	-1.7	-12.2	8.8
Neck	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Back	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Spinal Cord Disturbance	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Upper Extremity	3	2	1.3	3	3	1.6	-0.3	-10.8	10.2
Lower Extremity	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Other	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
NON-UNION	0	0	0.0	7	6	3.2	-3.2	-13.6	7.3
OTHER PAIN	1	1	0.6	9	8	4.2	-3.6	-14.1	6.9
Back	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Headache	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Lower Extremity	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Shoulder	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
RESPIRATORY	2	2	1.3	1	1	0.5	0.7	-9.8	11.2
SPINAL DISORDER	4	4	2.5	9	5	2.6	-0.1	-10.6	10.4
"No subcategory for CerviCore"	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Non-Study Surgery	2	2	1.3	2	2	1.1	0.2	-10.3	10.7
Cervical - Study Surgery	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Non Cervical	1	1	0.6	6	3	1.6	-1.0	-11.5	9.5
TRAUMA	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
UPPER EXTREMITY NERVE ENTRAPMENT	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
UROGENITAL	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
WOUND ISSUE NON-INFECTION	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
OTHER	0	0	0.0	3	2	1.1	-1.1	-11.5	9.4
Subjects with at least 1 adverse event		15			28				

Notes:
[1] Exact 95% binomial confidence interval without PS adjustment.

Definitely Device- or Procedure- Related Serious Adverse Events

There were 3 M6-C™ subjects (1.88%) and 8 control subjects (4.23%) with at least one SAE definitely related to the device or procedure. Based on the lower and upper bounds, there were no notable observed differences in the reported device- and procedure- related SAEs between the two study groups.

Table 14: Counts and Percentages of Subjects with Specific Serious, Definitely Device/Procedure Related Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	**No. of Evemts**	**No. of Pts.**	**% of Pts.**	**No. of Evemts**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DEATH	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
DYSPHAGIA\DYSPHONIA	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Dysphagia	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
NEUROLOGICAL	3	2	1.3	3	3	1.6	-0.3	-10.8	10.2
Spinal Cord Disturbance	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Upper Extremity	2	1	0.6	3	3	1.6	-1.0	-11.5	9.5
NON-UNION	0	0	0.0	5	5	2.6	-2.6	-13.1	7.9
RESPIRATORY	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
SPINAL DISORDER	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Non-Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
WOUND ISSUE NON-INFECTION	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Subjects with at least 1 adverse event		3			8				

Notes:
[1] Exact 95% binomial confidence interval without PS

Adverse Events Requiring Subsequent Surgical Intervention

Some adverse events resulted in subsequent surgical interventions at the index level. Subsequent surgical interventions (SSIs), prospectively classified as revisions, removals, reoperations or supplemental fixations, qualified as study failures in concert with FDA's Guidance Document, Clinical Data Presentations for Orthopedic Device Applications (2004). There were 3 SSIs in the M6-C™ group and 9 SSIs in the ACDF group.

Table 15: SSI Summary Table – ITT (PS Selected) Cohort through 24 Months

SSI	**M6-C™ (n=160)**	**ACDF (n=189)**
Revision	0 (0.0%)	2 (1.1%)
Removal	1 (0.6%)	3 (1.6%)
Reoperation	1 (0.6%)	1 (0.5%)
Supplemental Fixation	1 (0.6%)	3 (1.6%)
Total	**3 (1.9%)**	**9 (4.8%)**

Table 16: SSI by Time of Occurrence

SSI	Event Time Course (months)						Total (events)
	<1.5	1.5-3	3-6	6-12	12-18	18-24	
M6-C™							
Revision	-	-	-	-	-	-	0
Removal	-	-	-	-	1	-	1
Reoperation	1	-	-	-	-	-	1
Supplemental Fixation	-	-	-	1	-	-	1
Total	**1**	**-**	**-**	**1**	**1**	**-**	**3**
ACDF							
Revision	-	-	-	-	-	2	2
Removal	-	-	-	1	2	-	3
Reoperation	1	-	-	-	-	-	1
Supplemental Fixation	-	-	-	2	-	1	3
Total	**1**	**-**	**-**	**3**	**2**	**2**	**9**

Based on the results presented in **Table 15**, the SSI incidence rate is 1.9% for the M6-C™ subjects and 4.8% for the control subjects. In the M6-C™ group, one subject required posterior decompression (reoperation) at the index level (C5-C6) 1 month postoperatively, one subject required posterior fusion (supplemental fixation) at C4-C6 at 12 months postoperatively, leaving the M6-C™ Artificial Cervical Disc in place and intact, and one subject had their M6-C™ Artificial Cervical Disc removed with additional treatment at C3-C7 at 17 months.

Adjacent Level Disease and Symptoms

Adjacent level disease or symptoms which required subsequent surgical intervention up to 24 months were documented and are reported in **Table 17**. This table reports all known adjacent level surgeries and not the total number subjects with adjacent level disease/symptoms. The rates were comparable: 3.1% (5/160) for the M6-C™ group compared to 2.1% (4/189) for the ACDF group.

These data should be interpreted in the context that adjacent level data were not collected in the historical control subjects.

Table 17: Subsequent Surgical Interventions (SSI) including Level(s) Adjacent to Index Level through 24 Months

Group	Index Level	Event	Time to SSI	Description of SSI
M6-C™	C5-C6	Neck and right shoulder and arm pain along with numbness in right arm/hand.	12 Months	Posterior fusion from C4-C6
M6-C™	C5-C6	Neck pain and bilateral arm pain/ radiculopathy	12 Months	Microdiscectomy C3-C7 and 3-level M6-C™
M6-C™	C4-C5	Continued neck pain with right arm pain/radiculopathy	24 Months	ACDF C6-C7 and TDR C5-C6
M6-C™	C5-C6	Continued neck pain with right arm pain/ radiculopathy	24 Months	TDR C6-C7
M6-C™	C5-C6	New onset bilateral arm radiculopathy	24 Months	ACDF at C6-C7; M6-C™ at C5-C6 left in place
ACDF	C5-C6	Right arm pain and radiculopathy	3 Months	ACDF C6-C7
ACDF	C5-C6	Progressive severe left upper extremity pain and weakness	14 Months	ACDF C5-C7
ACDF	C5-C6	Increasing pain in the shoulder blade	17 Months	Posterior fusion C5-C7
ACDF	C4-C5	Increased neck and right arm pain/radiculopathy	20 Months	ACDF C3-C4, C5-C6; removal of hardware at C4-C5

Neurological Status

Neurological success was defined as maintenance or improvement in neurologic status at 24 months. As such, neurologic failure at 24 months was any decrease in neurologic function compared to baseline. At 24 months, 150 (93%) M6-C™ subjects and 144 (76.1%) control subjects were evaluated for this endpoint.

Table 18: Neurological Decrease from Baseline at 24 Months - ITT (PS Selected) Cohort

Neurological Component	M6-C™			ACDF		
	N	n	%	N	n	%
Sensory	150	6	4.0%	164	5	3.0%
Reflexes	150	3	2.0%	164	16	9.8%
Motor Function	150	3	2.0%	164	1	0.6%
Total*	**150**	**10**	**6.7%**	**164**	**21**	**12.8%**

*Total number of subjects; subjects may have one or more components with decrease from baseline.

At Month 24, ten (10) M6-C™ subjects were considered neurological failures (6.7%) and twenty-one (21) ACDF subjects were considered neurological failures (12.8%).

Adverse events categorized as neurological were as follows:

Table 19: Summary of Neurological Adverse Events

	M6-C™		ACDF	
	Events	**Subjects**	**Events**	**Subjects**
Total	68	46	115	73
Device-related	0	0	14	12
Serious	5	4	8	8
Serious, Definitely device- or procedure- related	3	2	3	3

Effectiveness Results

Primary Overall Success Analysis

The primary study endpoint is success rate assessed at 24-months after treatment. The success rate is a composite endpoint including both safety and effectiveness measures:

1. No supplemental surgical procedure at the index level
2. NDI improvement of 15 points
3. No device /procedure definitely related SAE
4. Neurological success (maintained or improved from baseline)

The data presented in **Table 20** demonstrate the non-inferiority of the M6-C™ Artificial Cervical Disc to ACDF controls on the overall primary endpoint. The counts and percentages provided for the M6-C™ and ACDF groups are not adjusted for PS subclass. The device group difference and 90% confidence interval lower bound (LB) and upper bound (UB) are calculated after controlling for PS subclass. Therefore, the reported difference does not match the difference between the presented unadjusted percentages. Subjects who are missing outcome data at the Month 24 time point who were not a prior terminal failure are excluded from the overall composite success assessment and addressed in missing data analyses in **Table 21**. This includes 26 ACDF subjects from the M6-C™ IDE study in the PS cohort who had not yet reached the month 24 time point following surgery.

For the composite success using subjects with complete data at month 24, the unadjusted success rate was 86.8% for M6-C™ group compared with 79.3% for the ACDF group. Adjusted for PS subclass, the difference between the M6-C™ and ACDF was 5.2%. The lower-bound of the 1-sided 95% confidence interval (identical to the lower-bound of the two-sided 90% confidence interval) for the group difference controlling for PS subclass was -2.1%. Since -2.1% is greater than -10%, the results from this comparison demonstrate that the study success criterion for non-inferiority has been achieved.

Using multiple imputation to account for missing data, the adjusted success rate was 85.7% for the M6-C™ group compared with 78.9% for the ACDF group, with the difference between the M6-C™ group and ACDF groups being 6.9%. The lower-bound of the 1-sided 95% confidence interval for the group difference controlling for PS subclass was -0.9%. Since -0.9% is greater than -10%, the results from this comparison demonstrate that the study success criterion for non-inferiority has been achieved.

In all components of the composite endpoint, the M6-C™ population performed numerically better than the ACDF controls. The largest numerical difference was present in the NDI component of the primary endpoint with a group difference of 3.7% adjusted for PS subclass.

Table 20: ITT (PS Selected) Cohort[1] Descriptive Comparisons of the Percentages of Subjects Achieving Month 24 Overall Success with PS Adjusted Group Differences and Two-Sided 90% CI's for the Overall Success Endpoint and its Components

	M6-C™ [5]			ACDF [5]			M6-C™ - ACDF[6]		
	N	n	%	N	n	%	Diff	LB	UB
Overall Success (Completed Cases)	152	132	86.8	164	130	79.3	5.2	-2.1	12.5
ITT (PS Selected) using Multiple Imputation (MI)[2,3]	160	---	85.7	189	---	78.9	6.9	-0.9	14.7
Per Protocol (Completed Cases)[4]	152	---	86.0	164	---	80.8	5.2	-2.1	12.5
(1) No supplemental surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation)[7]	160	157	98.1	189	180	95.2	3.0	-0.2	6.3
(2) NDI Responder (improvement of at least 15 points)[8]	147	133	90.5	154	131	85.1	3.7	-2.8	10.2
(3) No Device/Procedure Definitely Related SAE	160	157	98.1	189	181	95.8	1.8	-1.3	5.0
(4) Neurological Success (maintenance or improvement compared to baseline)[8,9]	150	149	99.3	164	162	98.8	0.7	-1.2	2.5

Notes:

[1] Includes all M6-C™ subjects (N=160) and control subjects selected into a propensity score subclass (N=189).

[2] The primary ITT analysis set includes all M6-C™ subjects (N=160) and controls selected into a propensity score subclass (N=189). Among 72 prospective controls, 46 were selected into a PS subclass. 39 (86.7%) were evaluable for overall success. Overall, among all 189 PS selected controls, 164 (86.8%) were evaluable for primary overall success endpoint. 152 of 160 (95%) M6-C™ subjects were evaluable for Month 24 overall success.

[3] A fully conditional specification (FCS) approach was used to produce 20 multiply imputed completed data sets. To implement the MI, the overall success endpoints were determined at intermediate time points. The FCS approach was used to accommodate non-monotonicity in the pattern of missing overall success over time and requires models to be specified for each variable with missing values. All models included PS subclass and treatment group. Overall success variables were sequentially added to account for longitudinal temporality. The model for Month 24 included PS subclass, treatment groups, and all intermediate overall success values.

[4] Since there were no exclusions from the ITT analysis set due to protocol violations the Per Protocol analysis set is a completers analysis set. The Per Protocol (PP) analysis set includes N=152 M6-C™ subjects and N=164 ACDF controls that were evaluable for Month 24 Overall Success

[5] All counts and percentages presented for subjects meeting the overall success endpoint (completed cases) and components of overall success are not adjusted for PS subclass, with the exception of the overall success endpoint in the ITT (PS Selected) using Multiple Imputation cohort and the protocol assessment that are adjusted for PS subclass.

[6] Device group differences and two-sided 90% confidence intervals (CI) for group differences were calculated controlling for propensity score (PS) subclass using Proc GENMOD with dist=binomial, link=logit, and ilink option in LSMEANS statements. The LB of the two-sided 90% CI is identical to the LB of the one-sided 95% CI. For overall success and NDI, PS subclass was included in the model as a stratification variable (df=4). The very high success rates for the other variables required that the ordinal PS subclass be included in the model as a continuous variable (df=1).

Note that in this table, the PS-adjusted group difference in success rates does not equal the difference in the unadjusted percentages since these do not control for PS subclass. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

[7] One M6-C™ subject died on relative day 18. This subject is included in this row as not experiencing an SSI. This subject experienced an SAE on day 8 that was classified as definitely related to the device or procedure and is included in row (3) as an SAE failure.

[8] NDI Responder is censored for terminal failure (SSI and device / procedure related SAE). Neurologic success is not censored for terminal failure.

[9] Neurological success for the primary endpoint was adjudicated for clinical relevance to the subject's index level by the CEC for the subjects who exhibited a numerical decline in neurological status.

When imputing all missing data as either successes or failures, the non-inferiority assessment is maintained, with the lower bound of the confidence interval being greater than -10% for both measurements.

The "best case" and "worst case" assessments for the M6-C™ group were developed via modeling, as the inclusion of the PS sub-classification into the model creates another dimension to the missing data analysis, with

the "worst case" combination not necessarily being the case where all missing M6-C™ subjects are considered failures and all missing ACDF subjects are considered as successes. In the "worst case" assessment for the M6-C™ group the lower bound of the confidence interval is -8.4%, indicating that even in the "worst case" assessment the lower bound of the confidence is greater than -10% and, thus, non-inferiority is met.

Table 21: ITT (PS Selected) Cohort Month 24 Overall Success Comparison and Missing Value Sensitivity Analyses for PS Adjusted Month 24 Overall Success and Device Group Differences with Two-Sided 90% CI's

	M6-C™ [4]			ACDF [4]			M6-C™ - ACDF [4]		
	N	n	%	N	n	%	Diff (%)	LB[5]	UB
ITT (PS Selected) using Multiple Imputation (MI)[1,2]	160	---	85.7	189	---	78.9	6.9	-0.9	14.7
Per Protocol (Completed Cases)[3]	152	---	86.0	164	---	80.8	5.2	-2.1	12.5
All Missing as Success	160	---	86.6	189	---	83.6	3.0	3.0	9.6
All Missing as Failure	160	---	82.6	189	---	68.9	13.8	6.0	21.6
Best Case (M6-C missing as success, ACDF as failures)	160	---	87.4	189	---	69.5	17.9	10.5	25.3
Worst Case (M6-C missing as failures, ACDF as success)	160	---	81.8	189	---	83.0	-1.2	-8.4	5.9

Notes:

[1] The primary ITT analysis set includes all M6-C™ subjects (N=160) and controls selected into a propensity score subclass (N=189). Among 72 prospective controls, 46 were selected into a PS subclass. 39 (86.7%) were evaluable for overall success. Overall, among all 189 PS selected controls 164 (86.8%) were evaluable for primary overall success endpoint. 152 of 160 (95%) of M6-C™ subjects were evaluable for Month 24 overall success.

[2] A fully conditional specification (FCS) approach was used to produce 20 multiply imputed completed data sets. To implement the MI, the overall success endpoints were determined at intermediate timepoints. The FCS approach was used to accommodate non-monotonicity in the pattern of missing overall success over time and requires models to be specified for each variable with missing values. All models included PS subclass and treatment group. Overall success variables were sequentially added to account for longitudinal temporality. The model for Month 24 included PS subclass, treatment groups, and all intermediate overall success values.

[3] Since there were no exclusions from the ITT analysis set due to protocol violations the Per Protocol analysis set is a completers analysis set. The Per Protocol (PP) analysis set includes N=152 M6-C™ subjects and N=164 ACDF controls that were evaluable for Month 24 overall success. Percentages in this row adjust for PS subclass and and not determined as n/N. This is why the n column is suppressed.

[4] Estimated overall success rates for each device group as well as the device group differences and 90% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using Proc GENMOD with dist=binomial and link=logit. The ilink option in the lsmeans statement was used to obtain estimated success rates and standard errors on the probability scale. The lower bound (LB) of the 90% CI is equivalent to the LB of the 1-sided 95% non-inferiority CI. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

[5] The Study Success criterion is a 1-sided 95% CI LB for the overall success that is greater than or equal to -10% in both the ITT and PP analysis sets. Since LB = -0.9% > -10% and -2.1% > -10%, the Study Success criterion is achieved.

Secondary Effectiveness Analyses

This section focuses on secondary clinical endpoints from a number of relevant domains (i.e., Neck Disability Index (NDI), Visual Analog Scale (VAS), Short-Form Questionnaire (SF-36/SF-12), and Radiographic Measurements, which were assessed at preoperative (baseline) and at prescribed clinical intervals throughout the follow-up period. In addition, Odom's criteria and patient satisfaction were assessed post-operatively at 24 months. Overall, subjects treated with the M6-C™ Artificial Cervical Disc exhibited significant improvement across the broad spectrum of secondary analyses.

Table 22: Secondary Effectiveness Subject Outcomes at 24-Months Compared to Baseline – ITT (PS Selected) Cohort

Component	M6-C™ (N=160)	ACDF (N=189)
NDI Improvement ≥ 15 points	133/147 (90.5%)	131/154 (85.1%)
VAS Neck Pain Improvement ≥ 2.0cm	134/147 (91.2%)	120/154 (77.9%)
VAS Worse Side Shoulder/Arm Pain Improvement ≥ 2.0cm	133/147 (90.5%)	123/154 (79.9%)
SF-12/SF-36 PCS Maintenance or Improvement	143/147 (97.3%)	132/148 (89.2%)
SF-12/SF-36 MCS Maintenance or Improvement	114/147 (77.6%)	114/148 (77.0%)
Patient Satisfaction*	138/150 (92.0%)	156/160 (95.1%)
Odom's Criteria (Excellent or Good)	142/150 (94.6%)	146/164 (89.0%)
Work Status (Working Full/Part Time w/ or w/out Restrictions)	127/152 (83.6%)	130/171 (76.0%)
Overall Pain Medication Usage (# of Subjects Using)	21/150 (14.0%)	68/178 (38.2%)
NSAID Usage (# of Subjects Using)	15/150 (10.0%)	36/178 (20.2%)
Opioid Usage (# of Subjects Using)	3/150 (2.0%)	27/178 (15.2%)

*Historical control satisfaction categories were dichotomized into "yes" or "no"

Neck Disability Index (NDI)

Table 23: Descriptive Statistics including Two-Sided 95% CI's for the Neck Disability Index (NDI) – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	54.8	14.1	54.0	26.0	96.0	189	51.9	14.5	50.0	30.0	90.0	-0.1	-3.3	3.1
Week 6	156	22.4	15.2	21.0	0.0	64.0	186	29.0	18.8	27.0	0.0	86.0	-5.3	-9.3	-1.2
Month 3	153	15.4	14.7	12.0	0.0	64.0	179	22.2	18.4	18.0	0.0	82.0	-5.9	-9.9	-1.8
Month 6	152	13.1	13.8	9.0	0.0	70.0	176	19.8	18.8	14.0	0.0	72.0	-5.8	-9.8	-1.7
Month 12	149	12.1	13.6	8.0	0.0	62.0	168	18.1	18.9	10.0	0.0	78.0	-5.9	-10.0	-1.8
Month 24	147	12.1	14.4	6.0	0.0	64.0	154	17.9	19.3	12.0	0.0	80.0	-5.4	-9.7	-1.1

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 24: Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in NDI Score of at Least 15 Points with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	156	125	80.1%	186	128	68.8%	4.8	-5.1	14.7
Month 3	153	138	90.2%	179	143	79.9%	7.2	-0.6	15.0
Month 6	152	141	92.8%	176	142	80.7%	8.5	0.9	16.0
Month 12	149	139	93.3%	168	145	86.3%	3.4	-3.5	10.2
Month 24	147	133	90.5%	154	131	85.1%	3.7	-4.1	11.5

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Success for the Neck Disability Index (NDI) was defined as an improvement of at least 15 points on a 100-point scale at 24 months. At 24 months, 147 M6-C™ subjects and 154 control subjects were assessed for this parameter. Mean scores at 24 months were 12.1 and 17.9 for the M6-C™ and control subjects, respectively. These scores represent a success rate of 90.5% and 85.1%, respectively.

It should be noted that while the NDI questionnaires used in the historical control and in the M6-C™ study were identical, with the same relative weight assigned to each answer, the raw scores were converted to a 100 point scale in the M6-C™ study to facilitate comparison with the historical control, which reported NDI on a 100 point scale. This conversion is commonly performed and does not affect the comparability of the results.

Functional improvement assessed using NDI appears comparable in the study arms.

Visual Analog Scale (VAS) – Neck Pain

Table 25: Descriptive Statistics including Two-Sided 95% CI's for VAS Neck Pain – ITT (PS Selected) Cohort

	M6-C™ Neck Pain VAS						ACDF Neck Pain VAS						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	7.3	1.9	7.6	0	10	189	7.1	2.0	7.4	0	10	0.0	-0.5	0.4
Week 6	156	2.0	1.9	1.5	0	9	186	2.6	2.4	1.6	0	10	-0.5	-1.0	0.0
Month 3	152	1.4	1.9	0.4	0	8	179	2.2	2.5	1.3	0	10	-0.7	-1.3	-0.2
Month 6	151	1.2	1.7	0.4	0	9	176	2.2	2.5	1.2	0	9	-1.0	-1.5	-0.5
Month 12	148	1.2	1.7	0.2	0	8	168	2.0	2.7	0.5	0	10	-1.0	-1.5	-0.4
Month 24	147	1.1	2.0	0.1	0	10	154	2.2	2.7	0.8	0	10	-1.0	-1.6	-0.4

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 26: Improvement in VAS Neck Pain Scores of at Least 2.0 cm with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF [1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	156	138	88.5%	186	144	77.4%	9.7	1.4	17.9
Month 3	152	137	90.1%	179	146	81.6%	5.1	-2.7	12.9
Month 6	151	139	92.1%	176	136	77.3%	14.1	6.1	22.1
Month 12	148	136	91.9%	168	135	80.4%	12.3	4.4	20.1
Month 24	147	134	91.2%	154	120	77.9%	11.6	3.1	20.1

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Success for the Visual Analog Score (VAS) was defined as an improvement of at least 2cm on a 10cm scale compared to baseline at 24 months. The M6-C™ IDE study specified a baseline threshold score of 4cm, and the propensity method was used to match control subjects to this baseline value.

At 24 months, 147 M6-C™ subjects and 154 control subjects were evaluated for this parameter. The mean VAS scores at 24 months were 1.1 and 2.2, respectively. Success for this parameter was 91.2% and 77.9%, respectively. The M6-C™ Artificial Cervical Disc appears to be more effective in relieving neck pain than ACDF.

Visual Analog Scale (VAS) – Shoulder/Arm Pain (Worse Side)

Table 27: Descriptive Statistics including Two-Sided 95% CI's for VAS Shoulder/Arm Pain (Worse Side) – ITT (PS Selected) Cohort

	M6-C™ Shoulder/Arm Pain (worse side)						ACDF Shoulder/Arm Pain (worse side)						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	7.3	2.2	7.6	0	10	189	7.5	1.9	7.7	0	10	-0.1	-0.5	0.4
Week 6	155	1.2	2.0	0.2	0	9	186	2.5	2.7	1.1	0	10	-1.1	-1.7	-0.5
Month 3	152	0.9	1.8	0.1	0	8	179	2.3	2.6	1.3	0	9	-1.0	-1.6	-0.5
Month 6	151	0.7	1.6	0.1	0	9	176	2.2	2.6	0.9	0	9	-1.2	-1.7	-0.7
Month 12	148	0.9	1.9	0.0	0	10	168	2.1	2.8	0.5	0	10	-1.2	-1.8	-0.7
Month 24	147	0.8	1.8	0.0	0	9	154	2.4	2.9	1.0	0	10	-1.5	-2.1	-0.9

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 28: Improvement in VAS Shoulder/Arm Pain (Worse Side) Scores of at Least 2.0 cm with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF [1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	155	135	87.1%	186	150	80.6%	5.8	-2.3	13.9
Month 3	152	137	90.1%	179	144	80.4%	10.0	2.1	17.8
Month 6	151	139	92.1%	176	142	80.7%	13.7	6.1	21.3
Month 12	148	131	88.5%	168	138	82.1%	11.5	3.6	19.4
Month 24	147	133	90.5%	154	123	79.9%	14.5	6.3	22.7

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Pain in the shoulder/arm was also assessed at 24-months using the VAS with the same success criteria. At 24 months, 147 M6-C™ subjects and 154 control subjects were evaluated for this parameter. No threshold baseline score was required; however, the baseline scores were similar. At 24 months, mean VAS worse side shoulder and arm pain scores were 0.8 and 2.4 for the M6-C™ and control subjects, respectively. Success for this parameter was 90.5% and 79.9%, respectively. The M6-C™ Artificial Cervical Disc appears to be more effective in relieving shoulder and arm pain than ACDF.

SF-12/SF-36

Health-related quality of life was assessed using the SF-36 tool in the M6-C™ IDE study and the SF-12 tool in the historical control, which precluded pooling of the concurrent and historical control groups. The sponsor addressed this by calculating the subscores of PCS and MCS and pooling them. This is not a validated method and the outcomes should be viewed in this context.

- Physical Component Summary (PCS)

Table 29: Descriptive Statistics including Two-Sided 95% CI's for SF-12/SF-36 Physical Component Summary Scores – ITT (PS Selected) Cohort

	M6-C™ Physical Component Summary						ACDF Physical Component Summary						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	34.9	7.7	34.6	16.1	55.0	187	32.7	8.0	32.4	10.8	56.9	2.8	1.0	4.7
Month 6	151	50.7	8.9	53.2	14.5	63.4	170	47.2	10.6	50.0	19.4	68.9	2.3	-0.1	4.7
Month 12	148	51.3	8.6	54.0	23.5	65.2	164	48.8	10.4	51.7	15.9	70.0	2.4	0.1	4.8
Month 24	147	51.3	8.4	53.4	22.5	63.2	150	48.2	10.8	52.4	17.5	64.3	2.5	0.1	5.0

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/ disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 30: Descriptive Comparisons of the Percentages of Subjects Maintaining or Improving SF-12/SF-36 Physical Function Component Summary Score with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Month 6	151	143	94.7%	168	153	91.1%	2.6	-3.2	8.3
Month 12	148	141	95.3%	162	150	92.6%	2.0	-3.5	7.5
Month 24	147	143	97.3%	148	132	89.2%	7.6	1.6	13.6

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

At 24 months, 147 M6-C™ subjects and 148 control subjects were assessed. Both groups reported improvement of this score compared to baseline (measurement at pre-operative timepoint). The scores for the M6-C™ subjects were numerically higher.

- Mental Health Component Summary (MCS)

Table 31: Descriptive Statistics including Two-Sided 95% CI's for SF-12/SF-36 Mental Health Component Summary Scores – ITT (PS Selected) Cohort

	M6-C™ Mental Health Summary						ACDF Mental Health Summary						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	41.4	13.9	42.1	7.7	66.6	187	42.5	12.8	42.0	16.0	73.6	0.5	-2.6	3.5
Month 6	151	53.6	9.3	56.3	15.0	69.4	170	50.5	10.7	53.6	17.3	66.7	3.0	0.5	5.4
Month 12	148	53.0	8.9	55.9	15.8	64.6	164	49.7	11.3	52.9	9.6	66.3	3.3	0.7	5.8
Month 24	147	52.9	9.7	56.0	20.1	65.0	150	51.7	10.4	56.2	21.1	72.5	1.9	-0.7	4.4

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/ disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 32: Descriptive Comparisons of the Percentages of Subjects Maintaining or Improving SF-12/SF-36 Mental Health Component Summary Score with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Month 6	151	123	81.5%	168	132	78.6%	0.3	-9.0	9.5
Month 12	148	114	77.0%	162	115	71.0%	5.1	-5.2	15.5
Month 24	147	114	77.6%	148	114	77.0%	0.5	-9.5	10.6

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. P-values are from Mantel-Haenszel PS subclass stratified comparisons between device groups. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

At 24 months, 147 M6-C™ subjects and 131 control subjects were assessed for the MCS. When compared to baseline, both arms showed improvement and the rates were similar.

Odom's Criteria

The surgeon's rating of subject outcomes was assessed using Odom's criteria. Different definitions of the categories were used in the two studies, which precluded pooling of the concurrent and historical control groups. No method was available to address this issue and therefore no comparison could be made between the two study arms.

Table 33: Odom's Criteria – Month 24 – M6-C™ and ACDF Pooled Controls – ITT (PS Selected) Cohort

	M6-C™		ACDF	
Odom's Criteria	**n**	**%**	**n**	**%**
Excellent	113	75.3	106	64.6
Good	29	19.3	40	24.4
Fair	7	4.7	13	7.9
Poor	1	0.7	5	3.0

At 24 months, 150 M6-C™ subjects and 164 control subjects were assessed for this parameter. The majority of subjects in both arms were rated by the surgeon as "Excellent".

Patient Satisfaction

Different questions were used in assessing patient satisfaction and preclude direct comparison. The 5-point responses of the historical control were converted into a binary response and then pooled with the concurrent control for comparison to the Investigational group. As this not a validated method, no comparison can be made between the study arms.

Table 34: Patient Satisfaction with Surgery – Month 24 – M6-C™ and ACDF Control – ITT (PS Selected) Cohort

	M6-C™		ACDF	
Satisfaction	**n**	**%**	**n**	**%**
Yes	138	92.0	156	95.1
No	12	8.0	8	4.9
Would you have Surgery Again	**n**	**%**	**n**	**%**
Yes	140	93.3	154	95.1
No	10	6.7	8	4.9

At 24 months, 150 M6-C™ subjects and 162 control subjects were asked if they would have surgery again. The majority of subjects in both arms responded "Yes".

Radiographic Assessments

Radiographic data were collected from both study arms. There were differences in some radiographic assessments and definitions. Assessments were performed by the same independent core laboratory, but there was a temporal difference in these assessments. In instances where there were differences in definitions or assessments, the results were harmonized.

- Quantitative Radiographic Assessments

Rotation (Flexion to Extension)

Table 35: Flexion Extension Rotation (F to E) (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Pre-Op	153	8.33	4.95	180	8.02	4.93
Month 24	144	8.78	4.55	152	1.16	1.34

The flexion to extension measurement reflects the range of motion at the index level. At 24 months, 144 M6-C™ subjects and 152 control subjects were evaluated for this endpoint. The mean ROM at baseline was slightly higher for the M6-C™ subjects than the controls. At 24 months, motion was maintained for the M6-C™ subjects. Motion was reduced in the fusion controls.

Translation (Flexion to Extension)

Table 36: Translation (F to E) (mm) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Pre-Op	153	0.83	0.62	179	0.87	0.65
Month 24	144	0.82	0.55	152	0.13	0.16

Translational motion is a measure of stability. No difference was observed in the M6-C™ subjects. Translational motion was reduced in the fusion control subjects at 24 months.

Disc Angle

Table 37: Disc Angle (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	158	2.21	4.59	184	1.96	4.50
Month 24	149	7.21	4.98	152	5.87	4.57

At 24 months disc angle was increased in both cohorts, and the measurements were comparable.

Disc Height (Average)

Table 38: Average Disc Height (mm) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	158	3.22	0.73	183	3.32	0.81
Month 24	149	5.31	1.02	152	4.27	1.28

Disc height increased in both study arms at 24 months compared to baseline. The increase was numerically greater in the M6-C™ group.

AP Rotation (Left to Right)

Table 39: AP Rotation (L to R) (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	142	5.78	2.75	135	5.77	3.33
Month 24	149	6.88	3.25	124	1.34	1.22

Rotational motion was comparable at baseline for both arms of the study. At 24 months, motion was maintained in the M6-C™ group. Motion was reduced in the ACDF group.

- Qualitative Radiographic Assessments

Radiolucency was assessed in both the M6-C™ and ACDF groups according to the following definitions:

1. None: No radiolucent lines along the device/endplate interface
2. Mild: < 25% radiolucency
3. Moderate: 25 - 50% radiolucency
4. Severe: > 50% radiolucency

Table 40: Qualitative Assessment of Radiolucency – ITT (PS Selected) Cohort

	M6-C™		ACDF	
	n	%	n	%
1-None	144	96.0	156	98.7
2-Mild	6	4.0	0	0
3-Moderate	0	0	2	1.3
4-Severe	0	0	0	0

At 24 months, 150 M6-C™ subjects and 158 control subjects were evaluated for radiolucency. At Month 24, there was a 4% (6/150) rate of mild radiolucency in the M6-C™ group and a 1.3% (2/158) rate of moderate radiolucency in the ACDF group.

Device condition was only assessed in the M6-C™ group. At 24 months, 150 subjects were assessed for device condition. There were 4 radiographic observations of device loosening (2.6%) and no incidences of disassembly or device fracture.

At Month 24, 150 M6-C™ subjects and 159 control subjects were evaluated for subsidence. In M6-C™ group, subsidence of the device was measured; in the control group, subsidence of the graft was measured. One (1) M6-C™ subject and 2 control subjects showed subsidence.

There were no radiographic observations of migration in either the control or the M6-C™ group at any timepoint.

Fusion was assessed in the control subjects. The definition of fusion differed in the two studies. In order to pool fusion outcomes, the definition used in the M6-C™ IDE study was applied to the historical control. Fusion was defined as:

1. Evidence of continuous bridging bone across treated disc space; where bridging is defined as plain radiographic evidence of a continuous connection of bone from the superior vertebral body to the inferior vertebral body, AND
2. ≤2º total angular motion (from flexion to extension), AND
3. ≤1.25 mm translational motion (from flexion to extension).

Fusion was observed in 78.6% (125/159) of the control subjects at 24 months.

Heterotopic ossification (HO) was assessed only in subjects that received the M6-C™ Artificial Cervical Disc. 81 subjects were prescribed NSAIDs prophylactically for 6 weeks post-operatively for HO. At 24 months, 150 subjects were assessed for heterotopic ossification.

Heterotopic ossification was graded as follows:

Class 0: No evidence of osteophyte formation or heterotopic ossification.

Class I: HO is detectable in the front or sides of the vertebral body, or as islands of bone in the adjacent soft tissue, but is not in the disc space. Bone is not present between the planes formed by the two vertebral endplates.

Class II: HO is growing into the disc space. Bone is present between the planes formed by the two adjacent endplates but is not significantly blocking or articulating between adjacent vertebral endplates or osteophytes.

Class III: The range of motion of the vertebral endplates is blocked by the formation of HO and/or postoperative osteophytes on flexion-extension or lateral bending radiographs. However, the ossifications still allow some movement of the prosthesis.

Class IV: HO is causing bony ankylosis. An apparent continuous connection of bridging bone exists between the adjacent vertebral endplates with little or no motion occurring across the treated segment.

Table 41: Qualitative Assessment of HO at 24 Months – ITT (PS Selected) Cohort (M6-C™ Only)

Class	n	%
0	61	40.7
I	22	14.7
II	50	33.3
III	16	10.7
IV	1	0.7

At 24 months, 59.3% (89/150) of subjects had HO. One subject had Class IV heterotopic ossification at Month 24 (0.7%).

Pain Medication Use

Table 42: Overall Pain Medication Use (Any) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	129	80.6%	189	162	85.7%
Week 6	158	46	29.1%	189	91	48.1%
Month 3	156	30	19.2%	189	78	41.3%
Month 6	154	32	20.8%	186	76	40.9%
Month 12	152	27	17.8%	185	69	37.3%
Month 24	150	21	14.0%	178	68	38.2%

Table 43: Pain Medication Use (Anti-Inflammatory and Antirheumatic Products, Non-Steroids) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	81	50.6%	189	71	37.6%
Week 6	158	29	18.4%	189	13	6.9%
Month 3	155	14	9.0%	189	29	15.3%
Month 6	154	18	11.7%	186	38	20.4%
Month 12	152	18	11.8%	184	35	19.0%
Month 24	150	15	10.0%	178	36	20.2%

Table 44: Pain Medication Use (Opioid) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	71	44.4%	189	115	60.8%
Week 6	158	11	7.0%	189	62	32.8%
Month 3	155	9	5.8%	189	38	20.1%
Month 6	154	7	4.5%	186	32	17.2%
Month 12	152	8	5.3%	184	31	16.8%
Month 24	150	3	2.0%	178	27	15.2%

As shown **Table 42**, **Table 43**, and **Table 44** overall pain medication, anti-inflammatory and antirheumatic products, non-steroids (NSAIDs), and opioid use was markedly higher in the ACDF group compared to the M6-C™ group at Month 24. In the ITT (PS Selected) cohort at Month 24, 38.2% (68/178) of ACDF subjects reported overall pain medication usage compared to 14.0% (21/150) of M6-C™ subjects, 20.2% (36/178) of ACDF subjects reported NSAID usage compared to 10.0% (15/150) of M6-C™ subjects, and 15.2% (27/178) of ACDF subjects reported opioid usage compared to 2.0% (3/150) of M6-C™ subjects. This observed reduction in pain medication usage at later time points demonstrates an additional benefit of the M6-C™ Artificial Cervical Disc compared to ACDF.

Long Term Clinical Results (36 Months)

An analysis of the 36-month data using the same parameters safety and effectiveness endpoints was conducted. For subjects theoretically due for 36-month follow-up, the M6-C™ cohort had a follow-up rate of 82.3% (93/113) and the ACDF control cohort had a follow-up rate of 88.2%. **Table 45** shows the secondary effectiveness results at 36 months. While these analyses were not pre-specified, the results suggest that the M6-C™ Artificial Cervical Disc remains comparable to the ACDF control for clinical outcomes at 36 months.

Table 45: Secondary Effectiveness Subject Outcomes at 36 Months Compared to Baseline

Component	M6-C™(N=139)	ACDF (N=158)
NDI Improvement ≥ 15 points	82/88 (93.2%)	109/126 (86.5%)
VAS Neck Pain Improvement ≥ 2.0cm	80/87 (92.0%)	103/126 (81.7%)
VAS Worse Side Shoulder/Arm Pain Improvement ≥ 2.0cm	75/87 (86.2%)	105/126 (83.3%)
SF-12/SF-36 PCS Maintenance or Improvement	83/88 (94.3%)	107/122 (87.7%)
SF-12/SF-36 MCS Maintenance or Improvement	72/88 (81.8%)	99/122 (81.1%)
Overall Pain Medication Usage (# of Subjects Using)	7/89 (7.9%)	57/147 (38.8%)
NSAID Usage (# of Subjects Using)	6/89 (6.7%)	30/146 (20.5%)
Opioid Usage (# of Subjects Using)	3/89 (3.4%)	25/147 (17.0%)

At 36 months, differences in adverse event rates are noted between the M6-C™ and control groups, with higher percentages of any adverse event, any serious adverse event, and device related adverse events in the ACDF group, while there is a higher rate of procedure-related adverse events in the M6-C™ group (**Table 46**). This difference in procedure-related adverse events may be due to differences in the classification of procedure-related adverse events in the M6-C™ and historical control IDE studies.

Table 46: Comparisons of Summary Adverse Event Rates between M6-C™ and ACDF Groups with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 36 Months

	M6-C™ (I) (N=160)		ACDF (C) (N=189)		I vs. C[1]		
	n	%	n	%	Diff (%)	LB	UB
Any adverse event (per patient)[4]	111	69.4	160	84.7	-13.7	-23.0	-4.4
Any device related AE[2]	5	3.1	26	13.8	-11.3	-17.2	-5.4
Any procedure related AE[2,3]	60	37.5	51	27.0	12.1	1.8	22.5
Any AE related to device or procedure[2]	61	38.1	69	36.5	2.5	-8.3	13.2
Any serious AE	22	13.8	35	18.5	-5.6	-13.6	2.5
Serious AE that is either device or procedure related[2]	6	3.8	12	6.3	-2.7	-7.3	1.9
Deaths[3]	3	1.9	1	0.5	0.9	-1.4	3.3

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

[2] Includes possible, probable, or definite.

[3] The very low event rates for these variables required that PS subclass be included in the generalized linear model as a continuous variable (df=1) rather than as a stratification variables (df=4).

[4] Historical control follow-up exceed two-years in many cases. Therefore, in order to provide meaningful comparisons between groups, AEs with onset dates more than 1155 days (36 months + 60 days) post index surgery were excluded from primary safety tables for all subjects.

Conclusions Drawn from the Clinical Study

The preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of the M6-C™ Artificial Cervical Disc when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that the clinical benefits of the use of the M6-C™ Artificial Cervical Disc in terms of improvement in pain and disability, and the potential for motion preservation, outweigh the risks, both in terms of the risks associated with the M6-C™ Artificial Cervical Disc and surgical procedure when used in the indicated population in accordance with the directions for use, and as compared to the ACDF control treatment in the same indicated population.

PATIENT SELECTION AND TREATMENT

Individualization of Treatment

The risks and benefits should be carefully considered for each patient before use of the M6-C™ Artificial Cervical Disc. Factors such as the patient's weight, activity level, and compliance to weight bearing or load bearing instructions have an effect on the stresses to which to the prosthesis is subjected and may affect implant longevity.

Prior to implantation, it is important that the surgeon provide the patient with information regarding the operative procedure to include:

- Potential failure of the cervical disc prosthesis due to excessive load, wear and tear, or infection
- Life of the prosthesis is determined by several factors, including body weight and daily activities
- Cervical disc prosthesis must not be subjected to overloading through extreme strain, or through work-related or athletic activities
- Revision surgery may be necessary if the prosthesis fails

- In the event of revision surgery, it may not be possible to restore segmental motion
- At regular intervals, the patient must undergo follow-up examinations of the cervical disc prosthesis

During the post-operative period, in addition to mobility and muscle therapy, it is of particular importance for the physician to keep the patient well informed regarding potential adverse events associated with an artificial disc prosthesis. Any damage to the weight-bearing structures may give rise to loosening, dislocation, subsidence, loss of height, or migration, as well as other serious complications. To ensure the earliest possible detection of such catalysts of dysfunction, the cervical disc prosthesis must be checked periodically post-operatively using appropriate techniques.

See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS for more information regarding patient selection and treatment. Consult M6-C™ Artificial Cervical Disc Operative Technique Manual for additional important information regarding implanting the device.

PACKAGING

The M6-C™ Artificial Cervical Disc is provided pre-packaged and sterile. It is intended for single use only. Do not use the M6-C™ Artificial Cervical Disc if the package is opened or damaged. The M6-C™ Artificial Cervical Disc is Ethylene Oxide (EO) sterilized. The use by date of the sterile device is provided on the external package label.

Resterilization of the prosthesis is prohibited. Any unused prosthesis in which the packaging has been opened or damaged or may otherwise be contaminated should be returned to Orthofix. Contact Orthofix for specific instructions on device return (Refer to Contact Information section below). The M6-C™ Artificial Cervical Disc is provided pre-assembled in a sterile package. Aseptic technique must be used while opening the packaging for the correctly sized prosthesis and transferring the device to the sterile field.

The M6-C™ Artificial Cervical Disc sterilization tray and associated surgical instruments are supplied non-sterile and must be cleaned and sterilized prior to use according to the instructions in the Orthofix document *Care and Handling Instructions for M6-C™ Surgical Instruments*.

The instruments are shipped and stored in the sterilization tray which has identifying markings and specific locations for each instrument. Instruments may also be shipped individually in packaging that is labeled according to its contents.

Store the instruments in their original packaging or in the sterilization tray. Store the sterilization tray in normal hospital environmental conditions. Do not remove the M6-C™ Artificial Cervical Disc from its packaging until it is ready to be placed in the operating room sterile field.

HANDLING

All instruments and implants should be treated with care. Improper use or handling may lead to damage and/or possible malfunction. Instruments should be checked to ensure that they are in working order prior to surgery. All instruments should be inspected prior to use to ensure that there is no unacceptable deterioration such as corrosion, discoloration, pitting, cracked seals, etc. Non-working or damaged instruments should not be used and should be returned to Orthofix.

Carefully inspect the sterile package before opening. Do not use after the use by date. If the integrity of the sterile packaging has been compromised or damaged, contact your local Orthofix representative for return and replacement information. **DO NOT USE IF ANY DEFECTS ARE NOTED.**

It is necessary for the prosthesis to be kept in the original packaging, in a clean, dry, temperate location under normal atmospheric pressure. Storage conditions must maintain the integrity of the prosthesis, associated ancillary instrumentation, and the respective packaging.

CLEANING

REFER TO THE *CARE AND HANDLING INSTRUCTIONS FOR M6-C™ SURGICAL INSTRUMENTS* PRIOR TO USE.

STERILIZATION

The M6-C™ Artificial Cervical Disc is provided sterile. The implant may not be resterilized for any reason. No implant should be re-used once it comes into contact with human tissue.

The M6-C™ Surgical Instruments are provided non-sterile and must be sterilized by the user prior to surgery. REFER TO THE *CARE AND HANDLING INSTRUCTIONS FOR M6-C™ SURGICAL INSTRUMENTS* PRIOR TO USE.

CONFORMANCE TO STANDARDS

The M6-C™ Artificial Cervical Disc is composed of titanium alloy (per ASTM 1472), commercially pure (CP) titanium plasma spray coating (per ASTM 1580), ultra-high molecular weight polyethylene (UHMWPE), and polycarbonate urethane (PCU).

UNIQUE DEVICE IDENTIFICATION (UDI)

A unique serial number is laser-marked on each M6-C™ Artificial Cervical Disc, and the serial number is included on individual patient labels supplied with each implant for use in the patient's hospital record.

PRODUCT COMPLAINTS

Any health care professional (e.g., customer or user of this system), who has complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effectiveness and/or performance, should notify Orthofix. Further, if the device (implant or instruments) ever "malfunctions," (i.e. does not meet any of its performance specifications or otherwise does not perform as intended) or may have caused or contributed to the death or serious injury of a patient, Orthofix should be notified immediately by telephone or written correspondence. When filing a complaint, please provide the device name and serial number, lot number, your name and address, and the nature of the complaint. Complaints may also be reported directly to Medwatch at http://www.fda.gov/medwatch. In the event that the M6-C™ Artificial Cervical Disc requires removal for any reason, follow the instructions provided below in the DEVICE RETRIEVAL section.

DEVICE RETRIEVAL

Please contact Orthofix to receive specific instructions regarding the preferred method for explant handling and transport as well as data collection, including histopathological, mechanical, patient, and adverse event information. Please refer to M6-C™ Artificial Cervical Disc Operative Technique Manual for step-by-step instructions on the required operative technique for device removal. All explanted devices must be returned to Orthofix for analysis.

It is preferred that no cleaning, decontamination or sterilization be performed at the hospital. Some surgical centers may require that the device be decontaminated or sterilized prior to leaving the facility. Note that many sterilization methods will damage the device (e.g., autoclaving, immersion in alcohol), and the effects of other methods are unknown. Rinsing with water or saline is acceptable. If decontamination and sterilization are required, 10% neutral buffered formalin is best. If cleaning, decontamination, or sterilization is performed, note what cleaning methods and materials were used.

It is preferred that the explanted device is packed "dry" (no fluid) or wrapped in formalin-soaked gauze. The device can be gently rinsed with water or saline to remove excess blood and fluids.

Send the explanted device in a leak-proof container, with the date of removal, explanting surgeon, and any known information regarding initial implantation, reasons for removal, and adverse event information. Please

note that the explanted M6-C™ Artificial Cervical Disc should be removed as carefully as possible in order to keep the implant and surrounding tissue intact if possible. Also, please provide descriptive information about the gross appearance of the device in situ, as well as descriptions of the removal methods, i.e., intact or in pieces. Orthofix will request additional information regarding the reason for removal, patient information and associated clinical outcomes.

NOTE: All implant removals must be reported immediately to Orthofix.

CONTACT INFORMATION

Orthofix
3451 Plano Parkway
Lewisville, TX 75056 USA
www.orthofix.com
888-298-5700
OSI-CustomerService@orthofix.com
M6info@orthofix.com

Manufactured by:
Spinal Kinetics LLC, an Orthofix Company
501 Mercury Drive
Sunnyvale, CA 94085, USA
888-298-5700

A complete Summary of Safety and Effectiveness (SSED), and labeling information for the M6-C™ Artificial Cervical Disc may be obtained at www.fda.gov by searching PMA number P170036.

Definitions of Symbols on Device Label

	Caution: Consult Accompanying Documentation
	Read Instructions Prior to Use: www.orthofix/ifu.com
	Sterile with Ethylene Oxide Gas
	MR Conditional
	Single Use Only / Do Not Reuse
	Catalog Number
	Lot Number
	Serial Number
	Use by Date
	Manufacturer

PK 0255 Rev 01