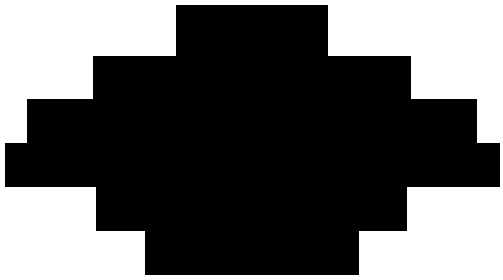
The Investigational Plan for the Evaluation of the ACADIA® Facet Replacement System
Protocol Number: 1020-9052
IDE#: G060073



Revision K

Confidential **Do Not Copy**

This investigational protocol contains confidential information for use by the principal investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title:	The Investigational Plan for the Evaluation of the ACADIA® Facet Replacement System
Protocol ID#:	Protocol Number: 1020-9052
Device:	The ACADIA® Facet Replacement System (AFRS)
Study Objective:	The primary objective of this study is to evaluate the safety and effectiveness of the AFRS through 24 postoperative months compared to an instrumented posterolateral fusion control.
Study Design:	• Multi-center clinical trial at up to 30 investigational sites • Prospective, randomized, concurrently-controlled trial • Control: Instrumented posterolateral fusion • 200 Minimum/500 Maximum Investigational and 100 Minimum/250 Maximum Control patients using 2:1 randomization • Up to 60 non-randomized investigational training cases (two per site)
Study Duration/ Follow-up Period:	Study Duration: 48-58 months Follow-up: 6 week, 3, 6, 12 and 24 month postoperative time points, and annually thereafter as required by FDA
Indication for Use:	The AFRS Study will include patients who have lateral, lateral recess and/or central stenosis at the L3 to S1 level requiring decompression and facetectomy. The operative level will receive either the test or control treatment. Adjacent lumbar vertebrae levels may be treated through decompression as required to treat stenosis that does not result in complete facetectomy or fusion.
Inclusion Criteria	• Is 21-85 years of age and skeletally mature; • Undergone at least six cumulative months of conservative treatment prior to surgery including any of the following: medications, NSAIDs, physical therapy, bracing, chiropractic manipulation, modified activities of daily living, epidural injections, facet block injections; • Lateral, lateral recess and/or central canal stenosis as demonstrated by compression of the thecal sac and/or cauda equina, nerve root impingement by either osseous or non-osseous elements or evidence of hypertrophic facets with encroachment into the central canal or lateral recess at the involved level as determined by MRI, CT scan, plain film or myelography; • Disc height measuring ≥ 4 mm at the operative level; • Persistent leg, thigh and/or buttock symptoms, including pain, numbness, burning or tingling with a minimum leg pain score of 40mm as measured with the Visual Analogue Scale (VAS) Index; • A score greater than 2 on a scale of 1-5 on the Zurich Claudication Questionnaire (ZCQ) Symptom Severity (SS) Score; • A score greater than or equal to 2 on a scale of 1-4 on the ZCQ Physical Function (PF) Score; • A candidate for a decompression with full facetectomy at the operative level; • A candidate for an instrumented posterolateral fusion; • Willing and able to comply with postoperative and routinely scheduled clinical and radiographic evaluations; • Lives in the immediate area and has no plans to relocate to another geographic

area before the completion of the study, or lives outside the immediate area and is willing to comply with scheduled postoperative visits with a designated physician;
- Signed a patient informed consent specific to this study.

Exclusion Criteria

- Previous surgical procedure at the operative or adjacent level except for one of the following: micro-discectomy, laminectomy, lamino/foraminotomy, rhizotomy, IDET, and/or interspinous spacer;
- Previous lumbar fusion or disc replacement procedure;
- Osteoporosis as defined by Simple Calculated Osteoporosis Risk Estimation (SCORE) screening questionnaire score of 6 or greater and DEXA bone density measured T-score ≤ -2.0;
- Greater than Grade I spondylolisthesis or retrolithesis, as defined by the Meyerding Grading Classification, at the operative level;
- Spondylolisthesis any grade, as defined by the Meyerding Grading Classification at levels other than at the operative level;
- Scoliosis of the lumbar spine (defined as more than 11° Cobb angle), as indicated by plain X-ray films;
- Primary diagnosis of discogenic back pain due to torn, herniated, inflamed or irritated disc or other pathology where the patient exhibits axial back pain from degenerative disc disease;
- Acute traumatic pars fracture at the operative or adjacent level vertebral body;
- Spinal stenosis at more than three lumbar segments;
- Experienced acute trauma to the lumbar spine within the last 24 months;
- Active infection at the operative level, or a systemic infection including prior or pending treatment for HIV or Hepatitis C;
- Physically or mentally compromised (*i.e.*, being currently treated for a psychiatric disorder, senile dementia, Alzheimer's disease, presence of alcohol or substance abuse) in a manner that would compromise his or her ability to participate in the clinical study;
- Diagnosed systemic disease (*i.e.*, Paget's disease, muscular sclerosis, amyotrophic lateral sclerosis (ALS), renal osteodystrophy, metastasis to vertebrae, Lupus, or ankylosing spondylosis) that may affect the patient's welfare or overall outcome of the research study;
- Immunologically suppressed or immunocompromised;
- Insulin-dependent diabetes mellitus (type I diabetes);
- Currently undergoing long-term steroid therapy (treated in the last 6 months with systemic corticosteroids);
- Metabolic bone disease (i.e., osteomalacia, and/or osteogenesis imperfecta);
- Is of child-bearing potential, and is either pregnant or interested in becoming pregnant during the duration of the study;
- Medically significant obesity as defined by a Body Mass Index (BMI) of > 40 kg/m^2. BMI = (weight in pounds $\times$ 703) $\div$ (height in inches $\times$ height in inches);
- Active malignancy: a history of any invasive malignancy (except non-melanoma skin cancer), unless the patient has been treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 5 years;

- Known allergy to cobalt chromium or titanium;
- Used any investigational drug or device within the past 30 days;
- Pending litigation related to back pain or injury;
- Is a prisoner.

Primary Endpoint:

The primary study endpoint for this study is individual patient success at 24 months. Individual patient success will be defined as follows:

- Improvement in the ZCQ by a minimum of 0.5 for both Symptom Severity (SS) and Physical Function (PF) scores at 24 months as compared to baseline.
- Maintenance or improvement in neurological outcome at 24 months.
- No subsequent surgical intervention at the level of treatment (including device failures requiring revision, removal, re-operation and supplemental fixation).
- No serious device-related adverse events.

Secondary Endpoints:

- Maintenance or improvement of the components of the primary ZCQ;
- Maintenance or improvement in patient function, as measured by the Oswestry Disability Index (ODI) questionnaire;
- Maintenance or improvement of the leg and back VAS pain scores;
- Maintenance or improvement in the components of the SF-36 Quality of Life Questionnaire;
- Changes in quantitative radiographic measures including disc height, vertebral range of motion and translation;
- Changes in qualitative radiographic measures including fusion; assessment, device migration and presence of radiolucencies;
- Radiographic Success
- Maintenance or improvement in neurological status;
- Incidence, severity and device or procedure relatedness of all adverse events over the 24-month study assessment period;
- Components of primary endpoint (surgical revisions, reoperations, removals, supplemental fixation);
- Return to normal activities of daily life;
- Change in work status and time to return to work;
- Narcotic medication usage;
- Length of hospital stay;
- Duration of surgical procedure and instrumentation time;
- Blood loss;
- Rehabilitation utilization.

Investigational Sites:

Up to 30 Investigational Sites

Study Sponsor:

Globus Medical, Inc.
Valley Forge Business Center
2560 General Armistead Avenue
Audubon, PA 19403
610-930-1800

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACRONYM	DESCRIPTION
AE	Adverse Event
AFRS	ACADIA® Facet Replacement System
AP	Anterior-Posterior
BMI	Body Mass Index
CRF	Case Report Form
CS	Clinically Significant
CT	Computed Tomography
DEXA	Dual Energy X-ray Absorptiometry
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IDET	Intradiscal Electrothermic Therapy
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NCS	Not Clinically Significant
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ODI	Oswestry Disability Index
PF	Physical Functioning
PHI	Personal Health Information
PI	Principal Investigator
PLF	Posterolateral Lumbar Fusion
QA	Quality Assurance
SAE	Serious Adverse Event
SLR	Straight Leg Raise
SS	Symptom Severity
UADE	Unanticipated Adverse Device Effect
US	United States
VAS	Visual Analog Scale
ZCQ	Zurich Claudication Questionnaire

1.0 INTRODUCTION

1.1 Background

Chronic spinal pain is the leading cause of disability in the industrialized world.[1] It has been estimated that 65% to 80% of the people in the United States will suffer an episode of low back pain during their lifetime.[2] In 1997, low back pain was estimated to have a total impact of $171 billion in the industrial setting of the United States. In 1990, the estimated cost of medical treatment for low back pain alone was $13 billion.[3] Low back pain is acknowledged as a large, costly and growing problem in industrialized countries.

The origin of low back and leg pain is varied and may include muscular, neurological and skeletal components. The most common indication for elective lumbar surgery is pain that is refractory to non-surgical treatment. The indications for reconstructive surgery to treat painful spinal conditions include instability, degenerative spondylolisthesis, scoliosis, stenosis and degenerative disc disease.[4] Many of these conditions are associated with degeneration of the spine which often occurs at an early age and progresses as the patient gets older.[5] This degeneration is associated with the mobile joint segments that comprise the lumbar spine.

At each level of the spine there is a three joint complex that allows for motion of the segment while preserving stability. This three joint complex consists of the disc and two facet joints. While the disc is a fibrocartilagenous joint, the facet joints are synovial joints consisting of articular cartilage, synovial fluid and fibrous capsule. The nature of the degenerative process differs between the discs and facet joints. However, due to their close relationship and function, changes in one joint will invariably affect the remaining two. It has been shown that changes to the disc structure are accompanied by facet osteoarthritis.[6] The two lowest motion segments of the lumbar spine are most affected by this degeneration process with disc degeneration and facet osteoarthritis increasing with age.[7,8,9] The degeneration of the motion segment leads to abnormal motion, instability and joint collapse. Eventually this can lead to spondylolisthesis due to asymmetric alignment of the facets with associated facet osteoarthritis and stenosis that contributes to increased pain and loss of function.

Facet joint osteoarthritis due to wear and motion is characterized by facet hypertrophy, thickening of the joint and osteophyte formation resulting in lateral, lateral recess and/or central canal stenosis. Mooney and Robertson demonstrated that the facet joint contributed to pain through the use of intra-articular facet injections.[10] It is estimated that 15-40% of low back pain is attributed to the facet joint.[11,12] Treatments for facet generated problems include decompression, facetectomy and posterior fusion. Although these treatments address the symptoms of pain, they may result in further destabilization and in the case of fusion loss of motion. It has also been reported that fusion with loss of motion transfers stresses to the adjacent motion segments creating additional degeneration and instability in these adjacent segments.[13, 14]

Historically, degeneration and instability of the joint and associated stenosis has been addressed with fusion. There could be a meaningful patient benefit by replacing the current practice of posterior fusion with facet arthroplasty. This approach involves the replacement of the degenerated facet with an articulating joint while resolving the associated stenosis. A facet arthroplasty system allows for an anatomic reconstruction of the facet joint after decompression and removal of the degenerated facet. Like the original facet joint, the replacement implant is designed to reproduce facet motion while restoring normal stability and kinematics. Instrumentation allows for precise and reproducible placement of the inferior and superior articulating implants. The cobalt chrome articulating components are aligned and secured at their natural anatomical position on the pedicle.

The ACADIA® Facet Replacement System (AFRS) has been designed on the principals that have allowed other total joint arthroplasty procedures to provide significant patient benefits. These guiding principals include:

- Anatomically-based implant design
- Reproducible surgical technique
- Elimination of pain

Globus Medical acquired the ACADIA® Facet Replacement System from Facet Solutions, Inc., in January 2011, and is now the sponsor of the associated Investigational Device Exemption (IDE) clinical trial.

1.2 Device Name

The device under clinical investigation is the ACADIA® Facet Replacement System (AFRS).

1.3 Purpose

The purpose of this study is to evaluate the safety and effectiveness of the AFRS in patients with lateral, lateral recess and/or central canal stenosis due to facet degeneration at a single level from L3 to S1 who require a lumbar decompression and facetectomy compared to an instrumented posterolateral fusion control group. Safety of the AFRS device will be evaluated by the incidence, severity and device or procedure relatedness of all adverse events over the 24 month assessment period as compared to the control group. Effectiveness of the AFRS will be based on the improvement in symptom-related questionnaire scores, function, and neurological status.

1.4 Intended Use

The AFRS device is intended for use in patients with acquired degenerative lateral, lateral recess and/or central canal stenosis at a single level from L3 to S1 that require decompression and facetectomy and have failed to improve with at least six cumulative months of conservative treatment.

Acquired Degenerative Stenosis is defined as a narrowing of the lateral, lateral recess and/or central canal resulting in compression of the thecal sac and/or cauda equina, nerve root impingement by either osseous or non-osseous elements or evidence of hypertrophic facets with encroachment into the central canal or lateral recess at the involved level as determined by MRI, CT scan, plain film or myelography.

In addition, patients should be candidates for, and willing to undergo, an instrumented posterolaterol fusion control procedure for the treatment of their acquired degenerative stenosis.

1.5 Study Objectives

The primary objective of this study is to evaluate the safety and effectiveness of the AFRS device through 24 postoperative months compared to an instrumented posterolateral fusion procedure.

More specifically, the primary study objective is to demonstrate that patient success, evaluated at 24 months in patients treated with the investigational device, is not inferior to subject success at 24 months in patients treated with the control procedure, where patient success is based on the following defined measures: The Zurich Claudication Questionnaire (ZCQ), neurological deficit, and the need for subsequent surgical intervention (at the level of treatment) and/or device removal and absence of serious, device-related adverse events.

Patients will also be evaluated during the course of the study for all adverse events and surgical interventions, and the relationship of these events and interventions to the investigational device. All adverse events and surgical interventions will be tabulated and reported for each assessment time period.

3.0 STUDY DESIGN AND METHODOLOGY

3.1 Study Design

The pivotal evaluation of the AFRS investigational device will incorporate a multi-center, prospective, randomized, and concurrently controlled study design. Up to 30 sites will enroll and treat a minimum of 300 patients and a maximum of 750 patients into the study. In addition, up to 60 training cases (two per clinical site) may be completed by participating investigators, at the discretion of the Sponsor and participating site clinicians.

The investigational group will consist of at least 200 patients who receive the AFRS device. The control group will consist of at least 100 patients who will receive an instrumented posterolateral fusion. This number is based upon the sample size required to provide reasonable assurance of safety and effectiveness using the concurrent control and allowing for 15 percent loss to follow-up. The patients will be allocated to treatment assignment using a 2:1 randomization scheme.

The outcome measures in this study will include the following: the SF-36 questionnaire, the ZCQ, the ODI, a neurological assessment, a symptomatic pain assessment, as measured with the VAS Index, a patient satisfaction questionnaire, and an independent radiological assessment. In addition, outcome measures will be included to support potential reimbursement with healthcare providers. Patients in both treatment groups will be followed for 24 months postoperatively.

3.2 Study Scope

3.2.1 Participating Institutions

The pivotal trial will utilize a maximum of 30 clinical sites. A list of participating institutions will be provided semi-annually to the FDA as required by regulations.

3.2.2 Patient Population

The AFRS Study will include patients as specified in the Inclusion/Exclusion criteria. Study patients will have lateral, lateral recess and/or central stenosis at a single level from L3 to S1 requiring decompression and facetectomy. Detailed enrollment criteria can be found in the Patient Selection section of this Protocol.

Patients will receive either the investigational or control treatment, using a posterior approach through a midline incision to treat lateral, lateral recess and/or central canal stenosis. All patients will receive a decompression and complete facetectomy. The operative level will receive either the test or control treatment. Up to two adjacent additional levels may be treated through decompression as required to treat stenosis that does not result in complete facetectomy or fusion.

Patients randomized into the investigational group will receive the AFRS device. Those randomized to the control group will receive an instrumented posterolateral fusion.

If the assigned device cannot be placed in the patient during the surgical procedure, this patient will be considered a treatment failure. This patient should receive treatment at the discretion of the principal investigator and must be followed per the protocol through hospital discharge and/or the resolution of any procedure-related adverse events that have occurred.

3.3 Study Duration

It is anticipated that the overall duration of the pivotal phase of the AFRS study will be approximately 8 years. This estimate is based upon a projected patient enrollment period of 4-5 years, including the period of time (~2 years) under the previous sponsor, Facet Solutions. Follow-up visits will occur for the subsequent 24 months while all patients reach the 24 month postoperative time point, with data analysis and report generation accounting for an additional 4-6 months. The follow-up period may increase up to 10 years as needed to address postmarketing studies that may be required by the FDA during the approval process.

3.4 Control Procedure

Upon completion of the decompression procedure, patients randomized to the control procedure will undergo an instrumented posterolateral fusion (PLF), Autograft bone recovered from the decompression procedure and/or the iliac crest, if necessary, will be used to support the fusion procedure. The autograft will be supported with allograft bone, including demineralized bone matrix, as needed based on the Investigator's determination of required volume. The use of bone morphogenetic protein (BMP) will be prohibited.

3.5 Study Endpoints

3.5.1 Primary Endpoint

The primary study endpoint for this study is individual patient success at 24 months. Individual patient success will be defined as follows and each component of the primary endpoint will be adjudicated by the Clinical Event Committee:

- Improvements in the ZCQ score by a minimum decrease of 0.5 versus baseline for both Symptom Severity (SS) and Physical Function (PF) scores.
- Maintenance or improvement in neurological outcome at 24 months.
- No subsequent surgical intervention at the level of treatment (including device failures requiring revision, removal, re-operation and supplemental fixation).
- No serious device-related adverse events (see paragraph below.)

[redacted]

4.0 PATIENT SELECTION AND ENROLLMENT

All patients presenting with acquired degenerative lateral, lateral recess and/or central canal stenosis at a single level from L3 to S1 who require decompression and facetectomy and have failed to improve with at least six months of conservative treatment are potential study candidates and will be approached for consent prior to any data collection by a member of the institution's research team. A screening and enrollment log will be provided to study sites to maintain a cumulative log of all screened patients.

Every effort will be made to establish eligibility of the participants prior to enrollment. Only patients who meet all eligibility criteria and have signed an IRB/IEC approved consent form are considered to be enrolled in the study. Patients who are consented but not randomized or randomized but are withdrawn prior to initiation of surgical procedures are considered a screen failure for this study. Reasons for screening failure will be documented on the site screening log. All treated patients will be evaluated, as defined by protocol through 24 months, and annually thereafter as required by FDA.

Patients may not be enrolled in the AFRS study without first granting their consent. No study specified procedures may be completed until patient has signed an approved Informed Consent form. The informed consent process is accomplished by providing the patient with a copy of and allowing the patient adequate time to review, the Informed Consent Form. The contents of this form are discussed by the participating clinical trial site staff with the patient, while allowing adequate time for questions. Patients indicate they are willing to participate in the study, by signing and dating the site's current IRB/IEC approved Informed Consent form.

A patient should not sign the Informed Consent Form if s/he is not willing to accept either the investigational or control treatment as established by the randomization process. Following consent, the patient will be randomized into either the AFRS (investigational) or posterolateral fusion (control) group.

All patients screened for this study should be recorded but only consented patients will receive a study number. All consented patients will be assigned a unique patient number where the first two digits represent the investigative site and the last three digits represent the patient number (e.g. 01-001 represents the first consented patient at site 01). Patients are considered enrolled only after they have signed the informed consent and met all eligibility requirements. Patients will be identified by this assigned number for the duration of their participation in the study.

Randomization will be performed on a per-patient basis, blocked by center to maintain a 2:1 mix of patients in the investigational and control groups at each institution. Randomization must occur prior to surgery and only after the patient provides written informed consent, completes all baseline procedures and meets the requirements of the study inclusion and exclusion criteria. Sites are reminded that enough time should remain between randomization and surgery to allow sufficient time for insurance authorization.

As specified earlier, each Investigational Site may complete up to two training cases in advance of randomizing patients into the study. These cases provide an opportunity for the Investigator to become familiar with the technique and instrumentation. Training cases will not be randomized but will be followed per the protocol and analyzed as a separate population.

Any patient enrolled , whether randomized or not, will be assigned a patient number. The reason for failure to randomize or failure to treat will be recorded in his/her study records. For enrolled (consented & eligible) patients who **are not** treated, the following information will be recorded in the patient's study file:

- Demographic information
- Inclusion/exclusion criteria
- Reason for failure to randomize

If a randomized patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomization plan until a sufficient number of patients have been treated per each group.

All patients treated in the study are considered to be "follow-up eligible" and will be required to adhere to the follow-up schedule as outlined in **Appendix 1**. Patients that withdraw consent after receiving treatment will not be required to undergo follow-up after withdrawal; however, these patients will still be considered part of the patient cohort. No patient will be removed from the study unless the patient has withdrawn his or her consent before treatment or no treatment was ever attempted.

4.1 Inclusion/Exclusion Criteria

Before entry into this study, each patient will be evaluated by the investigator to determine if s/he satisfies the eligibility criteria for this trial. To be eligible, the patient must meet all of the characteristics in the "Inclusion Criteria" and none of the characteristics listed in the "Exclusion Criteria" as listed below.

4.1.1 Inclusion Criteria

- 21-85 years of age and skeletally mature;
- Undergone at least six cumulative months of conservative treatment prior to surgery including any of the following: medications, NSAIDs, physical therapy, bracing, chiropractic manipulation, modified activities of daily living, epidural injections, facet block injections;
- Lateral, lateral recess and/or central canal stenosis as demonstrated by compression of the thecal sac and/or cauda equina, nerve root impingement by either osseous or non-osseous elements or evidence of hypertrophic facets with encroachment into the central canal or lateral recess at the involved level as determined by MRI, CT scan, plain film or myelography;
- Disc height measuring $\geq$ 4 mm at the operative level;
- Persistent leg, thigh and/or buttock symptoms, including pain, numbness, burning or tingling with a minimum leg pain score of 40mm as measured with the VAS;

- Score greater than 2 on a scale of 1-5 on the ZCQ Symptom Severity Score
- Score greater than or equal to 2 on a scale of 1-4 on the ZCQ Physical Function Score;
- Candidate for a decompression with full facetectomy at the operative level;
- Candidate for an instrumented posterolateral fusion;
- Willing and able to comply with postoperative and routinely scheduled clinical and radiographic evaluations;
- Lives in the immediate area and has no plans to relocate to another geographic area before the completion of the study, or lives outside the immediate area and is willing to comply with scheduled postoperative visits with a designated physician;
- Has signed a patient informed consent, specific to this study.

4.1.2 Exclusion Criteria

- Previous surgical procedure at the operative or adjacent level except for one of the following: micro-discectomy, laminectomy, lamino/foraminotomy, rhizotomy, IDET, and/or interspinous spacer;
- Previous lumbar fusion or disc replacement procedure;
- Osteoporosis as defined by Simple Calculated Osteoporosis Risk Estimation (SCORE) screening questionnaire score of 6 or greater and DEXA bone density measured T-score ≤ -2.0;
- Greater than Grade I spondylolisthesis or retrolithesis, as defined by the Meyerding Grading Classification, at the operative level;
- Spondylolisthesis any grade, as defined by the Meyerding Grading Classification at levels other than at the operative level;
- Scoliosis of the lumbar spine (defined as more than 11° Cobb angle), as indicated by plain X-ray films;
- Primary diagnosis of discogenic back pain due to torn, herniated, inflamed or irritated disc or other pathology where the patient exhibits axial back pain from degenerative disc disease;
- Acute traumatic pars fracture at the operative or adjacent level vertebral body;
- Spinal stenosis at more than three lumbar segments;
- Experienced acute trauma to the lumbar spine within the last 24 months;
- Active infection at the operative level, or a systemic infection including prior or pending treatment for HIV or Hepatitis C;
- Physically or mentally compromised (*i.e.*, being currently treated for a psychiatric disorder, senile dementia, Alzheimer's disease, presence of alcohol or substance abuse) in a manner that would compromise his or her ability to participate in the clinical study;
- Diagnosed systemic disease (*i.e.*, Paget's disease, muscular sclerosis, amyotrophic lateral sclerosis (ALS),renal osteodystrophy, metastasis to vertebrae, Lupus, or ankylosing spondylosis) that may affect the patient's welfare or overall outcome of the research study;

- Immunologically suppressed or immunocompromised;
- Insulin-dependent diabetes mellitus (type I diabetes);
- Currently undergoing long-term steroid therapy (treated in the last 6 months with systemic corticosteroids);
- Metabolic bone disease (i.e., osteomalacia, and/or osteogenesis imperfecta);
- Is of child-bearing potential, and is either pregnant or interested in becoming pregnant during the duration of the study;
- Medically significant obesity as defined by a Body Mass Index (BMI) of > 40 kg/m^2. BMI = (weight in pounds × 703) ÷ (height in inches × height in inches);
- Active malignancy: a history of any invasive malignancy (except non-melanoma skin cancer), unless the patient has been treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 5 years;
- Known allergy to cobalt chromium or titanium;
- Used any investigational drug or device within the past 30 days;
- Pending litigation related to back pain or injury;
- Is a prisoner.

5.0 STUDY PROCEDURES

The AFRS device will be clinically evaluated utilizing a standardized protocol as described below. The protocol has been designed to minimize variations in patient selection, surgical technique, postoperative management, patient evaluation, and documentation of results. To further assure consistency, each investigator will be trained in all aspects of the protocol, including the surgical technique and appropriate documentation.

Study patients will be evaluated pre-operatively, postoperatively and upon discharge, and at 6-weeks, 3, 6, 12 and 24 months postoperatively. In addition, patient follow-up will be completed annually after the 24-month time point as required by the FDA. The evaluations to be completed at each study visit will include radiographic, pain, function and neurological assessments. A summary of the data collection requirements is presented in **Appendix 1**. Included in the summary is a list of acceptable time windows for patient follow-up to be completed at each study time point. A detailed description of the assessment to be performed at each study visit is provided below.

5.1 Screening/Pre-Procedure

Patients presenting with stenosis will potentially be eligible for participation in the study. Before being considered for enrollment into this clinical evaluation or receiving any study-specific diagnostic tests and/or questionnaires to further determine eligibility, the Informed Consent Form must be completed and signed by the patient.

Once an Informed Consent Form has been successfully completed, the patient will be evaluated for his or her ability to meet the inclusion and exclusion criteria. Only those individuals who meet all of the inclusion criteria and none of the exclusion criteria are to be enrolled in the study. A list of consented patients excluded from enrollment into this study, or considered patient screen failures will be maintained for each investigation site. The following screening procedures and baseline data are collected for all patients.

5.1.1 Patient History

Patient demographics and medical history will be completed by the physician or assigned medical personnel. Specific parameters include:

- Age
- Gender
- Height/weight
- Smoking status
- Work status
- Education level
- Duration of pain
- Concurrent health conditions
- Medication use
- Previous surgeries/treatments

- Previous conservative treatment modalities

The patient should demonstrate failure to improve with conservative, non-surgical treatment for a minimum period of six months. Conservative, non-surgical treatment options may include, but is not limited to, medications, NSAIDs, physical therapy, bracing, chiropractic manipulation, modified activities of daily living, epidural injections, facet block injections;

Those patients who are smokers will be advised that they need to stop smoking for a period of 6 weeks after the procedure in order to be eligible for study participation.

Female patients of childbearing potential must have a negative pregnancy test within 14 days prior to treatment and must agree to avoid pregnancy during the course of the study

For those patients that enter the study with a previous surgery, information is collected on the case report form to provide as much detail as possible on the nature of the surgery including type, date, parameters of bone or device removal or other information that may be useful in analyzing the procedure and its affect on the patient.

A comprehensive physical examination will be conducted at baseline and any abnormal findings will be recorded on the CRF. Physical examinations at follow-up visits will be symptom directed only.

5.1.2 MRI, CT Scan, Plain Film, Myelography

Radiographic methods will be completed pre-procedure to verify the presence of lateral, lateral recess and/or central canal stenosis per the criteria outlined in inclusion/exclusion section above. If a study candidate has received a CT scan or MRI of his/her spine within six months prior to study screening, the Investigator may use CT/MRI to verify study eligibility for this criteria.

5.1.3 DEXA Scan

Patients will be administered the Simple Calculated Osteoporosis Risk Estimation (SCORE) questionnaire. Those patients who receive a total score of 6 or greater will need to have a DEXA scan completed. Patients with a T-score equal to or less than (-) 2.0 will be excluded from the study. If a study candidate has received a DEXA scan of his/her spine within the previous six months of study screening, the Investigator may use the T-score results to determine study eligibility for this criteria.

5.1.4 Disc Height

Radiographic assessment of the disc height will be used to screen out patients with a compromised disc and potential degenerative disc disease. The operative-level disc height must be greater than or equal to 4.0 mm in order for patients to qualify for enrollment into the study. For the purposes of patient eligibility the determination of this measurement will be made by the Investigator.

5.1.5 Radiographic Assessment

The following radiographs will be taken during pre-procedure screening to establish a baseline for future follow up visits:

View	Position	Image Type
Lateral	Standing Neutral	Lateral
Lateral	Flexion-Extension	Flexion, Extension
AP	Standing Neutral	AP
AP	Lateral Bending	Left Lateral Bending, Right Lateral Bending

The radiographs will be independently evaluated for the following quantitative measurements at the operative and adjacent levels:

- Range of Motion: Calculated from the flexion-extension and lateral bending radiographs
- Intervertebral Translation: Calculated from the flexion-extension radiographs
- Disc Height: Calculated from the static lateral and AP radiographs.

The recommended radiographic protocol detailing the procedures is found in **Appendix 2**.

5.1.6 Function

A pre-operative assessment of function will be made to establish a baseline for comparison to postoperative results. Specifically, the patient will complete the ZCQ and ODI questionnaires in order to measure pain and function. These forms are completed by the patient only.

5.1.7 Neurological Assessment

A neurological assessment[15] will be completed and is performed by the physician or designee (as specified on the site delegation/ signature log). Whenever possible, every effort should be made to use the same individual to perform a patient neurological assessment for the duration of the study. Specific pre-operative neurological evaluation parameters include:

- Reflexes (patellar (L2, L3, L4) and Achilles tendon (S1)) will be measured (left and right) and recorded using a 3-point scale: 0 (absent, trace); 1 (normal) or 2 (hyperreflexic, clonus).

- Straight Leg Raising (SLR) (L4, L5) will be measured (left and right, sitting and supine) and recorded using a 2-point scale: 0 (0°-70° positive test) or 1 (70°+ negative test).

- Sensory Function will be measured by nerve root distribution using a light touch technique with results recorded using a 2-point scale: 0 (decreased, anesthetic or hyperesthetic) or 1 (normal). The following dermatomes will be evaluated based on level of use:

L1	Anterior Quadriceps
L2	Anterior Thigh
L3	Anterior Knee
L4	Medial Foot
L5	Dorsal Foot
S1	Lateral Foot

  A figure detailing the location of the required dermatomes is located in **Appendix 3**.

- Muscle Strength will be measured for individual muscle groups and recorded using a 5-point scale: 0 (No evidence of contractility), 1 (Slight contractility, no joint motion), 2 (Joint motion with gravity eliminated), 3 (Some joint motion against gravity), 4 (Full joint motion against gravity, some resistance) or 5 (Full joint motion against gravity, full resistance).

  The following muscles will be evaluated based on the level of use using the noted motor evaluations:

L1-L2	Iliopsoas	Hip Flexion
L2-L4	Quadriceps	Knee Extension
L4-L5	Anterior Tibial Group	Ankle Dorsal flexion
L4-S1	Gluteus Maximus	Hip Extension
L5	Hallucis Longus	Great Toe Dorsiflexion
L5-S1	Hamstrings	Knee Flexion
S1	Flexor Hallucis	Ankle Plantar Flexion

5.1.8 Pain

A pre-operative assessment of bilateral leg and back pain will be made to establish a baseline for comparison to postoperative results. Right leg, left leg and back pain will be evaluated by the patient using a 100 mm Visual Analog Scale (VAS). The VAS consists of three horizontal lines, one each for the right leg, left leg and back. The patient denotes his/her pain level by placing a vertical line along its length. To qualify for the study, one leg VAS score must be equal to or greater than 40 mm as measured and recorded by the clinical staff on the VAS questionnaire document.

5.1.9 Quality of Life

The patient's quality of life information will be captured using the SF-36 Quality of Life questionnaire. This questionnaire is to be completed by the patient.

5.2 Randomization Procedure

Patients will be randomly assigned on a two to one (2:1) basis to either the treatment or control group. Randomization will be stratified by clinical center and permuted block randomization will be performed within strata. The block size will be variable and randomly chosen from small multiples of 3. The randomization schedules for the study will be prepared in advance by the study statistician or designee. Investigational sites and the Sponsor will not have access to the randomization schedules.

Treatment assignments will be provided by the statistician for each site completed either by sealed envelopes or an electronic web-based program. If envelopes are used, they will be sealed and sequentially numbered with one envelope per patient. Once distributed to the sites, they will remain sealed until a prospective patient had passed all study criteria. The study coordinator or designee will open the envelope to determine treatment assignment prior to the procedure, allowing sufficient time for insurance authorization. The assignment card will be attached to the Case Report Form. Patient will be blinded to treatment until after the procedure.

Alternatively, a web-based randomization program may be utilized by sites where treatment assignment is made after verification of proper informed consent execution and study eligibility.

Any patient consented, whether randomized or not, will be assigned a patient number. The reason for failure to randomize or failure to treat will be recorded in his/her study records.

If a randomized patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomization plan until a sufficient number of patients have been treated for each group.

5.3 Operative Procedure

Following the surgery, details of the surgical procedure are documented including:

- Operative date, time, clinical site location, investigator performing surgery
- Treatment assigned, device used and traceability
- Vertebral levels treated, decompression performed, procedure and instrumentation time, blood loss
- Source of bone for fusion
- Antibiotics and/or deep vein thrombosis prophylaxis used pre-, intra-, and/or post-operatively, if applicable
- Intra-operative complications

Immediately following surgery, the patient is transported to the surgical recovery area and monitored according to the hospital/physician protocol for surgeries of this nature. The patient may be released from the recovery room to the nursing unit when s/he has met the

hospital's criteria for discharge from the recovery area. Immediate postoperative care will be dictated by the hospital or physician's standard care protocol regarding post-anesthesia recovery. Patients shall be encouraged to ambulate after surgery as soon as is medically reasonable.

Unforeseen events (findings or procedures) may occur during decompression/spinal preparation procedure(s) prior to implantation of the ACADIA® Facet Replacement System or Control System. These unforeseen events are those that are not planned as part of this surgery (eg, a drop in oxygen saturation intraoperatively, evidence of an acute myocardial infarction, allergic reaction to an antibiotic, etc). Unforeseen events that are emergent in nature should be recorded as AEs and the investigator should reassess the patient's suitability for continued participation in this study.

If an intraoperative decision is made to perform a procedure other than what was intended for study enrollment, the patient will be withdrawn from the study and will be followed for safety as a separate "Not Treated" cohort. If a randomized patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomization plan until a sufficient number of patients have been treated per each group.

5.4 Patient Discharge

Prior to discharge, patients are examined and evaluated for the presence of any adverse events that may have occurred between the operative procedure and discharge. Patient discharge from the hospital will be accomplished according to standard hospital/physician practice. Patients are eligible for discharge based on the following criteria:

- Patient is able to ambulate
- Surgical wound is confirmed as intact, with no signs of infection
- Patient bodily functions are active

Patient discharge from the hospital will be accomplished according to standard hospital/physician practice. Prior to discharge the patient may be fitted with a brace at the investigator's discretion. The brace will be removed at the 6-week follow up visit or earlier based on the Investigator's discretion.

The following data is collected at discharge:

- Static AP radiographs
- Static lateral radiographs
- Duration of hospital-stay and hospital discharge date
- Pain and antibiotic medication use
- Adverse events

Bone growth stimulators are not to be used during the course of this study. This study does not specify the use of prophylactic antibiotic medications. Medications may be administered at the discretion of the physician. After discharge, patients are not to receive

epidural spinal injections or nerve blocks for pain relief within six weeks of a scheduled study visit, as this will confound the collection of pain and function data.

Additionally, patients receiving post-procedure denervation procedures, at the index level, within the 24 month follow up evaluation period will be considered study failures.

Patients will be instructed to avoid smoking and use of systemic (IV, PO or transdermal patch) steroidal therapy during the first six weeks of post procedure bone healing and informed that this may affect their recovery. For the purposes of this study, use of inhalers containing steroids are not considered systemic use.

All patients will receive postoperative rehabilitation therapy as directed by the investigator with the objective or improving strength, flexibility and mechanics. This therapy will not be standardized as the program is required to be specific for each patient's need. Bending and lifting should be avoided during the first 6 week period postoperative period.

The discharge instructions contained in **Appendix 4** (or site equivalent) will be explained and provided to the patient upon hospital discharge.

5.6 Patient Follow-Up

Patient follow-up will be completed postoperatively; at hospital discharge, at 6 weeks and 3, 6, 12, and 24 months as outlined in the Assessment Schedule located in **Appendix 1.** After 24 months, patients will be evaluated annually, as required by FDA. The study assessments required at each follow-up visit are detailed below.

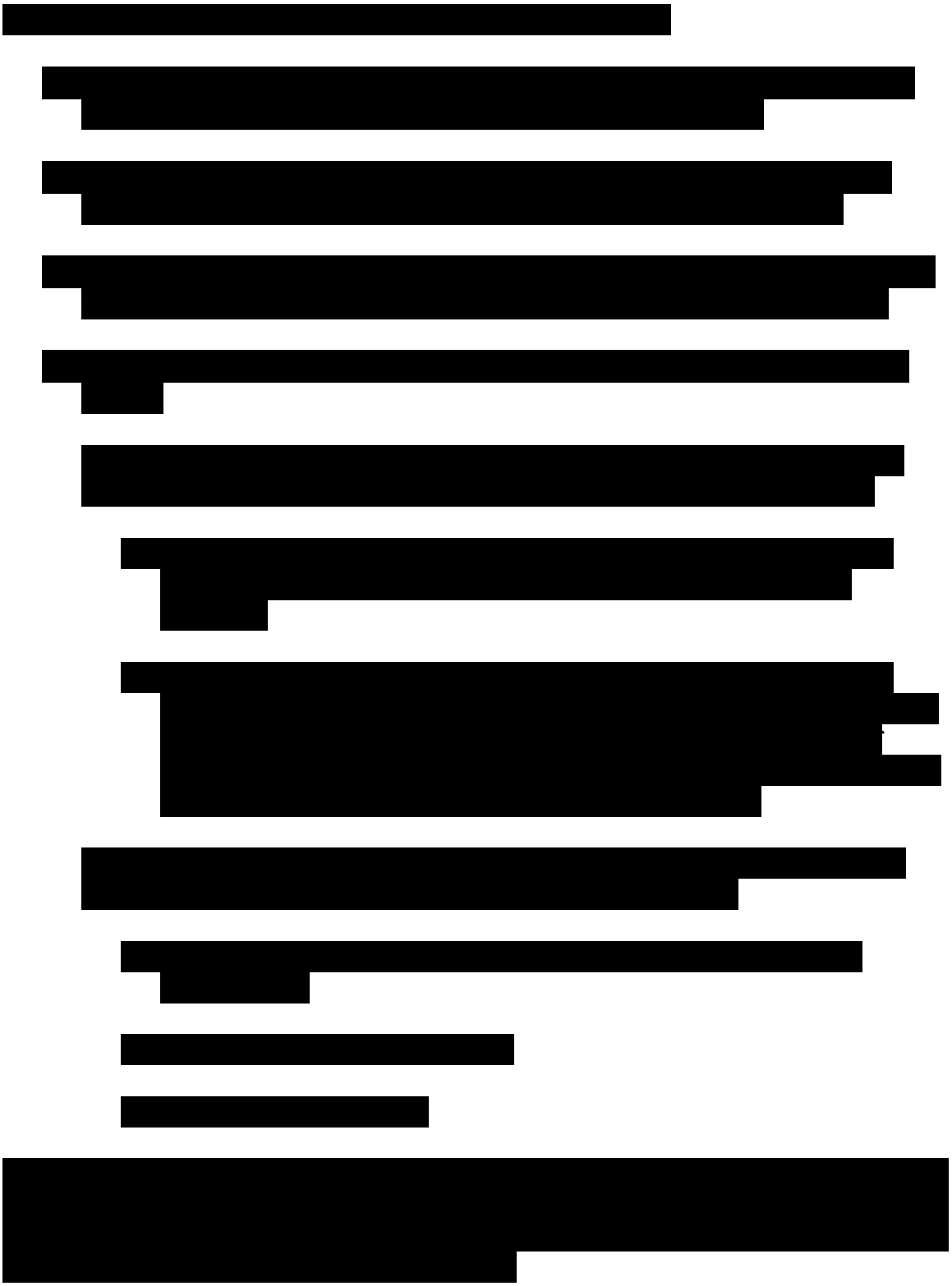
All questionnaires related to patient outcome will be completed at each visit independently by the patient prior to any clinical evaluations and will be administered by study personnel who are not healthcare providers directly associated with the study.

Patients who undergo removal, revision, or reoperation of, or supplemental fixation to, the investigational or control device will continue to be followed for safety and effectiveness outcome data.

5.6.1 Radiographic Assessment

The following radiographs will be taken during the follow-up visits. At the 6 week follow-up visit, only the standing neutral lateral and AP radiographs are taken. At the 3, 6, 12, 24 month time points, and annually as required by FDA, all listed radiographs are taken.

View	Position	Image Type
Lateral	Standing Neutral	Lateral
Lateral	Flexion-Extension	Flexion, Extension
AP	Standing Neutral	AP
AP	Lateral Bending	Left Lateral Bending, Right Lateral Bending



5.6.2 Function
The patient will complete the ODI and ZCQ Questionnaires for the purposes of measuring function. Both evaluations will be completed by the patient at their 6 week, 3, 6, 12 and 24 month follow-up visits, and annually as required by FDA.

5.6.3 Neurological Assessment
The neurological assessment will be completed and is performed by the physician or designee as specified on the site delegation/ signature log. Whenever possible, every effort should be made to use the same individual to perform a patient neurological assessment for the duration of the study. The specific postoperative neurological evaluation parameters are outlined in section 5.1.7 above. The evaluation will be completed at 6 weeks, 3, 6, 12 and 24 months, and annually as required by FDA. A decrease in any one of the measures compared to baseline will be considered an adverse event and should be documented on the appropriate CRF.

For the purposes of determining patient success for the primary endpoint, a successful neurological outcome is defined as: Maintenance or improvement in sensory, motor function, reflexes and muscle strength.

The results of this exam will be adjudicated by the CEC for the purposes of defining patient success.

5.6.4 Pain
Bilateral leg and back pain will be recorded by the patient and measured using the VAS Index. This evaluation will be completed by the patient at their 6 week, 3, 6, 12 and 24 month study follow-up visits, and annually as required by FDA.

5.6.5 Patient Satisfaction
Patient satisfaction with the procedure s/he received AFRS (investigational) or posterolateral fusion (control) will be assessed by the use of a brief satisfaction questionnaire. The questionnaire will be completed by the patient at 6 weeks, 3, 6, 12 and 24 months postoperatively, and annually as required by FDA.

5.6.6 Quality of Life
Quality of life indicators will be evaluated through the use of the SF-36 Quality of Life Questionnaire. This questionnaire will be administered to and completed by the patient at the 6 week, 3, 6, 12 and 24 months postoperative study visit time points, and annually as required by FDA.

5.6.7 Medication Use
Patient medication use, including pain injections, will be recorded and categorized by group. Medication evaluations will be completed at 6 weeks, 3, 6, 12 and 24 months, and annually as required by FDA.

Antibiotics and pain medications administered while the patient is in the recovery room after the spinal fusion surgery will not be recorded. Other medications, taken while in the recovery room, do not need to be recorded unless they are given for an AE. If a patient is medicated or receives other non-study therapy for an abnormal clinical laboratory evaluation (unless this is standard of care or for a pre-existing condition), it will be recorded as an AE. All pain medications and use of postoperative epidural injections and denervation procedures will be recorded. Patients receiving denervation procedures at the index level before the 24 month follow up visit will be considered study failures.

5.6.8 Return to Normal Activities/Work

Patient's ability to return to normal activities of daily living, utilization of rehabilitation and ability to return to work will be will be assessed by the use of a brief questionnaire. The questionnaire will be completed at 6 weeks, 3, 6, 12 and 24 months postoperatively and annually as required by FDA.

5.6.9 Adverse Events

Adverse events (AEs), including Serious Adverse Events (SAEs), will be captured intraoperatively and during all study follow-up visits. Adverse event definitions and reporting requirements are detailed in Section 6.0: Adverse Event Reporting. All reported AEs will be followed until resolution or completion of the study or postmarket study, as required by FDA.

5.6.10 Symptom Directed Physical Exam

A symptom directed physical examination will only be conducted during follow-up visits if a patient has reported signs or symptoms not previously identified during the previous study visit. Any abnormal findings will be recorded on the appropriate CRF.

5.7 Patient Discontinuation

All patients enrolled into the current study and who have undergone one of the study treatments, will be followed for 24 months postoperative and until all FDA requirements are met, potentially up to 10 years postoperative. Acceptable reasons for not evaluating a patient through the follow-up period include:

a) Patient Lost to Follow-Up: Unable to locate patient despite documented attempts to notify the patient via telephone and by certified mail. A patient will not be considered lost to follow-up until the last scheduled follow-up visit (24 month study time point).

b) Patient Request to Terminate: The patient requests to terminate his/her involvement in the study, therefore withdrawing his/her consent to participate in the study (the investigator must thoroughly document the reasons for termination).

c) Patient Death: If possible, an autopsy and/or death certificate should be obtained in order to document the cause of death.

If a patient discontinues from the study (regardless of the reason), the investigator will record the reason for withdrawal on the appropriate CRFs. Every effort shall be made to have discontinued patients (as appropriate) return for an "Early Termination Visit" to collected the required safety evaluations as detailed in the protocol.

6.0 ADVERSE EVENT REPORTING

6.1 Adverse Events

An Adverse Event (AE) is defined as any undesirable clinical occurrence in a patient, whether it is considered to be device-related or not. Adverse events may occur intraoperatively or postoperatively, and are reported on the Adverse Event Form (SA10). Conditions that existed or occurred prior to treatment in this study may only be considered adverse events if the patient's condition worsens or requires additional treatment.

AEs will be classified and tabulated by the following:

1. Their relationship to the investigational device (AFRS implant) or control (posterolateral fusion) procedure, depending on the patient's randomization into the trial;
2. Their relationship to the AFRS implant (investigational arm) or posterolateral fusion hardware (control arm) itself,
3. The severity of clinical event;
4. The action taken to treat the event; and
5. The outcome of the event.

Serious adverse events and deaths are considered adverse events, and will be listed and reported separately. Unanticipated adverse device effects will be recorded and reported in accordance with FDA regulations.

The determination of whether an adverse event is classified as a Serious Adverse Event (SAE) or Unanticipated Adverse Device Effect will be based on the definitions contained in this section, while also taking into account the clinical judgment of the investigator.

Adverse events will be coded by the Clinical Events Committee, based on the body system (e.g. gastrointestinal) and categorization of events appropriate to the condition.

6.1.1 Adverse Event Term

An adverse event term is determined by the investigator/site coordinator, based on the patient's symptom or condition, and is described on the form. Potential adverse events may include, but are not limited to, the following:

- Implant breakage;
- Component disarticulation;
- Component degradation;
- Implant displacement/dislocation;

- Pedicle disruption/failure;
- Allergic reaction to implant materials;
- Reaction to implant wear debris;Fracture/damage to pedicle;
- Fracture/damage to spinous process;
- Failure of bone to heal around implant;
- Bone resorption;
- Non-union, delayed union;
- Bursitis;
- Vessel damage/bleeding;
- Nausea and/or vomiting;
- Superficial infection;
- Deep wound infection;
- Hematoma at surgical site;
- Incisional pain;
- Pulmonary embolism;
- Stroke;
- Myocardial infarction;
- Coronary episode;
- Pneumonia;
- Kidney failure;
- Bowel obstruction
- Dural tear;
- Thrombosis;
- Nerve injury;
- Neuropathy
- Cauda equina syndrome;
- Transverse process fracture;
- Pseudomeningocele;
- Paralysis;
- Spinal fluid leakage;
- Spinal cord damage;
- Bone fracture;
- Spinous process fracture;
- Spondylosis;
- Heterotopic bone formation;
- Scoliosis;
- Kyphosis;
- Segmental instability;
- Decrease in neurological function;
- Worsening leg and/or back pain;
- Worsening pain associated with stenosis;
- Degeneration at adjacent level(s);

- Respiratory distress;
- Wound dehiscence;
- Wound swelling;
- Death

6.1.2 Relationship to Procedure

The relationship between an adverse event and the surgical procedure (investigational or control treatment) will be assessed on the basis of the following definitions:

- **Definitely Related:** Clear-cut temporal association and no other possible cause.

- **Probably Related:** Clear-cut temporal association and a potential alternative etiology that is not apparent.

- **Possibly Related:** Temporal association is less clear and other etiologies are also possible.

- **Probably Not Related:** Temporal association and the nature of the event is such that the surgical procedure is not likely to have had any association with the observed event (cause and effect relationship improbable but not impossible)

- **Definitely Not Related:** There is no temporal association and/or evidence exists that the event is definitely related to another etiology

6.1.3 Relationship to Device

The relationship between an adverse event and the implanted device (investigational or control) will be assessed on the basis of the following definitions:

- **Definitely Related:** Clear-cut temporal association and no other possible cause.

- **Probably Related:** Clear-cut temporal association and a potential alternative etiology that is not apparent.

- **Possibly Related:** Temporal association is less clear and other etiologies are also possible.

- **Probably Not Related:** Temporal association and the nature of the event is such that the device is not likely to have had any association with the observed event (cause and effect relationship improbable but not impossible)

- **Definitely Not Related:** There is no temporal association and/or evidence exists that the event is definitely related to another etiology

6.1.4 Severity

The severity of an adverse event will be assessed according to the World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects. The following definitions are used:

- **Mild (Grade 1):** The adverse event is noticeable to the patient but does not interfere with routine activity. The adverse event does not require implant removal.

- **Moderate (Grade 2):** The adverse event interferes with routine activity but responds to symptomatic therapy or rest. The adverse event does not require implant removal.

- **Severe (Grade 3):** The adverse event significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the adverse event may require removal of the implant.

- **Life-threatening (Grade 4):** The adverse event may require removal of the implant. The patient is at immediate risk of death.

6.1.5 Action Taken

Adverse events or treatment failures may lead to further actions as required to resolve the adverse event. The following actions will be identified for each adverse event:

- **None:** No further actions taken to resolve adverse event

- **Medication:** Medications are prescribed to treat the adverse event

- **Index Level Surgery:** A procedure at the original involved level in which all or part of the original implant configuration is modified or removed, with or without replacement, or additional surgical instrumentation is implanted. This includes decompression, surgical repair of a dural tear, wound debridement, irrigation and drainage at the original level. (Details are submitted on a Surgical Intervention Form SA11.)

- **Other:** Any additional procedure that is not one of the above categories

An index level surgery that is a revision, removal, reoperation, or supplemental fixation will be classified as a treatment "failure". Other index level surgery, such as debridement, irrigationa and drainage, and repair of a dural tear, will not be classified as a treatment "failure". All patients having secondary surgical procedures will be followed for the duration of the study for safety, in accordance with Section 5.6.

6.1.6 Outcome

The outcome of each adverse event will be identified as one of the following categories:

- **Resolved:** The adverse event has been resolved and is no longer continuing
- **Temporary Disability:** Disability that is short term and is not considered a permanent disability
- **Permanent Disability:** Disability that has been determined to be permanent and not temporary
- **Death:** Death of the patient due to the adverse event

6.2 Serious Adverse Events

Serious adverse events (SAEs) are defined as adverse events that are life-threatening, or ones that result in permanent impairment of a body function or permanent damage to a body structure, or they necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

An SAE is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Any Serious Adverse Event must be reported to Globus Medical, Inc. by the investigator within 24 hours of first learning about the event. An Adverse Event Case Report Form must be sent to Globus Medical within ten working days of knowledge of the event to the fax number listed on the case report form. The event is documented on the Adverse Event Case Report Form, with SAE denoted on the form. Participating Institutional Review Boards will be notified in accordance with their respective procedures.

6.3 Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life threatening problem or death caused by or associated with the device if that effect, problem or death **was not previously identified in nature, severity or degree of incidence in the investigational plan,** or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of subjects.

Any unanticipated adverse device effects must be reported to Globus Medical, Inc. within 24 hours of first learning about the event. A written report must be made to Globus Medical, Inc. within ten working days of knowledge of the event to the fax number listed

on the case report form. The event is documented on the Adverse Event Case Report Form, with UADE denoted on the form. The Institutional Review Board must also be notified within ten working days or sooner depending on their requirements.

Globus Medical, Inc. will also notify the appropriate regulatory agencies, and all participating investigators and Institutional Review Boards in writing within ten working days after learning of any unanticipated adverse device effects.

6.4 Patient Death

Patient death during the investigation must be reported by fax to Globus Medical, Inc. within 24 hours of the Investigator's knowledge of the death. Notification of death must include a brief statement of the relevant details and be signed by the Investigator or Co-Investigator. A copy of the death records, death certificate and an autopsy report (if performed) must be sent to Globus Medical, Inc.

6.5 Subsequent Surgical Interventions

All additional surgeries are to be reported, and are reported according to Section 6.1.5 Action Taken. Details are reported on the Surgical Intervention Form (SA11). Surgical procedures subsequent to the original surgery will be categorized as follows:

- A revision is a procedure that adjusts or in any way modifies or removes *part* the original implant configuration with or without replacement of a component, and may also include adjusting the position of the original configuration.

- A removal is a procedure where *all* of the original implant configuration is removed with or without replacement.

- A reoperation is any surgical procedure at the involved level that does not require removal, modification, or addition of any components of the system (excluding surgical repair of a dural tear, irrigation and drainage, or wound debridement).

- A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted at the involved level.

[redacted]

If an adverse tissue reaction is suspected before or during revision, report specific observations (operative site and device), any histological data (biopsy), MRI/CT, and metal allergy data on SA11, in addition to the operative report and chart notes.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Analysis Populations

Primary Analysis Population:

The principal analysis of the primary and secondary endpoints will utilize the intent-to-treat (ITT) patient population. The ITT population will include all randomized subjects for whom surgery is attempted. Subjects for whom surgery is attempted but not successfully completed will be considered treatment failures. Randomized subjects in whom surgery is not attempted will be described in detail in a separate section of the study report.

Secondary Analysis Populations:

The primary and secondary objectives will be further analyzed using an as-treated (AT) analysis performed on all randomized subjects according to the treatment actually received.

The primary and secondary objectives will be further analyzed using a per protocol (PP) analysis performed on an evaluable patient population. The evaluable population will consist of all ITT subjects that: [1] meet critical study eligibility criteria and have no significant protocol deviations based on Clinical Events Committee assessment; [2] have the assigned procedure completed; and [3] completed the 24-month follow-up assessment.

Training Population:

This patient population will include all non-randomized AFRS treated patients enrolled during the pivotal phase of the trial as training cases at the site. A maximum of two patients per site for a total of 60 patients will be included in this cohort. Training cases will be described separately from randomized patients in the final study report and will be presented primarily using descriptive statistics. This patient population will be used to understand the learning curve in the use of the device by assessing the results of the Training cases relative to those obtained in the Treatment group arm of the randomized study.

An additional presentation of the safety data in which all of the patients treated with the AFRS device (non-randomized and randomized) are combined as one cohort and compared to the control group will be included.

8.2 Primary Objective

The primary objective is to establish that AFRS (treatment) is non-inferior to fusion (control) at 24 months as assessed by subject success. [redacted]

[redacted]

8.3 Randomization, Sample Size, and Analysis Plan

This study is designed to adaptively determine the proper sample size. Possible sample sizes are 300, 450, 600, and 750 (maximum). Randomization will follow a 2:1 (treatment:control) allocation ratio and be stratified by site, using a blocked randomization scheme with blocks of randomly varying sizes. Further details on the randomization process are provided in **Section 5.2**.

In addition to the planned interim analyses that will determine the sample size, there will be several interim analyses conducted for the purpose of possibly declaring an early win. The first of these will occur when 300 subjects have completed 2 years of follow-up. If the trial does not stop for success at that analysis, a second analysis will occur when 450 have completed 2 years of follow-up. If the trial does not stop for success at that analysis, a final analysis will occur when the entire enrolled cohort has completed 2 years. It is not necessary for the trial to have stopped enrollment in order for the interim "Early Win" analyses to occur. For example, the first Early Win analysis (when 300 have completed 2 years) will occur even if the trial is still enrolling (i.e., the sample size determination algorithm has not determined the final sample size). Of course, if the final sample size is 300, there can be only 1 Win analysis (when the full cohort has reached 2 years); if the final sample size is 450, there can be only 2 Win analyses (when 300 have reached 2 years and when the full cohort has reached 2 years).

The sample size determination analyses and the "Early Win" interim analyses are triggered by different circumstances (number enrolled versus number completing 2 years) and are expected to follow different analysis schedules (i.e., although it is possible, a sample size analysis and an early win analysis are unlikely to occur simultaneously).

Further details on this analysis plan are given below.

Determination of Non-Inferiority and Superiority ("Win" Analyses)

Interim "Win" analyses are scheduled to occur when 300 and 450 subjects have completed 2 years of follow-up. A final analysis will occur when the entire enrolled cohort has completed 2 years of follow-up. At each of these analyses, the probability of non-inferiority Pr($H_{\delta=0.15}$ | data) will be calculated, based on all observed data, including predicted 2-year outcomes for those subjects who have not reached 2 years.

Determination of Sample Size

The sample size is guided by a standard frequentist non-inferiority power analysis.

1 Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.

2 Hintze, J. (2004). NCSS and PASS, Number Cruncher Statistical Systems. Kaysville UT. www.ncss.com.

3 Jennison C and Turnbull BW, *Group Sequential Methods with Applications to Clinical Trials*. Boca Raton: Chapman & Hall, 2000, p 27, 30.

[redacted]

[redacted]

The sample size determination algorithm is thus defined as follows. When $N = N_i$ subjects are enrolled (N_i = 300, 450, 600), two predictive probabilities are calculated:

- PP_{win} = Pr(Eventual Win | Data, δ=0.10, $N=N_i$ is the final sample size)
- PP_{fut} = Pr(Eventual Win | Data, δ=0.15, N=750 is the final sample size)

If PP_{win} exceeds a suitably high threshold W_i, subject accrual will stop because final success looks probable even using δ=0.10. On the other hand, if PP_{fut} is less than a suitably low threshold F_i, subject accrual will stop and futility will be declared. If neither of these conditions obtains, enrollment will continue to the next larger sample size (450, 600, 750). Thresholds W_i and F_i are listed in **Table 8.3.1**. Further detail on the calculations of the predictive probabilities is given below under the heading "Predictions."

[redacted]

8.4 Predictions

Predicted values of 2-year outcomes for those subjects who have not reached 2 years will be based on the intermediate outcomes measured at 6 months and 12 months. 3 month data will not be used in any of the predictive modeling. During this time, patients are continuing the post-operative healing process and may not be appropriate for this purpose.

At the time point of an interim analysis, there will be 4 types of subjects: subjects with complete 2-year data; subjects with 1-year data but no 2-year data; subjects with 6-month data but no 1-year or 2-year data, and subjects who are have begun the study but do not yet have 6-month or 1-year data. For those with 6-month or 1-year interim data but no 2-year data, subjects will be considered to be one of the following:

a) successes (i.e., meet all the criteria to be treatment successes, except that this is measured at 6 months or 1 year rather than 2 years)
b) recoverable non-successes (i.e., do not meet the criteria to be successes, but it is still possible that they might become successes at 2 years)
c) failures (i.e., subjects who cannot meet the definition of success at 2 years because of an event such as a device removal or re-operation.)

Subjects without 2-year follow-up data will thus be considered to be in one of 14 states (7 for each treatment group). The 7 states are:

- no interim data
- success at 6 months
- recoverable non-success at 6 months
- failure at 6 months
- success at 1 year
- recoverable non-success at 1 year
- failure at 1 year

Interim failures can be imputed to be failures at 2 years, with certainty. For each of the remaining 10 states (5 for each treatment group), the probability of becoming a success at 2 years is modeled via a Beta (a,b) prior distribution which is updated to a Beta(a+S, b+F) distribution, based on the number S and F of subjects who went on from that state to become 2-year successes and failures, respectively. For example, if, in the treatment group at an interim analysis time point, 70 of 100 subjects with 2-year data are successes, and if 50 of the 70 two-year successes also met the definition of success at 1 year, then the transition probability from the 1-year success state to the 2-year success state will be modeled as Beta (a+50, b+20). At an interim analysis time point, any treatment-group subjects residing in the success-at-1-year-but-without-2-year-data state will have their 2-year outcome predicted on the basis of this Beta(a+50, b+20) distribution. **Figure 8.4.1** graphically depicts the various transitions for a generic treatment group (treatment or control). The numerical example above would apply to transition #2 in the figure.

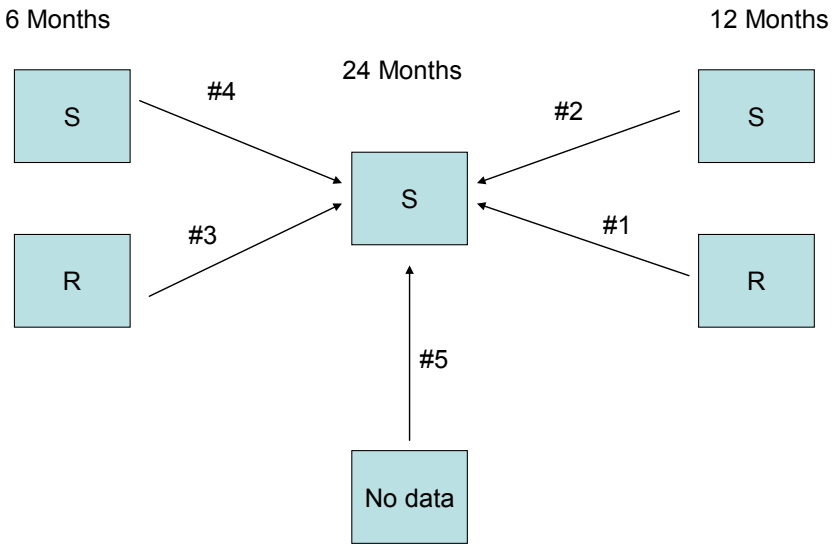


Figure 8.4.1. Graphical depiction of transitions from interim states (S = Success, R = Recoverable Non-Success, No Data) to 2-year Success. Each transition is assigned a Beta (a,b) prior distribution which is updated as data are gathered.

[redacted]

4 Lipscomb B, Ma G, Berry D, "Bayesian predictions of final outcomes: regulatory approval of a spinal implant," *Clinical Trials*, Vol. 2, No. 4, 325-333 (2005)

[redacted]

Prior Distributions for Transition Probabilities

The transitions of **Figure 8.4.1** are all assigned Beta(a,b) prior distributions. For "sample size looks," the values of a and b are tabulated in **Table 8.4.2** and graphically depicted in **Figure 8.4.2**. These values represent the trial sponsor's knowledge and belief about the relationship of the various interim states to the final state. At the times when sample size decisions must be made, the number of subjects who have completed 2 years (and thus provide information on the transition probabilities) will generally be insufficient to make good sample size decisions without including some additional information. Therefore, in all sample size determination analyses, the transitions are given informative priors, as tabulated in **Table 8.4.2**. However, for all "win looks," only flat priors ($a = b = 1$) for the transitions will be used.

Table 8.4.2 Parameters for Prior Distributions of the Transition Probabilities used in the determination of sample size. For all "win" analyses, *a* and *b* are set to 1.

		Transition #				
		1	**2**	**3**	**4**	**5**
Parameter	***a***	411.97	386.55	229.80	204.00	234.50
	b	644.36	29.09	153.20	51.00	100.50

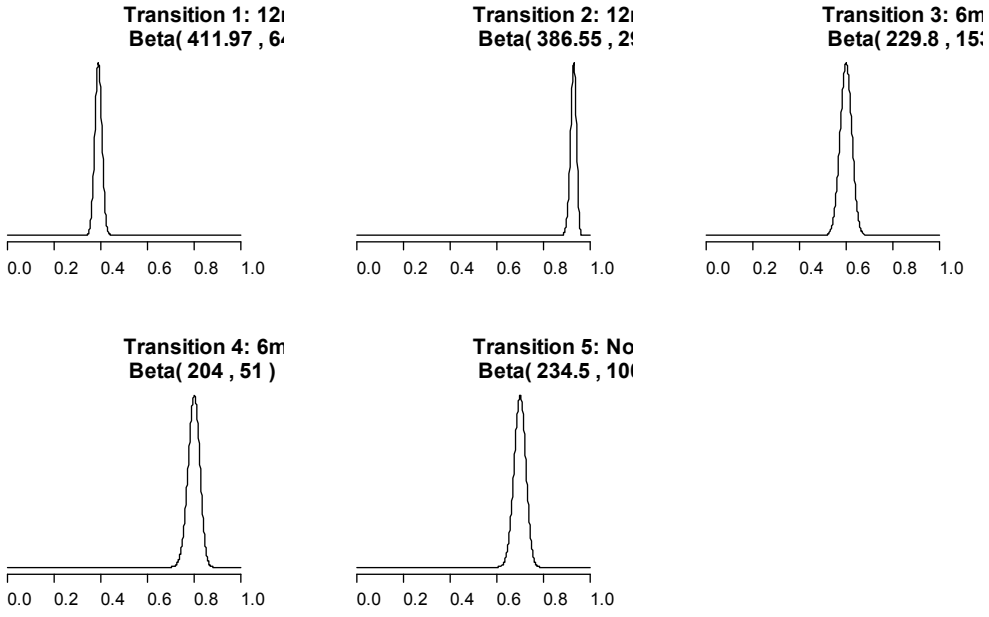


Figure 8.4.2 Prior Distributions of the Transition Probabilities used in the determination of sample size. For all "win" analyses, *a* and *b* are set to 1 for all transitions.

8.5 Operating Characteristics

The design described above has been subjected to intensive simulations in order to evaluate its anticipated performance in practice. In the simulation, the proportion of simulated trials that result in a declaration of non-inferiority is the estimated power when $P_t > P_c$ and the estimated type I error when $P_t \leq P_c$. The *estimated* operating characteristics are based on 10000 simulated trials per scenario, with predictions (in each of the 10000 trials) based on 5000 draws from each of the transition probability distributions. In order to generate data for this simulation, several assumptions about enrollment rates and correlations had to be made. These are described (and varied) in **Appendix 6**.

8.6 Missing Data and Sensitivity Analyses (Primary Objective)

By design, the analysis of the primary objective (at both the interim and final time points) will predict 2-year outcomes for any subjects without measured 2-year outcomes, based on transitions from interim states and the experience of those who went on from those states to provide complete 2-year data. This is true whether the missing 2-year outcomes are due to being enrolled later in the trial (as happens for many subjects at the interim analysis) or some other cause, such as loss to follow-up (which will likely apply at both the interim and final analyses). Several additional analyses are planned which will explore the sensitivity of the main conclusions to this prediction for subjects whose missing 2-year outcomes cannot be explained by simply being enrolled late (i.e., subjects who are known to be lost to follow-up or whose 2-year visit window has closed without a measured outcome). In these analyses and for such subjects, 2-year outcomes will be imputed according to the model described below.

As with the primary analysis, any such subject will be viewed as belonging to one of several states. These are the same states used in the primary analysis:

- no interim data
- success at 6 months
- recoverable non-success at 6 months
- failure at 6 months
- success at 1 year
- recoverable non-success at 1 year
- failure at 1 year

Interim failures can be imputed to be failures at 2 years, with certainty. For each of the remaining states, the probability of becoming a responder at 2 years will be modeled via a logistic formulation. Based on the number S and F of subjects who went on from that state to become 2-year successes and failures, respectively, a logistic regression of the following form will be fit:

$$\text{logit}(\, p \,) = \beta_0$$

where the parameter β_0 will be assigned a vague $N(0,10^2)$ distribution. The posterior distribution for β_0 will then be shifted by a biasing constant γ and will be back-transformed to the probability scale as:

$$p^* = \text{logit}^{-1}(\beta_{0+} \gamma)$$

The 2-year outcome for any subject belonging to this state but lost thereafter will be imputed based on this distribution of p^*. The case $\gamma = 0$ contains no bias and corresponds essentially to the primary analysis.

By varying γ, we can examine the impact of a biasing influence on the study results. The values $\gamma = -\infty$ and $\gamma = +\infty$ correspond to setting all such observations to be failures or successes, respectively. The impact of various values of γ will examined and presented in a sensitivity analysis, representing both positive and negative biases for the two groups.

[redacted]

8.7 Secondary Objectives

General Considerations for Secondary Objectives

While there are many pre-specified secondary objectives, only the first five are designated as objectives for which FDA-approved labeling claims may be sought, and only for the results measured at the 24-month time point. The rest of the secondary objectives have been pre-specified but are intended to be explanatory and supportive in nature, and not the basis of specific labeling claims.

As indicated in "Analysis Methods for Secondary Objectives," below, flat or diffuse prior distributions have been identified for all secondary objective analyses. For any hypothesis test, a posterior probability greater than 95% for any hypothesis will be considered to constitute evidence in favor of the hypothesis, in the same sense that a frequentist analysis would reject a null hypothesis when $p < 0.05$ and call it "statistically significant." However, for the subset of secondary objectives on which labeling claims may be sought, the posterior probability threshold for making the claim is somewhat more stringent. See the section entitled "Multiplicity Considerations," below.

Zurich Claudication Questionnaire (ZCQ) – Physical Function Domain (PF)

The ZCQ PF domain scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \mu_t - \mu_c < \delta$$

where μ_t and μ_c are the average PF scores in the treatment and control groups, respectively, and δ is the margin of non-inferiority. [redacted]

[redacted]

Zurich Claudication Questionnaire (ZCQ) – Symptom Severity Domain (SS)

The ZCQ SS domain scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \mu_t - \mu_c < \delta,$$

where μ_t and μ_c are the average SS scores in the treatment and control groups, respectively, and δ is the margin of non-inferiority. [redacted]

[redacted]

Back Pain on Visual Analog Scale (VAS)

The back pain VAS scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For inference, the relevant hypothesis is

$$H: \mu_t - \mu_c < 0,$$

where μ_t and μ_c are the average back pain VAS scores for subjects in the treatment and control groups, respectively. [redacted]

SF-36 Physical Composite Score (PCS)

The SF-36 PCS scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: p_t - p_c > -\delta,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who improve by at least 15% relative to baseline. [redacted]

SF-36 Mental Composite Score (MCS)

The SF-36 MCS scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: p_t - p_c > -\delta,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who improve by at least 15% relative to baseline. [redacted]

Radiographic Assessment of Flexion-Extension Range of Motion

Assessment of Flexion-Extension Range of Motion for subjects in each treatment group will be summarized at baseline and at each of the 3-, 6-, 12-, and 24-month time points. At 24 months, a statistical test will be conducted. For inference, the relevant hypothesis is

$$H: \mu_{T(24)} - \mu_{T(B)} > 0,$$

where $\mu_{T(24)}$ and $\mu_{T(B)}$ are the average flexion-extension range of motion scores for subjects in the treatment group at 24 months and baseline, respectively. [redacted]

Radiographic Success

Radiographic Success rate will be summarized for each treatment group at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: p_t - p_c > -\delta,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who achieve radiographic success. [redacted]

Neurological Assessment

A neurological assessment will be conducted at 3-, 6-, 12-, and 24-months, and summarized. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \ p_t - p_c > -\delta,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, whose neurological assessment status relative to baseline is maintained or improved. [redacted]

Leg Pain on Visual Analog Scale (VAS)

The leg pain VAS scores for subjects in each treatment group will be summarized separately by the more symptomatic and less symptomatic legs of each subject, as measured at baseline. For inference, the relevant hypothesis is

$$H: \ \mu_t - \mu_c < 0$$

where μ_t and μ_c are the average VAS scores for the more symptomatic legs (or less symptomatic legs, as appropriate) in the treatment and control groups, respectively. [redacted]

Oswestry Disability Index (ODI)

The ODI scores for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \mu_t - \mu_c < \delta$$

where μ_t and μ_c are the average ODI scores in the treatment and control groups, respectively. [redacted]

[redacted]

Adverse Events

All Adverse Events (AEs) will be tabulated and summarized as counts and percentages by treatment group. AEs will also be cross-tabulated separately according to treatment group and:

- Severity (Mild, Moderate, Severe)
- Seriousness (Serious, Non-serious)
- Device-Relatedness (Related, Not Related)
- Surgery-Relatedness (Related, Not Related)

In addition, the occurrence of any Unanticipated Adverse Device Effects (UADE) will be listed. The classification of severity, relatedness, and anticipated nature of AEs will be made by the Clinical Events Committee (CEC).

Summaries will include counts, percentages, and 95% Bayesian credible intervals for the difference in proportions between treatment groups. An analysis of safety outcomes which combines all AFRS treated patients (randomized and non-randomized) compared to control patients will also be performed. The statistical method for dichotomous outcomes (e.g., device-relatedness, surgery-relatedness) will be the Bayesian version of a comparison of proportions, described below. The statistical method for trichotomous outcomes (e.g., Severity) will be the Bayesian version of a comparison of polytomous outcomes, described below.

Surgical Revisions, Reoperations, Removals, and Supplemental Fixation

The incidence of a composite of surgical revisions, reoperations, removals, and supplemental fixation at the index level for subjects in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \ p_t - p_c < 0$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who experience one or more of the defining surgical events. The statistical method will be the Bayesian version of a comparison of proportions (with predictions), described below.

Radiographic Measurements

Radiographic measurements in each treatment group will be summarized at the 3-, 6-, 12-, and 24-month time points. Continuous radiographic endpoints are disc height, vertebral range of motion, and translation. For these, statistical summaries will include means, medians, standards of deviation, and 95% central Bayesian credible intervals for the means and mean differences over time between treatment groups, where appropriate. Dichotomous radiographic endpoints are fusion, device migration, and the presence of radiolucencies around the hardware and screws. For these, statistical summaries will include proportions and 95% Bayesian credible intervals for the proportions and, where appropriate, the difference in proportions between treatment groups.

Return to Normal Activities of Daily Life

The proportion of subjects able to return to "Most" or "All" of the activities of daily life will be summarized at the 3-, 6-, 12-, and 24-month time points. Statistical summaries will include proportions and 95% Bayesian credible intervals for the proportions and the difference in proportions between treatment groups. The statistical method will be the Bayesian version of a comparison of proportions, described below.

Return to Work

For subjects in each treatment group, the time from date of surgery to date of return to work will be computed and summarized with descriptive statistics. It is possible that some subjects will never return to work and be censored in this analysis, either at the end of the study or at the point of death or loss to follow-up, so the statistical technique will be the Bayesian Survival Analysis, described below. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

ZCQ Patient Satisfaction Domain Score

The ZCQ Patient Satisfaction domain scores will be summarized for subjects in each treatment group at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: \mu_t - \mu_c > 0$$

where μ_t and μ_c are the average satisfaction scores in the treatment and control groups, respectively. [redacted]

[redacted]

Narcotic Medication Usage

The proportions of subjects in each treatment group who are not on narcotic pain relieving medications and in whom an epidural injection, denervation procedure or other procedure for pain management has not been performed at the index level will be summarized at the 3-, 6-, 12-, and 24-month time points. For the 24-month time point, a statistical test will be conducted. The relevant hypothesis is

$$H: p_t - p_c > 0,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who are not taking narcotic medications and have not had pain management procedures at the index level. [redacted]

Length of Hospital Stay

The length of hospital stay will be calculated for each subject (with the day of surgery = Day 0) and summarized by treatment group. A statistical test of the difference in length of stay between treatment groups will be conducted. The relevant hypothesis is

$$H: \mu_t - \mu_c < 0$$

where μ_t and μ_c are the average stays in the treatment and control groups, respectively. It is anticipated that the distribution of hospital stays will be somewhat skewed, so the data will be ranked and the statistical method will be the Bayesian version of the Wilcoxon Rank-Sum test, described below. If a subject should die in hospital before being discharged, that subject will be assigned a length of stay that is 1 day greater than the maximum observed length of stay for any patient.

Duration of Procedure

The duration of the procedure will be summarized for the treatment and control groups. Statistical summaries will include means, medians, and standards of deviation, as well as 95% credible intervals for μ_t, μ_c, and $(\mu_t - \mu_c)$. A statistical test will be conducted on the hypothesis

$$H: \mu_t - \mu_c < 0$$

where μ_t and μ_c are the average procedure durations in the treatment and control groups, respectively. The statistical method will be the Bayesian version of a t-test, described below.

Instrumentation Time

The portion of the procedure time that is due to Instrumentation Time will be summarized for the treatment and control groups. Statistical summaries will include means, medians, and standards of deviation, as well as 95% credible intervals for μ_t,, μ_c, and $(\mu_t - \mu_c)$. A statistical test will be conducted on the hypothesis

$$H: \mu_t - \mu_c < 0,$$

where μ_t and μ_c are the average instrumentation times in the treatment and control groups, respectively. The statistical method will be the Bayesian version of a t-test, described below.

Procedural Blood Loss

The blood lost by subjects during the implant procedure will be summarized for the treatment and control groups. Statistical summaries will include means, medians, and standards of deviation, as well as 95% credible intervals for μ_t,, μ_c, and $(\mu_t - \mu_c)$. A statistical test will be conducted on the hypothesis

$$H: \ \mu_t - \mu_c < 0$$

where μ_t and μ_c are the average blood loss in the treatment and control groups, respectively. The statistical method will be the Bayesian version of a t-test, described below.

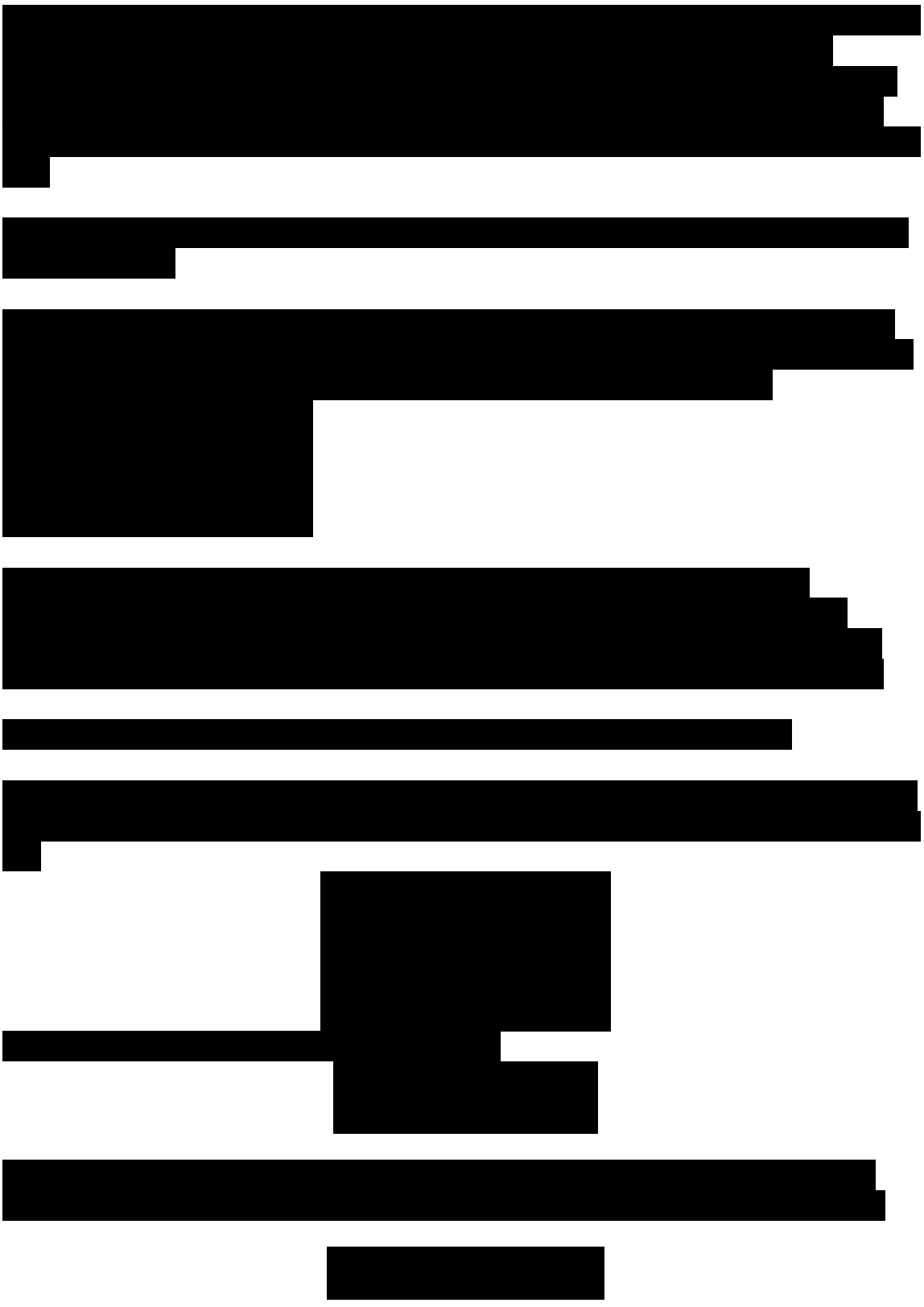
Rehabilitation Utilization

The proportions of subjects in each treatment group who utilize rehabilitation therapy will be summarized at the 3-, 6-, 12-, and 24-month time points. A subject will be considered to have used rehabilitation therapy at 6 months if he/she has used rehabilitation therapy at any time between the 3-month and the 6-month visits, and similar for each of the other time points. A statistical test will be conducted for each time point. The relevant hypothesis is

$$H: \ p_t - p_c < 0,$$

where p_t and p_c are the proportions of subjects in the treatment and control groups, respectively, who have utilized rehabilitation therapy since the last (surgery to 3 months, 3 months to 6 months, 6 months to 12 months, 12 months to 24 months) follow-up visit. The posterior probability of superiority Pr(H | data) will be reported. The statistical method will be the Bayesian version of a comparison of proportions, described below.

[redacted]



[redacted]

8.9 Poolability Analyses

To evaluate differences among sites in the study, summary tables by site will be presented and compared for important baseline variables, including demographics and medical history, baseline clinical variables, and procedure variables, as well as for the primary and secondary endpoint variables. Centers with fewer than seven participants will be pooled. Continuous variables will be presented by site in terms of percentiles (e.g., median, 25th and 75th percentile). For categorical parameters, data will be summarized by site using relative frequencies.

Comparisons will be made across sites for selected baseline variables. Continuous data will be compared across sites using a one-way analysis of variance, with a term for site. A two-factor ANOVA with treatment group and site as factors will be used to assess differences among sites and site by treatment interactions. Dichotomous data will be similarly analyzed via logistic regression analysis. If variables are observed to differ by study site, that variable and/or study site may be identified for special consideration in subsequent analyses.

The site effect will be further examined in a multivariable analysis to determine if site is independently associated with outcome. Tests for differences in rates of the primary outcome between treatment groups across sites will be performed using a logistic regression model with terms for sites, treatment assignment, and site-by-treatment interaction. If an association between center and treatment effect is identified, center differences will be further evaluated by assessing the endpoint with and without the center(s) for which the differences are observed, so that the impact of the center(s) can be assessed.

A similar evaluation of poolability will be undertaken for the following subgroups: 1) anatomical stenosis location (lateral, lateral recess or central), 2) number of levels requiring decompression, 3) presence or absence of spondylolisthesis at either the treatment or adjacent level, 4) smoking status during the study..

9.0 RISK/BENEFIT ANALYSIS

There are certain risks associated with the use of the AFRS device, including risks that are associated with any surgical procedure, risks that are generally associated with spinal intervention procedures and risks that are unique to the use of a Facet Arthroplasty Implant. Below is a detailed explanation of these potential risks and the means by which they may be minimized, as well as a justification for conducting the study.

9.1 Surgical Risks

There are risks related to any surgical procedure as well as procedures specific to spinal intervention. Surgical risks associated with this procedure include: vessel damage/bleeding; superficial infection; deep wound infection; hematoma at surgical site; incisional pain; pulmonary embolism; stroke; myocardial infarction; coronary episode; pneumonia; kidney failure; bowel obstruction; dural tear; thrombosis; nerve injury; cauda equina syndrome; transverse process fracture; pseudomeningocele; paralysis; spinal fluid leakage; spinal cord damage; bone fracture; spinous process fracture; spondylosis; heterotopic bone formation; scoliosis; kyphosis; segmental instability; decrease in neurological function; worsening back pain; worsening pain associated with stenosis; respiratory distress; wound dehiscence; wound swelling.

It is expected that the risks and complication rates strictly associated with the procedure would be similar to those associated with other posterior fixation procedures.

9.2 Implant Risks

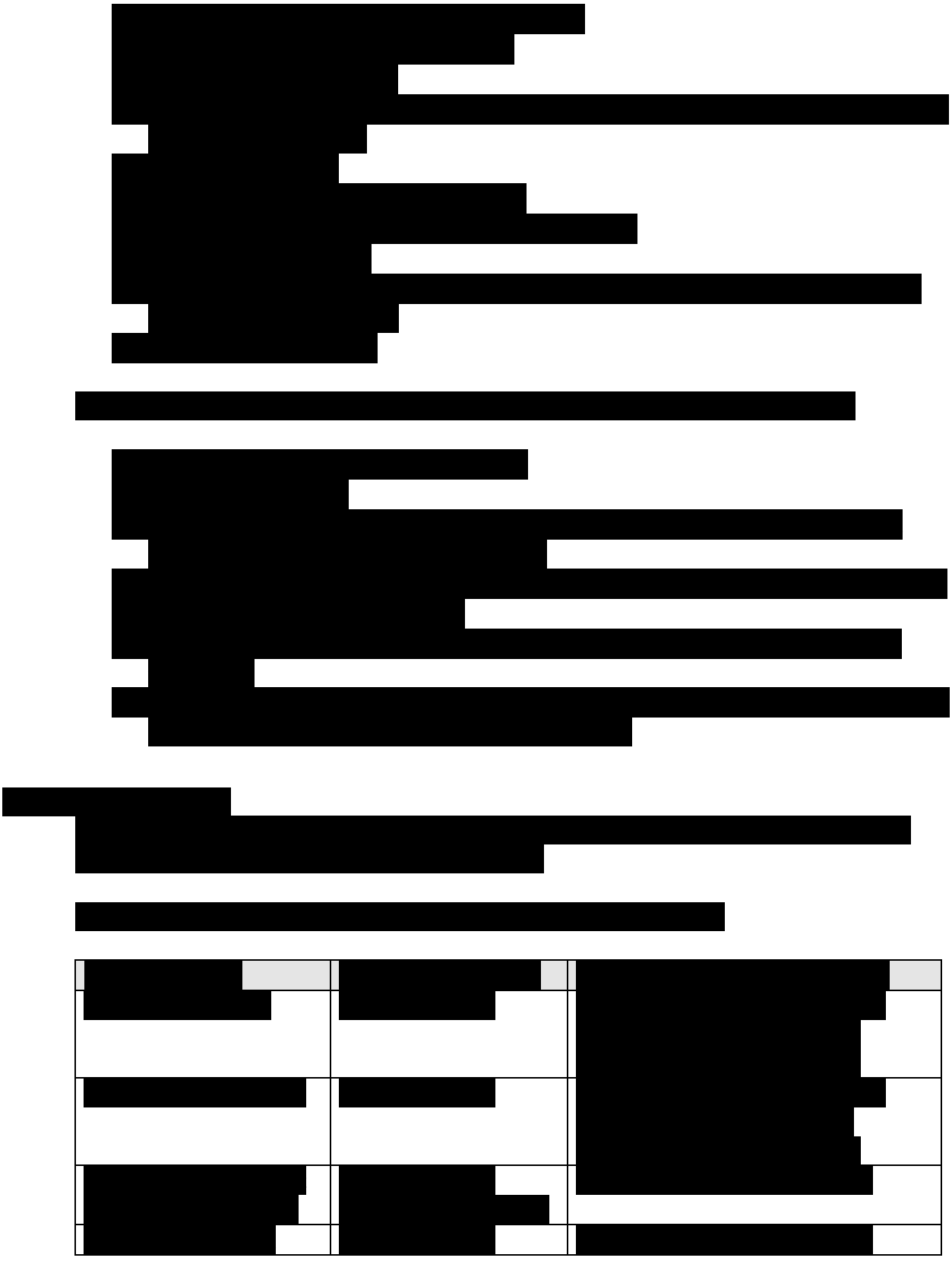
In addition to the risks listed above, the AFRS implant may be associated with unique risks associated with its instrumentation, implant design and the use of cobalt chrome and Hydroxyapatite materials in the implant. These risks include implant breakage; component disarticulation; component degradation; implant displacement; pedicle disruption/failure; allergic reaction to implant materials; and reaction to implant wear debris.

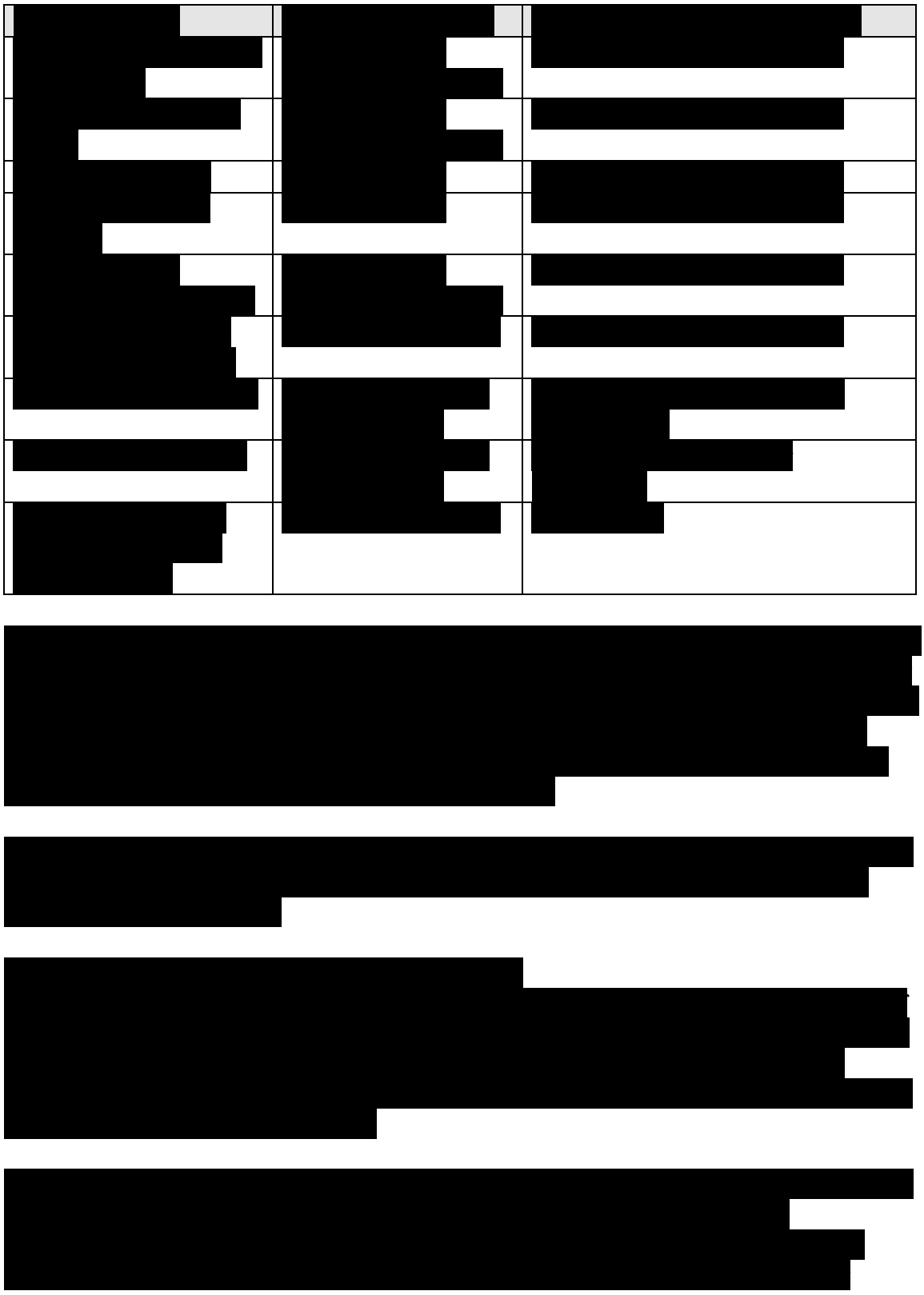
9.4 Justification for Investigation

Although there are risks associated with the AFRS, many of these risks are similar to those seen with other spinal devices that are implanted through a posterior approach. From a procedural standpoint, these devices have shown a satisfactory history of clinical use. In addition, appropriate steps have been taken to minimize the risks associated with the device design and materials. A successful Facet Arthroplasty procedure can enable patients to avoid fusion of the facets which is currently the typical treatment for stenosis of this nature. This procedure and device potentially allows patients to resume near-normal level activity, whereas allowing further disease progression can result in worsening disability.

Furthermore, the Facet Arthroplasty Implant offers the patient the potential ability to maintain motion and stability at the facet joint that otherwise would be lost as a result of a posterior fusion procedure and is an advantage over existing spinal treatments.

As noted above, there are substantial potential benefits associated with the AFRS and the risks associated with the procedure have been identified and minimized where possible. Thus, the balance of potential risks and benefits associated with the Facet Arthroplasty Implant warrants further clinical research and justifies this investigation.



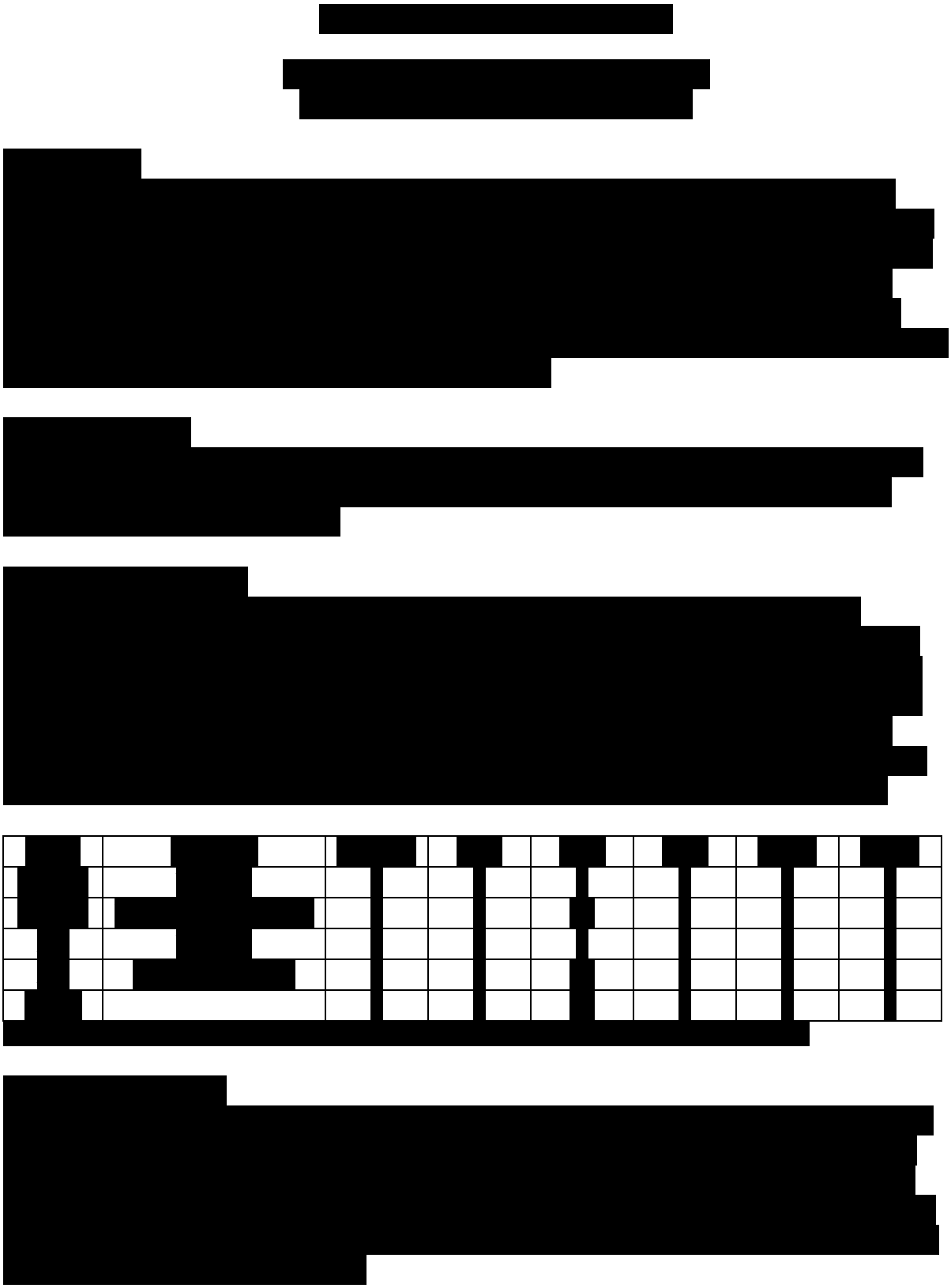


[redacted]

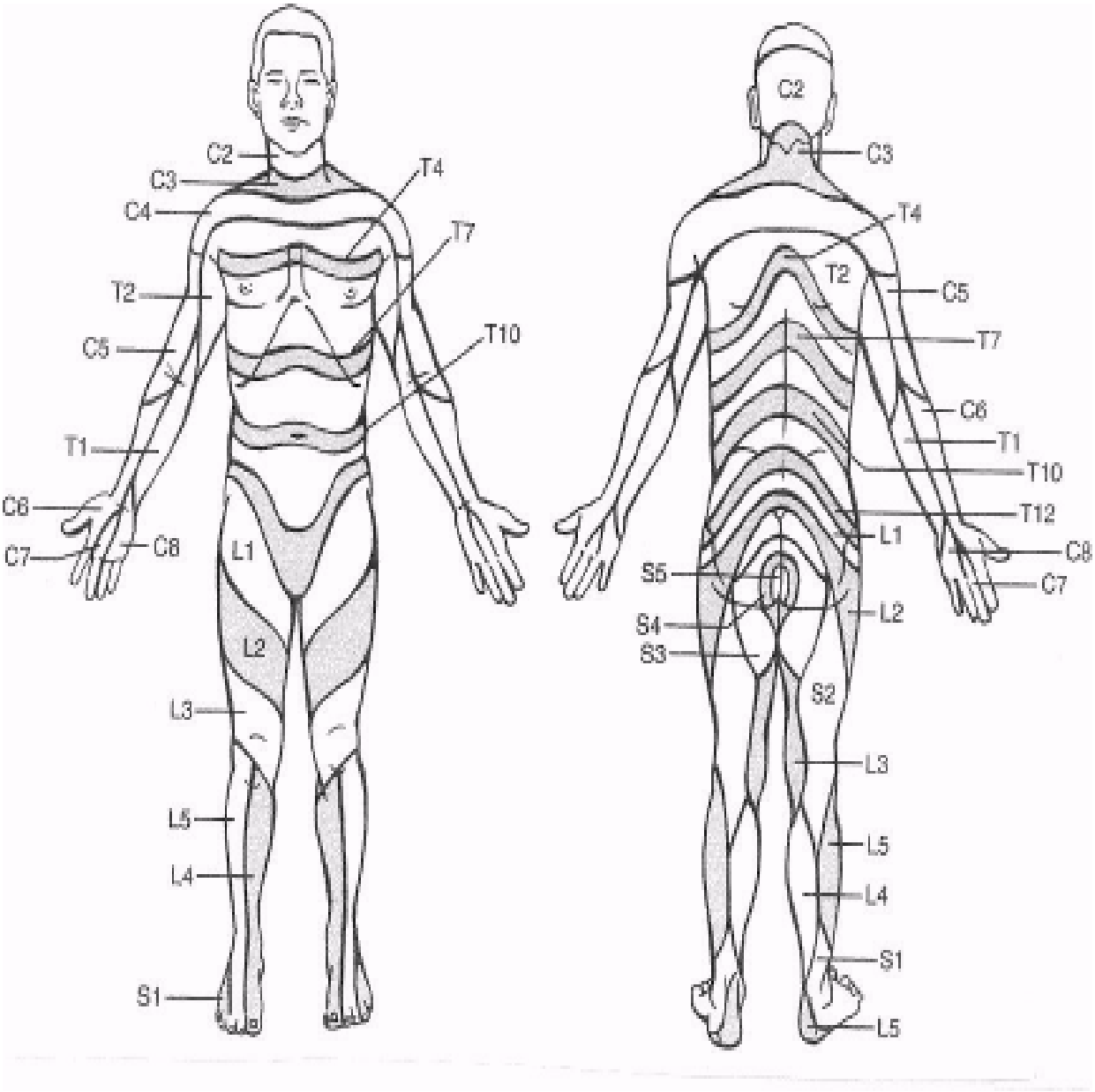
[redacted]

APPENDIX 1: STUDY SUMMARY

Evaluation	Screening/ Enrollment	Procedure/ Discharge	6 weeks (±2 weeks) postop	3 months (±2 weeks) postop	6 months (±1 month) postop	12 months (±2 months) postop	24 months (±2 months) postop & annually
Informed Consent	√						
Medical History	√						
Physical Exam	√		√	√	√	√	√
Medication use	√		√	√	√	√	√
CT, MRI, Myelography	√						
DEXA Scan (patients with SCORE ≥6)	√						
Disc Height Measurement	√						
Static lateral, A/P standing Radiographs	√	√	√	√	√	√	√
Standing Flexion/Extension Radiographs	√			√	√	√	√
Standing Lateral Bending Radiographs	√			√	√	√	√
ODI and ZCQ	√		√	√	√	√	√
SF-36	√		√	√	√	√	√
Neurological Exam	√		√	√	√	√	√
VAS	√		√	√	√	√	√
Patient Satisfaction			√	√	√	√	√
Adverse Events		√	√	√	√	√	√



APPENDIX 3: DERMATOME LOCATIONS


C2
C3
C4
T2
C5
T1
C6
C7
C8
T4
T7
T10
L1
L2
L3
L5
L4
S1
C2
C3
T4
T2
C5
T7
C6
T1
T10
T12
L1
C8
C7
S5
S4
S3
L2
S2
L3
L5
L4
S1
L5

APPENDIX 4: PATIENT DISCHARGE INSTRUCTIONS

AFR System Study Discharge Instructions

The following instructions are provided by the investigator to the patient upon discharge

Please follow these instructions closely to prevent complications and to increase the probability of acceptable surgical results.

1. Restrict your sitting to a minimum until you are seen in your physician's office. You may sit briefly for meals and for bathroom use. When you do sit, be sure to use a chair with good back support.
2. Avoid driving for 2 weeks. However, you may ride as a passenger on short trips
3. Do not stoop, bend or twist your back. Do not lift or participate in sports activities. Use your discomfort as a guide for most activities. Further instructions on activities and work limitations will be provided when you are seen for follow up in your physician's office.
4. Avoid back exercises for one month.
5. You may shower after your physician has given permission to do so.
6. Please discuss your return to work status with your physician or his/her office assistant.
7. Many people have some increase in pain a week or so after surgery. This is normal as there is swelling when healing takes place. The pain usually resolves in a few days.
8. Please call the physician's office if there are any signs of infection (i.e. fever, chills, redness, wound problems and increased pain).
9. If you have significantly increased pain that is not relieved by your pain medication, difficulty walking, difficulty passing your urine or moving your bowels, call your physician's office or go to the emergency room.
10. If you have any other questions or concerns or believe that you have any other difficulties, please call your physician's office.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

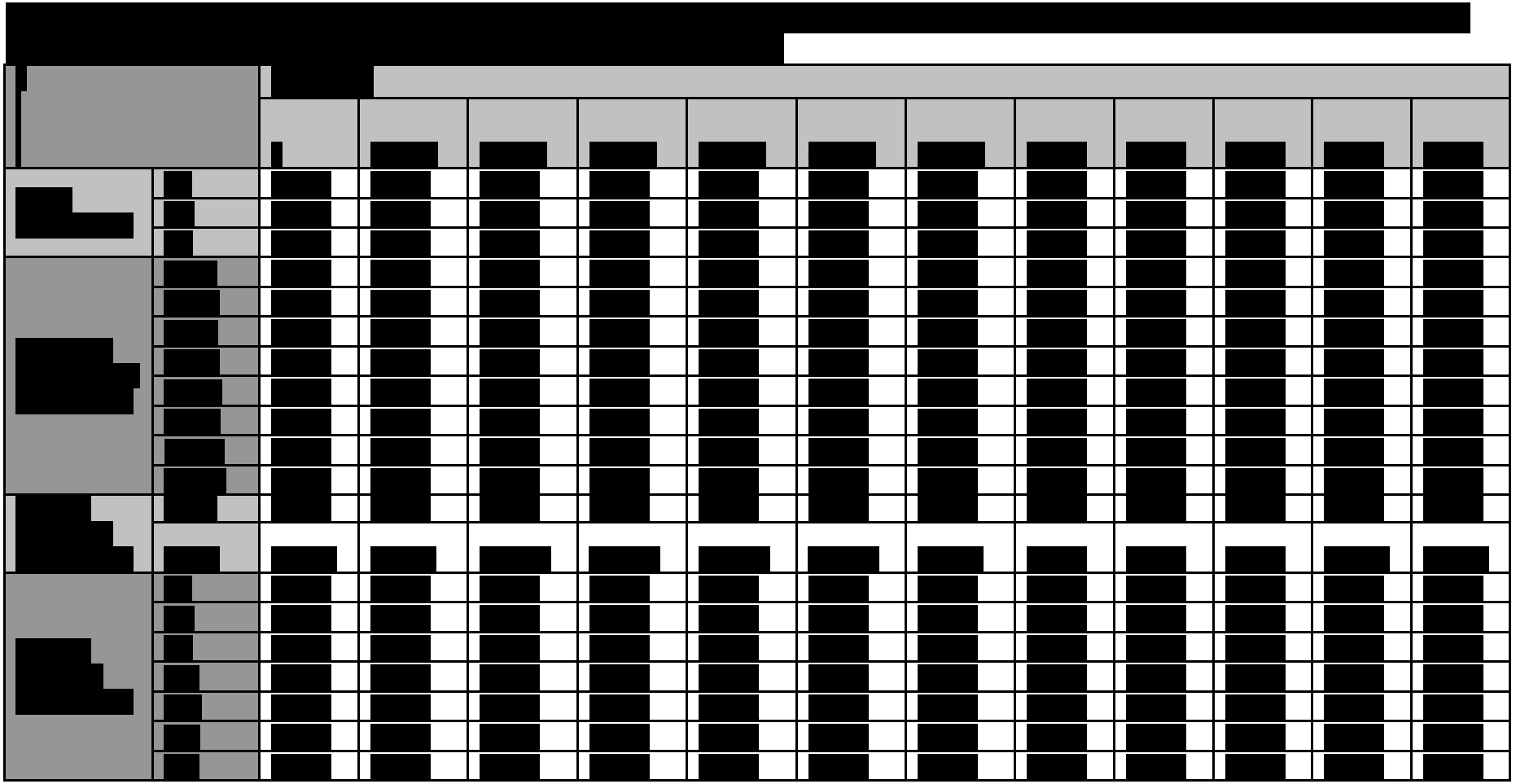
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

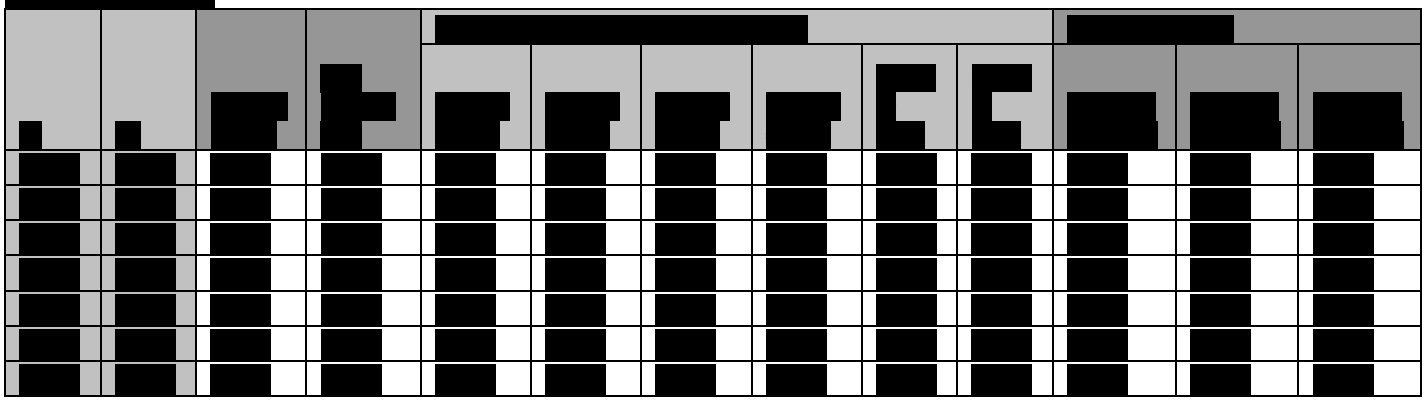
[redacted]

[redacted]

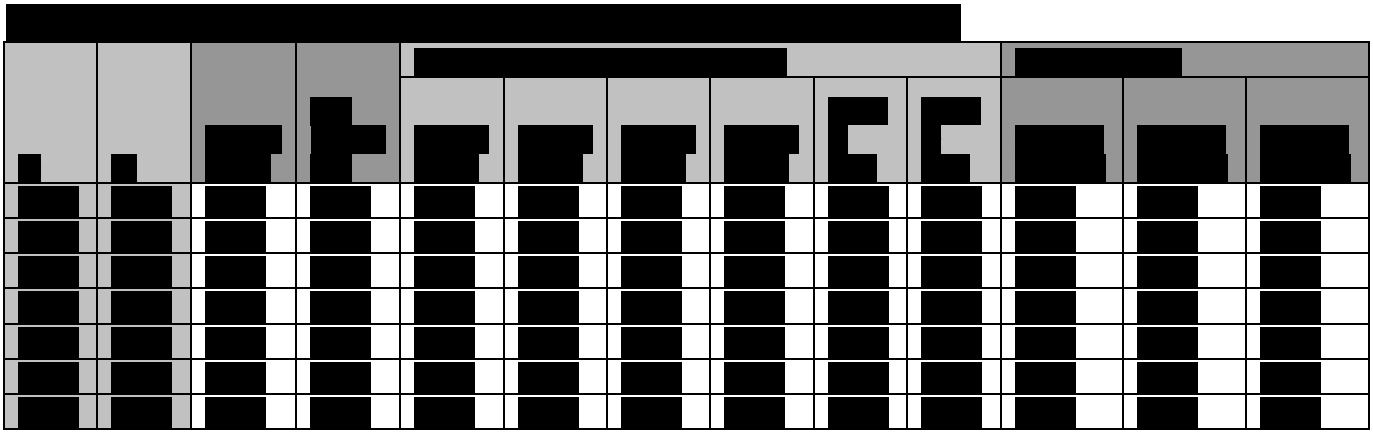
[redacted]

[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

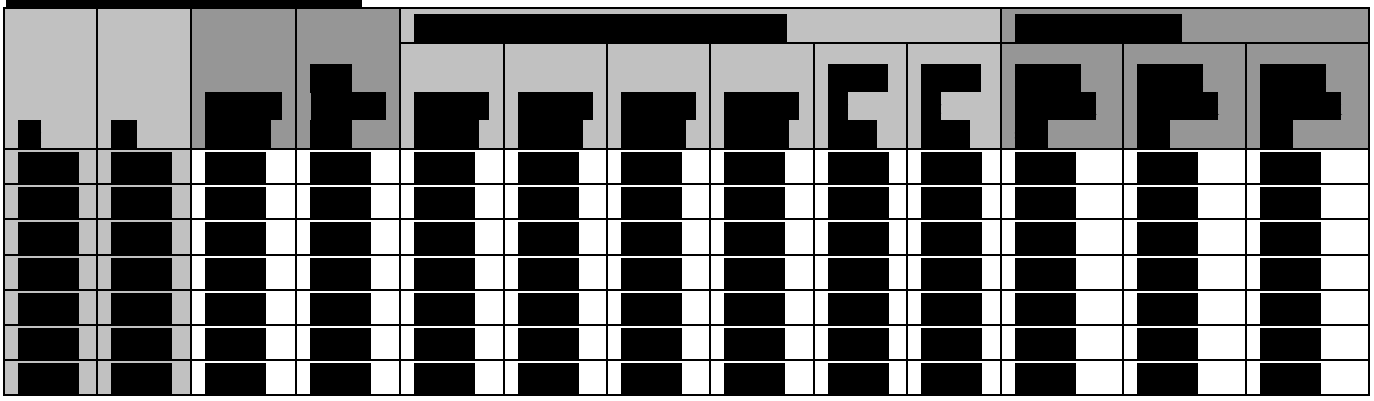
[redacted]

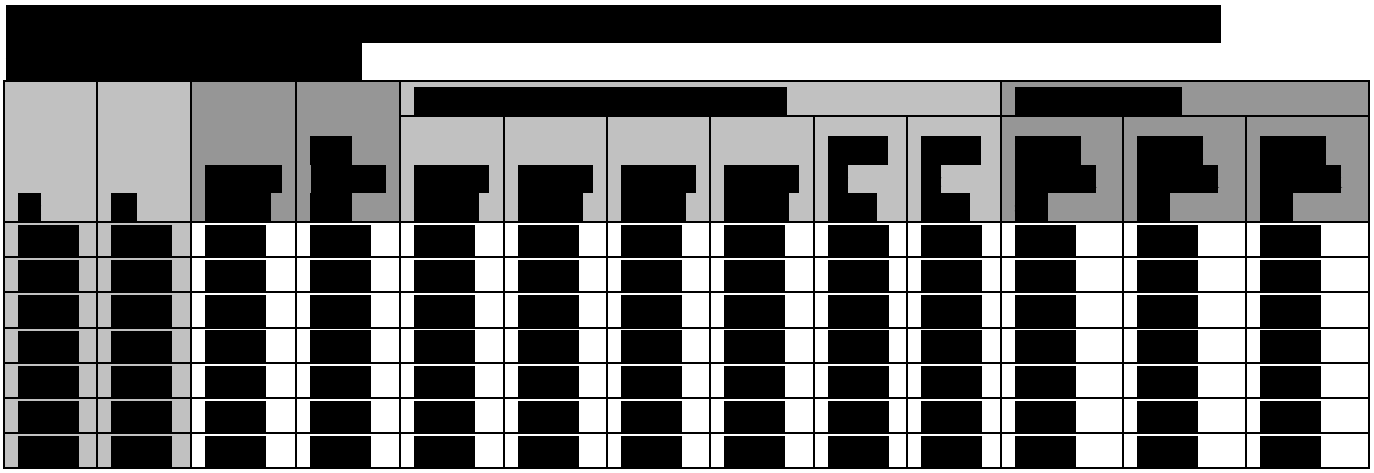
[redacted]

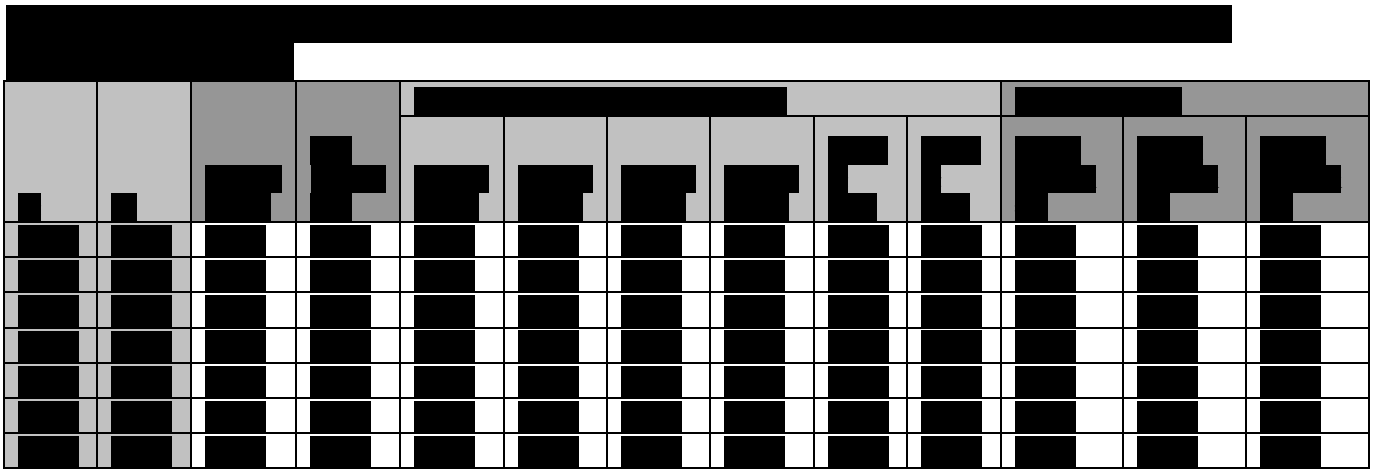
[redacted]

[redacted]

[redacted]







[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

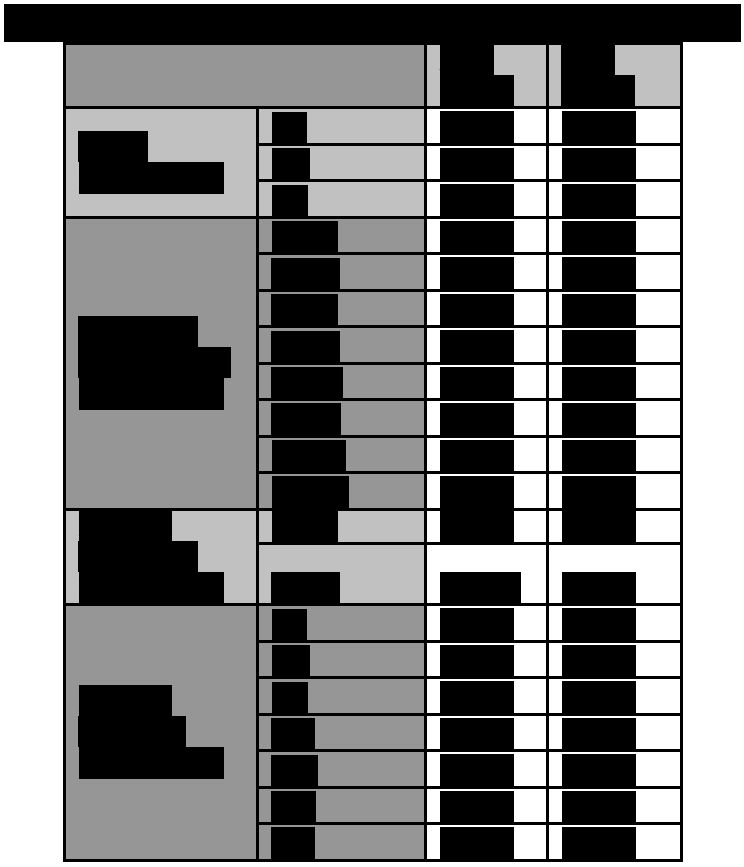
[redacted]

[redacted]

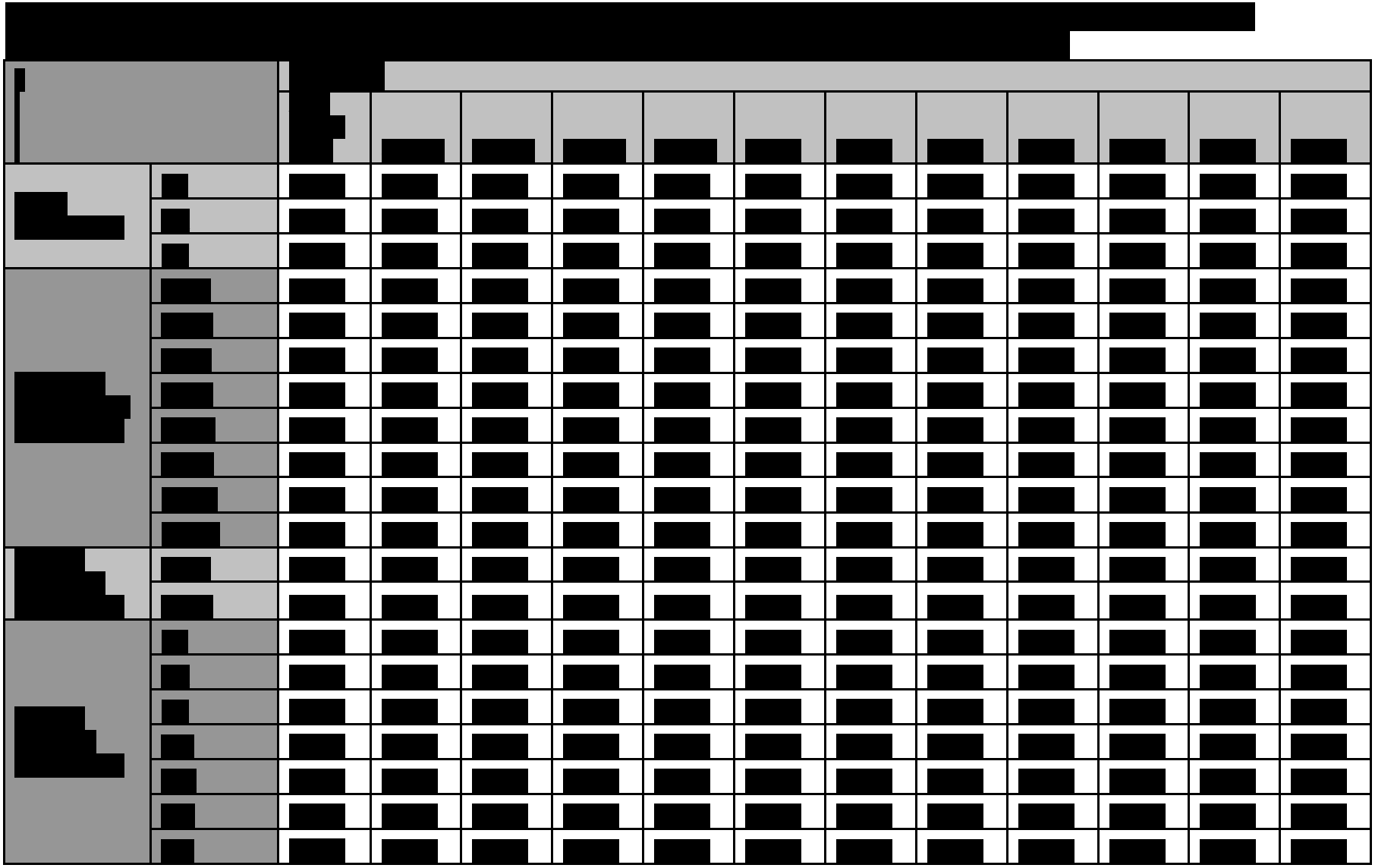
[redacted]

[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													