# K2M Post Market Clinical Study Protocol

A Comparison of Complication Rates between Lateral Approaches to the Lumbar Spine: K2M RAVINE® Far Lateral System versus NuVasive XLIF®

Clinical Protocol CA-002

Revision 4

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# 1 PROTOCOL SYNOPSIS

***Primary Objective:*** To evaluate the incidence of complications resulting from far lateral spine surgery utilizing the K2M RAVINE® Lateral Access System (RAVINE) with ALEUTIAN® Lateral Interbody Spacer System or CASCADIA® Lateral Interbody Spacer System versus literature reported results for the NuVasive XLIF® system (XLIF) in the treatment of degenerative disc disease (DDD) with up to Grade 1 spondylolisthesis.

***Study Design:*** Prospective, non-randomized (single-arm) multi-center study

***Follow-Up Evaluations:*** Clinical evaluations of patients implanted with ALEUTIAN or CASCADIA using the RAVINE system will be conducted at initial post-op, 3 months, 6 months, 12 months and 24 months post-procedure. Adverse events will be monitored continuously.

***Effectiveness Assessment:*** Effectiveness measurements include the following:

- Back, Hip/Buttock, and Leg Pain 10cm Visual Analog Scale (VAS)
- Evaluation of the Incidence of Thigh Pain and Dysesthesia
- Quantitative and Qualitative Radiographic Assessments
    - Fusion Assessment
    - Device Status
- Oswestry Low Back Pain Disability Index (ODI)
- SF-12v2 Health Survey, including SF-6D Utility Index assessment
- Patient Satisfaction
- Odom's Criteria
- Perioperative Assessments
    - Surgery Time
    - Anesthesia Times
    - Estimated Blood Loss
    - Neuromonitoring
- Length of Hospital Stay
- Return to Work/School
- Use of Narcotics Post-Surgery

***Safety Assessment:*** Safety will be assessed by:

- The evaluation of all adverse events including device related, procedure related and additional serious adverse events.
- Additional surgical intervention at the operative site including the need for removals, revisions, re-operations or supplemental fixation required to modify the device
- The incidence and severity of any psoas muscle injury, genital femoral nerve injury and lumbar plexus injury will be determined for all patients

***Study Subjects:*** Patients eligible for study enrollment will have a primary diagnoses limited to degenerative disc disease (DDD) with up to Grade 1 spondylolisthesis at L2-S1 requiring surgical intervention at one or two contiguous levels. Qualified patients

will have confirmed failure of conservative therapy as well as plain film imaging studies. Subjects must be ≥ 18 years old at the time of enrollment.

***Device Evaluation Group:*** K2M RAVINE Lateral Access System with ALEUTIAN Lateral Interbody Spacer System cleared for marketing and distribution under 510(k) K113138 or K2M RAVINE Lateral Access System with CASCADIA Lateral Interbody Spacer System cleared for marketing and distribution under 510(k) K150480.

***Comparative Group:*** Historical, literature control of reported results with the use of the NuVasive XLIF system for far-lateral spinal stabilization.

***Sample Size:*** Two-hundred twenty-two (222) total subjects at up to 15 clinical sites. Sites are considered a Principal Investigator and their Sub-Investigators who are covered by a single Institutional Review Board's (IRB's)/Ethics Committee's (EC's) oversight and approval.

Subject enrollment will be capped so that no single site contributes more than approximately 20% of cases.

***Investigator Selection:***

- Appropriate patient population for trial indication
- An investigator must have completed a minimum of three surgeries using the RAVINE system. If a surgeon does not have experience in using the RAVINE system, their first three (3) patients will be considered roll-in patients and the results from these patients will be analyzed against the entire cohort to determine if a learning curve exists. If a surgeon has previously completed three (3) surgeries using the Ravine system, there will be no stratification of their data.
- Experience in clinical trial execution
- Dedicated research infrastructure
- Local institutional review board (IRB)/Ethics Committee (EC) for research oversight or ability to use central IRB/EC
- Standard of Care (SOC) compatible with or capable of complying with the protocol requirements including but not limited to:
  - Neurological assessment, with specific evaluation of the incidence of thigh pain and/or dysesthesia after surgery
  - Use/Collection of patient reported outcome measures – ODI; Back, Hip/Buttock, and Leg VAS; SF-12v2
  - Follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months
- Insofar as possible, sites for the study will be distributed regionally and by type of institution and level of investigator experience, patient volume and research experience so that any unanticipated and potentially prognostic factors may then be balanced both geographically and demographically in the study.

# 2 INTRODUCTION

## 2.1 Study Purpose

The purpose of this study is to evaluate the complication rate of the RAVINE Lateral Access System with the ALEUTIAN Lateral Interbody Spacer System or the CASCADIA Lateral Interbody Spacer System compared to the literature reported results with the NuVasive XLIF® system, with particular interest in the incidence of thigh/leg pain and dysesthesia.

## 2.2 Background and Significance

Degenerative disc disease is a spinal condition caused by the breakdown of intervertebral discs. As a result of aging, the spine begins to show signs of wear and tear as the discs dry out and shrink. These age-related changes can lead to arthritis, disc herniation, or spinal stenosis, which can put pressure on the spinal cord and nerves and may cause back pain. Spinal fusion is often utilized as the final treatment after conservative method attempts have failed.

Minimally invasive (MI) fusion surgeries have been developed to treat disorders of the spine with less disruption to the muscles. This can result in quicker recovery, decreased operative blood loss, and the speed that patients return to normal function. While most MI access systems maintain the common table-mounting design, spine-fixated retractors provide stabilization of the exposure irrespective of patient movement on the operating table. Without the threat of compromising the surgical field through a disturbance in patient position, the retractors can shift relative to the patient and therefore potentially reduce complications associated with retractor placement and pressure.

## 2.3 Device Description

The RAVINE Lateral Access System (K2M, Leesburg, VA) is a far-lateral, spine-fixated dual blade retractor system that allows for a muscle splitting transpsoas approach. Used in conjunction with the ALEUTIAN Lateral Interbody Spacer System or the CASCADIA Lateral Interbody Spacer System, an anterior fusion can be established with potentially less post-operative neurological and muscle damage. If required, supplemental stabilization can be achieved utilizing the K2M SERENGETI® Minimally Invasive Retractor System, a flexible percutaneous delivery system that allows for direct visualization and access to the posterior screw heads for simple rod insertion of the K2M DENALI® Spinal System, K2M EVEREST® Spinal System, or K2M EVEREST® MI XT Spinal System. Alternatively, supplemental fixation can be achieved utilizing the K2M CAYMAN® Minimally Invasive Plate System, a low profile plate and screw system specifically designed for insertion through the RAVINE Lateral Access System's true muscle-splitting Retractor.

The ALEUTIAN Lateral Interbody Spacer System was cleared for marketing under 510(k) K113138 and the CASCADIA Lateral Interbody Spacer System was cleared for marketing under 510(k) K150481. The surgical technique guides for both interbody spacer systems include the RAVINE Lateral Access Retractor System as instrumentation (Class I). The SERENGETI Minimally Invasive Retractor System was included in the surgical technique guide for the DENALI Minimally Invasive Screw System, cleared under 510(k) K112037. The EVEREST Spinal System was cleared for marketing under 510(k) K103440. The CAYMAN Minimally Invasive Plate System was cleared for marketing under 510(k) K131533. The EVEREST MI XT Spinal System was cleared for marketing under 510(k) K151727.

## 2.4 Surgical Procedure

The implantation using the RAVINE system should be performed according to the standard of care of the Investigator, and in accordance with K2M's Instructions for Use and Surgical Technique Manual for the RAVINE Lateral Access System with the ALEUTIAN Lateral Interbody Spacer System or the CASCADIA Lateral Interbody Spacer System. Supplemental stabilization with the either the SERENGETI Minimally Invasive Retractor System or the CAYMAN Minimally Invasive Plate System, if required, should be performed according to the Instructions

for Use provided by K2M. RAVINE cases utilizing minimally invasive (percutaneous or mini-open) supplemental fixation with facet screws or competitive pedicle screw, thoracolumbar plate systems, if required, should be performed according to the Instructions for Use of the manufacturer.

## 2.5 Indications for Use

The RAVINE system is to be used for far lateral access to the spine for surgical interventions indicated for the use of ALEUTIAN Lateral or CASCADIA Lateral implants. When used as a lumbar intervertebral body fusion device, the ALEUTIAN Lateral and CASCADIA Lateral implants are indicated for spinal fusion procedures to be used with autogenous bone graft in skeletally mature patients. The lumbar IBF implants are intended for use at either one level or two contiguous levels in the lumbar spine, from L2 to S1, for the treatment of degenerative disc disease (DDD) with up to Grade 1 spondylolisthesis. DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies. The lumbar device is intended to be used in patients who have had six months of non-operative treatment.

In the cases where a supplemental stabilization is necessary after the anterior placement of the IBF implant, the SERENGETI Minimally Invasive Retractor System or the CAYMAN Minimally Invasive Plate System can be utilized. The SERENGETI system is a disposable set of surgical access devices for use only in conjunction with the DENALI Minimally Invasive Spinal System or the EVEREST Degenerative Spinal System. The DENALI and EVEREST systems are non-cervical spinal fixation devices intended for posterior, non-pedicle fixation for DDD and spondylolisthesis among other indications outside the scope of this study. The CAYMAN Minimally Invasive Plate System is a low profile plate and screw system specifically designed for insertion through the RAVINE Lateral Access System's true muscle-splitting Retractor. The CAYMAN Minimally Invasive Plate System is indicated for use via the lateral or anterolateral surgical approach in the treatment of thoracic and thoracolumbar (T1-L5) spine and for use as an anteriorly placed supplemental fixation device for the lumbosacral level below the bifurcation of the vascular structures (L5-S1).

## 2.6 Benefits and Risks

### 2.6.1. *Potential Benefits*

There is no guarantee that the subject will experience any immediate or direct benefits with the use of this device system or for taking part in this study.

### *2.6.2. Potential Risks*

Potential risks identified with the use of this device system include those associated with any spinal surgery resulting in neurological, cardiovascular, respiratory, gastrointestinal, or death. Additionally, with the use of a far lateral access system, potential risks also include those associated with the inherent psoas muscle splitting accompanying such an approach; particularly thigh pain, dysesthesia, and neurological complications.

A full listing of potential risks of the device and the surgical procedure can be found in **Section 9.5 Potential Risks and Anticipated Adverse Events**.

## 2.7 Mitigation of Risks

Operative and acute periprocedural risks for the patients enrolled in this study are mitigated by restricting the use of the device to skilled neurological and orthopedic spine surgeons trained and experienced in the proper surgical technique to implant the respective devices. Long-term risks such as device migration/failure and pseudoarthrosis are mitigated by proper patient selection and implanting the devices in accordance with the Surgical Technique

Manuals for the ALEUTIAN Lateral Interbody Spacer System or the CASCADIA Lateral Interbody Spacer System, the RAVINE and the SERENGETI or CAYMAN Minimally Invasive Plate System (if applicable) systems and the use of the surgical instruments provided by K2M; and by following accepted standard care in this population for far lateral fusion surgery.

# 3 INVESTIGATOR/SITE SELECTION

The investigators selected to participate in this clinical study will be responsible for conducting the study according to the requirements of the protocol. Each site will have a designated Principal Investigator and may have Sub-Investigators. Investigators/sites will be selected for participation in the study according to the following criteria:

The Investigator/Site must have:

- Expertise in clinical areas relevant to the study, including a background in spine surgery, sufficient experience in clinical research and an adequate patient population with adult spine disorders
- Completed a minimum of three (3) surgeries using the RAVINE system. If a surgeon does not have experience in using the RAVINE system, their first three (3) patients will be considered roll-in patients and the results from these patients will be analyzed against the entire cohort to determine if a learning curve exists. If a surgeon has previously completed three (3) surgeries using the Ravine system, there will be no stratification of their data.
- Experience in participating in clinical studies and have adequate personnel and a dedicated research infrastructure including a Study Coordinator to adequately perform the tasks required by the clinical protocol
- Local institutional review board (IRB)/Ethics Committee (EC) for research oversight or ability to use central IRB/EC
- A practice in a medical facility equipped appropriately to fulfill the surgical and patient contact requirements of the study
- A standard of care (SOC) compatible with or capable of complying with the protocol requirements including but not limited to:
    - Neurological assessment, with specific evaluation of the incidence of thigh pain and/or dysesthesia after surgery
    - Use/Collection of patient reported outcome measures – ODI; Back, Hip/Buttock, and Leg VAS; SF-12v2
    - Follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months
- (Be willing to) sign a Clinical Research Agreement and abide by the agreement for the duration of the study.
- (Be willing to) provide financial disclosure; including updating the disclosure during the study if the financial status changes.

Insofar as possible, sites for the study will be distributed regionally and by type of institution and level of investigator experience, patient volume and research experience so that any unanticipated and potentially prognostic factors may then be balanced both geographically and demographically in the study.

## 3.1 Investigator Training

Training sessions in proper surgical technique and trial performance for the Principal Investigator, all Sub-Investigators and research coordinators will be provided by the sponsor prior to initiation of the study at each site.

# 4 STUDY METHODS

## 4.1 Study Design

Prospective, non-randomized (single-arm) multi-center study to evaluate the incidence of complications and the patient effectiveness outcomes using the RAVINE system as compared to the literature reported complications and outcomes for the XLIF system when utilized in the surgical treatment of symptomatic DDD with up to Grade 1 spondylolisthesis. If required, supplemental stabilization may be achieved using the SERENGETI posterior percutaneous retractor system, the CAYMAN Minimally Invasive Plate System, or another appropriate minimally invasive (percutaneous or mini-open) system.

## 4.2 Treatment Group

Patients treated with the RAVINE system that had:

- A diagnosis of DDD with up to Grade 1 spondylolisthesis at L2-S1, confirmed clinically and radiographically, requiring surgical intervention
- One or two contiguous levels requiring surgical intervention
- Inadequate response to conservative medical care over a period of at least 6 months
- An age at time of enrollment of ≥ 18 years old

## 4.3 Control Group

Literature reported outcomes of adult patients (≥ 18 years old) with lumbar DDD between L2-S1 who presented with up to a Grade 1 spondylolisthesis at one or two contiguous levels, for whom the NuVasive XLIF far-lateral system was used during their surgical intervention.

## 4.4 Sample Size

Two-hundred twenty-two (222) total subjects at up to 15 clinical sites. Sites are considered a Principal Investigator and their Sub-Investigators who are covered by a single Institutional Review Board's (IRB's)/Ethics Committee (EC) oversight and approval.

Subject enrollment will be capped so that no single site contributes more than approximately 20% of cases.

# 5 STUDY OBJECTIVES/OUTCOMES

## 5.1 Primary Effectiveness Objective

The primary effectiveness objective is:

To evaluate the improvement of the Back VAS and the Leg VAS at 24 months as compared to pre-op time periods. Information on all reports of pain/numbness/tingling and the location of symptoms will be captured and evaluated.

## 5.2 Primary Safety Objectives

The primary safety objectives are:

- The evaluation of all adverse events including device related, procedure related and additional serious adverse events.
- Additional surgical intervention at the operative site including the need for removals, revisions, re-operations or supplemental fixation required to modify the device
- The incidence and severity of any psoas muscle injury, genital femoral nerve injury and lumbar injury will be determined for all patients

All adverse events will be documented on a continuous basis and reviewed by K2M Clinical Research Staff. Information regarding all device failures including instrument breakage, implant breakage, subsidence, migration, or expulsion will be captured.

*5.2.1 Device and Procedure Related Adverse Events*

Device and procedure related adverse events will be documented and reported to the sponsor, including the need for removals, revisions, re-operations or supplemental fixation required to modify the device.

## 5.3 Secondary Objectives

Secondary objectives are expected to further define the safety and patient outcomes for effectiveness of the K2M device. Secondary objectives include:

*5.3.1 Visual Analog Scales*

The severity of back, hip/buttock, and leg pain will each be evaluated in all study subjects using a 10-cm visual analog scale (VAS).

*5.3.2 Incidence of Thigh Pain/Dysesthesia*

A neurological evaluation of the patient, with specific evaluation of psoas muscle weakness, radiating radicular pain, knee extension weakness, dorsiflexion weakness, plantarflexion weakness and anterior thigh numbness will be performed by the healthcare staff and will also be addressed through a patient questionnaire entitled Patient Symptom Questionnaire.

*5.3.3 Oswestry Disability Index*

The Oswestry Disability Index (ODI) is one of the principal condition-specific outcome measures used in the management of spinal disorders. The ODI is the most commonly outcome measures in patients with low back pain. It has been extensively tested, showed good psychometric properties, and applicable in a wide variety of settings. This patient-reported outcome measure is a 10 item questionnaire that evaluates disability and functional impairment associated with back problems. This validated instrument includes items that relate to subjective symptomatology and activities of daily living (pain intensity, personal care, lifting, walking, sitting, standing, sex life, traveling). Each item is scored from 0 up to 5, with higher scores corresponding to greater disability. A total

ODI score is determined by adding the scores of the individual questions and dividing that total by the maximum possible score (i.e., 50 if all questions are answered) to yield a percentage. Therefore, the ODI score ranges from 0% to 100%. An improvement by at least 15 percentage points will be considered a success.

*5.3.4 Health-Related Quality of Life*

Health-related quality of life will be evaluated in all study subjects using the SF-12v2 Health Survey. This shortened and simplified version of the SF-36 makes the questionnaire less ambiguous for patients. It has a self-administered form that makes it easy to read and complete, and that reduces missing responses. The physical and mental component summary scales, referred to as PCS-12 and MCS-12 will be evaluated against published normative values and a 15% improvement in these scores will be used as an assessment of success. To calculate the true value of a treatment, the scores from the SF-12v2 will be converted into a utility index (SF-6D), which considers not only how many years a medical intervention can add to a patient's life, but also the quality of that life. Use of the SF-6D does not expand the questions administered to the patient.

5.3.5 Radiographic Assessments

Quantitative and qualitative radiographic assessment of the pre and post-operative AP, and Lateral, Flexion/Extension images will be performed and submitted. Radiographic assessments being performed include:

- Qualitative Assessment
  - Device Condition
  - Device Subsidence
  - Device Migration
- Radiographic Assessment of Fusion/Non-fusion
  - Bony Bridging
  - Radiolucency
  - Development of Pseudoarthrosis

*5.3.6 Patient Satisfaction*

At the 12 month and 24 month follow-up visits, subjects will be asked whether they were satisfied with the outcome of their surgery (Yes/No) and whether they would repeat the operation (Yes/No).

*5.3.7 Odom's Criteria*

At the 24 month follow-up visit, the Investigator will rate the clinical disposition of each study subject according to Odom's Criteria as follows:

**Excellent:** all pre-operative symptoms relieved, able to carry out daily occupations without impairment.

**Good:** minimum persistence of pre-operative symptoms, able to carry out daily occupations without significant interference.

**Fair/Satisfactory:** relief of some pre-operative symptoms but physical activity is significantly limited.

**Poor:** symptoms or signs unchanged or worse.

*5.3.8 Surgery Time*

The length of the surgical procedure from the initial incision to final closure will be captured from the Anesthesia Record.

*5.3.9 Anesthesia Time*

The length of time the patient is under anesthesia will be captured from the Anesthesia Record.

### *5.3.10 Estimated Blood Loss*

The amount of blood loss over the entire length of the surgery, documented on the Anesthesia Record, will be captured.

### *5.3.11 Neuromonitoring*

The type(s) and any abnormal result(s) of neuromonitoring systems utilized during the surgery will be captured.

### *5.3.12 Length of Hospital Stay*

The length of hospital stay from the date of hospital admission to the date of discharge will be calculated.

### *5.3.13 Return to Work/School*

The ability to and the time it takes for the subject to be cleared to return to work/school from the date of surgery will be documented.

### *5.3.14 Use of Narcotics Post-Surgery*

The types and dosages of any narcotics taken by the patient post-surgery will be documented.

# 6 STUDY ENDPOINT

## 6.1 Primary Study Endpoints

The primary effectiveness endpoint is the improvement Back VAS and Leg VAS at 24 months as compared to pre-op time periods.

# 7 STUDY POPULATION

## 7.1 Sample Size

Two-hundred twenty-two (222) total subjects at up to 15 clinical sites, geographically distributed throughout US.

## 7.2 Inclusion and Exclusion Criteria

To be eligible to participate in the study, a subject must meet all of the Inclusion Criteria and none of the Exclusion Criteria.

**Inclusion Criteria**

1. Diagnosis of DDD with up to Grade 1 spondylolisthesis, confirmed clinically and radiographically, requiring surgical intervention at one or two contiguous levels between L2-S1
2. Inadequate response to conservative medical care over a period of at least 6 months
3. Willing and able to comply with the requirements of the protocol including follow-up requirements
4. Willing and able to sign a study specific informed consent
5. Skeletally mature and ≥ 18 years of age at the time of enrollment

**Exclusion Criteria**

1. Active systemic infection or infection at the operative site
2. Co-morbid medical conditions of the spine or upper/lower extremities that may affect the lumbar spine neurological and/or pain assessment
3. Metabolic bone disease such as osteoporosis that contradicts spinal surgery
4. History of an osteoporotic fracture
5. History of an endocrine or metabolic disorder (e.g., Paget's disease) known to affect bone and mineral metabolism
6. Taking medications that may interfere with bony/soft tissue healing including chronic steroid use
7. Known allergy to titanium, cobalt chrome or PEEK
8. Rheumatoid arthritis or other autoimmune disease or a systemic disorder such as HIV, active hepatitis B or C or fibromyalgia
9. Current medical condition (e.g., unstable cardiac disease, cancer) that may result in patient death or have an effect on outcomes prior to study completion
10. Pregnant, or intend to become pregnant, during the course of the study
11. Severe obesity (Body Mass Index > 40)
12. Physical or mental condition (e.g., psychiatric disorder, senile dementia, Alzheimer's disease, alcohol or drug addiction) that would interfere with patient self-assessment of function, pain or quality of life
13. Involved in current or pending spinal litigation where permanent disability benefits are being sought
14. Incarcerated at the time of study enrollment
15. Current participation in an investigational study that may impact study outcomes

## 7.4 Study Duration

Study subjects will be expected to participate in this study for 24 months following surgery, with follow-up evaluations at initial post-op, 3 months, 6 months, 12 months, and 24 months.

# 8 STUDY ENROLLMENT/EVALUATIONS

## 8.1 Patient Screening and Enrollment

Consecutive patients who potentially meet the study inclusion and exclusion criteria will be screened for eligibility. Diagnostic imaging studies to confirm the diagnosis of DDD with up to Grade 1 spondylolisthesis between and including the levels of L2-S1, must be completed within 180 days of the planned date of surgery (provided there have been no significant changes in the patient's clinical presentation). If, at an interim point following the initial imaging, and prior to surgery, the subject experiences a significant change in his/her clinical presentation, the changes should be documented and the images repeated. Patients will be screened as follows:

- Consecutive patients are potentially eligible for entry into the study based on their age and whether their medical condition appears to generally fit the characteristics specific to this study.
- Patients who agree to enter the study must sign the approved informed consent form.
- A patient is considered enrolled in the study after signing the IRB/EC approved informed consent. Consented patients complete the remainder of the screening process to confirm study eligibility. Patients who do not fulfill the screening criteria are considered Screening Failures and will be documented on the Screening & Enrollment Log. Screening failures will not count against the total number of subjects eligible for analysis.
- Subjects who have signed the informed consent and fulfilled the Inclusion/Exclusion criteria are then scheduled for surgery. It is important that surgery be scheduled within 90 days from the date that the subject completed the required pre-operative questionnaires for the study and within 180 days from the date of the required pre-operative X-rays (provided there have been no significant changes in the patient's clinical presentation). The following should be considered when evaluating whether or not the change in clinical presentation is considered significant: an increase in related pain of approximately 3 points (on VAS scale from 0-10), a change in the location of the pain, deteriorating neurological status or other conditions where repeat radiographic studies may be necessary. The objective is to ensure that the patient still meets the eligibility criteria based on the medical judgment of the surgeon.

Once a patient is enrolled into the study, they will need to be given a unique subject identifying number (Subject ID) that will be used to capture de-identified information. For this study, the following standardized format will be used: *Site Identifying Number (2 digits)-Subject Identifying Number (3 digits)*. Your site identifying number will be assigned by the Sponsor, and the subject identifying number should start with 001 and continue accordingly during patient enrollment. For example, if the site identifying number issued to you is Site 03, and you are enrolling your second patient into the study, their Subject ID would be 03-002. A Patient Information Log will be provided to you to keep as a cross reference for study subjects.

## 8.2 Pre-Operative Evaluation

All subjects will complete the ODI, VAS, and SF-12v2 questionnaires within 90 days prior to the scheduled surgery. All patient questionnaires should be completed during the visit, preferably prior to the patient interacting with the Investigator or other clinical staff. A pertinent medical history will be documented and all subjects will undergo a standard neurological examination including assessments of sensation, motor function, and reflexes.

### *8.2.1 Pre-Operative Assessment*

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Pertinent History and Physical including Current Symptoms, Height, Weight, and Tobacco Use

- Work/School Status
- Current Medication for Spine Problem
- Neurological Examination
- AP and Lateral X-rays
- Back, Hip/Buttock, and Leg VAS
- Oswestry Disability Index
- SF-12v2
- Patient Symptom Questionnaire
- Adverse Event assessment

## 8.3 Hospitalization/Surgery/Discharge

Subjects will be admitted to the hospital according to the Investigator's standard for non-cervical spine surgery. Prophylactic antibiotics may be administered prior to surgery in accordance with the surgeon's standard of care and anesthesia will be administered per standard operating procedures. The device will be implanted in accordance with methods detailed in the instructions for use for the respective device systems.

Data points required on the Operative case report form must be documented at the time of surgery. Intra-operative adverse events must be recorded.

A Subject may be excluded from the study intra-operatively at the discretion of the Investigator if unexpected findings/occurrences dictate deviation from the intended study procedure. Justification for an intra-operative exclusion and alternative surgical procedure must be fully documented in the subject's medical record and on the Study Exit case report form. A subject who is excluded intra-operatively will be considered an overall treatment failure.

If the patient experienced an adverse event(s) during the hospitalization it should be documented and recorded on an Adverse Event case report form. The subject may be instructed to return to normal activity at the discretion of the Investigator.

Additional post-operative restrictions may be imposed according to the standard of care normally utilized by the Investigator. In addition, subjects should be instructed to notify the Investigator if experiencing untoward events including but not limited to noticeable pain, numbness, tingling, or weakness that does not decrease with rest, swelling of the lower extremities that does not decrease, or increased pain, erythema, edema or drainage from the surgical incision. The Investigator should then determine if an evaluation is warranted.

### *8.3.1 Surgery/Hospital Discharge Evaluation*

- Date of Hospital Admission
- Date of Surgery
- Date of Hospital Discharge
- Implanting Surgeon
- Implanted System Detail
- Surgery Detail/Concomitant Procedures
- Surgery Time (initial incision to closure)
- Anesthesia Time
- Fluoro Time
- Estimated Blood Loss
- Neurological Examination
- Back, Hip/Buttock, and Leg VAS
- Oswestry Disability Index
- SF-12v2

- Patient Symptom Questionnaire
- Adverse Event assessment – Surgery Through Discharge

## 8.4 Post-Operative Follow-Up Visits

All subjects will be required to return for follow-up visits at initial post-op, 3 months, 6 months, 12 months, and 24 months post-procedure. Data collected at each follow-up visit must be confirmable by source documents and the appropriate case report forms must be completed. All patient questionnaires should be completed during the visit, preferably prior to the patient interacting with the Investigator or other clinical staff. If a site requires multiple follow-up visits within the "initial post-op" timeframe (discharge to 8 weeks post-op), only the latter of the visits will be utilized for data collection. Requirements at each post-operative follow-up visit are as follows:

### *8.4.1 Follow-Up Evaluations and Data – Post-Op through 24 Months*

- Work/School Status (including release for return to work/school) (all visits)
- Current Symptoms (all visits)
- Medication (taken for spine problem since last contact) (all visits)
- Neurological Examination (all visits)
- AP and Lateral X-rays (6 Month, 12 Month, and 24 Month visits)
- Flexion/Extension X-rays (12 Month and 24 Month visits)
- Fusion Assessment (per X-rays and/or CT Scan as determined by the investigator)
- Back, Hip/Buttock, and Leg VAS (all visits)
- Oswestry Disability Index (all visits)
- SF-12v2 (all visits)
- Adverse Event assessment (all visits)
- Patient Symptom Questionnaire (all visits)
- Patient Satisfaction (12 and 24 Month visits only)
- Odom's Criteria (24 Month visit only)
- Study Exit

## 8.5 Unscheduled Follow-Up Evaluation

Subjects may return to the clinic at a time point that is not a scheduled follow-up visit. If the Investigator determines that the return visit is related to the study device or procedure, the Unscheduled Visit portion of the Follow-Up case report form should be completed. If a subject requires a device or procedure related re-operation including supplemental fixation, revision and/or device removal as a result of an unscheduled visit, the Sponsor should be notified immediately and an Adverse Event case report form should also be completed. The requirements for an unscheduled visit are as follows:

- Reason for Visit/Current Symptoms/Pertinent history
- X-rays and/or CT Scan, as needed (if done, a minimum of AP/Lateral for all unscheduled visits that are attributable to a spine-related condition)
- Neurological Examination
- AP, Lateral and Flexion/Extension X-rays
- Flexion/Extension X-rays (12 Month and 24 Month visits)
- Back, Hip/Buttock, and Leg VAS
- Oswestry Disability Index
- SF-12v2
- Patient Symptom Questionnaire
- Adverse Event assessment

## 8.6 Schedule of Evaluations

### *8.6.1 Schedule of Evaluations*

| **Interval →** **Assessment ↓** | Pre-Op | Operative/ Discharge | Initial F/U (Discharge to 8 wks post-op) | 3 Mo F/U (± 2 wks) | 6 Mo F/U (± 1 mo) | 12 Mo F/U (± 2 mos) | 24 Mo F/U (± 2 mos) | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | |
| Demographics | X | | | | | | | |
| Pertinent History | X | | | | | | | X |
| Work Status/ Current Symptoms | X | | X | X | X | X | X | X |
| Medications for Spine Problems | X | | X | X | X | X | X | X |
| Neurological Examination | X | X | X | X | X | X | X | X |
| AP & Lateral X-rays | X | | | | X | X | X | If needed |
| Flexion/Extension X-rays | | | | | | X | X | If needed |
| ODI | X | X | X | X | X | X | X | X |
| Back, Hip/Buttock and Leg VAS | X | X | X | X | X | X | X | X |
| SF-12v2 | X | X | X | X | X | X | X | X |
| Patient Symptom Questionnaire | X | X | X | X | X | X | X | X |
| Hospitalization and Surgery Data | | X | | | | | | |
| Adverse Event Assessment | X | X | X | X | X | X | X | X |
| Patient Satisfaction | | | | | | X | X | |
| Odom's Criteria | | | | | | | X | |
| Study Exit | | | | | | | X | |

## 8.7 Pregnancy during Study Participation

If a subject becomes pregnant during the study, the sponsor should be notified as soon as possible. The subject will remain in the study, but during the pregnancy the study follow-up visit(s) will be modified to exclude the X-ray imaging requirements. At follow-up visits after the pregnancy, the required X-rays should again be performed. Information related to the pregnancy and outcome should be maintained by the site and documented by the Sponsor in monitoring reports during periodic visits.

## 8.8 Protocol Deviations

The Protocol must be followed closely, and the Investigators should not deviate from the protocol unless in the opinion of the Investigator a deviation from the protocol is in the best interest of safety for the subject. A deviation from the Protocol should be reported to the sponsor as soon as possible after the deviation is noted. In addition, during routine monitoring visits the monitor may determine a protocol deviation and initiate the protocol deviation process. All protocol deviations must be documented on a Protocol Deviation case report form. For the scientific integrity of the study, protocol deviations must be kept at a minimum. If a site has an unacceptable number of protocol deviations that cannot be explained due to patient safety, the issue will be discussed with the site and corrective action will be considered.

In the event a patient questionnaire is not completed during a visit, permission may be obtained from the sponsor to have that questionnaire mailed into the site within a reasonable amount of time.

## 8.9 Subject Lost to Follow-Up

Every attempt will be made to have all subjects complete the follow-up visit schedule as specified in the protocol. A subject will not be considered lost to follow-up unless efforts to obtain compliance are unsuccessful. If a subject misses a follow-up visit, the site must document attempts to contact the subject by phone twice. If both contact attempts are unsuccessful, a certified letter from the Investigator must be sent to the subject's last known address indicating the subject's commitment to the study and site contact information to arrange a visit. If the subject does not respond, only then will the subject be considered lost to follow-up. If a subject is lost to follow-up, a Study Exit case report form, including a full description of the attempts to locate the subject, must be completed.

## 8.10 Subject Withdrawal

Subjects have the right to withdraw their consent at any time during the study. If a subject requests to withdraw from the study, all information regarding the subject's withdrawal and disposition must be recorded in the subject's medical record. A Study Exit case report form, including a full description of the circumstances related to the withdrawal, must be completed.

## 8.11 Study Case Report Forms

The Sponsor will provide Case Report Forms (CRFs) to the sites for the study, on paper or electronically, as available. Data should be entered with a black ink on the specified locations of the CRFs. On paper CRFs, if an error is made, the incorrect entry should be crossed out with a single horizontal line, the correct entry written next to it, and the correction initialed and dated by the person making the correction. Copies of the CRFs for the study are included as an appendix to the protocol.

### *8.11.1 List of Case Report Forms*

- Inclusion/Exclusion
- Pre-Operative
- Operative/Discharge
- Follow-Up Form Covering:
  - Initial Post-Op Follow-Up Visit (discharge to 8 weeks post-op)
  - 3 Month Follow-Up Visit ± 2 Weeks
  - 6 Month Follow-Up Visit ± 1 Month
  - 12 Month Follow-Up Visit ± 2 Months
  - 24 Month Follow-Up Visit ± 2 Months
  - Unscheduled Visit
- Patient Questionnaires
  - Oswestry Disability Index
  - Back, Hip/Buttock and Leg Visual Analog Scale (VAS)
  - SF-12v2
  - Patient Symptom Questionnaire
- Adverse Event
- Protocol Deviation
- Study Exit

# 9 ADVERSE EVENTS

## 9.1 Definitions

*9.1.1 Adverse Event*

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject undergoing surgery in this trial which does not necessarily have a causal relationship with this intervention. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the one of the devices, whether or not the event is considered causally related to the use of the device. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

*9.1.2 Serious Adverse Event*

Any AE that results in one or more of the following is considered a Serious Adverse Event (SAE): death, life threatening situation, inpatient hospitalization, persistent or significant disability/incapacity, and other medically important events. Definitions of SAEs are:

**Death**: the subject dies during participation in the study.

**Life threatening situation**: the subject is at risk of death at the time of the event, but does not refer to the hypothetical risk of death if the AE were more severe or were to progress.

**Inpatient hospitalization**: a subject requires hospitalization or prolongation of an existing hospitalization, including medical or surgical intervention to prevent permanent impairment to a body structure or body function during participation in a clinical study.

**Persistent or significant disability/incapacity**: any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions. This includes the inability to work, but is not intended to include transient interruptions of daily activities.

**Other medically important events**: important medical events that may not result in death, be life-threatening, or require hospitalization (including emergency room visits) but may be considered a serious AE when, based upon medical judgment, they may jeopardize the subject.

Reports of all Serious Adverse Events, as classified by the Investigator, will be reviewed on a periodic basis by the Medical Monitor.

*9.1.3 Subsequent Surgical Interventions*

The cause for subsequent surgical interventions should be listed as a serious adverse event.

Subsequent surgical interventions are classified as follows:

**Revision**: a procedure that adjusts or in any way modifies the original implant configuration. A revision may also include adjusting the position of the original configuration.

**Removal**: a procedure where all of the original system configuration are removed with or without replacement.

**Supplemental Fixation**: a procedure in which additional instrumentation not under study in the protocol is implanted.

**Reoperation**: any surgical procedure at the involved level that does not require removal, modification, or addition of any components to the system.

## 9.2 Adverse Event Reporting

Any AE that occurs during the subject's participation in the study will be recorded on the Adverse Event case report form. Pre-existing medical conditions or symptoms occurring prior to the initiation of the study will not be reported as AEs but a worsening of a pre-existing medical condition or symptom will be reported as an AE. Pain, neurological status and functional impairment should be considered AEs when a subject's complaint for any of these symptoms results in an unscheduled visit or when a subject presents with new or worsening symptoms as compared to a previous visit.

All AEs will be followed until the event is resolved or considered to be stable. Relevant source documentation must be available to confirm the occurrence of an AE and must be provided to the sponsor upon request.

### *9.2.1 Serious Adverse Event Reporting*

Independent of the relationship to the study device or device procedure, the site must report SAEs to the Sponsor immediately upon becoming aware of the events and subsequently submit the appropriate CRFs within 10 working days. SAEs will be investigated and reported to the FDA if they fall within the appropriate guidelines for Medical Device Reporting (MDR). The site must also report SAEs to the reviewing Institutional Review Board (IRB)/Ethics Committee (EC) according to IRB/EC requirements.

The site must confirm the SAE in appropriate source documents and provide detailed information pertaining to the event to the sponsor and reviewing IRB/EC if requested.

## 9.3 Adverse Event Severity

The Investigator will be asked to characterize the severity of each AE as mild, moderate or severe. The assessment is subjective and the Investigator will use medical judgment to compare the reported AE to similar types of events observed in clinical practice. Guidelines for AE severity assessment are as follows:

**Mild:** The AE is transient and easily tolerated by the subject. No medical treatment required.

**Moderate:** The AE causes the subject discomfort and interrupts the subject's usual activities. Medical treatment required to alleviate or lessen the impact of this untoward condition.

**Severe:** The AE causes considerable interference with the subject's usual activities may be incapacitating and may require hospitalization. See **Section 9.1.2. Serious Adverse Events.**

## 9.4 Adverse Event Association

The relationship of all AEs to the device, the procedure or general surgery will be classified by the Investigator as not related, possibly related, probably related or definitely related.

**Not related**: The AE is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the study device, procedure or general surgery.

**Possibly related**: The causal and/or temporal relationship to the study device, procedure or general surgery, is equally or less likely than other plausible explanations.

**Probably related:** The causal and/or temporal relationship to the study device, procedure or general surgery, is likely or significantly more likely than other plausible explanations.

**Definitely related**: A clinical event that can only be attributed to the device, procedure or general surgery.

## 9.5 Potential Risks and Anticipated Adverse Events

### *9.5.1 General Surgery Risks*

General surgical risks are but may not be limited to:

- Airway Obstruction
- Anaphylaxis
- Anesthesia Related
- Atelectasis
- Blood Clots, including Pulmonary Emboli
- Cardiac Arrest
- Cardiac, Other
- CVA
- Death
- Decompensation
- Deep Vein Thrombosis
- Epidural Fibrosis
- Epidural Hematoma or Bleeding
- Excessive Blood Loss
- Hemorrhage Possibly Requiring a Blood Transfusion
- Infection, Deep Wound
- Infection, Superficial Wound
- Infection, Urinary Tract
- Infection, Other
- Myocardial Infarction
- Phlebitis
- Pleural Effusion
- Pneumonia
- Pneumothorax
- Poor Tissue Healing
- Retained Sponge
- Septicemia
- Suture Abscess
- Transfusion Reaction
- Vascular or Blood Vessel Injury
- Wound Dehiscence

### *9.5.2 Lateral Access and with or without Supplemental Fixation for Fusion Surgery Risks*

Lateral Access with or without Supplemental Fixation for Fusion surgical risks are but may not be limited to:

- Allergic Reaction to the Implant/Retractor Materials
- Bowel or Bladder Dysfunction
- Disc Height Loss
- Dural Tear (with or without Cerebrospinal Fluid Leak)
- Dysesthesia or Numbness
- Erosion due to Implant
- Failure to Relieve Symptoms, including Unresolved Pain
- Foot Drop
- Foreign Body Reaction
- Genital Numbness
- Kyphosis or Hyper-Extension
- Loss of Spinal Flexibility
- Muscle and Tissue Injury or Damage
- Nerve Injury
- Nerve Root Injury
- Osteolysis
- Pain, New Onset
- Pain, Unresolved
- Paralysis
- Pseudoarthrosis
- Sexual Dysfunction
- Spinal Cord Damage
- Spinal Degeneration
- Spinous Process Fracture
- Surgical Intervention at Incorrect Levels
- Tingling
- Thigh Pain
- Vertebral Body Fracture
- Weakness

### *9.5.3 K2M Device Risks*

Risks specific to the RAVINE, ALEUTIAN Lateral, CASCADIA Lateral, SERENGETI, DENALI Minimally Invasive, EVEREST Minimally Invasive, and CAYMAN Minimally Invasive Systems are but may not be limited to:

- Bone Graft Migration
- Bone Graft Subsidence
- Device Instability
- Device Malposition
- Device Migration
- Device Subsidence
- Disengagement – from Bone
- Disengagement – Screw/Rod Interface
- Foreign Body Reaction
- Material Degradation
- Plate Breakage
- Prominent Implants
- Retractor breakage
- Rod Breakage
- Rod Interface Disengagement
- Screw Back-out
- Screw Breakage
- Screw/Rod Interface Slide
- Set Screw Loosening

# 10 SITE REGULATORY REQUIREMENTS

## 10.1 Institutional Review Board (IRB)/Ethics Committee (EC) Approval

Prior to enrolling subjects in the study, site IRB/EC approval must be obtained according to 21 CFR Part 56. IRB/EC approval must be maintained by the site throughout the study. The IRB/EC approval letter(s) must be maintained in the study files at all times.

## 10.2 Study Specific Informed Consent

The informed consent process when executed properly provides sufficient information about study procedures so that a potential participant can voluntarily make a reasonable decision about participation, based on an understanding of the purpose, potential risks and anticipated benefits (if any) of the study. Informed consent is not a waiver of rights.

A study specific sample informed consent will be provided to each site prior to the IRB/EC process. The sample informed consent should be used as a template for creating the IRB/EC specific informed consent. Prior to submission of the proposed informed consent to the reviewing IRB/EC, the Sponsor must review the informed consent for completeness according to the protocol and according to 21 CFR Part 50. Potential study subjects should be offered informed consent according to the process outlined in **Section 8.1 Patient Screening and Enrollment**.

Patients must not be offered informed consent until written proof of IRB/EC approval is attained. The patient should be given the opportunity to take home a copy of the informed consent to review and discuss with family members or acquaintances prior to signing. Potential study subjects must also be given the opportunity to discuss the procedure, risks, benefits, alternative treatments and study requirements prior to signing the informed consent. Patients should be informed that they are free to refuse participation in this study and refusal will not affect their medical treatment. If patients elect to participate, it should be made clear that they may withdraw from the study for any reason and at any time without prejudicing further care.

A copy of the signed and dated IRB/EC approved informed consent should be given to all subjects.

## 10.3 Regulatory Documents

Prior to patient enrollment, the following documents must be provided to the Sponsor and be on file at the site:

- Curriculum vitae and copy of medical license for Principal and Sub-Investigators
- IRB/EC approval letter and IRB/EC roster
- IRB/EC approved informed consent form
- Signed Clinical Research Agreement
- Signed Investigators Agreement for Principal and Sub-Investigators, as required
- Finalized budget agreement
- Financial disclosures for the Principal and Sub-Investigators
- Site Initiation documentation

# 11 SITE VISIT/MONITORING PROCEDURES

Monitoring of the study will be a continuous process conducted in accordance with 21 CFR 812.46 and applicable Sponsor procedures. Monitoring will be performed by qualified clinical research personnel, or designees, of K2M.

## 11.1 Site Qualification Visit

Prior to selecting an Investigator for participation in the study a Qualification visit will be performed. The purpose of the visit is to confirm that the Investigator/investigative site has adequate staff, including a designated Study Coordinator, and facilities to perform the study according to the requirements of the protocol.

## 11.2 Study Initiation Visit

Prior to enrolling subjects at a study site, a Site Initiation Visit will be performed. The purpose of the visit is to confirm that the site continues to be qualified for participation and to review the Investigator/site responsibilities and requirements for the study. Site training will be performed and will include:

- Review of the clinical protocol and data collection process
- Monitoring requirements
- IRB/EC requirements
- Informed Consent process
- Review of site records

## 11.3 Periodic Monitoring Visits

Periodic site monitoring visits will be performed during the study by a designated study monitor assigned by the Sponsor. The purposes of the visits are to confirm compliance to the protocol, review regulatory documents, accurate and complete records are being maintained and to compare source documents to completed CRFs for completeness and consistency. The initial monitoring visit to a site will be scheduled soon after the first 2 to 5 patients are enrolled in the study and may occur prior to the first surgery. The frequency of subsequent visits will be dependent upon the rate of enrollment and site performance on previous monitoring visits. If possible, monitoring visits will be performed at least quarterly. Specific assessments during a monitoring visit include:

- Continued site acceptability
- Compliance to the protocol
- IRB/EC approval status
- Use of the approved informed consent
- Adequacy of source documents
- Complete and accurate CRFs
- Reporting of adverse events
- Protocol deviations
- Site records

If it is determined during a monitoring visit that there are significant non-compliance issues at a site, including adherence to the protocol or applicable regulatory requirements, the issues will be discussed with the Investigator and Study Coordinator and the site will be instructed how to gain compliance. If continued non-compliance is detected on a subsequent monitoring visit, it may be necessary to terminate site participation in the study.

## 11.4 Final Close-Out Visit

At the completion of the last long-term follow-up visit at each site a final close-out visit will be performed. The purpose of the visit will be to:

- Review site records
- Reconcile all outstanding data queries
- Review the records retention requirements for the study
- Review the final IRB/EC requirements for the study

# 12 STATISTICAL METHODS

## 12.1 Study Design

Prospective single-arm controlled, multi-center study to evaluate the patient outcomes and incidence of complications using RAVINE compared to the literature reported results with the XLIF system for the surgical treatment of patients with symptomatic DDD with up to Grade 1 spondylolisthesis.

## 12.2 Study Hypothesis

The primary effectiveness endpoint is the improvement Back VAS and Leg VAS at 24 months as compared to pre-op time periods. The primary hypothesis of this trial is that the clinical performance of the K2M RAVINE system is non-inferior to the clinical performance achieved and reported with the NuVasive lateral system.

A PubMed literature review was conducted to assemble relevant publications utilizing results from minimally-invasive far lateral fusion surgeries utilizing the XLIF system in patients with symptomatic DDD with up to Grade 1 spondylolisthesis. Searches included all peer-reviewed journals published between January 2000 and April 2013. Articles were selected for review if at least a portion of the represented cases included minimally-invasive far lateral surgery with or without minimally-invasive supplemental stabilization. Sample sizes, patient populations, evaluated variables, results, and recorded complications were assessed for each selected article.

Only data regarding VAS back and leg outcomes of XLIF cases in patients with symptomatic DDD with up to Grade 1 spondylolisthesis were incorporated into the VAS score tables used for statistical analysis. Articles were entirely excluded from the statistical analysis if results combined data from cases with multiple diagnoses not included in this study or if data were extracted through meta-analysis.

The following tables give the VAS Back and VAS Leg improvements found from included studies:

**VAS back**

| Paper # | n | Preop | Last FU | Difference of means | Weighted difference | Sum of weighted differences | Sum of sample sizes | Average difference of means |
|---|---|---|---|---|---|---|---|---|
| 1[1] | 30 | 3.90 | 2.90 | 1.00 | 30.00 | 889.53 | 237 | 3.75 |
| 2[2] | 84 | 5.89 | 1.37 | 4.52 | 379.68 | | | |
| 3[3] | 93 | 7.25 | 2.80 | 4.45 | 413.85 | | | |
| 4[4] | 30 | 6.80 | 4.60 | 2.20 | 66.00 | | | |

**VAS leg**

| Paper # | n | Preop | Last FU | Difference of means | Weighted difference | Sum of weighted differences | Sum of sample sizes | Average difference of means |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | 7.50 | 2.90 | 4.60 | 138.00 | 560.10 | 153 | 3.66 |
| 2** | | | | | | | | |
| 3 | 93 | 5.80 | 2.10 | 3.70 | 344.10 | | | |
| 4 | 30 | 5.40 | 2.80 | 2.60 | 78.00 | | | |

** No Leg VAS separately detailed in paper for this study

The study hypothesis for both the Back and the Leg VAS is that the RAVINE system is non-inferior to other systems post-surgery. The hypotheses can be written:

H0: $\mu_R \leq$ OPC
H1: $\mu_R >$ OPC

where $\mu_R$ is the mean VAS of the RAVINE system, the Objective Performance Criteria (OPC) is 3.25.

### 12.3 Sample Size

A total sample size of 222 subjects was selected for the study. Assuming the true mean difference between pre-op and 24 month follow-up VAS is 3.66 and the standard deviation is 2.0, a sample size of 189 subjects provides >87% power to detect a statistically significant difference between the mean post-op VAS and the OPC of 3.25 using a one-sided one-sample t-test at a significance level of 0.05. In order to account for approximately 15% attrition, based on clinical experience, 222 subjects will be enrolled.

### 12.4 Analysis Populations

Analysis Populations are defined as follows:

- The Intent-to-Treat (ITT) population includes all enrolled subjects.
- The Per-Protocol population includes all enrolled subjects who have no major protocol violations (defined as not meeting inclusion/exclusion criteria or not being consented properly) and have 24 month VAS scores.

The effectiveness analysis will be performed on the Per Protocol population. Analysis of the ITT population considering several missing data imputations will be confirmatory of the Per Protocol analysis. Safety summaries will be performed on the ITT population.

### 12.5 Analysis of Primary Endpoint

The primary effectiveness endpoint will be evaluated on the Per Protocol population by a one-sided one-sample t-test of the RAVINE system which is measured as the difference between the pre-op and 24 month post-op Back VAS and the Leg VAS as compared to 3.25, the literature reported differences.

As secondary analyses, the comparison of the difference between the pre-op and 24 month Back VAS and Leg VAS will be repeated as follows:

- Considering ITT subjects with available 12 or 24 month data only. In the event that a subject has 12 month data but no 24 month data, the 12 month VAS scores will be used. Subjects without 12 or 24 month VAS measurements will be excluded.
- A Last Observation Carried Forward (LOCF) approach for all ITT subjects

### 12.6 Safety Analyses

Incidence rates of adverse events will be provided descriptively in tabular form for each study group for the overall adverse event rate, serious adverse event rates, revision rates, removal rates, etc. at each follow-up interval.

### 12.7 Supplementary Analysis

Other ancillary variables such as demographics, baseline variables, surgical variables and post-op pain medication usage will be summarized by mean, standard deviation, median (if appropriate), and range for continuous measures, and frequency and percent for categorical measures.

Graphical methods such as bar graphs, box and whiskers plots, and star plots may be employed to compare the study groups simultaneously for multiple variables.

## 12.8 Methods to Minimize Bias

Quantitative radiographic evaluations will be conducted by an independent central radiology laboratory using validated digitization software. Lastly, this trial includes several well-validated patient-reported outcome measures (e.g., VAS, ODI, SF-12v2). When providing follow-up self-reports of these outcomes, subjects will remain blinded to their previous responses on these instruments so as to not bias their current reports. When conducting follow-up neurological examinations, every effort will be made to blind the Investigators to the ratings provided at earlier intervals.

Insofar as possible, sites for the study will be distributed regionally and by type of institution and level of investigator experience, patient volume and research experience so that any unknowable and potentially prognostic factors may then be balanced both geographically and demographically in the study arms.
We will evaluate the subjects from each site to assess poolability of the data. Sites will be examined for adherence to the requirements of the protocol, baseline demographic and relevant clinical characteristics.

# 13 SITE RESPONSIBILITIES

## 13.1 Investigator

Principal Investigators selected by K2M to participate in this clinical study assume overall responsibility for the performance of the study at the site.

Specifically, the Investigator will assume the overall responsibility for:

- Obtaining IRB/EC approval
- Conducting the study according to the clinical protocol and applicable, federal, state and local regulations and the signed Clinical Research Agreement
- Providing financial disclosure according to federal regulations
- Proper execution of the approved informed consent
- Protecting the rights, safety and welfare of study subjects
- Appropriate source documents to verify study data
- Reviewing and signing all CRFs for subjects enrolled in the study
- Oversight and training of site staff given study related responsibilities

## 13.2 Study Coordinator

The Study Coordinator is designated by the Investigator to assume site management responsibilities. Specifically, the Study Coordinator is responsible for:

- Managing the IRB/EC submission and approval process
- Managing study activities according to the clinical protocol and applicable, federal, state and local regulations and the signed Clinical Research Agreement
- Ensuring proper execution of the approved informed consent
- Protecting the rights, safety and welfare of study subjects
- Maintaining appropriate source documents to verify study data
- Ensuring that CRFs are complete, reviewed and signed by the Investigator at the completion of patient contacts and before scheduled monitoring visits
- Ensuring that radiographic images are submitted, as required
- Management of additional staff members given study related responsibilities

If the Investigator designates a replacement Study Coordinator at any time during the performance of the study, the Sponsor must be notified immediately. A Sponsor designee will arrange to visit the site as soon after the notification as is feasible to ensure that the replacement Study Coordinator has the ability and is adequately trained to function in that capacity.

# 14 RECORDS AND REPORTS

All Sponsor and site records may be subject to regulatory inspection and must be retained for a period of 2 years following, a) the date the investigation is completed or terminated, or b) the records are no longer required to support a regulatory submission, whichever is longer. The Sponsor will notify the site in regard to length of record retention at the completion of the study.

## 14.1 Investigator/Site Records

Investigator/site records must be maintained and updated as necessary. Records will be reviewed during the site initiation visit and on subsequent monitoring visits to ensure adequacy and completeness of records. Investigator/site records include, but may not be limited to:

- Original and All Subsequent IRB/EC Approval Letters
- Original and All Subsequent (if applicable) Approved Informed Consents
- IRB/EC Roster
- IRB/EC Updates/Reports as Required by Reviewing IRB/EC
- Final Protocol and Subsequent (if applicable) Protocol Amendments
- Other Required Reports
- Relevant Correspondence between the Investigator, IRB/EC and K2M
- Signed Clinical Research Agreement
- Signed Investigators Agreement for Principal and Sub-Investigators, as required
- Financial Disclosure Documents
- Copies of Curriculum Vitae for the Investigator and Sub-Investigators
- Site Signature & Responsibility Log
- Site Monitoring Log
- Signed Informed Consents
- Completed Case Report Forms

## 14.2 Investigator/Site Reports

The Investigator/site is responsible for the preparation and submission of reports to the Sponsor, IRB/EC and applicable Regulatory agencies. The following reports are required:

**Serious Adverse Events**: Submitted to the Sponsor within 10 working days of first learning of the event and to the reviewing IRB/EC as required

**Withdrawal of IRB Approval**: Sponsor must be notified within 5 working days

**IRB/EC Updates/Reports**: Submitted to the reviewing IRB/EC as required

**Failure to Obtain Informed Consent**: Submitted to the Sponsor and reviewing IRB/EC within 5 working days after realizing the failure

**Final Report**: Submitted as required to the reviewing IRB/EC

## 14.3 Sponsor Records

The Sponsor will maintain site specific study files including:

- Copy of the Original and All Subsequent IRB/EC Approval Letters
- Copy of the Original and All Subsequent (if applicable) Approved Informed Consents
- IRB/EC Roster
- Copy of IRB/EC Updates/Reports as Required by Reviewing IRB/EC
- Other Required Reports
- Relevant Correspondence between the Investigator, IRB/EC and K2M
- Signed Clinical Research Agreement
- Signed Investigators Agreement for Principal and Sub-Investigators, as required
- Financial Disclosure Documents
- Copies of Curriculum Vitae for the Investigator and Sub-Investigators
- Site Initiation Report
- Site Monitoring Reports
- Completed Case Report Forms

In addition, the Sponsor will maintain a Study Central File including, but not limited to:

- Final Protocol and Subsequent (if applicable) Protocol Amendments
- Clinical Research Agreement and Investigators Agreement Template, as applicable
- Composite Listing of Adverse Events
- Data and Data Analysis
- Interim (if applicable) and Final Summary

## 14.4 Sponsor Reports

The Sponsor is responsible for the preparation and submission of reports to the Site and applicable Regulatory agencies. The following reports are required:

**Serious Adverse Events**: Submitted to the FDA only if they meet the requirements for MDR reporting

**Final report**: Submitted to all sites upon completion of the study and final data analysis

Reports not listed may be made by the Sponsor to Regulatory agencies and to the sites if additional notifications are necessary.

# 15 PUBLICATION POLICY

Data resulting from the conduct of this study are considered confidential information. Abstracts, book chapters, articles, white papers peer-reviewed manuscripts and other publications (all of which are "Publications") resulting from the study can originate from the sponsor or from Investigators participating in the study; provided, however, any Publications shall be governed by and in compliance with the terms of Section VIII of the Clinical Evaluation Research Agreement.

# 16 REFERENCES

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