Circumferential Vertebral Reconstruction of Osteoporotic Compression Fractures Using a Novel Bipedicular Peek Implant (RECONSTRUCT)
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Circumferential vertebral **RECONSTRUCT**ion of osteoporotic compression fractures using a novel bipedicular peek implant (RECONSTRUCT)

Protocol Number: WIUSA 1

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Sponsor: Hyprevention SAS

Version Number: V3

03 June 2024

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE PAGE

By signing below I confirm that:

1) I have read this protocol (Version 3; dated 03 June 2024 , and it contains all necessary details for conducting this study; and

2) I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

_____

Principal Investigator's Signature Date

_____

Principal Investigator's Name

_____

Site Name

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

Circumferential vertebral **RECONSTRUCT**ion of osteoporotic compression fractures using a novel bipedicular peek implant (RECONSTRUCT STUDY)

Study Description:

Multi-center, prospective, single arm study conducted on 30 subjects followed to 6 months post-operatively

Objectives:

Primary Objective: Ability to enroll

Secondary Objectives:

1) To evaluate intraprocedural technical performance.
2) To evaluate fracture stability over time at the target level.
3) To evaluate incidence of adjacent and remote level vertebral compression fractures during follow up period
4) Response to treatment in terms of pain reduction andfunctional status over time

Endpoints

Feasibility will be determined based upon the ability to successfully enroll 30 patients over the study period. Performance outcomes and safety outcomes will be observed over time. Performance endpoints comprise functional (Visual Analog Scale, Eq5D questionnaire, Oswestry disability index, Roland Morris disability questionnaire) and radiologic variables (vertebral height maintenance, segmental kyphotic angle, subsequent adjacent and remote vertebral fractures, subsequent same level vertebral compression fractures). Safety endpoints will include adverse events and frequency of secondary surgical intervention.

Inclusion Criteria

- Age ≥ 50
- Osteoporotic compression fractures of the thoracolumbar spine (T1 – L5)
- Up to three levels can be fractured and treated but at least one of the three need to be treated with V-STRUT; the level to be treated with study device is at the discretion of the enrolling investigator
- Fracture age of ≤ 12 weeks as indicated by onset of pain or known antecedent traumatic event with corresponding evidence of acuity on MRI (T1 and STIR sequences) or radioisotope bone scan
- ODI ≥ 30/100 at screening visit and VAS ≥ 60 at screening visit.
- Failure of conservative management strategies for compression fractures resulting in inadequately controlled pain and/or patient immobility
- Patient has failed non-operative medical therapy as defined by one of the following definitions set forth by the American College of Radiology:[1]
    - For a patient rendered nonambulatory as a result of pain from a VCF, pain persisting at a level that prevents ambulation despite 24 hours of analgesic therapy; or
    - For a patient with sufficient pain from a VCF such that physical therapy is intolerable, pain persisting at that level despite 24 hours of analgesic therapy;
    - For a patient with pain from a VCF, unacceptable side effects such as excessive sedation, confusion, or constipation as a result of the analgesic therapy necessary to reduce pain to a tolerable level.
- Magerl classification A1.1, A1.2, A1.3, A2.1, A2.2 and A3.1 type fractures; pediculosomatic junction fractures and other fractures involving vertebral pedicles
- Appropriate pedicle diameter to receive 4.5mm, 5.5mm diameter or 6.5mm diameter implants
- ASA < 4.

Exclusion Criteria

- Patient clearly improving on conservative treatment
- Any contra-indication or allergy to implant material or cement
- Systemic infection or infection located in the spine
- Any medical condition including but not limited to anemia, coagulation disorders, fibromyalgia, algoneurodystrophy, Paget's disease, uncontrolled diabetes that would preclude the patient from having surgery or would impede the benefit of surgery
- Neurologic signs or symptoms related to the fracture or the impeding pathological fracture
- Less than one third of the original vertebral body height remaining.
- Unstable fractures or neoplasms with posterior involvement
- Damages of the posterior wall
- Sclerotic cancellous bone
- Pedicles not large enough to accept V-STRUT©

instrumentation and implants

- Pregnancy (women of childbearing potential must have a negative pregnancy test to participate)
- Pre-existing or clinically unstable neurologic deficit
- Spinal canal compromise causing clinical manifestations of cord, neural foramen, or nerve root compression at the level to be treated
- Any physical exam evidence of myelopathy or radiculopathy
- Pain based on clinical diagnosis of herniated nucleus pulposus or severe spinal stenosis (progressive weakness or paralysis)
- Bed bound prior to incident fracture
- Spondylolisthesis > Grade 1 at target VB
- Any underlying systemic bone disease other than osteoporosis (e.g., osteomalacia, osteogenesis imperfect, Paget's disease, etc.)
- A medical contraindication to spinal surgery and/or general anesthesia, such as coagulopathy and/or taking warfarin (Coumadin) or other anticoagulant or anti-aggregate therapy including antiplatelet agents on regular basis for coagulopathy (with a threshold for normal being INR≤1.5, PTT within lab normal range, and platelet count > 100,000)
- Disabling back pain due to causes other than acute fracture
- Severe cardiopulmonary deficiencies
- Any evidence of alcohol or drug abuse
- Uncontrolled psychiatric illness or severe dementia
- Involved in medical litigation including workers' compensation
- Any previous surgical treatment (material or cement) in the targeted vertebra

Study Population:	Male and female adult patients with acute osteoporotic (patient age >50) compression fractures, less than or equal to 12 weeks of age associated with severe pain (VAS $\geq$ 6/10) at baseline
Phase:	Post-market registry.
Description of Sites/Facilities Enrolling Participants:	Mount Sinai will act as both an enrollment center and the CRO for this study. Three additional sites will be included along with Mount Sinai.
Description of Study Intervention:	The study device is V-STRUT© Vertebral Implant manufactured by Hyprevention SAS (VIP - Vertebral Implant PEEK), FDA cleared under K191709 and K240084, indicated for use in the treatment of vertebral fractures in the thoracic and lumbar spine from T1 to L5. It is intended to be used in combination with PMMA bone cement. VIP procedure is a minimally invasive/percutaneous vertebral augmentation (PVA), image guided procedure. Two VIP devices are implanted in each to be treated vertebra. A cavity is drilled allowing the introduction of the implant posteriorly through the pedicle and the vertebral body up to the anterior wall. A part of the implant is embedded into the pedicle, thus providing posterior support. The other part of the device, located in the vertebral body, presents a central canula and lateral perforations, which allow acrylic bone cement diffusion, filling of the vertebral body, filling and fixing the implant, and supporting of the upper endplate. The combination of the implant and the cement allows the treatment of vertebral fractures. VIP exists in 3 (4.5, 5.5, 6.5 mm) different diameters and multiple lengths between 25 to 60 mm to accommodate individual patient's anatomy of thoracic and/or lumbar vertebrae from T1 to L5. The implant is made of radio transparent polymer, PEEK (Polyetheretherketone as per ASTM F2026), is MRI safe and includes visualizing markers made of tantalum (as per ASTM F560). VIP is implanted with a specific instrumentation (V-STRUT© Instrumentation Set (reusable) and V-STRUT© Guide Wire).

Figure 1: Views of the VIP device in a vertebra (A- Perspective. B- Top view. C- Side view. D- Back view)

Study Duration: 36 months (24 months enrollment, 6 months follow-up, 6 months for final report)

Participant Duration: 6 months

1.2 SCHEMA

Visit#	Timing	Purpose	Description
0	Day 0	Screening	- Screen potential participants by inclusion and exclusion criteria - MRI +/- CT evaluation (vertebral body and pedicles fractures) - Obtain informed consent - Obtain history document - Visual Analog Scale (VAS) Pain Assessment - Health Questionnaire Eq5d Questionnaire - Oswestry Disability Index (ODI) - Roland Morris Disability questionnaire - Medication/Analgesic requirements - Total n=25
1	Day 1	Operative visit	- Treatment with V-STRUT© - On table dyna CT or post-operative CT after treatment or prior discharge - Medication/ Analgesic requirements
2	Day 14 (Window: ± 3 days)	Post-op follow-up	Clinical exam: - Wound site evaluation - Neurological exam - Visual Analog Scale (VAS) Pain Assessment - Health Questionnaire Eq5d Questionnaire - Oswestry Disability Index (ODI)

			- Roland Morris Disability questionnaire - Medication/ Analgesic requirements
3	Day 30 (Window: ± 7 days)	Post-op follow-up	Clinical and radiological exam: - Visual Analog Scale (VAS) Pain Assessment - Health Questionnaire Eq5d Questionnaire - Oswestry Disability Index (ODI) - Roland Morris Disability questionnaire - Radiographic evaluation (AP and lateral standing) - Medication/ Analgesic requirements
4	Day 180 (Window: ± 1 month)	Post-op follow-up	Clinical and radiological exam: - Visual Analog Scale (VAS) Pain Assessment - Health Questionnaire Eq5d Questionnaire - Oswestry Disability Index (ODI) - Roland Morris Disability questionnaire - Radiographic evaluation (AP and lateral standing xrays) and CT examination (vertebral body and pedicles) - Medication/ Analgesic requirements

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -0	Treatment Visit 1, Day 1	Study Visit 2 Day 14 +/-3	Study Visit 3 Day 30 +/- 3	Study Visit 4 Month 6 +/-21 day
Informed consent	X				
Demographics	X				
Medical history	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X
Treatment		X			
CT Scan Intra Op OR D/C		X			X
Visual Analog Scale (VAS) Pain Assessment	X	X	X	X	X
Oswestry Disability Index (ODI)	X	X	X	X	X
Health Questionnaire EQ-5D-5L Questionnaire	X		X	X	X
Roland Morris Disability Questionnaire	X		X	X	X
Radiologic/Imaging assessment	X	X		X	X
Adverse event review and evaluation	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to collect clinical and radiologic data regarding use of the VIP implant (V-STRUT© manufactured by Hyprevention) in the treatment of symptomatic , acute (≤ 8 week) vertebral compression fractures who have failed conservative care strategies (as described above). The device is FDA approved for this indication (FDA 510(k) clearance K101709 obtained in March 2020). The device is also being studied in France on 20 patients (NTC03580434). Nine have been enrolled to date and preliminary results have been published on 6 patients (see summary below).[2]

Multiple standards setting organizations acknowledge vertebroplasty (VP) and balloon kyphoplasty (BKP) as safe, efficacious, and durable procedures in appropriate patients with painful osteoporotic when performed in accordance with published standards.[1] These procedures relieve fracture pain by stabilizing the fracture site using cement. In patients with painful osteoporotic fractures that may benefit from vertebral height restoration, alternative interventional techniques include percutaneous

vertebral augmentation (PVA), which combine cement injection with implantable devices. Two such devices, SpineJack® and KIVA®, have been evaluated in two separate prospective randomized trials.[3]

Outcomes for the Spinejack® device were evaluated in 68 osteoporotic patients in the SAKOS Study (NCT0246180) and outcomes in 144 osteoporotic patients treated with the KIVA® device were evaluated in the KAST Study (NCT01123512). In both of these trials, a control arm involving BKP was used (73 patients in SAKOS study and 141 patients in KAST Study). In contrast to currently available implantable devices, which aim primary to restore vertebral height,[5] the transpedicular V-STRUT© implant aims to prevent progression of postoperative fractures and continued vertebral body compression by distributing axial load to the posterior column of the spine.

This study is a multi-center, prospective pilot study intended to obtain clinical and radiologic outcomes data on the V-STRUT© implant in osteoporotic compression fractures. Study endpoints will focus on pain relief, functional improvement and quality of life measures and incidence of subsequent fractures at adjacent levels. A total of 30 patients will be enrolled across all four sites.

Regarding clinical data collection, the studies conducted on the alternatives, SAKOS and KAST have been used as reference to determine objectives and endpoints for osteoporotic patients.

2.2 BACKGROUND

Vertebral compression fractures affect an estimated 1.4 million patients in the world annually and incidence rates rise exponentially with age, especially in women.[6 7] Outcomes following non-interventional management of these injuries are generally poor, largely as a consequence of opioid requirements, prolonged immobilization, and bedrest. [8-10] As a result, interventional techniques such as BKP and VP with or without implantable devices are currently regarded as the standard of care for select patients with acute painful osteoporotic compression fractures.[1]

The VIP implant (V-STRUT© manufactured by Hyprevention) has undergone both clinical and pre-clinical testing. Static and dynamic bending of the implant has been evaluated to demonstrate that the product is capable of supporting in-situ loading, and increase fracture load and energy to fracture. Testing was conducted on the implant alone, without cement and without support below the implant, and used a loading force of 21.6 N (corresponding to the anatomical load the implant alone should receive in-vivo). Results demonstrated a static yield load >21 N and run-out load ≥ 21.6 N (5 million cycles). The implant was neither broken nor bent during testing, indicating that it can support in-situ loading (static and dynamic) without failure.

Further, biomechanical study conducted on osteoporotic human vertebrae has been conducted comparing the VIP implant to vertebroplasty in order to assess the biomechanical efficacy of this implant in resurrecting and fortifying the osteoporotic vertebra following a vertebral body fracture.[11]

In this study, a total of 17 vertebrae from 3 human osteoporotic spine segments (T9-L5) were selected. Vertebral compression fractures were generated by eccentric compressive loading until a height reduction of 25%. Then the vertebrae were either fixed using vertebroplasty technique (control group; n=8) or by vertebral augmentation with the VSTRUT © implant combined with bone cement (device group; n=9). A new compressive loading was performed in the same conditions. Maximal load and stiffness, as well as total energy to fracture were measured.

Fracture force and energy to fracture were both increased either after V-STRUT© implantation or vertebroplasty compared to when the initial fracture was generated. Mean increase percentage between the initial value and the post-treatment value for each parameter were +77% vs +39% regarding fracture load and +126% vs +99% for energy to fracture, for the device group vs vertebroplasty group respectively. No pedicle fractures were observed in both groups, nor implant breaking or bending in the device group. These results show that V-STRUT© combined with bone cement has the ability to reinforce the vertebral body strength, with an at least equivalent biomechanical performance as vertebroplasty.

A clinical study (NCT03580434) is in progress in France, and preliminary results on 6 patients have been published.[3] From February 2019 to December 2019, 6 consecutive patients (3 men and 3 women; mean age 55 ± 8 years; range 40–64 years) who had percutaneous transpedicular fixation with cementoplasty for the treatment of VCF (5 tumor lesions, 1 traumatic) were included. The procedure duration, length of hospital stay, and complications were reported. Visual analog scale (VAS) and the Oswestry disability index (ODI) for pain and disability were assessed before and 2 months after the procedure.

The mean procedure duration was 74 ± 47 min (range 20–140 min). The median length of hospital stay was 3 days (range 2–63) after the procedure. Only minor adverse events occurred (4 asymptomatic cement leakages) and there were no severe complications. No cases of procedural site fracture during follow-up were noted (median 198 days; range 78–238 days). The mean VAS score decreased from 6.2 ± 1.8 mm (median 6 mm; range 4–9 mm) before the procedure to 1.7 ± 2.1 mm (median 1; range 0–5 mm) after the procedure. The ODI decreased from 36 ± 14% (range 18–54%) before the procedure to 23 ± 10% (range 11–30%) at 2-months follow-up. These preliminary clinical results suggest that percutaneous transpedicular fixation of VCF by PEEK implants with cementoplasty appears feasible and safe.

The use of V-STRUT© in current practice has started in the USA, and preliminary data on the first two patients are shown below:

Case	Anesthesia	Treated Level	Pathology	Implant #1	Implant #2	Cement	Volume of	Cement leakage	Symptomatic	Duration (min)	Hospitalization stay (days)
1	MAC	L1	Osteoporosis	5.5 L45	5.5 L40	Vertecem 2	9	N	N	18	0
2	MAC	L2	Osteoporosis	5.5 L55	5.5 L50	Vertecem 2	10	N	N	20	0

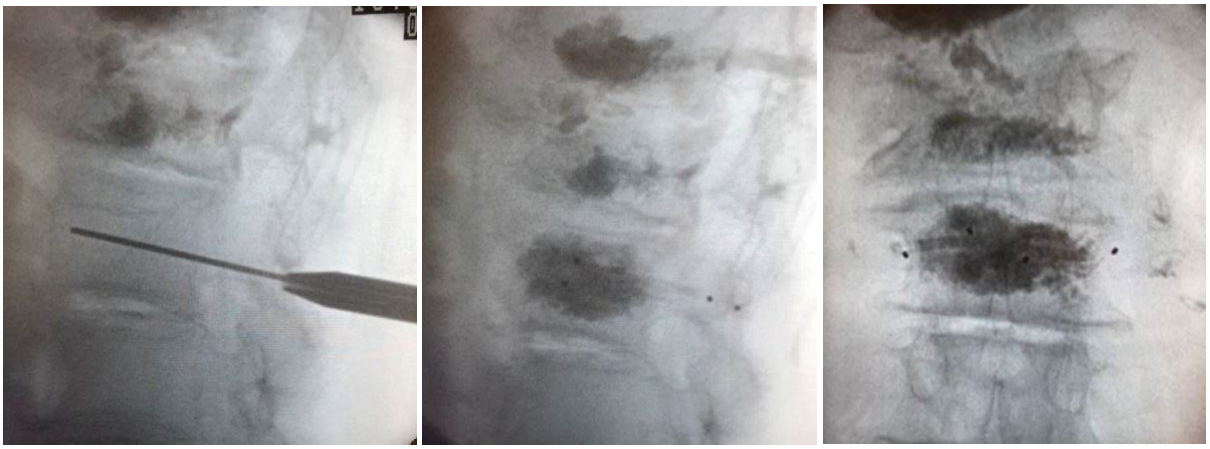
VAS score

Case	Pre-Op	Hospital discharge	2 Months
1	8	0	0
2	9	1	0

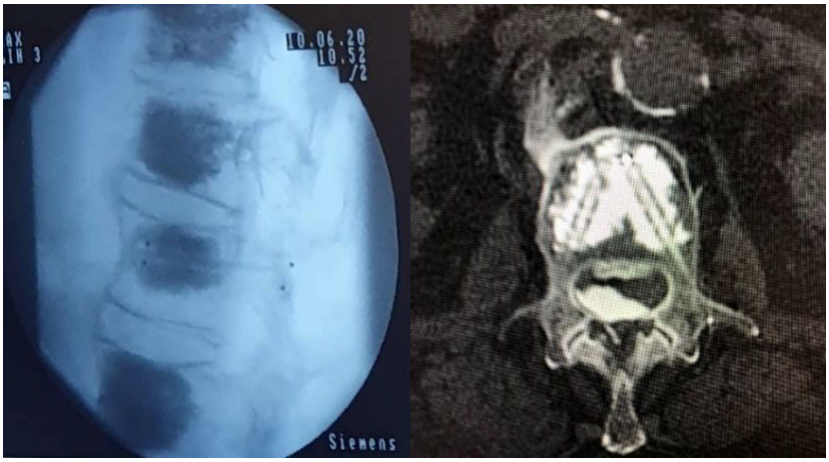
ODI Index

Case	Hospital discharge	2 Months
1	69	5
2	73	8

Case 1:



Cases 2:



2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Clinical risks have been assessed through pre-clinical study, literature review and a pre-market clinical study.

These risks are identified in the Instructions For Use (http://instructions.hyprevention.com/) that were part of the FDA review for clearance (K191709 and K240084).

Side effects possibly associated with the use of VIP are the same as for other percutaneous spinal procedures.

Those may include:

- Cement leakage
- Anterior displacement of bone fragments, or vascular puncture
- Hematoma, bleeding, hemorrhage, embolism
- Pain
- Inflammatory reaction, infection, cutaneous necrosis
- Anaphylaxis
- Dural tear, neurological complications
- Secondary fracture, subsidence, fracture of the pedicle, implant migration, implant fracture, or initial lesion aggravation.

Some of these undesirable side effects may lead to lengthening of the procedure or to a new surgery.

This list may not include all complications caused by the surgical procedure itself (including anesthesia and radiation). This list may not include all the undesirable side effects related to the cement: refer to the cement manufacturer's instructions for use.

There are no physical, psychological, social, legal, economic risks for the participant of the study. The technique proposed is equivalent to other technique. The patient will receive a detailed information on the technique and the alternative from the investigator and will accept freely to participate to the study by signing the inform consent.

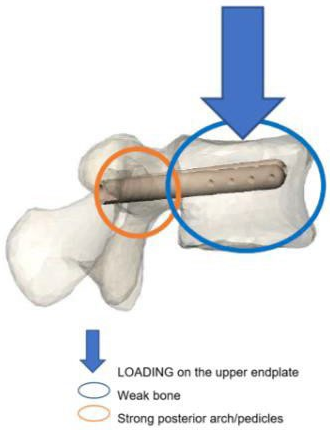
2.3.2 KNOWN POTENTIAL BENEFITS

The anticipated clinical benefits of the treatment using the VIP device are:

- Pain reduction, immediate and long term (assessed by VAS score and Analgesic requirements)
- Improved functional and quality oflife measures, immediate and long term (assessed by Oswestry disability questionnaire, EQ-5D-5L and Roland Morris DisabilityQuestionnaire)
- Maintenance of vertebral height over time (assessed by radiographic follow-up)
- Stability of treated level with absence of ongoing collapse or deformity during the followup period

Maintenance of vertebral height at the treated level and a decrease in the likelihood of adjacent vertebral compression fractures is predicted due to the transpedicular implants ability to create a bridge between the anterior, middle and posterior columns. The implant is designed to redistribute load received on the superior vertebral endplate to the posterior arch.

Figure 1: VIP device principle



2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

VIP is a new technique to treat vertebral fracture; however, numerous similar techniques already exist and are used on a daily base worldwide. The initial clinical experience did not show any risk.

The treated population will be the same as the population managed with equivalent instrumented vertebral augmentation techniques (SpineJack® Implant, Kiva® Implant) that have provided good clinical results in terms of pain and functional outcomes according to literature and safety database reviews.[3 4]

When using VIP implant, the standard of care will be like the other techniques and there is no additional risk anticipated.

The investigators involved in the study are experimented practitioners of the other techniques and have a very good understanding and practice of the other techniques. They will be trained adequately to the VIP technique and supported by product specialists during the implantation.

The treatment will be done in the same facilities as for the reference techniques, meaning operative room for surgical treatment, with trained technical team/OR staff.

The expected benefits of the VIP are to be at least equivalent to the reference techniques in term of performance: pain reduction and long-term fracture fixation, and we do not anticipate any performance issues.

Therefore, we believe the benefits of using VIP to treat vertebral compression fracture due to osteoporosis outweighs the risks.

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. To evaluate the efficacy of the treatment with VIP to reduce pain without device related adverse events	Feasibility endpoint: Ability to enroll 30 patients. • Safety endpoint: Absence of device-related serious adverse events, defined as device-related adverse events (device migration, device fracture) or symptomatic cement extravasation requiring surgical re-intervention or retreatment at the index level, including revision,	The primary purpose of this pilot study is to the demonstrate the feasibility of enrolling the target patient population. This outcome measure will be used to inform the recruitment plan for a future larger multicenter study.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	removal, reoperation, and/or supplemental fixation.	The absence of device-related serious adverse event is a major endpoint to assess the device safety as part of its efficacy.
Secondary		
1. To evaluate technical performance. 2. To evaluate efficacy to maintain performance. 3. Secondary feasibility endpoints	Technical Performance: • Procedure duration • Volume of cement injected per level • Asymptomatic cement leakage • Fluoroscopy time and dose • % Vertebral height restoration at end of procedure Performance Efficacy: • Incidence of progressive collapse/deformity at treated level post augmentation • Incidence of adjacent level vertebral compression fractures • Incidence of remote and same level vertebral compression fractures • Reduction in vertebral fracture-related pain at all time intervals to 6 months from baseline as measured by a 100 mm VAS scale (minimum clinically significant response is reduction of pain at 6 months by > 20 mm) • Time to mobilization post procedure for inpatient	The technical performance of the device is assessed by measuring per-operative endpoints. The VIP implant is designed to redistribute the force through the pediculosomatic junction and decrease the rate of progressive collapse and deformity at the treated level. This outcome will be monitored throughout the trial. Pain is the primary reason why patient will receive vertebral fracture treatment. Reduction in pain is a key secondary endpoint to assess the efficacy of the VIP technique. Pain can be measured at baseline and during the follow-up visits to

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	admitted patients immobilized due to pain • Change in analgesic/narcotic requirements from pre to post out to 6 months • Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by the 100-point Oswestry Disability Index (ODI) • Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by Health Questionnaire EQ-5D-5L • Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by Roland Morris Disability Questionnaire • Vertebral height maintenance at all radiologic time points to 6 months post augmentation Feasibility: • Lost to follow up rates at each time point	demonstrate effectiveness of the VIP to reduce pain and maintain pain reduction. Knowing the patients treated will present a minimum pain level of 60mm at baseline, a 20mm reduction allow to assess a significant pain reduction (30%). The long-term efficacy is assessed by measuring the maintenance of the post-op immediate endpoints. In addition, to assess efficacy, it is important to show patient function maintenance or improvement. The Oswestry Disability Index is a Low Back Pain Disability Questionnaire frequently used to assess function and very often report in the literature.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a multi-center, prospective, single arm, post-market pilot study that will include four sites for recruitment and enrollment. A total of 30 eligible subjects with a diagnosis of osteoporotic fractures of

the thoracolumbar spine, as confirmed by MRI scan, and who are treated with the Vertebral Implant PEEK (VIP) device, will be asked to join the registry. No placebo or control will be utilized during this study.

The procedure using the VIP device will be performed under local anesthesia with sedation or general anesthesia if indicated by anesthesiology recommendation. The procedure instruments have been validated. The investigator will be adequately trained and the manufacturer will provide technical assistance during the implantation. Based on prior research with the device, no serious adverse events related to the device are anticipated when the surgical technique is strictly followed. Cement leakage will not exceed rates reported previously in the literature (SpineJack® 47.3%, Kyphoplasty 41.0% (SAKOS Study)) The operating time should not be longer than the equivalent techniques, such as kyphoplasty or implants, as the procedure includes equivalent surgical steps. This is reported as approximately 30 minutes within the SAKOS study.[3]

For ambulatory patients, we expect same day discharge following the procedure. For patients who are already inpatient at the time of screening due to admission for pain control, discharge post operatively will be determined by best clinical judgment and patient medical and rehabilitation requirements.

Patients fracture related pain should be reduced at 6 months by > 20 mm from baseline on the VAS. Patient functional status should be maintained or improved from baseline parameters. The rate of adjacent or remote level vertebral compression fractures encountered during the follow up period should be in line with or less than rates reported in the available literature.

To minimize bias, and ensure a homogeneous patient population, patient selection will strictly conform to the following parameters:

- Magerl classification A1.1, A1.2, A1.3, A2.1, A2.2 and A3.1 type stable vertebral compression fractures, pediculosomatic junction fractures and other fractures involving vertebral pedicles
- No evidence of unstable fracture type on radiological evaluation
- Included fractures will be located in the thoracic and/or lumbar spine from T1 to L5,
- Only 1 - 3 acutely fractured levels are to be treated per patient; at least 1 of the three must be treated with V-STRUT
- Pain level $\geq$ 6 at the time of the procedure, by self-assessment VAS,
- ASA < 4,
- Recency of fracture ($\leq$ 12 weeks of age) must be demonstrated by history and/orimaging
- Failure of conservative management as described by the consensus statement from American College of Radiology (ACR)

All investigators will be trained according to the same training plan.

3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As discussed in Section 2.2, the VIP implant has undergone both biomechanical testing and preliminary clinical evaluation. This multi-center, prospective single-arm pilot study has been designed with the intention of achieving two goals: 1) to inform the design of larger controlled clinical trials in the future; and 2) to assess the safety of the study device within the patient sample.

Inclusion and exclusion criteria were selected to create a patient cohort representative of those commonly treated by BKP or instrumented vertebral augmentation (SpineJack®, Kiva®). Restrictions on pedicle size were selected according to the device instructions for use. The feasibility endpoints of loss to follow-up and ability to enroll were selected in order to inform per-center recruitment goals for a future controlled multicenter study. The primary safety endpoint was selected to ensure the absence of device-related serious adverse events within the study population.

The selection follow-up timepoints and secondary endpoints for efficacy and technical performance was informed by the design of previous randomized trials assessing currently available vertebral implants. The secondary efficacy outcome of progressive collapse/deformity at the treated level after augmentation was selected in order to assess a unique feature of the study device, which is intended to prevent progressive collapse by distributing loading force on the vertebral body to the posterior spinal column. Secondary outcomes will be used to select primary outcome measures for future controlled trials.

3.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) in Section 1.3.

4 STUDY POPULATION

Study subjects will be recruited from the emergency department and neurology and neurosurgery services at three institutions, under the responsibility of each site investigator. Patients with a diagnosis of osteoporotic fractures of the thoracolumbar spine, as confirmed by MRI scan, will be prospectively enrolled, according to the eligibility criteria.

4.1 INCLUSION CRITERIA

In order for the study participant to be considered for enrollment, the patient must meet all of these parameters:

- Age $\geq$ 50
- Osteoporotic compression fractures of the thoracolumbar spine (T1 – L5)
- Up to three levels can be fractured and treated but at least one of the three need to be treated with

V-STRUT; the level to be treated with the study device is at the discretion of the enrolling investigator

- Fracture age of ≤ 12 weeks as indicated by onset of pain or known antecedent traumatic event with corresponding evidence of acuity on MRI (T1 and STIR sequences) or radioisotope bone scan
- ODI ≥ 30/100 at screening visit and VAS ≥ 60 at screening visit.
- Failure of conservative management strategies for compression fractures resulting in inadequately controlled pain and/or patient immobility
- Patient has failed non-operative medical therapy as defined by one of the following definitions set forth by the American College of Radiology:[1]
    - For a patient rendered nonambulatory as a result of pain from a VCF, pain persisting at a level that prevents ambulation despite 24 hours of analgesic therapy; or
    - For a patient with sufficient pain from a VCF such that physical therapy is intolerable, pain persisting at that level despite 24 hours of analgesic therapy;
    - For a patient with pain from a VCF, unacceptable side effects such as excessive sedation, confusion, or constipation as a result of the analgesic therapy necessary to reduce pain to a tolerable level.
- Magerl classification A1.1, A1.2, A1.3, A2.1, A2.2 and A3.1 type fractures; pediculosomatic junction fractures and other fractures involving vertebral pedicles
- Appropriate pedicle diameter to receive 4.5mm, 5.5mm diameter or 6.5mm diameter implants
- ASA < 4.

4.2 EXCLUSION CRITERIA

Potential candidates will not be enrolled if any of these parameters pertain to their current state of being:

- Patient clearly improving on conservative treatment
- Any contra-indication or allergy to implant material or cement
- Systemic infection or infection located in the spine
- Any medical condition including but not limited to anemia, coagulation disorders, fibromyalgia, algoneurodystrophy, Paget's disease, uncontrolled diabetes that would preclude the patient from having surgery or would impede the benefit of surgery
- Neurologic signs or symptoms related to the fracture or the impeding pathological fracture
- Any previous surgical treatment (material or cement) in the targeted vertebra
- Less than one third of the original vertebral body height remaining
- Unstable fractures or neoplasms with posterior involvement
- Damages of the posterior wall
- Sclerotic cancellous bone
- Pedicles not large enough to accept V-STRUT© instrumentation and implants
- Pregnancy (women of childbearing potential must have a negative pregnancy test to participate)
- Pre-existing or clinically unstable neurologic deficit
- Spinal canal compromise causing clinical manifestations of cord, neural foramen, or nerve root compression at the level to be treated
- Any physical exam evidence of myelopathy or radiculopathy

- Pain based on clinical diagnosis of herniated nucleus pulposus or severe spinal stenosis (progressive weakness or paralysis)
- Bed bound prior to incident fracture
- Spondylolisthesis > Grade 1 at target VB
- Any underlying systemic bone disease other than osteoporosis (e.g.,osteomalacia, osteogenesis imperfect, Paget's disease, etc.)
- A medical contraindication to spinal surgery and/or general anesthesia, such as coagulopathy and/or taking warfarin (Coumadin) or other anticoagulant or anti-aggregate (anti-platelet agents) on regular basis for coagulopathy (with a threshold for normal being INR≤1.5, PTT within lab normal range, and platelet count > 100,000)
- Disabling back pain due to causes other than acute fracture
- Severe cardiopulmonary deficiencies
- Any evidence of alcohol or drug abuse
- Uncontrolled psychiatric illness or severe dementia
- Involved in medical litigation including workers' compensation

4.3 SCREEN FAILURES

Participant who are consented to participate in the registry and who did not receive the VIP treatment (example: during the treatment the pedicle appears to be too small and the treatment was limited to vertebroplasty) will exit the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment is the dialogue which takes place between an investigator and a potential participant or legal authorized representative (LAR) prior to the initiation of the informed consent process. It begins with the identification, targeting, and enlistment of participant for the study. Recruitment will be competitive, and to minimize selection bias, consecutive patients meeting pre-defined eligibility criteria will be enrolled.

Staff members of the emergency, orthopedics, pain medicine and Neurology/Neurosurgery departments should be made aware of this registry and in-serviced about its protocol to facilitate rapid screening and recruitment. It is expected that the study team and study coordinator (or other designated members of the study staff) will be informed about all patients who present a diagnosis of osteoporotic compression fractures of the thoracolumbar spine, as confirmed by MRI scan; these patients will be reviewed by appropriate members of the study staff immediately to determine eligibility for participation in the study.

All enrollments will be tracked using an electronic data capture system. The site investigator will be required to maintain a screening log for patients who are found ineligible to participate in the study, documenting the reason(s) for exclusion from the current study. The study coordinator at each site is required to enter the screening log data into the study database on a monthly basis.

4.5 INFORMED CONSENT AND ENROLLMENT

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation.

Paper consent forms and electronic consent forms will be Institutional Review Board (IRB) approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will beprovided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The informed consent must be obtained by either the clinical site PI or other members of the study team who are qualified to perform this task and whose names are listed on the Delegation of Authority Log.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

The study device is V-STRUT© and manufactured by Hyprevention. The device is indicated for use in the treatment of vertebral fractures in the thoracic and lumbar spine from T1to L5. It is intended to be used in combination with PMMA bone cement.

The Instructions for Use and surgical technique are available on the following link:
http://instructions.hyprevention.com/

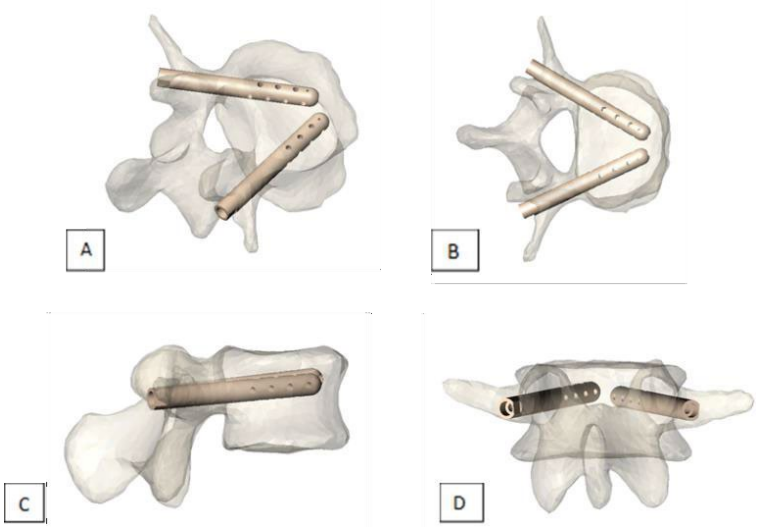
Vertebral Implant PEEK (VIP) procedure is a minimally invasive/percutaneous vertebral augmentation (PVA), image-guided procedure. Two VIP devices are implanted in each to be treated vertebra. A cavity is drilled allowing the introduction of the implant posteriorly through the pedicle and the vertebral body up to the anterior wall. A part of the implant is embedded into the pedicle, thus providing posterior support. The other part of the device, located in the vertebral body, presents a central canula and lateral perforations, which allow acrylic bone cement diffusion, filling of the vertebral body, filling and fixing the implant, and supporting of the upper endplate. The combination of the implant and the cement allows the treatment of vertebral fractures.

VIP exists in 3 different diameters and multiple different lengths to accommodate individual patient's anatomyof thoracic and/or lumbar vertebrae from T1 to L5.

The implant is made of radio transparent polymer known as polyetheretherketone (PEEK) and includes visualizing markers made of tantalum. It is MRI safe.

VIP is implanted with a specific instrumentation (V-STRUT© Instrumentation Set (reusable) and V- STRUT© Guide Wire).

Figure 1: Views of the VIP device in a vertebra (A- Perspective. B- Top view. C- Side view. D- Back view)



5.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

5.2.1 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

V-STRUT® Vertebral Implant is manufactured by Hyprevention SAS. It is packaged in individual packaging and provided sterile.

5.2.2 PRODUCT STORAGE AND STABILITY

See Instruction for Use (*http://instructions.hyprevention.com/*): no specific storage conditions are needed.

Shelf-life stability: 5 years.

5.2.3 PREPARATION

V-STRUT© Vertebral Implant instructions for use are available on the following link: *http://instructions.hyprevention.com/*

In addition, Instructions for Use for the associated instrumentation in available on the same link. In this Instructions all information related to the instruments handling, cleaning, sterilization, and maintenance are provided.

5.3 STUDY INTERVENTION COMPLIANCE

The site investigator is responsible for patient selection and evaluation, adherence to the protocol, and collection of data. The study must be conducted in accordance with applicable regulation and any conditions of approval imposed by the IRB. Investigators may delegate functions to other members of the study staff; however, the investigator remains responsible for the conduct of the study.

The investigator must identify a primary study coordinator to assist with administrative aspects of the study. The investigator is responsible for ensuring that the investigation is conducted according to this protocol and that signed informed consent is obtained from the subject prior to their inclusion in the study. It is the investigator's responsibility to ensure that all staff assisting with the study have appropriate qualifications, are fully instructed and trained on the study procedures and will respect confidentiality.

A delegation of authority (DOA) log and training records will be maintained by each site detailing activities that have been designated to other research team members by the site investigator.

Comprehensive training (approximately 2 hours each for both the coordinator and investigator) is required before a site is activated. Early review of data is made possible by real time entry of data into the electronic data capture system with source document validation and daily monitoring.

The site investigator is required to report protocol deviations (in accordance with IRB jurisdiction) within 24 hours of occurrence or as soon as it is discovered to the CRO study monitor. If the quality assurance monitor discovers an undocumented major deviation during a monitoring activity, the monitor will notify the investigator immediately. Each sites coordinator will report deviations as they are discovered to the local IBR in accordance with local requirements.

5.4 CONCOMITANT THERAPY

Any patient may be partnered with fracture reduction techniques that may include using on table postural correction or with the use of an inflatable bone tamp, or directable bone curette for cavity creation prior VIP implantation.

5.4.1 RESCUE MEDICINE

In case of failure of the treatment and need for revision, a revision procedure is provided in the Instructions for Use: *http://instructions.hyprevention.com/*

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Cancelling or aborting the surgical procedure does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The study may be modified or discontinued at any time by the sponsor, IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

Subjects withdrawn early from treatment or who withdraw consent or are lost to follow-up will not be replaced. If a subject is withdrawn early from treatment due to a clinical safety endpoint, we expect standard clinical judgment to be applied to continue to monitor the subject until resolution of the event. Participant follow-up should continue according to the schedule of assessments.

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The subject or legal representative has the right to withdraw consent to continue participating in the study and to complete follow-up assessments. At the time of consent withdrawal, the site personnel will discuss with the subject or legal representative the level of their consent withdrawal to determine if they are willing to agree to phone contact to determine vital status, or no further contact at all. The date and reason for patient withdrawal should be recorded on the End of Study Case Report Form(CRF).

6.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit on a weekly basis. The site investigator and research staff will be encouraged to counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or studyfile.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 EFFICACY ASSESSMENTS

Efficacy endpoints:

- Reduction in vertebral fracture-related pain at all time intervals to 6 months from baseline as measured by a 100 mm VAS scale (reduction of pain at 6 months by > 20 mm).

- Change in analgesic/narcotic requirements from pre to post out to 6 months: Decrease in analgesic/narcotic requirement should be reached or reduction in vertebral fracture-related pain and no increase in analgesic/narcotic requirements.

- Time to mobilization post procedure for inpatient admitted patients immobilized due topain, should be compared to the alternative treatments as presented in SAKOS Study (Length of hospital stay 3.8+/-3.6 days with SpineJack and 3.3+/-2.4 days with balloon kyphoplasty).

- ODI score decrease at all time intervals to 6 months from baseline measured should be compared to the alternative treatments as presented in SAKOS Study (at 1-month post-surgery-44.2 +/-21.2 for SpineJack and -39.9+/-23.7 for BK, at 6 months -48.3+/-19.0 for SpineJack and -43.2+/-22.3 for BK) and as presented in KAST Study, improve or maintain ODI score at 99.2% for KIVA.

- Health Questionnaire EQ-5D-5L at all time intervals to 6 months from baseline measuredshould be compared to the alternative treatments as presented in SAKOS Study (at 1-month post-surgery 0.45+/60.29 for SpineJack® and 0.42+/-0.29 for Balloon Kyphoplasty, at 6 months0.50 +/-0.26 for SpineJack© and 0.48+/-0.27 for BK).

- Incidence of progressive fracture at the treated level at 6 months should be compared to the common rate (SpineJack® 6.3%, BK 9.0%).

- Incidence of adjacent fractures at 6 months will not exceed the common rate (SpineJack® 9,4%, BK 22.3% to 25.0%, Kiva® 20.9%).

- Vertebral height restoration and maintenance achieved should be compared to alternative techniques showing a restoration between baseline and 6 months of -7.70 to +9.90, mean 1.14 +/-2;61, median 0,90 for SpineJack® and -9.70 to 5.30, mean 0.31+/-2.22, media 0.50 for BK.

7.2 SAFETY AND OTHER ASSESSMENTS

The registry will comply with all local, legal, regulatory, and Institutional Review Board (IRB) requirements. The national principal investigator will be responsible for ensuring that all site treating investigators report all AEs, including SAEs, to the competent authority and independent ethics committees/institutional review boards based upon federal regulations and local/IRB policies.

Information about all AEs, whether expected or unexpected, volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected and recorded on the Adverse Event form and followed as appropriate. In addition, the site principal investigator, or his designate, will report required SAEs to regulatory authorities, per reporting regulations, within 7 from the sponsor/CRO becoming aware of such AEs.

The principal investigator, or their designate, will ensure that the treating investigators will collect the following information, at minimum, for AEs:

- Study name
- Patient identification (e.g., subject number, sex, age)
- Event (preferably a diagnosis)
- Device
- Reporter identification (e.g., name or initials)
- Causality
- Outcome

We will utilize the following definitions as listed below. Details about SAEs relevant to the registry are described under Adverse Events and Serious Adverse Events below. We will use the FDA Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf*, to evaluate all unexpected events and adverse reactions.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient temporally associated with the use of an investigational product, whether or not considered related to the investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the product, whether or not considered related to the product. For marketed products, this also includes failure to produce benefits (i.e., lack of efficacy), abuse, or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition. New conditions detected or diagnosed after investigational product administration even though it may have beenpresent prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication

Examples of an AE do not include:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads tothe procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to hospital)
- The disease being studied, or signs/symptoms associated with the disease unless more severe than expected for the subject's condition

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
    - The term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe
- Inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office orout-patient setting. Complications that occur during hospitalization are AEs.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- The term incapacity means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance which may interfere or prevent everyday life functions, but do not constitute a substantial disruption
- A congenital anomaly/birth defect
- It is considered a significant medical event by the investigator based on medicaljudgment

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.3 CLASSIFICATION OF AN ADVERSE EVENT

7.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant'sdaily activities.
- **Moderate** – Events result in a low level ofinconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to"serious."

7.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratorytest

result, occurs in a plausible time relationship to the study intervention and cannot be explained by concurrent disease or other drugs or chemicals.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to the study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying diseaseprovide plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of the study intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.3.3.3 EXPECTEDNESS

The site investigator at each site will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the studyintervention.

7.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW -UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reportable AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study monitor will record all reportable events with start dates occurring any time after the procedure until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the site investigator will inquire about the occurrence of AE/SAEs since the last visit. Adverse events will be followed for outcome information until resolution or stabilization, or until end of study.

7.3.5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events (SAEs) occurring until participation in study has ended must be recorded on the AE CRF on the study's electronic data capture (REDCap) within 24 hours from AE onset or investigators' first knowledge of these AEs. All non-serious AEs must be reported within 5 business days of discovery. The site investigator, study coordinator, or designee is responsible for entering all AEs and SAEs and updating the information (e.g., date of resolution, action taken) in a timely manner.

The principal investigator, or their designate, must collect the following information, at minimum, for AEs:

- Patient identification (e.g., subject number, sex, age)
- Event (preferably a diagnosis)
- Device (if applicable)
- Severity, Causality, and Expectedness of the AE
- Outcome

An Independent Medical Safety Monitor will review and adjudicate all reported adverse events, and may request relevant medical records if needed.

7.4 UNANTICIPATED PROBLEMS

7.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures thatare described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known orrecognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

7.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the coordinating center team. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, oroutcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be entered into REDCap and reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to REDCap and the IRB within 5 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by aninstitution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 days of the IRB's receipt of the report of the problem from the investigator.

The investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Endpoints:

The study will be conducted based upon the hypothesis that (1) enrollment of 30 patients will be achieved; and (2) that there will be no significant device related adverse events. There will be no statistical hypothesis testing.

- Secondary Endpoints:

All secondary endpoints will be reported descriptively, and will be used to inform the design of a future larger multicenter study. There is no *a priori* hypothesis regarding secondary outcomes.

8.2 SAMPLE SIZE DETERMINATION

Thirty patients will be enrolled across three sites. Following completion of this pilot study, the data obtained will be used to design a subsequent comparative study to other implants or BKP in patients with osteoporotic compression fractures. This will allow a more direct comparison with other vertebral implants used in the management of this patient group (SAKOS Study : 68 patients treated with SpineJack® and 73 with BK). The design of the larger study will be directly informed by results of the pilot in terms of outcome measures, lost to follow up rates, and adherence to outcome time points.

8.3 POPULATIONS FOR ANALYSES

All analysis will be conducted according to intention to treat.

8.4 STATISTICAL ANALYSES

8.4.1 GENERAL APPROACH

This is a multi-center prospective pilot study. Qualitative data will be presented with their number and percentage. For quantitative data, mean, median, minimum and maximum as well as standard deviation and interquartile range will be described. 95% confidence intervals will be calculated. For all the variables, number of available and missing observations will be specified. A of notable findings will be presented.

8.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary feasibility endpoint is the ability to enroll 30 patients. This is a single endpoint. Enrollment will be presented as count data. Evaluation of this endpoint will not require statistical hypothesis testing.

The primary safety endpoint is the absence of device-related serious adverse events. This is a summary endpoint defined as device-related adverse events (device migration, device fracture) or symptomatic cement extravasation requiring surgical re-intervention or retreatment at the index level, including revision, removal, reoperation, and/or supplemental fixation. This will be presented as count data and proportions. Evaluation of this endpoint will not require statistical hypothesis testing. There will be no imputation for missing data, and lost to follow-up will be reported.

8.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be evaluated regardless of the outcome of the primary endpoints. Secondary endpoints for technical performance include the following single measures:

- Procedure duration (interval)
- Volume of cement injected per level (interval)
- Asymptomatic cement leakage (binary; observed on intra-procedural imaging)
- Fluoroscopy time and dose (interval)
- Percent Vertebral height restoration at end of procedure (interval; observed onintra-procedural imaging)

Secondary endpoints for efficacy include the following repeat measures:

- Reduction in vertebral fracture-related pain at all time intervals to 6 months from baselineas measured by a 100 mm VAS scale (interval)
- Time to mobilization post procedure for inpatient admitted patients immobilized due topain (interval)
- Change in analgesic/narcotic requirements at all time points (interval)

- Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by the 100-point Oswestry Disability Index (ODI) (interval)
- Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by Health Questionnaire EQ-5D-5L (interval)
- Maintenance or improvement in function at all time intervals to 6 months from baseline as measured by Roland Morris Disability Questionnaire (interval)
- Vertebral height maintenance at all radiologic time points to 6 months (interval) compared to immediate post-operative imaging
- Presence and count of adjacent and remote level fractures (interval)
- Presence and count of progression of same level fractures (interval)
- Presence of subsequent fracture on the treated level (interval)

Interval data will be summarized using descriptive statistics including mean, median, standard deviation, interquartile range, minimum and maximum. A 95% two-sided binomial proportion confidence interval will be reported using a normal approximation to the binomial. Categorical variables will be summarized using frequency counts and percentages. All analysis will be conducted according to intention to treat. Missing data will be handled by listwise deletion, and the number of patients missing reported data points will be reported. Count data for patients lost to follow-up at each time point will be reported.

8.4.4 SAFETY ANALYSES

The primary safety endpoint is the absence of device-related serious adverse events. This is a summary endpoint defined as device-related adverse events (device migration) or symptomatic cement extravasation requiring surgical re-intervention or retreatment at the index level, including revision, removal, reoperation, and/or supplemental fixation. This will be presented as count data and proportions. Evaluation of this endpoint will not require statistical hypothesis testing. There will be no imputation for missing data, and lost to follow-up will be reported.

Adverse events will be coded using MedRA, counted once per effected patient, and presented according to severity, and relationship to the study device or procedure. Tabulated reports will include actions taken, outcome, and time period according to the following classification: (1) intraprocedural, (2) within 24 hours of procedure and (3) after 24 hours post-procedure. Adverse events leading to premature discontinuation from the study intervention and those that are serious treatment-emergent will be presented either in a table.

8.4.5 BASELINE DESCRIPTIVE STATISTICS

For continuous variable, baseline characteristics will be summarized using descriptive statistics including mean, median, standard deviation, interquartile range, minimum and maximum. A 95% two-sided binomial proportion confidence interval will be reported using a normal approximation to the binomial.

Categorical variables will be summarized using frequency counts and percentages. A summary table will be reported with key baseline characteristics, including subject demographics, admission functional assessments, and lesion evaluation results.

8.4.6 PLANNED INTERIM ANALYSES

No interim analyses are planned.

8.4.7 SUB-GROUP ANALYSES

Data will be reported with regard to the entire cohort. Subgroup reporting based upon age, sex, race/ethnicity, or other demographic characteristics is not warranted due to the small sample size of this pilot study.

8.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be tabulated by measure or timepoint.

8.4.9 EXPLORATORY ANALYSES

No exploratory analyses are planned.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 MONITORING OF STUDY PROGRESS AND RECRUITMENT

The national principal and sponsor will monitor recruitment progress at the site on a monthly basis to address any issues and concerns. The national principal investigator and sponsor will also monitor accrual of subjects on an ongoing basis throughout the study and will conduct formal reviews of the overall recruitment on a monthly basis.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, investigators, and the sponsor. If the study is prematurely terminated or suspended, the national principal investigator will ask site investigators to promptly inform study participants, the Institutional Review Board (IRB). The

sponsor provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and FDA.

9.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or FDA requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be entered into an electronic data capture (REDCap) and stored on a server within the Mount Sinai Health System. Sites other than Mount Sinai will be given login credentials and full access to REDCap. Each site will only have access to their own patient data, as assigned by Data Access Groups. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and research staff will be secured, and password protected. The national principal investigator, sponsor, and CRO will have access to all study data. At the end of the study, study data will be de-identified and archived.

9.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Mount Sinai. After the study is completed, the de-identified data will be archived and stored on the Mount Sinai neurosurgery research shared drive, a cloud-base system that required duo factor authorization. Permission to transmit data to the sponsor will be included in the informed consent.

9.1.5 KEY ROLES AND STUDY GOVERNANCE

National Principal Investigator	**Medical Monitor #1**	**Medical Monitor #2**
Reade De Leacy MD	*Douglas Beall MD*	*Sean Tutton MD*
Mount Sinai Hospital	*Oklahoma Spine Hospital*	*Froedert Hospital, Medical College of Wisconsin*
1450 Madison Avenue, New York, NY, 10028	*1800 S Renaissance Blvd, Edmond, OK, 73013*	*8750 William Coffey Dr, Milwaukee, WI, 53226*
212-241-8897	*405-601-2325*	*414-801-8416*
reade.deleacy@mountsinai.org	*db@clinrad.org*	*stutton@mcw.edu*

A data and safety monitoring board will be established which will incorporate three individuals. The studies medical monitor, a second physician not involved in enrolling in the study and a statistician.

9.1.6 SAFETY OVERSIGHT

Safety oversight will be provided under the direction of the medical monitors. Their responsibility will be the oversight of safety of trial participants, review of the safety reports, requesting additional data/information (if necessary), and advising the principal investigator and sponsor regarding continuation/ discontinuation of the study. The medical monitors will meet after 15 enrollments have completed the 6 month follow up and then again, once all 30 subjects have completed the 6 month follow up. During each meeting, study progress, and accumulated safety data with particular attention to mortality, SAEs, and safety endpoints will be discussed

The medical monitors will make decisions regarding continuation, discontinuation, or modification of the study in order to protect the safety of the study participants. The study may be modified or discontinued at any time by OHRP, the FDA, and the local IRB as part of their duties to ensure that research subjects are protected.

9.1.7 CLINICAL MONITORING, QUALITY ASSURANCE, AND DATA CONTROL

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with International

Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Data should be independently entered by the designated personnel at each enrollment site into REDCap. Data must be entered within f5 working days following the completion of any study visit. SAEs should be entered into REDCap within 24 hours of first knowledge of the occurrence of these events. It is critically important to the effective and efficient conduct of the study that ALL data be entered in a timely manner. An hardcopy of the case report forms (CRFs) will be made available to each site as part of the start-up package to be used as worksheets to capture the required data for the study.

The data management staff within the Mount Sinai CRO will perform verification, consistency checks, and quality assurance on the data regarding missing data or queries on CRF data. They will maintain direct contact with site staff to ensure the study is conducted according to the Good Clinical Practice Guidelines and all applicable regulations.

An experienced clinical research monitor will be assigned to perform remote source data verification during the study. Remote monitoring will occur on a weekly basis. The monitor will query any data points that do not match the source documentation. All informed consent and HIPAA documents will be verified by the clinical research monitor. In addition to data verification, the monitor will evaluate site regulatory documents. The CRFs and corresponding source documents will be made available to the monitor via REDCap and Florence eBinders. It is also expected that the site PI, or a designated member of the research staff, will be addressing and resolving queries on a weekly basis. The close out monitoring visit will take place after the study is completed.

The monitor will prepare, at selected intervals, a summary report of screened and enrolled patients, completeness and quality of CRF data, status of enrolled patients, and a listing of SAEs and outcome events. The national principal investigator will review these reports and monitor the study performance (recruitment, compliance, protocol violations, and follow-up) and safety data on an ongoing basis. The study statistician will also generate a comprehensive statistical report bi-annually to the medical monitors, unless requested at more frequent intervals

9.1.8 DATA HANDLING AND RECORD KEEPING

9.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Electronic copies of the CRFs will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the 21 CFR Part 11-compliant data capture system, REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the FDA. It is the responsibility of the FDA to inform the investigator when these documents no longer need to be retained.

9.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the principal investigator to use continuous vigilance to identify and report deviations within 24 hours of identification of the protocol deviation. All deviations must be addressed in study source documents and reported on REDCap. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The principal investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

9.1.10 PUBLICATION AND DATA SHARING POLICY

Upon the completion of the study, Mount Sinai's data management team will clean and analysis all data in preparation of manuscript writing and publication. The intention will be to publish together between the principal investigator and the sponsor.

Following publication, Mount Sinai will archive and store all associated data on its cloud-based system.

9.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
V2	12 Jul 2022	Transition of study from single center to multi-center includes: • Administrative and formatting changes to protocol • Removal of second Protocol Signature Page • Increased patient enrollment from 25 to 30 • Schema has been updated • Medical monitor role has been expanded	Further collaboration and funding provided by sponsor
V3	03 Jun 2024	Inclusion Criteria: • Treated levels from T9 – L5 changed to T1 – L5 • Clarify that 3 levels can be fractured and only 1 or 3 need to be treated with study device • Indicated expanded to include pediculosomatic junction fractures and other fractures involving vertebral pedicles • Allowing usage of new implant size available (4.5 mm) • Fracture age of < 12 weeks as indicated by onset of pain or known antecedent traumatic event with corresponding evidence of acuity on MRI (T1 and STIR sequences) or radioisotope bone scan Exclusion Criteria • Removed “of the pedicles” from “damages of the pedicles or posterior wall” • Removed “any radiographic evidence of pedicle fracture visible on pre-operative imaging”	• Device now available and approved to treat multiple levels • Including other types of fractures will boost enrollment • Approved device now available in additional size and the national PI would like to ensure all cases where device is used, have the opportunity to be enrolled into the trial • Upon reviewing recruitment challenges with current sites, increasing fracture age from 8 to 12 weeks will allow for more potential subjects. • Exclusion criteria was edited to reflect that pedicle fractures are now eligible for enrollment due to expanded device indication

		Description of Study Intervention & Known Potential Risks • Added FDA clearance identification number: K240084 Study Duration • 36 months instead of 24 months Safety • The medical monitors will meet after 15 enrollments have completed the 6 month follow up and then again, once all 30 subjects have completed the 6 month follow up. During each meeting, study progress, and accumulated safety data with particular attention to mortality, SAEs, and safety endpoints will be discussed Other: • Increasing to 4 enrolling sites • Administrative and formatting changes to protocol	• To reflect updated device FDA clearance information • Accounting for a longer recruitment period as enrollment has not been met within the timeline previously mentioned • Given the slow enrollment, meeting every 3 months would not be efficient as there is not enough data available to complete a thorough review. Timeline for medical monitor meeting sessions is going to be based on enrollments and follow up completion. • More centers have expressed interest in participation, hence we have added a 4th site

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