A PROSPECTIVE, POST-MARKET ASSESSMENT OF NANOSS BIOACTIVE 3D IN THE POSTEROLATERAL SPINE

Post-Market Study Protocol
NB3D012012
Amendment 1

Version Date
10 JUNE 2013

Pioneer Surgical Technology, Inc. (Sponsor)
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I. SUMMARY OF MAJOR CHANGES FROM PROTOCOL V. 21 JUNE 2012

Section	Page	Change
N/A	1	Version date changed to 10 June 2013
III.	6	Definitions/Abbreviations added: AP, BMA, DXA, EXT, FLX, LAT, ODI, PEEK, PLIF, TLIF, VAS
IX.	13	Changed last sentence of 3rd paragraph to read: BMA and autograft are osteoinductive and, when combined with nanOss Bioactive, they form a cohesive and adhesive implant with a putty-like consistency.
		Changed FDA approved to FDA cleared throughout document
XI.A.	15	Added 24 months postoperative visit
XI.B.	15	Changed from treated level to treated segment throughout document
		Adjusted endpoints so definitions reside in the statistics section
XII.C.	16	Added "unless approved by Sponsor" to these lines regarding enrollment of smokers or more than 15 enrollees at 1 site
XII.D.	17	# 1: Changed eligibility age from 18 to 21 years
		# 2: Added bilateral specification
		# 3: Added or has the presence of progressive symptoms or signs of nerve root/spinal cord compression and fusion is clinically necessary.
XII.E	17	# 1: Changed to requires fusion at more than two segments
	18	# 8: Specified diabetes to uncontrolled diabetes type 1
	18	# 20: clarified workman's compensation eligibility
	18	Added intraoperative exclusion criteria:
		• Unilateral instrumentation was used.
		• A lateral or anterior technique/device was used to complete the procedure.
		• A synthetic bone void filler was used in and/or around the IBF device.
		• A non-PEEK IBF device was used to complete the procedure.
		• Less than 2.5 cc of autograft bone was used on each side of the posterolateral spine at each treated segment.
		• BMA was not used to rehydrate nanOss Bioactive 3D.
		• Bone graft material other than autograft bone, autologous BMA and nanOss Bioactive 3D was used in the posterolateral spine.
XIII.A.	21	Removed requirement for urine pregnancy test - only confirmation needed
		Changed 10-14 month postoperative visit to 12-14 months
		Added 24-26 month postoperative visit
		Added clarification for 24 month CT scan: If clinically indicated, participants will complete a Lumbar CT scan without contrast (e.g., PI determines there is a clinical need or the independent radiologist finds no bridging bone in the posterolateral spine).
XIII.B.	21	Simplified CRF details (moved from Study Visits & Procedures section)
XIII.C.	23	Placed surgical technique in Methods section (moved from Study Visits & Procedures section).
		Technique, locations of BMA and autograft harvest and amount total harvested added
XIII.D.	25	Specified x-ray guidelines
XIII.E.	25	Added 24 month postoperative visit x-rays to be transferred
XV.A.	29	Defined how quantitative assessments are performed
XV.B.	29	Defined how qualitative assessments are performed
XVI.C.	32	Added requirement for participants with no middle name. "If there is no middle initial a "-" may be used."
XVI.G	34	Specified follow-up windows for each postoperative visit, procedures performed and CRFs completed.
	35	Added 24 month postoperative visit
XVI.H	35	Added statement regarding protocol amendments
XIX.A	41	Added primary endpoint and statistical analysis
XIX.B	41	Added secondary endpoints and statistical analysis
XIX.C	42	Added quality assurance of the data

II. STUDY CONTACTS

A. Study PI

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B. Independent Radiological Review

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III. DEFINITIONS

AP - Anterior-Posterior x-ray
BMA – Bone Marrow Aspirate
CFR – Code of Federal Regulations
CRF – Case Report Form
CSA – Clinical Study Agreement
CT Scan – Computed Tomography scan
DDD – Degenerative Disc Disease
DXA - Dual-energy X-ray Absorptiometry
EXT - Extension x-ray
FDA – Food and Drug Administration
FLX - Flexion x-ray
IBF Device – Interbody Fusion Device
IRB – Institutional Review Board
LAT - Neutral Lateral x-ray
MRI Scan – Magnetic Resonance Imaging Scan
ODI - Oswestry Disability Index for lower back pain
PEEK - Polyether ether ketone
PI – Principal Investigator
PLF – Posterior Lumbar Fusion
PLIF – Posterior Lumbar Interbody Fusion
TLIF – Transforaminal Lumbar Interbody Fusion
VAS - Visual Analog Scale for pain (0 - 10 cm)

IV. REGULATIONS

This post-market, clinical study will be conducted in compliance with the CSA, the Post-Market Study Protocol that has received prior IRB approval and is consistent with applicable regulatory requirement(s).

The PI must agree to maintain complete confidentiality of the Study data until the Sponsor permits disclosure of any Study outcomes.

21 CFR 812

As devices that have been cleared for marketing and being investigated in accordance with its cleared indications and cleared labeling, the Study entitled "*A post-market, prospective assessment of nanOss Bioactive 3D bone void filler in the posterolateral spine*" is exempt from IDE regulations according to 21 CFR 812.2(c)(2).

A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

21 CFR 822 and Section 522 of the Federal Food, Drug and Cosmetic Act

The Study is not being conducted in accordance with a required post-market surveillance plan ordered by the FDA (21 CFR 822 or Section 522 of the Federal Food, Drug and Cosmetic Act).

V. SITE REQUIREMENTS

The following Essential Documents must be submitted to the Sponsor:

1. Written IRB approval of the Study. The content of the approval shall contain, at a minimum:
    a. Name and address of reviewing IRB.
    b. PI name and address.
    c. Date of IRB review and approval of the following documents.
        i. Study protocol (include name or number and version)
        ii. Informed consent form (with version date listed)
            1. The IRB approved informed consent form should be stamped with the approval date.
        iii. CRFs (with version date listed)
        iv. Written information provided to participants (with version date listed)
    d. IRB approval expiration date

2. A statement that the IRB is organized and operates according to GCP and the applicable laws and regulations and an IRB roster (if available).

3. A completed *Protocol Signature Page*[A] signed & dated by the PI.

4. A completed and signed Financial Disclosure Form and updated curriculum vitae with current medical license and copies of any training documentation for the PI.

5. A completed and signed Financial Disclosure Form and updated curriculum vitae for any Sub-Investigator(s) that signs the Sub-Investigator Agreement in the CSA.

6. An executed CSA(s) and any other required agreements.

The Sponsor will assure appropriate Study-related training for each Study Site prior to initiation of the Study. Training may take place via telephone and/or by an on-site visit. Study training is completed by the PI, Sub-Investigator(s) and necessary Study personnel and documented.

A Study Site is approved to screen and enroll participants once the Sponsor is in receipt of and has approved the Essential Documents listed above; has completed the appropriate Study training and has submitted a copy of the completed *Delegation of Authority Log* signed and dated by the PI.

[A] Protocol Signature Page

VI. NANOSS BIOACTIVE 3D PRODUCT INFORMATION

A. Description

nanOss Bioactive 3D is a resorbable porous calcium phosphate bone void filler that provides a scaffold for the in-growth of new bone. nanOss Bioactive 3D is an osteoconductive implant with an interconnected porosity similar to human cancellous bone. The product is a semi-rigid three dimensional construct that consists of porous hydroxyapatite granules suspended within porous gelatin-based foam matrix. When hydrated with BMA and used with autograft, nanOss Bioactive 3D becomes a compressible and elastic sponge that allows the shape of the implant to conform to the defect maximizing direct contact with viable host bone.

nanOss Bioactive 3D is provided sterile by prior exposure to gamma irradiation and intended for single use only.

B. Indications

nanOss Bioactive 3D bone void filler is intended for bony voids or gaps that are not intrinsic to the stability of bony structure. These defects may be surgically created osseous defects or defects created from traumatic injury to the bone. The product is intended to be used in conjunction with BMA and autograft bone as a bone graft extender and gently packed into bony voids or gaps in the posterolateral spine. nanOss Bioactive 3D provides an open void/gap filler that resorbs and is replaced by the growth of new bone during the healing process.

C. Contraindications

Use of nanOss Bioactive 3D is contraindicated in the presence of one or more of the following conditions:

- Fractures of the epiphyseal plate.
- Metabolic or systemic bone disorders that affect bone or wound healing.
- Fractures for which stabilization of the fracture is not possible.
- Significant vascular impairment proximal to the graft site.
- Infected or contaminated wounds, or fractures for which intraoperative soft tissue coverage is not planned or possible.
- Acute and chronic infections in the surgical area (soft tissue infections; inflammatory, bacterial bone disorders, osteomyelitis).
- Impaired calcium metabolism.
- Treatment with steroids and other drugs affecting calcium metabolism.
- Immunosuppressant therapy.
- Use in the area of the open epiphyseal growth plate.
- Patients allergic to porcine collagen products.

A copy of the 510K approval letter for nanOss Bioactive 3D is included as a supplemental Study document.[B] A copy of the product labeling[C] and complete Instructions for Use is included as a supplemental Study document.[D]

D. Instructions for Use

Radiographic assessment of the defect site pre-operatively is essential to accurately evaluate the shape and volume of the defect. This assessment aids in treatment planning for appropriate product size and placement of nanOss Bioactive 3D and/or internal fixation devices.

E. Laboratory & Clinical Data

In a 26 week animal study using a single level bilateral rabbit posterolateral spinal fusion model, nanOss Bioactive 3D+autograft+BMA produced the same results as those seen in the rabbits that received autograft+BMA (control). Micro-computed tomography evaluation at 12 and 26 weeks found that both groups demonstrated new bone formation along the transverse-processes and in the middle of the fusion mass with extensive bone remodeling at the treated level. The study also included a group of animals that received Vitoss BA+BMA. After 26 weeks, the Vitoss group demonstrated new bone formation only on the transverse-processes (not in the middle of the fusion site) with minimal graft remodeling at the treated level.[E]

nanOss Bioactive 3D has been cleared by the FDA and is currently being sold within the U.S., but there is no clinical data on its use in the posterolateral spine.

[B] nanOss Bioactive 3D 510k letter
[C] nanOss Bioactive 3D labeling
[D] nanOss Bioactive 3D IFU
[E] Internal study document. MKT-434-A/117200

VII. STREAMLINE TL SPINAL SYSTEM PRODUCT INFORMATION

A. Description

The Streamline TL Spinal System consists of a variety of rods, polyaxial screws, transverse connectors, set screws and other connecting components used to build a spinal construct. The Streamline TL Spinal System may be used with the Streamline TL Crosslink, SpineWorks FixxSure Crosslink or the Quantum® Spinal System X-Link®. The components of this system should not be used with components of any other system or manufacturer. Instrumentation is also available to facilitate implantation of the device components.

The Streamline TL Spinal System is intended to help provide immobilization and stabilization of spinal segments as an adjunct to fusion of the thoracic, lumbar, and/or sacral/iliac spine. The implant components can be rigidly locked into a variety of configurations, with each construct being tailor-made for the individual case.

Sacral/iliac screws are designed for posterior fixation.

The implant components of the Streamline TL Spinal System are manufactured from the implant grade Ti6Al/4V ELI Alloy, Grade 23 (ASTM F136).

B. Indications

The Streamline TL Spinal System components are non-cervical spinal fixation devices intended as an adjunct to fusion for use as a pedicle screw (T1-S2), sacral/iliac screw fixation or as an anterolateral fixation system (T8 – L5). Pedicle screw fixation is limited to skeletally mature patients. These devices are indicated for all of the following indications: DDD (defined as discogenic back pain with degeneration of the disc confirmed by history and radiographic studies), spondylolisthesis, trauma, (i.e., fracture or dislocation), deformities or curvatures (i.e., scoliosis, kyphosis, and/or lordosis, Scheuermann's Disease), tumor, stenosis, pseudoarthosis, and failed previous fusion.

C. Contraindications

Certain degenerative diseases or underlying physiological conditions such as diabetes or rheumatoid arthritis may alter the healing process, thereby increasing the risk of implant breakage. Mental or physical impairment which compromises or prevents a patient's ability to comply with necessary limitations or precautions may place that patient at a particular risk during post-operative rehabilitation.

A copy of the complete Instructions for Use is included as a supplemental Study document.[F]

[F] Streamline TL Spinal System IFU

VIII. IBF DEVICES PRODUCT INFORMATION

A. Description

The Pioneer IBF device is an implantable device consisting of different footprints and heights which enable the surgeon to choose the implant best suited to an individual's pathology and anatomical condition. Supplemental anterior and/or posterior fixation is intended for use with the device to ensure stability of the spine and adequate compression of the implant. The spacer is intended to be used with autograft. The components are manufactured from PEEK, in order to allow radiographic imaging inside the implant to evaluate fusion status. The device can be implanted with currently available manual surgical instruments.

The components of this device are manufactured from a radiolucent polymer and include either Titanium or Tantalum radiographic markers. Mixing of implant components with different materials is not recommended, for metallurgical, mechanical and functional reasons.

B. Indications

The Pioneer IBF device systems are indicated for intervertebral body fusion of the spine in skeletally mature patients. The device systems are designed for use with autogenous bone graft to facilitate fusion. One device may be used per intervertebral space. The implants are intended to be used with supplemental spinal fixation cleared for the implanted level, such as the Quantum, LowTop or SlimFuse systems.

The Lumbar IBF device system is also intended for use at either one level or two contiguous levels in the lumbar spine, from L2 to S1, for the treatment of 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 to be used in patients who have had six months of non-operative treatment.

C. Contraindications

The Lumbar IBF devices should not be implanted in patients with any of the following: an active infection at the operative site or with an allergy to PEEK, titanium, titanium alloy or tantalum; prior fusion at the level(s) to be treated; or any condition not described in the indications for use.

A copy of the complete Instructions for Use is included as a supplemental Study document.[G]

[G] Pioneer IBF device IFU

IX. BACKGROUND INFORMATION

Spine fusion is one of the most common procedures performed in spinal surgery. It is estimated that more than 200,000 spine fusion procedures are performed each year in the United States.[H] The concept of spinal fusion was developed over 70 years ago and is generally attributed to Hibbs[I] and Albee[J], who devised posterior fusion techniques to control the progressive kyphosis associated with tuberculosis. Today, the emphasis of fusion techniques in the treatment of lumbar spinal deformity is to obtain segmental stability or to correct a deformity by internal fixation.[K]

There are several surgical approaches available to achieve a solid union; however PLF is one of the most common techniques used in spinal fusion.[L] Bone graft material obtained from the iliac crest is recognized as the "gold standard" against which all other graft materials are compared. However, several complications have been associated with the use of autogenous bone graft such as increased blood loss, donor site pain, increased operative time, risks of nerve injury, additional incision sites, and insufficient quantity of bone available to harvest from the donor site.

Considerable efforts have been expended to develop synthetic bone graft materials as replacements for iliac crest bone graft or to produce materials that extend autograft when the supply is limited. Developmental challenges surround the production of a synthetic material that maintains both the osteoinductive and osteoconductive properties of autograft. nanOss Bioactive, an FDA cleared bone void filler, contains 2 primary components: nanocrystalline hydroxyapatite providing an osteoconductive matrix and a collagen-based bioscaffold carrier, to form an adhesive and cohesive paste.[M] nanOss Bioactive is indicated to be gently packed into bony voids or gaps in the posterolateral spine in conjunction with BMA and autograft bone. BMA and autograft are osteoinductive and, when combined with nanOss Bioactive, they form a cohesive and adhesive implant with a putty-like consistency.

nanOss Bioactive 3D is also FDA cleared for use in the posterolateral spine. It is an osteoconductive implant with an interconnected porosity similar to human cancellous bone. The product is a semi-rigid three dimensional construct that consists of porous hydroxyapatite granules suspended within porous gelatin-based foam matrix. When hydrated with BMA and used with autograft, nanOss Bioactive 3D becomes a compressible and elastic sponge that allows the shape of the implant to conform to the defect maximizing direct contact with viable host bone.

[H] Boden, SD (2002). Overview of the Biology of Lumbar Spine Fusion and Principles for Selecting a Bone Graft Substitute. Spine, 27: S26-S31.
[I] Hibbs RA (1911). An operation for Pott's disease of the spine. J Am Med Assoc, 59: 433-6.
[J] Albee FH (1911). Transplantation of a portion of the tibia into spine for Pott's disease. J Am Med Assoc, 57: 885-6.
[K] Fraser RD (1995). Interbody, Posterior, and Combined Lumbar Fusions. Spine, 20: 167S-177S.
[L] Boden S, Schimandle J and Hutton W. An experimental lumbar intertransverse process spinal fusion model. Radiographic, histologic, and biomechanical healing characteristics. Spine 1995; 4(20): 412-20.
[M] K091031

X. STUDY OBJECTIVES AND PURPOSE

A. Purpose

nanOss Bioactive 3D has recently been cleared for use in the U.S., however, additional information is useful to assess its efficacy and gather information about its use and fusion results in the posterolateral spine.

The purpose of the Study is to assess fusion results in the posterolateral spine using nanOss Bioactive 3D mixed with autograft bone and BMA.

B. Objective

The objective of the Study is to gather information about fusion results, clinical & radiographic outcomes, complications/adverse events and patient reported outcomes in patients treated with nanOss Bioactive 3D mixed with autograft bone and BMA. The results of nanOss Bioactive 3D will be compared to those cited in literature.

XI. STUDY DESIGN

A. Study Type

This is a prospective, non-randomized and un-controlled post–market Study.

This is not an investigational treatment Study. nanOss Bioactive 3D is being studied in accordance with its cleared indications and cleared labeling. All participants will receive nanOss Bioactive 3D mixed with BMA and autograft in their posterolateral spine as part of their routine instrumented PLF surgery.

Clinic procedures will be related to standard of care for persons receiving treatment for posterior lumbar fusion surgery. Information from clinical notes, examinations, questionnaires, results of diagnostic tools, radiographs, tests and exams will be recorded for the Study at the following timepoints:

- Pre-Operative
- Surgery
- Discharge
- 6 Months Post-Operative
- 12 Months Post-Operative
- 24 Months Post-Operative

B. Study Endpoints[N]

X-rays as well as axial, coronal and sagittal CT reconstructions will be used to determine the presence of bridging bone in the posterolateral spine. The primary endpoint is treated segment fusion at 12 months post-operatively based on the following criteria:

- Presence of bridging trabecular bone; and
- < 5° Angular motion; and
- < 3 mm Translational motion.

Secondary evaluation parameters include:

1. The proportion of successfully fused treated segments 6 and 24 months postoperatively.
2. Improved postoperative pain, disability and physical-functioning scores compared to baseline values.
3. Overall satisfaction with the procedure.
4. The proportion of complications and adverse events.

[N] nanOss Bioactive 3D post-market study schedule of events

XII. SELECTION AND WITHDRAWAL OF PARTICIPANTS

A. Source of Participants

Participants will be recruited from the medical practices of the PI and are those that require and elect to have instrumented PLF surgery between L2 and S1 and which meet the inclusion and exclusion criteria listed below.

B. Number of Participants and Study Sites

Up to 60 participants may be enrolled in the Study from no more than 10 participating sites.

A maximum of 15 smokers may be enrolled in the Study.

- All inclusion criteria must be met and no exclusion criteria can be met.
- Verification with the Sponsor is required before enrolling a smoker in the Study.
- A Study Site may enroll no more than 5 smokers, unless approved by the Sponsor.
- This cohort of patients will be identified and analyzed separately.

C. Recruitment of Participants

It is estimated that there will be 50 participants total. Consented participants that drop out of the Study prior to surgery or that must be withdrawn due to eligibility conflicts that arise during surgery may be replaced, however, a new participant identification number must be reassigned.

Enrollment is competitive. Each Site is required to enroll at least 1 participant within 30 days of activation and may enroll no more than 15 participants, unless approved by the Sponsor. Each Study Site will be permitted a maximum of 1 year (from activation) to enroll their participants. Once open to enrollment, a Study Site must have consistent enrollment (or documentation of screen failures) each 30 day period. The Screening and Enrollment Log will be used as a record of site activity.

Surgeons are expected to meet the enrollment goals contained in the CSA. If enrollment goals are not met for 3 consecutive months, the Study Site will be closed and may be replaced by another Study Site (as deemed necessary by the Sponsor).

The Sponsor will permit in-office flyers[O] to be used to recruit participants. These must be approved by the Sponsor. The IRB is expected to review any *direct* advertising that a PI or Sub-Investigator proposes to be used to recruit participants.

[O] In-office flyers template

Notice of any financial relationship between the Sponsor and a PI or Sub-Investigator must be disclosed in the informed consent.

Participants may receive reimbursement for participating in the Study provided all appointments, procedures and forms are completed. Compensation will be in the form of a $50 US debit card issued following the 12 month and 24 month post-operative visit. Any proposed payment should be reviewed and approved by an independent IRB/EC. The compensation or any other benefit should also be consistent with the informed consent document.

D. Inclusion Criteria

The participant must exhibit all of the following:

1. Is at least 21 years of age and is skeletally mature.
2. Has symptomatic spinal stenosis secondary to DDD with up to Grade 1 spondylolisthesis at one or two adjacent segments from L2-S1 requiring bilateral, instrumented PLF surgery.
3. Has completed a minimum of 6 months of non-operative treatment or has the presence of progressive symptoms or signs of nerve root/spinal cord compression and fusion is clinically necessary.
4. Has pre-operative objective evidence of primary diagnosis confirmed by appropriate imaging studies (AP/Lateral/Flexion/Extension x-rays & an MRI or CT scan).
5. Is willing and able to return for post-treatment exams according to the follow-up called for in the protocol.
6. Is able to review, understand and sign the informed consent document.

E. Exclusion Criteria

The participant must not exhibit any of the following:

1. Requires fusion at more than two segments.
2. Has had previous fusion surgery at the segment(s) to be treated (previous discectomy, laminotomy, laminectomy or nucleolysis at the segment(s) to be treated $\geq$ 6 months ago is ok).
3. Has > 11^{o} lumbar scoliosis.
4. Has > 40 BMI.
5. Has > Grade 1 spondylolisthesis.
6. Smokes (see previous page).
7. Has osteoporosis, osteomalacia, Paget's disease or metabolic bone disease.
   Osteoporosis should be assessed at the time of the pre-operative evaluation based on the participant's history, physical examination and review of the radiographic evaluations (i.e., DXA scan). According to the World Health Organization (WHO):
   - A T-score of -1.0 or above is normal bone density (e.g., 0 and -0.9).
   - A T-score between -1.0 and -2.5 is low bone density or osteopenia (e.g., -1.1 and -2.4).
   - A T-score of -2.5 or below (e.g., -2.6 and -3.9) is osteoporosis. These patients must be excluded.

8. Has a disease that significantly inhibits bone healing (e.g., uncontrolled diabetes type 1, renal failure, impaired calcium metabolism).
9. Has a medical condition that requires or has a history of chronic steroid use (i.e., oral steroids), with the exception of inhaled/nasal corticosteroids steroids or has any medical condition that requires treatment with drugs known to interfere with bone healing.
10. Has a neurological disease (e.g., Parkinson's disease), a psychosocial disorder (e.g., suicidal, diminished capacity) or has a history of substance abuse which would preclude accurate evaluation or limit the ability to comply with study requirements.
11. Has either an active infection or infection at the site of surgery
12. Has a systemic disease (e.g., AIDS, HIV, active hepatitis, tuberculosis)
13. Has rheumatoid arthritis or other autoimmune disease.
14. Has spinal tumors.
15. Has an active malignancy (except non-melanoma skin cancer) or history of any invasive malignancy unless treated and in remission for at least five years.
16. Has a known sensitivity or allergies to porcine collagen, PEEK, tantalum or titanium.
17. Has active arachnoiditis.
18. Has fractures of the epiphyseal plate or fractures for which stabilization of the fracture is not possible.
19. Is a prisoner.
20. Is involved in spinal litigation at the treated segment(s) (workers compensation cases may be included if uncontested).
21. Is participating in another clinical study that would confound Study data.
22. Is pregnant or is interested in becoming pregnant while participating in the Study.

If any of the following criteria are met during the surgery, a participant may be excluded:

- Unilateral instrumentation was used.
- A lateral or anterior technique/device was used to complete the procedure.
- A synthetic bone void filler was used in and/or around the IBF device.
- A non-PEEK IBF device was used to complete the procedure.
- Less than 2.5 cc of autograft bone was used on each side of the posterolateral spine at each treated segment.
- BMA was not used to rehydrate nanOss Bioactive 3D.
- Bone graft material other than autograft bone, autologous BMA and nanOss Bioactive 3D was used in the posterolateral spine.

F. Participant Disposition or Lost to Follow-Up

It is expected that participants will complete the Study, and the PI will make every attempt to contact the participant to have the participant continue in the Study. If the participant is lost to follow up despite all attempts, the PI (or designee) will complete and sign the appropriate CRF.

The following are circumstances for which a participant would be identified as not continuing his or her participation in the Study:

- Lost to follow-up and no additional data is available on the participant's outcome.
- Participant died.

All information regarding the participant discontinuation in the Study will be recorded and includes:

- When the participant completes the Study.
- Indicates how the participant left the Study at their final visit.

For participants that are lost to follow-up, data from the visits that were completed will be used.

G. Withdrawal criteria

Participants will be advised that they may voluntarily withdraw from the Study at any time and will be instructed to notify the PI immediately. Participants may choose to withdraw for any reason and will be asked to reveal their reasons for withdrawal to the Sponsor.

A participant may be withdrawn from the Study without consent by the PI for any of the following reasons:

- The participant may relocate to another geographical area, which requires a change of the physician.
- The participant may be unable to continue participation in the Study due to some significant though unrelated condition or accident.
- The participant may be withdrawn from the Study by the PI or the Sponsor for noncompliance with the Study procedures.

All information regarding the participant discontinuation in the Study will be recorded and includes:

- When the participant completes the Study.
- Indicates how the participant left the Study at their final visit.

For participants that withdraw or are withdrawn, data from the visits that were completed will be used.

H. Duration of Participant Participation

The expected duration of participant participation is approximately 24 months.

I. Completion of the Study

When the last participant enrolled completes the Study, and the information has been recorded on the appropriate CRF, the Study will be considered as completed.

XIII. METHODS

A. Schedule of Events

Pre-operative, operative, discharge and post-operative follow-up data will be collected on all participants. The complete list of events is a supplemental document. A summary of the events is below.

Procedures	Pre-Op	Surgery	Discharge	6 Months +/- 4 weeks	12 Months + 8 weeks	24 Months + 8 weeks
Informed Consent & Eligibility Review	X					
Preoperative History & Physical	X					
Clinical & Neurological Evaluation	X		X	X	X	X
Surgery		X				
Discharge			X			
PI Radiological Assessment				X	X	X
Disposition						X
Routine X-rays (4 views)	X			X	X	X
Thin-slice (≤ 1.25 mm) lumbar CT scan w/o contrast with coronal and sagittal mpr					X	X*
Participant Forms (4)	X			X	X	X

* = If clinically indicated, participants will complete a lumbar CT scan without contrast (e.g., PI determines there is a clinical need or the independent radiologist observed no posterolateral bridging bone in the 12 month CT).

B. Data Collection

Copies of all forms will be provided and will include all relevant information from the protocol and are included as supplemental documents. Clinical data (i.e., no prior written or electronic record of data) may be directly reported on case report forms (CRFs) by the PI (or designee) or participant and considered to be source data.

There will be CRFs for the pre-operative, intra-operative, discharge and post-operative visits.

- The PI (or designee) will complete the following CRFs.
  - Pre-operative eligibility: CRF 1[P]
  - Pre-operative medical history: CRF 2[Q]

[P] CRF 1 - Pre-operative eligibility
[Q] CRF 2 - Pre-operative medical history

- Pre-operative clinical and neurological evaluation and diagnosis: CRF 3[R]
- Operative Data: CRF 6[S]
- Discharge Data: CRF 7[T]
- Post-operative clinical and neurological evaluation: CRF 8[U]
- Post-operative radiological evaluation: CRF 9[V]
- Participant disposition: CRF 12[W]
- Complications/adverse events: Complications/Adverse Events Form[X]

- The Participant will complete the following self administered questionnaires (completion of these CRFs should be supervised but not influenced):
  - Pre-operative demographics & work status: CRF 4[Y]
  - Pre-operative VAS for back and leg pain and medication use[Z]: CRF 5[AA]
  - Post-operative work status: CRF 10[BB]
  - Post-operative VAS for back and leg pain, medication use and satisfaction with procedure: CRF 11[CC]
  - ODI for lower back pain: CRF ODI[DD, EE,FF]
  - RAND 36-item health survey: CRF 36-Item HS[GG,HH]

C. Surgical Technique

This is a routine bilateral, instrumented PLF surgery where nanOss Bioactive 3D will be hydrated with autologous BMA and placed bilaterally on a bed of local autograft bone spanning the transverse processes of the treated segment(s). The procedure should generate enough local autograft bone for use in the posterolateral spine and the interbody space (if applicable).

[R] CRF 3 - Pre-operative clinical & neurological evaluation and diagnosis
[S] CRF 6 - Surgery Information
[T] CRF 7 - Discharge Information
[U] CRF 8 - Post-Operative Clinical & Neurological Evaluation
[V] CRF 9 - Post-Operative PI Radiological Assessment
[W] CRF 12 - Participant Disposition
[X] CRF Complications & Adverse Events
[Y] CRF 4 - Pre-Operative Demographics & Work Status
[Z] Wewers, M. E. and Lowe, N. K. (1990). A critical review of visual analogue scales in the measurement of clinical phenomena. Research in Nursing & Health, 13: 227–236.
[AA] CRF 5 - Pre-Operative Pain & Medication Use
[BB] CRF 10 - Post-Operative Work Status
[CC] CRF 11 - Post-Operative Pain, Medication Use & Satisfaction
[DD] Fairbank JCT, Couper J, Davies JB (1980). The Oswestry low Back Pain Questionnaire. Physiotherapy, 66: 271-273.
[EE] Steven Glassman, MD et al (2006). MOS Short Form 36 and Oswestry Disability Index outcomes in lumbar fusion: a multicenter experience. The Spine Journal, 6: 21-26.
[FF] CRF ODI
[GG] Hays, RD (1994). *Medical Outcomes Study (MOS) Measures of Patient Adherence.* Retrieved April 19, 2004, from the RAND Corporation web site: http://www.rand.org/health/surveys/MOS.adherence.measures.pdf.
[HH] CRF 36-Item HS

If an interbody fusion is performed, only a PLIF or TLIF with PEEK IBF devices (with autograft) may be performed. Pioneer hardware and instrumentation (e.g., Streamline TL pedicle screw system, T-Plus IBF device, Bullet-Tip IBF device) should be used on Study participants. Upon prior approval by the Sponsor, a posterior, thoracolumbar, titanium pedicle screw system cleared for use at the segment treated must be used on participants to obtain rigid stabilization.

It is suggested that graft be placed in the posterolateral spine after irrigation has taken place to minimize any loss of graft material.

The recommended total graft mass in the posterolateral spine is 20 cc per treated segment.

10cc of graft mass per side = 5cc autograft bone + 5cc nanOss Bioactive 3D

1. BMA

Autologous BMA will be used to hydrate the nanOss Bioactive 3D strip.

- 10 cc of BMA should be harvested for each treated segment.
- The BMA may be harvested from the pedicles of the lumbar vertebrae (following initial preparation of the pedicle screw path) or from the posterior iliac crest using conventional techniques.
- The sites of aspiration will be recorded.
- The amount of BMA used to hydrate the nanOss Bioactive 3D strip will be measured prior to use and recorded.

The volume of autologous BMA used to rehydrate nanOss Bioactive 3D should be appropriate for the selected size (see table below). Soak nanOss Bioactive 3D in the BMA using manual compression for at least 5 minutes to ensure complete uptake of the BMA. The length of hydration time will be recorded.

nanOss Bioactive 3D strip size	**Minimum Amount of BMA**
5cc: 25x50x4 mm	4 mL
10cc: 25x100x4 mm	8 mL
10cc: 25x50x8 mm	8 mL
20cc: 25x100x8 mm	16 mL

2. Local Autograft Bone

Local autograft bone will be used to make an autograft bed placed directly on the decorticated site(s) and spanning the transverse-processes bilaterally.

- 10 cc of autograft bone is recommended for each treated segment (5cc per side).
    - No less than 5cc of autograft bone may be used in the posterolateral spine for each treated segment (2.5cc/side).
    - Equivalent amounts of autograft bone placed bilaterally.

- The autograft bone may be harvested locally, the soft tissue cleaned from the bone and then morselized using conventional techniques.
- The amount of autograft bone placed bilaterally in the posterolateral spine will be measured prior to use and recorded.
- The sites and volume of autograft collection will be recorded.
- It will be documented how the autograft bone was morselized.

3. nanOss Bioactive 3D

nanOss Bioactive 3D will be placed on top of the bed of autograft bone spanning the transverse-processes of the treated segment bilaterally.

- 10 cc of nanOss Bioactive 3D should be used for each segment treated (5cc/side).
- The amount of nanOss Bioactive 3D placed on each side of the posterolateral spine will be recorded.
- Equivalent amounts of nanOss Bioactive 3D placed bilaterally (see description and images below).
    - Single segment procedure options following rehydration:
        - A 5cc (25x50x4 mm) nanOss Bioactive 3D strip may be applied to each side of the treated segment (2 strips).
        - A 10cc (25x50x8 mm) nanOss Bioactive 3D strip may be cut in half lengthwise and applied bilaterally at the treated segment (1 strip).
        - A 10cc (25x100x4 mm) nanOss Bioactive 3D strip may be cut in half and applied bilaterally at the treated segment (1 strip).
    - Two segment procedure options following rehydration:
        - A 5cc (25x50x4 mm) nanOss Bioactive 3D strip may be applied to each side of each segment (4 strips).
        - A 10cc (25x50x8 mm) nanOss Bioactive 3D strip may be cut in half lengthwise and applied bilaterally, spanning both segments on each side (2 strips).
        - A 10cc (25x100x4 mm) nanOss Bioactive 3D strip may be applied to each side spanning both segments on each side (2 strips).
        - A 20cc (25x100x8 mm) nanOss Bioactive 3D strip may be cut in half lengthwise and applied bilaterally, spanning both segments on each side (1 strip).

D. Radiological Studies

As part of routine care, participants have a series of pre-operative and post-operative radiographic studies performed. Pre-operative DEXA scans should only be performed as part of routine care for at risk patients.

1. LAT, FLX & EXT X-Ray Guidelines

The x-ray system should be set up according to standard protocol for lateral lumbar spine x-ray.

- Include the calibration marker around the subject's waist and in the field of view in all lateral x-rays.

2. AP X-Ray Guidelines

The x-ray system should be set up according to standard protocol for an AP lumbar spine x-ray.

- Do not include the calibration marker in this x-ray.

3. Lumbar CT Scan (without contrast) Guidelines

The CT manufacturer's spine imaging protocols should be followed as long as it specifies acquisition of original axial slices that are ≤ 1.25 mm thick.

- Sagittal and coronal reformatting is required. See the radiograph acquisition protocol for specific guidelines.
- The entire fusion mass at the treated segment(s) must be included.

E. Radiological Study Transmission

The following radiographic studies are required to be transmitted to the independent radiological reviewer as shown below:

- Pre-operative: Neutral AP/Lateral & Flexion/Extension x-rays.
  - Images should be within approximately 6 months.
- 6 Months Post-operative: Neutral AP/Lateral & Flexion/Extension x-rays.
- 12 Months Post-operative: Neutral AP/Lateral & Flexion/Extension x-rays & a thin-slice lumbar CT scan (without contrast) with sagittal and coronal reformatting.
- 24 Months Post-operative: Neutral AP/Lateral & Flexion/Extension x-rays & a thin-slice lumbar CT scan (without contrast) with sagittal and coronal reformatting, as applicable.

X-rays transmitted to the independent radiological reviewer should be in a format that permits electronic transmission. If this is not permitted at the site CDs/DVDs may be used. An Image Transmittal Form must be used with any x-ray transmission to the Independent radiologist.[II]
In order to accurately measure the x-rays, the following apply to post-operative plain x-rays:

- A scale should be placed on the plain x-rays for accurate measurements.
- The Right or Left side must be clearly indicated.
- The original, unformatted, thin-slice CT images must be sent to MMI along with all available orthogonal reformations.

[II] MMI Image Transmission Form (ITF)

F. PI Clinical & Neurological Assessment

As part of their routine care, participants will have a pre-operative, discharge and post-operative clinical & neurological assessments performed. The following information will be recorded:

Muscle Strength
Muscle strength for the right and left sides will be tested in the:

- Hip Flexors and Extensors
- Knee Flexors and Extensors
- Foot/Toe Dorsi-Flexors
- Foot/Toe Plantar-Flexors

Scoring will be recorded using the following scale:

0. Absent (total paralysis)
1. Trace (palpable or visible contraction)
2. Poor (active movement, gravity eliminated)
3. Fair (active movement, against gravity)
4. Good (active movement, against resistance)
5. Normal
6. Not-Testable

Sensory Deficit
Sensory deficit will be measured by conducting a pinprick test for pain, a temperature test with a cold object and a touch test using a cotton ball or something similar. These tests indicate the participant's ability to sense an external source. Scoring will be recorded using the following scale:

- None - if the tests are negative, the PI will indicate that there are no deficits detected on any dermatone.
- If the participant cannot sense any of the above items, then the test is positive. If any of the tests are positive, the physician will determine which dermatome (L1 – S1) is affected and on which side it occurred (Right or Left).

Reflexes
Reflexes will be graded for the Right and Left Patellar and Achilles. Scoring will be recorded using the following scale:

0. Absent/Trace
1. Decreased
2. Normal
3. Hyperactive

Straight Leg Raise
The Straight Leg Raise is where the participant lies supine on the examination table. The physician will lift the participant's leg upward supporting the foot and keeping the knee straight. The extent to which the leg can be raised without discomfort varies but normally the angle between the table and the leg measures approximately 70-80 degrees. Scoring will be recorded using the following scale:

1. If there is no pain, then the test is negative.
2. If the test is painful, the physician must determine whether the pathology is due to the sciatic nerve or to the participant's tight hamstrings. If the pain is due to the sciatic nerve, then the test if positive.

G. PI Radiological Assessment

Each PI will review the x-rays for any instances of heterotopic bone formation, hardware condition and any complications or adverse events. The PI will also assess the treated segment(s) according to the Lenke's classification of posterolateral fusion success[JJ] and record the results on the post-operative radiological assessment form according to the following criteria:

- Grade A - Definitely solid with bilateral trabeculated stout fusion masses present.
- Grade B - Possibly solid with a unilateral large fusion mass and a contralateral small fusion mass.
- Grade C - Probably not solid with a small fusion mass bilaterally.
- Grade D - Definitely not solid with bone graft resorption or obvious pseudoarthrosis bilaterally.

[JJ] Lenke LG, Bridwell KH, Bullis D, Betz RR, Baldus C, Schnoenecker PL. Results of in situ fusion for isthmic spondylolisthesis. *J Spinal Disord*. 1992; 5: 433-42.

XIV. COMPLICATIONS AND ADVERSE EVENTS

Safety assessment involves assessment of the complications, including subsequent surgical interventions and pain and neurological complication information. Pain, neurological and function symptoms should be considered complications when a patient's complaint for any of these symptoms results in an unscheduled visit or when a patient presents with new or worsening pain, neurological, and/or function symptoms as compared to the previous visit.

All non-serious operative and post-operative complications, whether or not they are related to the device, including both observed or volunteered problems, complaints, symptoms, physical signs, or diseases which occur during participation in the Study that were not present at the baseline evaluation, or were present at baseline but have worsened, are to be recorded by the PI and reported to the Sponsor.

- These should be reported to the Sponsor **no later than ten working days after the PI learns of the event**.
- This should be reported on the Complication/Adverse Event CRF.

Any serious and unanticipated serious adverse device events that have at least a possible relationship to nanOss Bioactive 3D are to be recorded on the Complication/Adverse Event CRF and reported to the Sponsor.

- These should be reported to the Sponsor **within 24 hours** of the PI becoming aware of the event via fax or email or telephone.
- The Sponsor will immediately conduct an evaluation of the events.

The Sponsor will ensure that the event is documented by the PI and reported to the appropriate authorities as required. The Sponsor has internal advisory boards composed of physicians that are available for questions and review of such events.

- A serious adverse event (SAE) is an anticipated AE that falls into one of the following categories: (a) death, (b) life-threatening adverse experience, (c) inpatient hospitalization or prolongation of hospitalization, (d) persistent or significant disability/incapacity, (e) congenital anomaly/birth defect, (f) important medical event that may jeopardize the participant and may require medical intervention to prevent an outcome listed in a-e above, or (g) any AE associated with the use of nanOss Bioactive 3D, the specificity or severity of which is not consistent with the risk information provided.
- An unanticipated serious adverse device effect (USADE) is an unanticipated serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, nanOss Bioactive 3D, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol, or any other unanticipated serious problem associated with nanOss Bioactive 3D that relates to the rights, safety, or welfare of participants.

XV. INDEPENDENT RADIOLOGICAL ASSESSMENT

A. Quantitative Measurements

Quantitative measurements (angular and translational motion) will be produced by trained analysts using Quantitative Motion Analysis software (QMA®, Medical Metrics, Inc.). The software is US FDA 510(k) cleared and has been validated to produce assessments of intervertebral motion accurate to less than 1 degree and 1 mm (Zhao et al, *J Biomech* 2005; Reitman et al, *Spine* 2004). The reproducibility of the measurements has also been validated (Pearson et al, *Spine* 2011).

The measurements will be produced from flexion-extension views at the treated segments 6, 12 and 24 (as applicable) months postoperatively:

- Angular Motion (in units of degrees): Rotation of the superior vertebra relative to the inferior vertebra. Angular Motion will be measured in the sagittal plane from flexion-extension films.
- Translational Motion (in units of mm): Displacement of the posterior-inferior corner of the superior vertebra in a direction defined parallel to the superior endplate of the inferior vertebra. Translational Motion will be measured in the sagittal plane from lateral flexion-extension films.

B. Qualitative Measurements

Qualitative assessments shall be performed by a single, independent radiographic reviewer that is board-certified, fellowship-trained, practicing neuro- or musculoskeletal radiologist. The following qualitative assessments shall be performed by a single, independent radiographic reviewer. The reviewer shall be a board-certified, fellowship-trained, practicing neuro- or musculoskeletal radiologist.

The qualitative assessments shall be conducted at the treated segments 6, 12 and 24 (as applicable) months postoperatively:

- Left & Right Posterolateral Bridging: X-rays as well as axial, coronal and sagittal CT reconstructions, when available, will be used to determine the presence of bridging. Assessment of bridging bone across the left and right posterolateral gutter, facet joint and/or transverse processes. Each treated segment will be graded separately. Posterolateral Bridging will be graded for each side (left and right) separately, and will include the entire posterolateral gutter, from the lateral-most aspect of the transverse processes to the medial-most aspects of the facet joints. Bridging between facet joints, between transverse processes, or between facet joint and transverse process will all be considered acceptable forms of bridging.
- Interbody Bridging: X-rays as well as axial, coronal and sagittal CT reconstructions,

when available, will be used to determine the presence of bridging. Assessment of bridging bone between the involved vertebral endplates. Each treated segment will be graded separately.

- Heterotopic Ossification
- Heterotopic bone formation will be evaluated to detect bone formation in unintended locations associated with the treatment.
- Hardware Condition: Assessment of device disassembly, loosening or fracture.
- Additional Observations: Other noteworthy observations will be documented at the radiologist's discretion.

XVI. STUDY VISITS AND PROCEDURES

A. Screening

The use of screening tests to assess whether prospective participants are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While a PI, Sub-Investigator or Study personnel may discuss availability of studies and the possibility of entry into the Study with a prospective participant without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not Study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining Study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research. The PI, Sub-Investigator or Study personnel should take extra care to clarify with their patient-participants why certain tests are being conducted.

Any participant that screen-fails prior to or following their consent should be tracked. The *Screening & Enrollment Log* will be maintained by the Site and submitted to the Sponsor as changes occur.

B. Enrollment

Participants who are eligible for inclusion in the Study will be asked to give his or her informed consent (*Template Informed Consent Document* is included as a supplemental document).[KK] This process will involve a discussion about the objectives of the Study, number of participants in the Study, follow up schedule and the procedure they will have including the surgical techniques and its foreseeable risks as well as potential benefits of participating in the Study.

The participant will be provided with the PIs contact details so that they can contact them with any questions. Participants will be informed that they are free to withdraw their consent at any time and this will not compromise any further medical care. In addition, the participant will be informed that the PI may terminate his/her participation without their consent.

The PI will also inform all participants that, should any unanticipated device related adverse effects occur during the Study which, in the opinion of the Sponsor, present unreasonable risks to the participants, all participants will be notified and participant enrollment will be terminated.

The participant will be informed by the PI that the Sponsor will verify that each participant has consented, in writing, to direct access to his/her original medical records for trial-related

[KK] Template informed consent document

monitoring, audit, IRB review, and regulatory inspection. Additionally, that his/her original medical records will be subject to review possibly by any legal authorities. This information will be used during the analysis of the results of the Study but the confidentiality of the participant will be maintained at all times.

A signed, written informed consent must be obtained from the participant by the PI (or designee) prior to the participant's involvement in the Study. Once a participant's consent has been obtained, a copy of the consent form will be provided to the participant. The original form will be maintained in the participant's research file. This consent is separate from the normal consent gained for any surgical procedures.

If the participant is a smoker, the Sponsor must be contacted prior to enrollment to ensure eligibility.

C. Unique Participant ID Assignment

At the time of enrollment, a participant Study number will be issued which will be used on the CRFs, electronic records of data and any other Study documentation relating to that participant. The Study Site will assign the participant number in the following format: site # - participant # - participant initials (e.g., 03-01-ABC).

- The site's two digit number (assigned by the Sponsor).
- The PI (or designee) will assign the participant's two digit number in the order the participants are consented (e.g., sequentially 01, 02, etc.).
- The participant's first, middle and last name initials will be used. If there is no middle initial a "-" may be used.

D. Pre-Operative Visit

As a participant in the Study, information from the participant's medical record and pre-operative assessment will be recorded to verify eligibility (CRF 1). This information will include:

- Medical charts will be reviewed by the Study doctors. Participant's medical histories and clinical information from standard pre-operative diagnostic tools and routine tests, scans, and procedures to confirm the diagnosis and segments needing surgical intervention will be used for the Study (CRF 2).
    - History and Physical: e.g., start date of complaints, diagnosis and segments needing surgical intervention, pain level, previous non-operative treatments and current analgesia use, previous surgeries at the operative level, etc.
        - Information in a participant's medical chart from a recent visit to the PI or Sub-Investigator may be used to complete the form.
    - Clinical and Neurological Examination: e.g., Test reflexes, sensory deficits, muscle strength and physical limitations (CRF 3).

        - Information in a participant's medical chart from a recent visit to the PI or Sub-Investigator may be used to complete the form.
    - Diagnostic Tools and Routine Tests: e.g., questionnaires, plain x-rays, CT scan, MRI, DXA, discogram, bone density scan, bloods, ECG when necessary.
        - MRI should be within approximately 11 months of the surgery date or as routinely prescribed per the PI's pre-operative care.
    - Routine plain x-rays will be taken, reviewed and transmitted (AP/LAT/FLX/EXT).
        - If all 4 x-rays were taken within the past 6 months, those x-rays may be transmitted to the independent radiologist.
- The participant will complete the following:
    - Women with the potential of being or becoming pregnant will confirm they are not pregnant.
    - Participant will complete self-administered questionnaires (CRF 4, CRF 5, CRF ODI and CRF 36-Item HS).

Completed CRFs should be faxed to the Sponsor following the visit. All completed plain radiographic films should be transmitted to MMI following the visit.

E. Surgery and Discharge Information

Operative and discharge reports shall be submitted to the Sponsor with the completed CRFs (participant name, medical record number or account number must be redacted). As a participant in the Study, information from the surgery, hospital stay and discharge will be recorded by the PI (or designee).

- CRF 6: Participants will be evaluated pre- and intra-operatively and information about the surgery and hospital stay notes/events/procedures/x-rays will be used for the Study. This information will include:
    - Date of surgery
    - Operated segment(s)
    - Duration of surgery (time)
    - Procedures performed
    - Devices used
    - Amount of autograft used in and around the IBF device (as applicable)
    - Amount of autograft used in the posterolateral spine
    - Amount of BMA used to hydrate nanOss Bioactive 3D
    - Amount of nanOss Bioactive 3D used
    - Location of autograft and BMA harvesting
    - Estimated amount of blood loss (cc)
    - Complications or adverse events

- Participants will be evaluated at discharge (CRF 7 and CRF 8):
    - Information about discharge notes/events/procedures/x-rays will be used for the Study. This information will include:

- Date of discharge
- Medication prescribed at discharge
- Type of orthotics prescribed
- Type of facility where participant was discharged
- Complications or adverse events

- A clinical and neurological examination will take place prior to discharge. The doctor will test reflexes, sensory deficits, muscle strength and physical limitations.

Completed CRFs should be faxed to the Sponsor following the discharge date. A de-identified operative report should be included with the CRFs.

F. Post-Operative Regimen

Post-operative patient management and care should follow the same regimen as routinely prescribed by the PI. The use of internal or external bone growth (or fusion) stimulators is not permitted on patients that participate in the Study.

G. Post-Operative Visits

As part of routine post-operative care, participants are evaluated periodically by the surgeon. Information from the participant's post-operative visits will be collected. Postoperative visit windows are based off of the participant's date of surgery.

1. 6 Months Postoperatively (6 months +/- 4 weeks):

Medical charts will be reviewed by the Study doctors.

- The PI or designee will perform a routine post-operative clinical and neurological evaluation and complete CRF 8.
- Routine plain x-rays will be taken, reviewed and transmitted (AP/LAT/FLX/EXT).
- The PI will assess fusion status using Lenke's criteria and complete CRF 9.
- The PI or designee will review for any complications or adverse events since their discharge from the hospital.
- The participant will complete the self-administered questionnaires (CRF 10, CRF 11, CRF ODI and CRF 36-Item HS).

2. 12 Months Postoperatively (12 months + 8 weeks):

Medical charts will be reviewed by the Study doctors.

- The PI or designee will perform a routine post-operative clinical and neurological evaluation and complete CRF 8.
- A thin-slice ($\leq$ 1.25 mm) lumbar CT scan (without contrast) with coronal and sagittal mpr will be taken and transmitted.
- Routine plain x-rays will be taken, reviewed and transmitted (AP/LAT/FLX/EXT).
- The PI will assess fusion status using Lenke's criteria and complete CRF 9.

- The PI or designee will review for any complications or adverse events since the 6 month postoperative visit.
- The participant will complete the self-administered questionnaires (CRF 10, CRF 11, CRF ODI and CRF 36-Item HS).

3. 24 Months Postoperatively (24 months + 8 weeks):

Medical charts will be reviewed by the Study doctors.

- The PI or designee will perform a routine post-operative clinical and neurological evaluation and complete CRF 8.
- If clinically indicated (including if no posterolateral bridging bone observed on the 12 month CT scan by the independent radiologist), a thin-slice (≤ 1.25 mm) lumbar CT scan (without contrast) with coronal and sagittal mpr will be taken and transmitted.
    - If the participant is asymptomatic and does not want another CT scan, they may opt out of the 24 month CT scan while remaining in the Study.
    - If a thin-slice lumbar CT scan with sagittal and coronal mpr was taken within 6 months of the 24 month appointment for the entire treated area, that CT may be transmitted to the independent radiologist instead of another CT being completed.
- Routine plain x-rays will be taken, reviewed and transmitted (AP/LAT/FLX/EXT).
- The PI will assess fusion status using Lenke's criteria and complete CRF 9.
- The PI or designee will review for any complications or adverse events since the 12 month postoperative visit.
- The participant will complete the self-administered questionnaires (CRF 10, CRF 11, CRF ODI and CRF 36-Item HS).
- The PI or designee will complete CRF 12.

Completed CRFs should be faxed to the Sponsor following each visit. All completed plain radiographic films and the CT scan should be transmitted to MMI following each visit.

H. Protocol Modifications & Deviations

Changes to the written Protocol must be approved by the Sponsor unless the change is made to assure the safety of the subject. Written approval by the PI's IRB will be obtained by the Sponsor prior to implementation of the amendment.

Deviations from the protocol will be recorded in the Protocol Deviation Log and submitted to the Sponsor and IRB as required by local regulations.

XVII. RISKS

The participant population for whom nanOss Bioactive 3D is intended is characterized by the inclusion and exclusion criteria and as described in the product labeling.

A. Risks Associated with Instrumented PLF Surgery

As with any operation, there are potential risks associated with spinal fusions and associated instrumentation.

Some of the most common complications following posterior lumbar fusion include:

- Adverse reactions to anesthesia
- Thrombophlebitis
- Infection
- Nerve damage
- Problems with bone graft
- Instrumentation/hardware problems (migration, fracture, failure, loosening)
- Muscle disruption
- Nonunion/delayed union
- On-going pain

Other less frequent complications may include:

- Adjacent segment disease
- Bowel or bladder incontinence
- Corrosion of metal hardware
- Damage to lymphatic vessels and or lymphatic fluid exudation
- Death
- Deep infection
- Device component fracture
- Epidural hematoma, dural tear
- Fracture of the pedicle or vertebral bone
- Hardware migration
- Hematoma or seroma at the implant site
- Hemorrhage
- Ileus
- Loss of bladder or bowel control
- Loss of fixation
- Muscle damage
- Nerve root injury
- Pain, infection or weakness from bone harvest location
- Pneumonia, bronchopneumonia or collapsed lung
- Pulmonary or systemic embolism
- Secondary surgery to remove hardware
- Stress shield bone
- Thrombosis
- Vascular injury or damage resulting in catastrophic or fatal bleeding
- Wound dehiscence

These lists describe the most common risks that could occur with this kind of surgery. There may be other risks that are not currently known.

B. Risks Associated with nanOss Bioactive 3D

The primary risk associated with nanOss Bioactive 3D is the lack of a solid fusion. There may be other risks that are not currently known. Risks associated with bone void fillers include:

- Hematoma
- Site drainage
- Bone fracture
- Infection
- Fracture or extrusion of the bone void filler
- Deformity of the bone at the site
- Incomplete or lack of osseous bone ingrowth
- Continued pain
- Allergic reaction - nanoss Bioactive 3D contains a porcine (pig) collagen product which is sterilized as part of the manufacturing process
- Revision surgery

C. Loss of Confidentiality

The Sponsor and Study Sites will put forth best efforts to make sure personal information from medical records is kept private. However, personal information may be given out if required by law. Organizations that may look at and/or copy medical records for research, quality assurance, and data analysis include IRBs, the Sponsor and/or the FDA.

If information from the Study is published or presented at scientific meetings, a participant's name and other personal information will not be used.

D. Risks Associated with the Lumbar CT Scan

CT scans involve the risks of radiation. Having a CT scan may mean some added discomfort to the participant, specifically, feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time.

E. Reproductive Risks

Pregnant women may not participate in the Study because the risks to an unborn baby are unknown. A pregnancy test will be given prior to surgery to confirm the participant is not pregnant.

Women of child-bearing potential should not become pregnant while participating in the Study. Female participants able to become pregnant are responsible for using an effective birth control method such as birth control pills, barrier method (condoms, diaphragm, and cervical cap), intrauterine device (IUD), hormone implants or surgical sterility while taking part in the Study.

A participant that thinks she has become pregnant during the Study must tell the PI or Study personnel immediately.

F. Unknown Risks

There may be other risks that are not currently known.

G. Minimization of the Risk

Risks to the patients who have agreed to participate in the Study will be minimized to the extent possible in several ways. The PI, Sub-Investigator and Study personnel participating in the Study will be trained to select the appropriate patient. Patient selection is of paramount importance; the inclusion and exclusion criteria have been carefully chosen to describe the best patient for the procedure. The PI and Sub-Investigator must demonstrate that they have had appropriate training/experience with nanOss Bioactive 3D as well as the anticipated complications associated with nanOss Bioactive 3D. The Sponsor will assure appropriate training for each PI and Sub-Investigator prior to initiation of the Study at each site.

A unique identification number is assigned to each participant. This number will be used on any material transferred out of the Study Site.

The PI will closely monitor for complications and adverse events and record them on the appropriate case report forms. The Sponsor will investigate any report of an unanticipated adverse event. If an unreasonable risk occurs, the Sponsor will terminate the Study.

H. Justification for Study

Low back pain impacts the lifestyle of many individuals and results in a diminished quality of life. There are no immediate benefit to participants, however, future participants may benefit from the information obtained in the Study. The Sponsor believes that the risk to the participant is justified.

I. Participant Benefit

There are no direct benefits for a Study participant. The information from the Study will help doctors and the Sponsor learn more about the use of nanOss Bioactive 3D in spinal fusion procedures and could help future patients with similar conditions.

J. Participant Costs

Since this is a Study is in line with standard of care and using the product according to its FDA cleared indications and cleared labeling, the Sponsor will not provide any products free of charge. The surgical facility/institution/Study Site is responsible for purchasing products through normal purchasing channels.

The surgical facility/institution/Study Site is responsible for submitting claims to third party payers (e.g. Medicare, insurance carriers, etc.), in accordance with all applicable laws and guidelines for such third party payers, all procedure, radiologic, or other expenses incurred in performance of the Study.

K. Participant Research Related Injury

If a participant experiences a complication from participation in the Study, then the participant may be treated for it at the surgical facility/institution/Study Site. The surgical facility/institution/Study Site is responsible for submitting claims to third party payers (e.g. Medicare, insurance carriers, etc.), in accordance with all applicable laws and guidelines for such third party payers, for the reasonable and necessary items and services to diagnose and treat the complication.

XVIII. PARTICIPANT ALTERNATIVES

Participants may receive the surgery and any of the products without having to participate in the Study.

A. Non-Operative Alternatives

Treatment of back pain without surgery may include the following:

- Physical therapy.
- Facet joint injections.
- Epidural steroid injections.
- Acupuncture.
- Back school.
- Behavior modifications.
- Ultrasound.
- Hot or cold compresses.
- Anti-inflammatory medications.
- Analgesic medications.
- Muscle relaxers.
- Corsets or braces.

B. Operative Alternatives

Treatment of back pain with surgery may include the following:

- Discectomy.
- Foraminotomy.
- Laminectomy.
- Laminotomy.
- Intradiscal electrothermal therapy (IDET).
- Intervertebral disc replacement surgery.

XIX. STATISTICAL METHODS

A. Primary Endpoint

The primary endpoint includes successful fusion of the treated segment(s) 12 months postoperatively based on the quantitative and qualitative assessments of the x-rays and CT scan. Fusion is defined as:

1. Presence of bridging trabecular bone [i.e. presence of left posterolateral bridging AND/OR right posterolateral bridging], **AND**
2. Angular motion < 5º, **AND**
3. Translational motion < 3 mm

The sample size and percentage of treated segments successfully fused will be presented. Sample sizes and percentages of treated segments successfully fused will be presented for different groups based on smoking status, age, sex, BMI, the number of segments treated and whether or not an IBF device was used.

Non-fusion will be defined as the failure to meet any one of the above criteria for fusion.

B. Secondary Endpoints

An assessment of secondary endpoints will include an analysis of the following to determine trends in the data;

1. Assessment of fusion 6 and 24 months postoperatively.
2. Pain score improvement using the VAS.
3. Physical disability score improvement using the ODI.
4. Physical-functioning improvement using the 36-Item HS.
5. Satisfaction with procedure.
6. No serious adverse event classified as related to nanOss Bioactive 3D or no device failure or subsequent intervention, excluding the removal of fixation after a solid fusion occurred.

The following additional data will be presented:

- The sample size and percentage of successfully fused segments 6 and 24 months postoperatively.
- Sample sizes and percentages of successfully fused segments for different groups based on smoking status, age, sex, BMI, the number of segments treated and whether or not an IBF device was used 24 months postoperatively.
- Demographic information will be presented as sample sizes and percentages.
- Satisfaction with procedure will be presented as sample sizes and percentages for each visit.

- Pain, physical disability and physical-functioning scores will be presented as sample sizes, means, standard deviations and ranges for each visit. The post-operative results will be compared to baseline levels.
- The proportion of clinical complications, reoperations, revisions, as well as unexpected adverse events will be calculated.

C. Quality Assurance of the Data

The accuracy and quality of the data obtained from the investigators and maintained by the Sponsor will be assured through a structured program of field auditing and internal review. All data received by the Sponsor during the course of the investigation will be internally processed to assure the accuracy and quality of the data.

XX. MONITORING

A. Monitors

The Sponsor will ensure that the Study is adequately monitored. The Sponsor will designate one or more appropriately trained and qualified individuals to monitor the Study. The monitor(s) will follow the Sponsor's established written procedures as well as those procedures that are specified by the Sponsor for monitoring the Study.

Monitors will be thoroughly familiar with the product(s), the protocol, written informed consent form and any other written information to be provided to participants, the Sponsor's SOPs, GCP, and the applicable regulatory requirement(s). Physicians, clinical research associates, paramedical personnel and nurses are acceptable to perform monitoring functions. A monitor does not need to be qualified to diagnose or treat the disease for which nanOss Bioactive 3D is intended. They will also be appropriately trained, and have the scientific and/or clinical knowledge needed to monitor the trial adequately.

B. Assessment

For the Study, the factors that will be considered in the determination of the number of monitors and the education, training or expertise necessary will include the following:

- Number of PIs conducting the Study.
- Number and location of the facilities in which the Study will be conducted.
- Type of product involved in the Study.
- Nature of the disease or condition under study.

The Sponsor may conduct an assessment visit and follow-up communication prior to initiating any Study to ensure that:

- The PI understands and accepts his/her obligation in conducting the Study.
- The PI and staff have sufficient time and access to the adequate number of patients required for the Study.
- The PI and staff understand the proper use and application of nanOss Bioactive 3D.
- The PI will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents.
- The PI understands his/her obligations for filing adverse events, annual reports and a final report to the IRB and providing the documentation to the Sponsor.
- The PI understands his/her responsibility for solicitation of Informed Consent signatures from the patients prior to the participants start in the Study.

C. Monitoring

Monitors act as the main line of communication between the Sponsor and the PI. As such, it is necessary to implement alternative training and communication methods for providing and documenting ongoing, timely training and feedback, as well as to provide notification of significant changes to Study conduct or other important information.

Study Site Monitoring will be performed centrally (to the extent appropriate and feasible) and through on-site visits. At a minimum, at least 1 annual on-site visit will take place for a Study Site with active participants until the Study is completed.

Completed CRFs may be submitted via a scan to a secure email, to a secure fax line or collected during on-site visits. If a Data Management vendor is utilized during the Study, original CRFs will be submitted via a courier service.

Throughout the course of the Study, the Sponsor and/or monitors will:

- Maintain contact with the PI and his or her staff and will conduct periodic visits to the Study Site to ensure completeness and accuracy of the data being collected, as well as any evidence which may be indicative of participant risk. Any discrepancies noted in the data will be resolved with the PI or an individual previously designated by the PI. When information is incomplete, every effort will be made to resolve it.
- Ensure that the Study is conducted in accordance with the signed CSA, the post-market protocol, and conditions, if any, imposed by the IRB and/or FDA. The Sponsor will note any noncompliance by the PI with any of these documents.
- Complete administrative and regulatory tasks as well as the collection and archiving of the required regulatory documents.
- Confirm Study Personnel included on the Delegation of Authority current curriculum vitae, licensure and training documentation, have proper licensure and/or experience and/or are trained and familiar with the laws and ethical standards governing the responsible conduct of research for the tasks assigned.
- Evaluate the quality of the overall conduct of the trial at a Study Site.
- Evaluate the accuracy and completeness of the records/CRFs/source documentation.
- Verify recorded data by reviewing source documents.
- Confirm participant eligibility.
- Verify that the initial informed consent was obtained appropriately, prior to any Study-specific procedures; the consent is dated; that the person conducting the informed consent discussion signed and dated the document; and that the date on the consent form is consistent with the Study entry date.
- Monitor data quality and potential protocol deviations.
- Collect completed CRFs and verify film transfers.
- Report of the incidence of reoperations, unexpected adverse events or complications.

XXI. FUNDING AND BUDGET

The Sponsor will pay for required IRB fees and other required Site fees as negotiated in the CSA. The Sponsor will compensate the Site for CRF completion, file maintenance, participant contact, transmittal of radiographs to the independent radiologist and site visit preparation as negotiated in the CSA. The Sponsor will not pay for procedures or fees not included in the executed CSA.