Cellentra™ Viable Cell Bone Matrix (VCBM) Anterior Cervical Discectomy and Fusion Outcomes Study (VCBM/MaxAn®)

Protocol Number CS-092-03

August 15, 2014

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PROTOCOL NUMBER: CP-092-03
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The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this Post Market Surveillance Validation will be conducted according to Good Clinical Practices and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.

It is agreed that the protocol contains all necessary information required to conduct the Post Market Surveillance Validation as outlined in the protocol.

It is agreed that all participants in this post market surveillance will provide written informed consent and/or a HIPAA Authorization (addendum to be provided by sponsor) and agree to the Post Market Surveillance Validation procedures as agreed by the Institutional Review Board or Independent Ethics Committee, if applicable.

SPONSOR:

_____
Print Name

_____ _____
Signature Date

PRINCIPAL INVESTIGATOR:

_____
Print Name

_____ _____
Signature Date

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1 Investigational Plan

1.1 Purpose

The purpose of this study is to assess the clinical, radiographic, functional and economic outcomes in patients who undergo ACDF procedures using Cellentra™ Viable Cell Bone Matrix (VCBM), cortical allograft spacers, and the MaxAn® Anterior Cervical Plate System.

2 Introduction

2.1 Background

Cervical degenerative disc disease (DDD) causing axial neck pain and/or radicular arm pain is a frequently diagnosed condition. When conservative therapies fail, operative intervention is often recommended. One such surgical procedure is the anterior cervical discectomy and fusion (ACDF). This procedure involves discectomy (removal of the damaged intervertebral disc) with fusion of the adjacent vertebral bodies, and can involve one or more spinal levels. It has a history of clinical success based upon relief of symptoms and favorable outcomes.[1,2] Autologous iliac crest bone grafts are frequently used for creating bony fusion of two vertebrae; however, bone harvesting is associated with short- and long-term morbidity and increased operative time.[3,4] Alternative grafts and instrumentation techniques have thus been utilized. The use of allograft eliminates the need for donor graft harvesting and its associated complications. Interbody cages/spacers provide initial stability, and by filling the disc space, require less structural bone graft. The spacers are manufactured from different materials such as titanium alloy, and PEEK; however, these can only be marketed for use with autograft as supplemental bone graft material, as per current US regulatory requirements. Machined allograft bone spacers are also available and can be used with allograft for supplemental fusion, thereby eliminating the need for donor site autograft material. Anterior cervical plating can provide immediate stability, maintain spinal alignment, prevent graft dislodgement and collapse, enhance fusion rates, and eliminate the need for external immobilization.

This study will assess outcomes in subjects who undergo ACDF procedures using the Cellentra™ Viable Cell Bone Matrix (VCBM) graft,

machined allograft interbody spacer, and the MaxAn® Anterior Cervical Plate System.

2.2 Device Description

Use of any other devices and/or graft materials for ACDF procedures in subjects enrolled in this study will be considered a protocol deviation.

Cellentra™ Viable Cell Bone Matrix (VCBM)

Cellentra™ VCBM is a human tissue allograft consisting of cryopreserved cancellous bone that contains naturally occurring viable cells within the cancellous bone matrix, combined with demineralized cortical bone matrix.

Indications for Use: Cellentra™ VCBM is an allogeneic bone graft containing naturally occurring viable donor cells intended for homologous use in the repair, replacement, reconstruction or supplementation of the recipient's tissue in musculoskeletal defects. These defects may be surgically created or from traumatic injury to bone.

Contraindications: Cellentra™ VCBM is contraindicated in patients with a sensitivity or allergies to any of the processing agents: Cryopreservation solution – Aqueous serum-free and protein-free electrolyte/mineral solution, Dimethyl sulfoxide (DMSO), Antibiotic Solution – Gentamicin Sulfate, Vancomycin, Amphotericin B, Dulbecco's Modified Eagle's Medium (DMEM). Processing Solution – Hydrochloric Acid, Acetic Acid, Phosphate Buffered Saline (PBS), water; use in immune compromised patients; or use as a standalone in load bearing applications.

Machined Allograft Interbody Spacers

Cellentra™ VCBM will be utilized in conjunction with LifeLink® cortical allograft spacers, available from Biomet under the catalog numbers of: LGAP915, LGAP916, LGAP917, LGAP918, LGAP919, LGAL915, LGAL916, LGAL917, LGAL918 and LGAP919. All allograft spacers are processed in accordance to AATB standards.

For the purposes of this study, Cellentra™ VCBM will be packed within the cavity of the allograft spacer.

MaxAn® Anterior Cervical Plate System

The MaxAn® Anterior Cervical Plate System provides a simple, efficient and innovative approach to anterior cervical plating. The system offers a decompression-based technique for cervical spine stabilization and introduces an innovative one-level plate technique that provides a direct relationship between the bone graft/spacer size and the position of the plate holes. The unique ability to obtain maximum screw angulation and place a fixed screw at any angle up to 30° cephalad on the superior end of the plate and up to 30°caudal on the inferior end of the plate allows for versatile screw placement close to the endplates. Note that the screws converge at 10° in the transverse plane and are not intended to have additional variability in that plane. The significant cephalad-caudal angulation affords the surgeon the opportunity to choose a smaller plate to help minimize the potential for adjacent level ossification.

The plate is low profile and allows for excellent intra-operative visualization of the vertebral end plate and graft. The system also provides a choice of fixed and variable self-drilling screws to provide the surgeon with multiple options.

The MaxAn® Anterior Cervical Plate System is an anterior cervical spinal fixation device made from titanium alloy (Ti-6Al-4VELI). Pre-contoured plates that conform to the natural lordotic curvature of the spine are available in one, two, or three level configurations. These offerings also range from 8.0mm to 72mm in length when measured from screw hole to screw hole. The system includes variable and fixed bone screws, which are available in 4.0mm and 4.5mm diameters in various lengths. The MaxAn® Anterior Cervical Plate System is cleared under premarket notification [510(K)] K080646.

Indications for Use: The MaxAn® Anterior Cervical Plate System is intended for anterior interbody screw fixation of the cervical spine. The system is indicated for use in the temporary stabilization of the anterior spine during the development of cervical spinal fusions in patients with degenerative disc disease (as defined by neck pain of discogenic origin confirmed by patient history and radiographic studies), trauma (including fractures), tumors, deformity (defined as 'kyphosis, lordosis, or scoliosis), pseudarthrosis, and/or failed previous fusions. The intended levels for treatment range from C2 -T1.

Contraindications for Use: The MaxAn® Anterior Cervical Plate System is contraindicated in patients with spinal infection or inflammation; morbid obesity; mental illness, alcoholism or drug abuse; pregnancy; metal sensitivity/foreign body sensitivity; inadequate tissue coverage over the operative site, open wounds local to the operative area, or rapid joint disease, bone absorption, osteopenia and/or osteoporosis. Osteoporosis is a relative contraindication since the condition may limit the degree of obtainable correction, the amount of mechanical fixation and/or intolerance.

3 Study Design

3.1 Design

This is a prospective single-arm multi-center study of Cellentra™ Viable Cell Bone Matrix (VCBM), cortical allograft spacers, and the MaxAn® Anterior Cervical Plate System when used in anterior cervical discectomy and fusion procedures. This study will enroll up to eighty (80) subjects across up to eight (8) clinical sites. Subjects will be recruited from a pool of patients presenting to investigators for an anterior cervical discectomy and fusion procedure.

3.2 Inclusion Criteria

Subjects will be considered for inclusion in this study if they satisfy all of the following criteria.

1. The subject is scheduled to undergo a two or three level primary spinal fusion surgery between the levels of C2-T1 (Cervical 2 to Thoracic 1) using Cellentra™ VCBM, allograft spacers, and the MaxAn® Anterior Cervical Plate System.
2. The subject is 18 years of age or older.
3. The subject was unresponsive to conservative treatment for at least 6 weeks unless clinically indicated sooner.
4. The subject has persistent neck, shoulder, or arm pain consistent with cervical degenerative disc disease confirmed by patient history and radiographic studies.
5. The subject must in the investigator's opinion, be psychosocially, mentally, and physically able to fully comply with this protocol including

the required follow-up visits, the filling out of required forms, and have the ability to understand and give written informed consent.

3.3 Exclusion Criteria

Subjects will be excluded from this trial if they satisfy any of the following criteria (Exclusion criteria 1, 2, 3, 4, 5, 10, and 13 are specific to the MaxAn® Anterior Cervical Plate).

1. Subject has an active local or systemic infection.
2. Subject is morbidly obese, defined as a BMI greater than 40.
3. Subject has a history (present or past) of substance abuse (recreational drugs, prescription drugs or alcohol) that in the investigator's opinion may interfere with protocol assessments and/or with the subject's ability to complete the protocol required follow-up.
4. Subject has inadequate tissue coverage over the operative site.
5. Subject has an open wound local to the operative area, or rapid joint disease, bone absorption, osteopenia, osteomalacia and/or osteoporosis.
6. Any previous cervical spinal surgery.
7. Subject has a condition requiring medications that may interfere with bone or soft tissue healing (i.e., oral or parenteral glucocorticoids, immunosuppressives, methotrexate, etc.) or immunocompromised.
8. Subject has any medical condition or extenuating circumstance that, in the opinion of the investigator, would preclude participation in the study.
9. Subject who does not meet the specific indications for use of the Cellentra™ VCBM or MaxAn® Anterior Cervical Plate System.
10. Subject is pregnant, lactating or interested in becoming pregnant during the duration of the study.
11. Subject is currently involved in another investigational drug or device study that could confound study data.
12. Subject is a prisoner.
13. Subject has a metal sensitivity/foreign body sensitivity.

14. Subject is involved in or planning to engage in litigation or receiving Worker's Compensation related to neck or back pain.
15. Subject has sensitivity or allergies to any of the processing agents. (See package insert for Cellentra™ VCBM).

3.4 Subject Screening Exceptions

No subject screening exceptions for inclusion or exclusion criteria will be granted for this study.

4 Study Procedure

4.1 Screening Assessments

4.1.1 Informed Consent

Subjects will be provided with an informed consent and will be given ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study specific procedures, that are not part of the investigator's standard of care begin. A copy of the informed consent will be given to the subject. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

All subjects who have agreed to participate in this study, and have signed informed consent and who meet the inclusion/exclusion criteria will be considered enrolled and assigned a subject ID number. Once a Subject ID number has been issued, it cannot be reassigned or used for another subject.

4.1.2 Medical History and Demographic Data

Within 60 days prior to the surgery date, the following information will be collected according to the parameters described by VCBM/MaxAn CRFs:

- Demographic data (including date of birth, employment status, smoking status and history of substance abuse)
- Medical history, including a complete history of spinal disorder(s) (non-operative or operative treatments performed)
- Physical examination (including height, weight, blood pressure and pulse)

- Neurological Assessment (motor, sensory & reflex assessments)
- Standard radiographs and/or CT scans
- Current pain medications and other drug therapies.

4.1.3 Pregnancy Screening

A pregnancy test will be performed and negative results will be on file for all female subjects unless sterilized or post-menopausal to ensure pregnant subjects are not enrolled into the study.

4.1.4 Clinical Assessment

The subject will undergo the following pain and function assessments within 60 days prior to the surgery date:

Pain/Function Disability Assessment: Pre-operatively the subject will complete the Neck Disability Index (NDI) Questionnaire. The questionnaire is a combined pain and function index. It will be used to assess the subject's neck pain and how that pain affects the subject's ability to manage in everyday life.

The questionnaire is divided into ten sections designed to assess limitations of various activities of daily living. Each section contains six statements and each statement describes a greater degree of difficulty in that activity than the preceding statement. The subject marks the one statement in each section, which describes his/her limitations most accurately. Each section is scored on a 0-5 scale, 5 representing the greatest disability. The scores for all sections are added together, giving a possible score of 50. If a subject marks two statements, the highest scoring statement is recorded as a true indication of his disability. If a section is not completed because it is inapplicable, the final score will be adjusted.

Neck and Shoulder/Arm Pain: Preoperatively all subjects will assess their neck and/or radicular shoulder/Arm pain in one or both arms using a visual analogue scale (VAS) from 0-10 cm with 10 being considered most painful.

Hip Pain: Preoperatively all subjects will assess their hip pain in both hips using a visual analogue scale (VAS) from 0-10 cm with 10 being considered most painful. Hip pain is being measured as some of the subjects will undergo bone harvesting for autograft from the iliac crest.

SF-36v2™ Health Survey: Preoperatively all subjects will complete a SF-36v2™ Health Survey as an outcome measure to assess quality of life.

Subject completed self-assessments will be collected preoperatively and postoperatively.

4.2 Perioperative and Postoperative Management

Surgeons will perform a 2 or 3 level anterior cervical discectomy and fusion per their customary care utilizing Cellentra™ VCBM, cortical allograft spacers and the MaxAn® Cervical Plate. Surgeons will perform the discectomy and endplate preparations and will insert the allograft spacer with Cellentra™ VCBM per their preferred insertion method.

Screws will be tightened and locked per the MaxAn® system ring locking mechanism instructions for use and the closure performed per the surgeon's normal ACDF customary care. Data will be collected during and immediately after the surgery according to the parameters described by the VCBM/MaxAn CRFs. This includes: duration of surgery, blood loss, OR time, length of hospital stay, instrumentation used, type of procedure, surgical level, biological augmentation, size of interbody spacer used and amount of Cellentra™ VCBM used. In addition, all intra-operative complications (e.g. excessive blood loss, hematoma, vascular injury, etc.) will be reported and recorded as a complication on the CRF.

Intra-operative (after hardware is completed) or immediate post-operative, x-rays will be obtained. These images will be transferred electronically via an internet connection to the independent imaging vendor and may be reviewed by Biomet Spine and an independent radiologist. Postoperative care will follow the standard of care at each institution for subjects who undergo anterior cervical fusion procedures.

4.3 Investigator Training

All investigators participating in this study will have adequate training and familiarity with surgical technique for ACDF procedures, cortical allograft spacers, Cellentra™ VCBM and the MaxAn® Anterior Cervical Plate System.

4.4 Follow-Up Assessments

Subjects will be asked to return postoperatively at 3 (± 2 weeks), 6 (± 2 weeks), 12 (± 1 month) and 24 (± 1 month) months for a clinical and radiographic exam. The following data will be recorded on the Case Report Forms (CRFs) and in addition, electronic data entry will be employed via an Internet connection when using the Electronic Data Capture (EDC) program, OpenClinica.

Clinical assessment: The investigator will carry out a clinical examination at the 3, 6, 12 and 24 month visit to assess:

- subject compliance with postoperative care instructions,
- Neurological Assessment (motor, sensory & reflex assessments)
- ability to return to work and normal activity, and
- any procedure related or device related complications since discharge from the hospital

Subject self-assessment:

- Each subject will be asked to complete a follow-up Neck Disability Index (NDI) form, SF-36 form and a Neck and Shoulder/Arm Pain VAS and Hip Pain VAS form at each follow-up visit.

Radiographic assessment: Each subject will undergo AP and lateral x-rays at the 3, 6, 12 and 24 month visits and flexion and extension x-rays at the 6, 12, and 24 visits as well as a CT scan at the 12 month visit to assess:

- Evidence of progression towards fusion
- Presence / absence of heterotopic bone at the fusion site or at the adjacent vertebral levels
- Evidence of plate and/or spacer migration or subsidence
- Evidence of adjacent level ossification

All x-ray and CT images collected during the follow-up visits will be transferred electronically via an internet connection to the independent imaging vendor.

4.5 Independent Radiographic Assessment

An independent radiographic analysis will be performed to evaluate all images and assess subjects' radiographic status. The following quantitative and qualitative assessments will be performed.

Fusion Determination

Fusion will be assessed by an independent radiologist using the subjects' 12 month visit x-ray and CT images. All x-ray and CT images will be transferred electronically via an internet connection to the independent imaging vendor. The subjects' 12 month CT images will be evaluated by an independent radiologist to determine fusion. In addition, the subjects' 12 month x-rays will be evaluated for fusion determination using the Bridwell anterior fusion grading system[5,6]. The Bridwell grading system is as follows:

- Grade I (definite) – Fused with remodeling and trabeculae
- Grade II (probable) – Graft intact, not fully remodeled and incorporated through, no lucencies
- Grade III (probably not) – Graft intact, but a definite lucency at the top or bottom of the graft
- Grade IV (no) – Definitely not fused, with resorption of bone graft or collapse

Radiographic Success: Radiographic success is defined as Grades I or II.
Radiographic Failure: Radiographic failure is defined as Grades III or IV.

The subjects' x-ray images from the 3, 6, and 24 month follow-up visits may also be assessed for fusion by an independent radiologist using the Bridwell grading system.

4.6 Success Criteria

4.6.1 Primary Measure of Effectiveness

The primary measure of effectiveness will be assessed by the improvement in the Neck Disability Index (NDI) score at 12 months. Subjects treated with Cellentra will be considered a success if they show a clinically meaningful improvement in NDI score (from baseline to 12 months) of 8 or more NDI points.

4.6.2 Primary Measure of Safety

The primary measure of safety will be determined by the percentage of adverse events as compared to published literature for cervical plate systems and allograft spacers with autograft or allograft.

4.6.3 Secondary Measure of Effectiveness

The secondary measure of effectiveness will be determined by fusion. A subject will be considered a success if fusion as assessed by an independent radiologist is a Grade I or Grade II at 12 months.

4.7 Subject Withdrawal

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the surgeon, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. If the subject is withdrawn for any reason at any time a final evaluation form will be completed.

Other Conditions for Withdrawal:

Any subject who develops a severe concurrent medical illness during the study should be withdrawn. This type of illness is defined as any illness that would hinder the subject's ability to return for scheduled follow-up appointments. Such a withdrawal will not be counted for the purposes of determining success or failure.

5 Complications

In addition to the standard operating procedures for reporting complications per hospital/physician protocol, all clinical events, including both observed or volunteered problems, complaints, symptoms, physical signs or disease which either occur during the study, having been absent at baseline, or, if present at baseline, appear to worsen during the clinical outcomes collection study are to be recorded as complications in the subject's medical record and on the appropriate case report form. In addition for any cleared device, or tissue product a Product Experience

Report (PER) must be completed per the manufacturer's customary complaint procedure (SOP 114.0.1 – Product Complaint Procedure).

Complications reported in the literature as most commonly associated with ACDF procedures include, but are not limited to, dysphagia, soft tissue or wound hematoma, recurrent laryngeal nerve palsy, cerebrospinal fluid leakage secondary to dural tear, esophageal or pharyngeal perforation, Horner's syndrome, vascular injury, mechanical failure of cervical instrumentation, and extrusion of bone graft material.[7]

Definition

A complication is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, performance, or any indication of the failure of a device or tissue product to meet a user or customer's expectations. The complaint may be the possible failure of a device, labeling, or packaging to meet any of its specifications after it is released for distribution.

6 Statistical Analysis Plan

6.1 Primary Objective and Sample Size Justification

The primary objective of this study is to show subjects who are treated with Cellentra have a clinically meaningful NDI improvement (from baseline to 12 months) of 8 or more NDI points. The secondary objective is to compare the results to published NDI changes in similar populations treated with standard of care bone grafts (autograft and allograft).

For subjects who have undergone an ACDF procedure, the minimal clinically important difference (MCID) in the change of NDI was determined to be 8 points[8,9]. In published literature, the reported improvement in NDI from baseline to 12 months was found to be similar between subjects who had an ACDF procedure performed with autograft and allograft. The average improvement in NDI ranged from 7 to 20 points (on an NDI scale from 0-50 points) [8, 10-14]. For the purposes of this sample size calculation an average 12 month NDI improvement of 14 points (SD: 12) was chosen, as Cellentra is expected to perform similarly to the standard of care.

Sample sizes were calculated to determine if subjects treated with Cellentra have clinically relevant improvements of at least 8 NDI points, and to compare Cellentra to published NDI changes under the standard of care (ACDF with allograft or autograft). As published studies have typically shown that subjects have an average of 14 points NDI improvement, we have assumed a non-inferiority margin of 6 NDI points such that changes in NDI score using Cellentra are no more than 6 NDI points smaller than the typical change of 14 using standard of care. Note that this margin is smaller than the MCID of 8 points.

Sample sizes were calculated assuming a 5% two-sided type 1 error rate and 97.5% power for a 1 sample t test. The Cellentra group will result in clinically relevant improvements in NDI if the lower bound of the 95% confidence interval does not overlap 8. Assuming a standard deviation of 12, this will be achieved if the mean NDI improvement is 11 points. Secondarily, this would provide some evidence that Cellentra results in NDI changes no less than 6 NDI points lower than the standard of care treatments, which result in an average change of 14 points. However, this claim must be made carefully, as different populations may experience different changes in NDI. Again, assuming a standard deviation of 12, if the lower bound of the 95% confidence interval overlaps 8, NDI changes of 14 or greater with Cellentra can be ruled out, suggesting that the standard of care may outperform Cellentra.

Definitions:

$\mu_{1:}$ the mean value of the ΔNDI_{12} in the study group (Cellentra)
μ_0: Clinically relevant change in NDI. The lower 95% confidence bound for ΔNDI of subjects at 12 months must be greater than μ_0.

The primary hypothesis is given by:

$$H_0: \mu_1 \leq \mu_0 \quad \text{versus} \quad H_1: \mu_1 > \mu_0$$

Assumptions:

$\alpha = 0.05$	Probability of Type I error
$\beta = 0.025$	Probability of Type II error: power = $1 - \beta$
$\mu_1 = 14$	Estimated ΔNDI from baseline to 12 months
$\mu_0 = 8$	Clinically Relevant Improvement

Sample sizes were calculated in R version 3.1.0.

In order to rule out NDI changes of less than 8 points, 64 subjects are required (5% type I error rate, 97.5% power). The sample size was increased by 25% to allow for possible attrition. This gives a sample size of 80 total Cellentra study subjects.

6.2 Inferential Methods

6.2.1 Significance Levels

Statistical tests will be performed using a 2-sided $\alpha = 0.05$ to compare changes in NDI.

6.2.2 Models for Continuous Measures

Continuous measures will be summarized using standard summary statistics (mean, standard deviation, and range). Changes in NDI will be evaluated using a 1 sample t-test. Secondary analyses may include multiple linear regression models in order to adjust for important covariates (such as age, sex, BMI, tobacco use, etc.).

6.2.3 Categorical Data Analyses

Categorical measures will be summarized using standard summary statistics (frequency and percentage of total).

7 Ethical and Regulatory Requirements

7.1 Code of Conduct

The Investigator will ensure that the clinical study is conducted in accordance with good clinical practice (GCP) and all regulatory and institutional requirements, including those for subject privacy, informed consent, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval and record retention, the Food and Drug Administration (FDA) Guidelines for the conduct of clinical trials, and the CPMP/ICH/135/95.

7.2 Reports

Clinical investigators must make the following required reports:

- Unanticipated Adverse Device Effects
- Withdrawal of IRB Approval
- Yearly report to Sponsor/IRB
- Other reports requested by a reviewing IRB or FDA

7.3 Institutional Review Boards (IRB)

The Investigator must obtain appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval before the study can be initiated. A copy of the written approval from the IEC/IRB and a copy of the approved informed consent form should be sent to the Sponsor. A list of the IEC/IRB members (including their Institution affiliations, gender makeup, and occupations); or a statement from the IEC/IRB specifying that the membership comply with applicable regulations is to be provided to the sponsor.

If the Investigator advertises for subjects, whether in a professional or consumer publication, radio, television or community notices, all advertising must receive prior approval by the Sponsor and the IEC/IRB.

Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by the Sponsor for submission to the IEC/IRB for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's medical record.

The Investigator must immediately forward to the IEC/IRB any written safety reports or updates from the Sponsor.

The Investigator must keep the IEC/IRB informed of the progress of the study at least annually.

7.4 Informed Consent

The Investigator must observe the requirements of the appropriate regulatory body by obtaining written informed consent. The Sponsor will supply a sample informed consent form. Whether or not the sample

informed consent form is used or adapted, the site will submit the proposed informed consent form to the Sponsor for review PRIOR to submission to the IEC/IRB. The informed consent form must be approved by the institution's designated IEC/IRB. Copies of the informed consent form used in the study must contain the IEC/IRB-approval stamp (if applicable) and version date.

Subjects will be informed of new information learned during the study, which may affect the subject's decision to continue participation in the study.

The study informed consent form must be obtained prior to the initiation of any study procedures. The subject (or the subject's legally authorized representative) must be allowed sufficient time to thoroughly read (or have explained to them), the informed consent form. The Investigator should answer any questions that the subject/representative might have. If the subject agrees to participate in the study, the subject must sign the informed consent form. The Investigator or a representative for the investigator, who is obtaining informed consent, must also sign the informed consent form. A copy of the signed consent form will be given to the subject and the original signed form will be retained in the patient's subject binder. The study staff should adequately and accurately document the sequence of actions in the consenting process as well as the date of the subject's signature on the informed consent form in the subject's medical chart to document that informed consent was obtained prior to initiating any study procedures.

Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

7.5 Source Documentation Requirements

Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the trial data submitted for review and analysis. Source documentation will include, but not be limited to, signed and dated consent form, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, pharmacy records, device accountability records, pregnancy tests and medical consultations (as applicable).

7.6 Subject Confidentiality

The Sponsor will maintain the confidentiality of the identity of all subjects enrolled in the study and the information contained in their records. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study records. The subject records will be made available as required for review by governing regulatory agencies such as FDA and a reviewing IEC/IRB, however to every extent possible; the subject's identities will not be disclosed.

Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is required and data collection must comply with the Standards for Privacy of Individually Identifiable Health Information, 45 CFR Part 160 and Part 164, as amended from time to time (the "Privacy Rule"), under HIPAA.

The case report forms do not include any subject identifying information in accordance with HIPAA. Therefore, once the data is entered in the online database a subject can no longer be identified. It is the responsibility of the investigator to maintain a list of subject identification and study ID numbers.

By assigning subjects a unique study ID number, their identity is protected in OpenClinica, an online database. The database is restricted, allowing a physician and his/her research associate to view and enter data from their enrolled subjects. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

7.7 Retention of Records by the Investigator

The Investigator will retain records for a period of 2 years following the date of study conclusion.

7.8 Data Reporting

7.8.1 Case Report Forms

Data for this clinical trial will be collected and documented on the patient Case Report Forms (CRFs) provided which may be in paper form or in an electronic form. Authorized study site personnel will complete CRFs only.

Since there is a potential for errors, inaccuracies, and misinterpretation in transcribing data onto the CRFs, originals or photocopies of all relevant records and reports, and copies of test results must be available at all times for inspection and comparison to the CRFs by the study monitor.

7.8.2 Final Report

Following completion of this trial, final reports will be issued as required.

7.9 Monitoring

The Investigator must allow regular inspection of all study records including CRFs, source documents and regulatory documents during the study by the monitor or a representative of the Sponsor. This measure is to ensure that the study is carried out and documented in accordance with the terms of this protocol, GCPs, ICH, IRB and if applicable federal regulations. The Investigator also agrees to allow inspections by members of any regulatory agencies at any point, if such inspections are requested.

In cooperation with the on-site staff, monitors will:

- Review all study documentation to ensure compliance with the protocol.
- Review data recording for each visit to verify the accuracy and completeness of the information on the CRFs against appropriate source documents.
- Review adequacy of enrollment rate.
- Review required regulatory documentation.

Biomet will monitor at least 20% of the sites during the course of the study. If inconsistencies in the data are found, an increased percent of monitoring will be performed.

7.9.1 Data Quality Assurance

Standardized subject case report forms will be provided for use at all Investigational Sites. The Investigator is responsible for completion and timely submission of the forms to the study Sponsor for data processing.

Data will be collected on all subjects pre-operatively, intra-operatively and postoperatively at 3, 6, 12 and 24 months. Electronic data entry will be employed via an Internet connection when possible, using our Electronic Data Capture (EDC) system OpenClinica. Access to the EDC program is limited to the physician or research associate. All users will be given a unique user name and password and will be assigned a specific role. The role determines the level of access granted to each user. Study monitors will have access to subject numbers only; any subject identifying information will be blocked. In the event the site does not have Internet access, data will be recorded on paper Case Report Forms (CRFs).

Incoming data are reviewed to identify inconsistent or missing data and complications. Data inconsistencies will be addressed through telephone calls, faxes, or emails to the Investigational Sites and during site visits. All hard copy forms and data files will be secured to ensure confidentiality.

7.9.2 Screened Subjects who are not enrolled

Only data for enrolled subjects will be monitored and entered into the database. Subjects who are screened for the study but are not enrolled for any reason will not be followed and the Sponsor will not evaluate their data. The sites may retain the screening case report forms for these subjects, at their discretion.

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APPENDIX 1

Case Report Forms (CRFs)

CLINICAL PROTOCOL CHANGE HISTORY

From Version	To Version	New Version Date	Change Page No.	Description of Changes
CS-092-01	CS-092-02	5-15-2014	1-3, 5, 11-25	Updated randomization process. Amended radiographic assessments to be performed by physicians and the independent radiologist. Added requirement for sites to send radiographic images to an independent imaging vendor instead of Biomet. Updated EDC system to OpenClinica. Aligned protocol to match updated CRF requirements. Corrected grammatical errors and adjusted formatting.
CS-092-02	CS-092-03	8-15-2014	All	Revised study design to a prospective single-arm multi-center study of Cellentra and MaxAn in ACDF procedures.