1. Title

Clinical and Radiographic Outcomes of BIO^4 Bone Matrix in Patients Undergoing 1 or 2-Level Anterior Cervical Discectomy and Fusion Surgery, CR-16-109, Full Board, Expiration Date 2/21/18

2. Principal Investigator

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3. Purpose

The goal of this study is to investigate the efficacy of BIO4 bone matrix in patients undergoing 1 or 2-level Anterior Cervical Discectomy and Fusion (ACDF) spine surgery. BIO4 is a viable bone matrix containing endogenous bone forming cells including mesenchymal stem cells, osteoprogenitor cells and osteoblasts as well as osteoinductive and angiogenic growth factors. BIO4 possesses all four characteristics involved in bone repair and regeneration: osteoconductive; osteoinductive; osteogenic and angiogenic (Roberts and Rosenbaum, 2012; Osiris Therapeutics; Bourke et al., 2003). It is an alternative to autograft that minimizes the potential for harvest site co-morbidities (Epstein, 2008, 2009; Eastlack et al., 2014).

Features for BIO4 include: next generation viable bone matrix; lot tested for the presence of VEGF (vascular endothelial growth factors) and 70% or greater cell viability post-thaw (Osiris Therapeutics); ready to use out of the package (no decanting required and thaws in 15 minutes); differentiated handling compared to the competition; contains on average at least 600,000 cells (endogenous bone forming cells including mescenchymal stem cells, osteoprogenitor and osteoblasts) per cc (Osiris Therapeutics); and non-immunogenic (Osiris Therapeutics). To date, no other non-cultured cellular bone allografts are promoted as supporting angiogenesis and all four components for bone formation. This study aims to investigate the efficacy of BIO4 bone matrix in patients undergoing 1 or 2-level ACDF spine surgery.

Specifically, the study aims to collect the data for ACDF model utilizing BIO^4 with Bio AVS Cervical Allograft (with graft window). Our null hypothesis is that in ACDF model, the clinical and radiographic outcomes of utilizing BIO^4 bone matrix with Bio AVS Cervical

Allograft are equivalent to historical high level published data of similar product (Data reported in Meta-analysis ACDF obtained from FDA disc arthroplasty trials).

This White Paper research on new Biologic Platform (BIO^4 Viable Bone Matrix) will enroll 20 patients. The study with the current sample size tends to serve as an exploratory pathway to another higher Level 1 study with a similar study design. Characteristics of subjects and clinical variables will be analyzed using means and standard deviations calculations. Independent t-tests will be used to compare the means of continuous variables. The normally distributed data will be presented as mean ± standard deviation. The non-normally distributed data will be expressed as medians (interquartile range) and will be analyzed via the Mann-Whitney's U test. Descriptive variables will be subjected to χ^2 analysis or Fisher's exact test as appropriate. The level of significance will be set at α=0.05. SPSS 14.0 for windows statistical software will be used for this study.

4. Procedures

This is a prospective study with the intent to investigate the efficacy of BIO^4 bone matrix in patients undergoing 1 or 2-level ACDF spine surgery. At the time a patient is scheduled for surgery, the patient's chart will be evaluated for inclusion/exclusion criteria. If a patient meets the criteria for the study, the study will be explained to the patient and consent obtained.

We will utilize the BIO^4 on label as a 361 HCT/P (human cell, tissue and cellular and tissue-based product) for homologous use for the repair, replacement or reconstruction of bone defects. Interbody fusion (1 or 2-level fusion) in conjunction with an allograft (hct/p) interbody spacer (anterior approach in the cervical spine with hardware) will be utilized. We will also use the Aviator Anterior Cervical Plating System for anterior intervertebral screw fixation of the cervical spine at levels C2-T1. The Aviator Anterior Cervical Plating System is intended for use as an aid in cervical spinal fusion and is intended for unilateral fixation. The Aviator plates are intended to be used with the Aviator bone screws. As a standard of care, there are alternative treatment options for patients who choose not to participate in the study. The patient may still receive ACDF surgery with BIO^4 bone matrix outside of the study. Additional alternative treatments include continuing conservative care or a different surgical treatment. Conservative care may include: bed rest, back brace, medications for pain, oral steroids, exercise and/or physical therapy, drug injections directly into the spine. The patient may also choose an alternative surgical procedure such as: removing part of the disc (called discectomy) and fusion, and/or removing a small amount of bone from the back of his/her spine (called laminectomy) to possibly help patient's symptoms. Some or all of these alternatives may or may not be appropriate for a given patient. The study doctor can discuss other options with the patient. Only the patient and his/her study doctor can decide if an alternative treatment is appropriate for their condition.

a. Location

Subjects will be recruited from the Seton Spine & Scoliosis Center, Austin, TX. Recruitment will continue until 20 subjects are enrolled and scheduled with 1 or 2-level ACDF spine surgery at levels C2-T1. All the surgeries will take place at Seton Medical Center Austin TX.

b. Resources

Not applicable

c. Study Timeline

The project will take about 12 months from data collection to dissemination of results.

5. Measures

In addition to the basic demographics (age, gender, BMI, smoking status) and operative details (operative time, total blood loss, time of ambulation and perioperative complications), the study aims to collect the data for the following: 1) radiological assessment of fusion (cervical spine x-ray and if needed, CT at 1 year follow up) as the primary endpoint; 2) Arthrodesis rates assessed using CT (1 year follow up, if needed) and AP, lateral, dynamic flexion-extension cervical spine x- rays pre-op, post-op 2~4 weeks (no flexion-extension) (10~34 days post op), 3 months (83~97 days post op), 6 months (173~187 days post op) and 1 year (primary data point outcome) (351~379 days post op); 3) revision rates (if any); 4) outcome scores (Visual Analog Scale, VAS and Neck Disability Index, NDI) pre-op, post-op 2 ~ 4 weeks, 3 months, 6 months and 1 year.

6. Participants

a. Target population

20 individuals who are skeletally mature with cervical pain would be considered as potential subjects for the study.

b. Inclusion Criteria:

- Ages18 -75 years
- Scheduled 1 or 2-level ACDF spine surgery
- The capacity to provide informed consent.
- Subject has one or more of the following diagnoses:
    i) Degenerative Disc Disease (as defined by neck pain of discogenic origin with degeneration of the disc confirmed by patient history and radiographic studies)
    ii) Trauma (including fractures)
    iii) Tumors
    iv) Deformities or curvatures (including kyphosis, lordosis, or scoliosis)

v) Pseudoarthrosis
vi) Failed previous fusion
vii) Decompression of the spinal cord following total or partial cervical vertebrectomy
viii) Spondylolisthesis
ix) Spinal stenosis

c. Exclusion Criteria

Patients with any of the following conditions will be excluded, or if enrolled and found to be ineligible and do not fit the inclusion criteria, will be withdrawn from the study.

- Patients with current or recent history of malignancy or infectious disease.
- The inability to provide informed consent.
- Subject has marked local inflammation
- Subject has any mental or neuromuscular disorder which would create an unacceptable risk of fixation failure or complications in postoperative care.
- Subject has a bone stock compromised by disease, infection or prior implantation which cannot provide adequate support and/or fixation to the devices.
- Subject has bone abnormalities preventing safe screw fixation.
- Subject has any open wounds.
- Subject has rapid joint disease, bone absorption, osteopenia, osteomalacia, and/or osteoporosis. Osteoporosis or osteopenia are relative contraindications, since this condition may limit the degree of obtainable correction and/or the amount of mechanical fixation.
- Subject has a documented or suspected metal sensitivity.
- Subject is pregnant.
- Subject has anatomical structures or physiological performance that would interfere with implant utilization.
- Subject has inadequate tissue coverage over the operative site.
- Subject has other medical or surgical conditions which would preclude the potential benefit of surgery, such as congenital abnormalities, immunosuppressive disease, elevation of sedimentation rate unexplained by other diseases, elevation of white blood count (WBC), or marked left shift in the WBC differential count.
- Note: The Aviator Anterior Cervical Plating System is not approved or intended for screw attachment to the posterior elements (pedicles) of the cervical, thoracic, or lumbar spine. The surgeon must consider the levels of implantation, patient weight, patient activity level, and other patient conditions which may impact on the performance of the system.

d. Benefits

There are no direct benefits to patients from being in this study. Information gathered in this study may benefit others who undergo this procedure in the future. Long term, studies

like this may help clinicians better understand the benefits of doing spine surgery with BIO[4] bone graft, BIO AVS cervical allograft and Aviator anterior cervical plating system.

e. Risks

All procedures will be performed by the Board Certificate Orthopedic Surgeons (principal and co-investigators) who have performed several such procedures in the past. The only risks that patients would be subjected to are same that are associated with any such procedures. There may be potential cancer risks associated with similar bone graft products. All the patients will be followed up closely post-operatively for any risks and treated accordingly. There may be confidentiality risks associated with the study. All efforts will be made to minimize this risk.

Subject's participation in this research is voluntary and will be allowed to discontinue from the study anytime he/she wishes to. If the subject choose not to participate, it will not affect his/her relationship with the study doctors or the study doctor's institution, or their right to health care or other services to which they are otherwise entitled at our center. Subject's participation may be stopped by the PI/Co-PI under the following or other circumstances: (1) to protect subject's health and safety, (2) because the subject fails to come in for his/her scheduled study visit, or (3) the study is stopped for any reason.

f. Recruitment

Subjects will be recruited from the Seton Spine & Scoliosis Center, Austin, TX. Recruitment will continue until 20 subjects are enrolled and scheduled with 1 or 2-level ACDF spine surgery at levels C2-T1.

g. Obtaining Informed Consent

The inclusion and exclusion criteria check list will be completed and consent obtained in private in a clinical setting at Seton Spine and Scoliosis Center. After the initial evaluations by investigators, they will address enrollment in the prospective study with his/her patient. Potential subjects will be educated about all essential aspects of the study including the requirements for enrollment, the study procedures, and all risks and benefits of participation. Potential subjects will be given the opportunity to ask questions. After questions have been answered, potential subjects that are interested in enrolling in the study will be asked to sign an informed consent. A copy of the signed informed consent documents will be given to the patient. In the event that a potential subject wishes to deliberate, shows any hesitation, or is not able to decide whether they will participate, the issue of enrollment will be deferred.

7. Privacy and Confidentiality

a. All the required study data will be collected by the study personnel at various study visits. All study personnel are the employed by the clinic and will have access to the patient medical records. During the patient visit, the outcome data such VAS and NDI will be collected on the VAS and NDI forms and scored will be transferred to the data

collection sheet. The forms will be filed in the patient binder. Clinical and demographic data will be captured from the medical record and mentioned in the data collection sheet. These data will be collected at Seton Spine and Scoliosis Center. Specifically, in addition to the basic demographics (age, gender, BMI, smoking status) and operative details (operative time, total blood loss, time of ambulation and perioperative complications), the study aims to collect the data for the following: 1) radiological assessment of fusion (cervical spine x-ray and if needed, CT at 1 year follow up) as the primary endpoint; 2) Arthrodesis rates assessed using CT (1 year follow up, if needed) and AP, lateral, dynamic flexion-extension cervical spine x- rays pre-op, post-op 2~4 weeks (no flexion-extension), 3 months, 6 months and 1 year (primary data point outcome); 3) revision rates (if any); 4) outcome scores (VAS and NDI) pre-op, post-op 2 ~ 4 weeks, 3 months, 6 months and 1 year.

b. The data collection sheet will not have any personal information of subjects (such as date of birth, SSN, etc.). Despite this, all the study documents will be stored locked in a locked office at the Spine Center. The initial data sheet will have a coded number on it, and this coded number will be used to collect follow-up study related information. Only the principal/co-investigators and the study coordinator will have access to the documents. The electronic data sheet will be stored on investigators and study coordinator's Seton computers which are password protected.

c. The study data will be kept for 2 years from the conclusion of the study.

d. Study participants will be assigned a study number, and their data coded and de-identified in the data bases. All efforts will be made to protect the privacy of subjects and maintain confidentiality of data collected. The data collection sheet will not have any personal information of subjects (such as date of birth, SSN, etc.). Despite this, all the study documents will be stored locked in a locked office at the Spine Center. The initial data sheet will have a coded number on it, and this coded number will be used to collect follow-up study related information. Only the principal/co-investigators and the study coordinator will have access to the confidential documents. These confidential documents will not be shared by other researchers for research purposes.

e. At a point after the conclusion of the research study and final analysis, all code and research-related records will be destroyed by study personnel by shredding or other means per discretion of the hospital policy for paper waste containing patient information.

8. Compensation

There will be no remuneration offered for participation in this study.