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STUDY PROTOCOL

Prospective, Randomized Three Arm Study of lumbar Spinal Fusion Graft Efficacy: Bone marrow aspirate concentrate & Allograft versus Recombinant Bone Morphogenetic Protein-2 (BMP) versus Control Group

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Study #S16-01160

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Purpose of Study and Background

Purpose of the Study

The aim of this investigation is to compare the use of bone marrow aspirate concentrate (BMAC) and allograft versus recombinant human bone morphogenetic protein-2 (BMP) versus the gold standard fusion in subjects undergoing elective lumbar spinal fusion with interbody support. The safety and efficacy of the surgical interventions will be evaluated by assessing fusion status and subjects' quality of life outcomes.

Rationale

Biologics are almost universally used as an adjunct in spinal fusions for osteoconductive (ability to serve as scaffold for bone growth), osteoinductive (ability to stimulate bone growing cells), and osteogenic (bone growth cells creating new bone) effects. However, the use of BMP is marginally very expensive and has well documented complications such as cancer, wound complication, and increased immediate post-operative pain. BMP is a commonly used adjunct for minimally invasive surgeries of the lumbar spine for its osteoconductive, osteinductive, and osteogenic effects without the need for autologous bone graft. Recent studies, specifically the study by Robert Johnson, M.D. using BMAC with allograft, and the study by Gan et al. using BMAC with beta-tricalcium phosphate during spinal fusion procedures have produced positive results comparable to BMP results. In addition, several recent studies using BMAC to treat bone non-unions and osteonecrosis (abnormal bone death) have been positive. Therefore, it is believed that BMAC with allograft has the same osteoconductive, osteoinductive, and osteogenic effects as BMP without including the same complications. Previous research conducted at our own institution has demonstrated clear efficacy in the usage of bone marrow aspiration and concentration for the treatment of high risk adult spinal deformity patients relative to iliac crest, in a randomized manner. This has been tremendously helpful in our attempt to reduce inefficiencies in the cost of patient. This study intends to further investigate and compare the efficacy and long term effects of anterior lumbar spinal fusions with BMAC and allograft to that of BMP in 2-4 level lumbar spine surgical cases. This study also attempts to enhance our understanding of the cellular mechanisms that correlate with outcomes, a point of deficiency in previous studies, by adding a cellular analysis component. Use of BMAC and allograft may be an alternative to BMP that will limit BMP's increased price, known increase of complications, and foreign antibodies. It is anticipated that there will be an increase in minimally invasive spine surgeries for lumbar degenerative disease which will expand the role and use of biologics due to suboptimal successful fusion rates without their usage. This increase in minimally invasive surgery has been reflected in the busy practices of the co-investigators of this trial who wish to study the comparative efficacy of the 2 main biologics currently in use as their standard practice.

For validity and to provide reference the 2 main biologics will be controlled with the auto graft gold standard fusion. In some applications, such as intervertebral disc fusion in the cervical and lumbar spine, allografts with internal fixation have rivaled the results of autogenous bone grafts. Studies by Bishop et al., Martin et al., and Zdeblick and Ducker have shown that using allograft bone in the anterior cervical spine during fusions is just as adequate as autograft bone. In addition, Savolainen et al. observed similar rates of fusion in autograft and allograft. Also, in the lumbar spine, anterior femoral ring allografts have been very successful when posterior instrumentation is

used. Also, posterior spinal fusions for scoliosis in adolescents have similar rates of fusion when comparing allograft and autograft. Still further comparison is needed and a study comparing autograft as a control in BMAC vs. BMP will fill a gap in the literature.

The high expense and limited indication of BMP products makes it necessary to apply for prior authorization from insurance companies of these products for usage by insurance companies. For the purposes of this study, standard of care in all aspects will be followed, and pre-operative authorization for use of BMP as well as BMAC will be obtained from insurance companies prior to the day of surgery. If authorization cannot be obtained prior to the day of surgery the subject enrolled will be counted as a screen fail. While both of these products are currently approved for use by the NYU/HJD operating room product and pricing committees, through the conduction of this research we will also be working with the NYULMC supply chain management team in vetting and determining the clinical cost effectiveness of these biologics.

Background

Currently, there are numerous orthopaedic graft adjuncts. These include bone morphogenetic proteins (BMP), autograft (iliac crest bone graft), graft substitutes, blood, bone marrow aspirate, platelet rich plasma (PRP), embryonic culture-expanded stem cells, and bone marrow aspirate concentrate (BMAC). Each graft adjunct involves unique advantages and disadvantages. Although BMPs and embryonic culture-expanded stem cells are osteoinductive and osteogenic, respectively, they are both associated with issues such as high cost and risk of side-effects. When using bone marrow aspirate, there is the issue of providing sufficient bioactivity via including a sufficient baseline concentration of stem cells. Hence, BMAC presents as a logical means of orthopedic grafting. Not only does BMAC demonstrate osteoinductive and osteogenic properties, but it also supplies a significantly higher stem cell concentration than sole BMA.

History of Mesenchymal Stem Cells as Drivers of Tissue Regeneration

Mesenchymal stem cells (MSC) were initially thought to be the most important cell because early technology was only capable of expanding and differentiating an MSC *in vitro*. This led to the conclusion that MSCs were the drivers of tissue regeneration and if enough of them were expanded and transplanted, we would have clinical success regenerating tissue. However, FDA randomized clinical trials using cultured MSCs have failed and recent presentations have shown a negative dose effect in cardiac disease (i.e. high dose less effective than medium dose). The new understanding is that these cells can be best used for immune modulation rather than tissue regeneration. This is important to slow intervertebral disc degeneration.

Current Understanding: Nonadherent Cells Drive Tissue Regeneration

It has been noted that nonadherent cells (bone marrow cells), not adherent cells (MSCs), drive tissue regeneration. For example, Chen et al. (1997) demonstrated that bone marrow cells (CD34+) can form fibroblasts, adipocytes, smooth muscle cells, and macrophages and can differentiate into functional osteoblasts. This finding was repeated by Mifune et al. (2008), in which they showed that CD34+ cells can differentiate to osteoblasts via an MSC intermediate.

Animal and clinical models have substantiated the finding that nonadherent cells (bone marrow cells) drive bone formation. Matsumoto et al. (2008) demonstrated that CD34+ cells delivered systemically or locally reliably formed functional bone greater than did controls. When these cells

were delivered in a matrix, fewer cells were required than systemic administration. Further, Hernigou (2005) and Edgard and Einhorn (2011) recommended "the use of concentrated whole bone marrow, which includes other cells in the stromal and hematopoietic lineages...as they provide an optimized physiological and cellular milieu for the promotion of osteogenesis and angiogenesis."

Overall, non-adherent cells drive tissue regeneration by: (a) up-regulating cytokine release, which stimulates additional HSCs and MSCs from intact bone to the site of damage (Jung 2008); (b) releasing BMPs (Jung); (c) up-regulating production of VEGF and other cytokines that support angiogenesis and vasculogenesis (Mifune 2008); and, (d) directly forming bone by differentiating into MSCs and then osteoblasts (Matsumoto 2006, 2008).

Advantages of Bone Marrow Aspirate Concentrate

In the bone marrow, there are two principal multipotent stem cells: stromal stem cells (SSC) and hematopoietic stem cells (HSC). There is roughly one SSC in every 250,000 cells in the marrow at age 35 and this ratio decreases with age. There is roughly one HSC in every 10,000-15,000 cells in the marrow (this ratio does not decrease with age). The issue is that with such a small concentration of SSCs and HSCs, without concentrating the BMA, there will be unpredictable healing, particularly in healing-impaired patients.

Hence, the use of BMAC is recommended. When provided in a clinical model, BMAC is given with allograft and this combination demonstrates the same angiogenic, osteoinductive, osteoconductive, and osteogenic properties as BMP. Further, BMAC exactly mimics and supplements the body's natural response to trauma by stimulating vasculogenesis and tissue regeneration.

Conclusions of previous clinical models

BMP has been used since 2002 in the lumbar spine to promote bony fusion since its approval by the FDA for use in anterior lumbar interbody fusion, and is now approved for use in posterior and transforaminal approaches. BMP augment bony growth is promoting MSC and osteoprogenitor cell differentiation into osteoblasts, which is very similar to BMAC. In a 2015 systematic review of lumbar fusion rates with the use of rhBMP-2, Galimberti et al showed interbody lumbar fusion rates ranging from 97.8-93.6%. However, as detailed in a review of randomized clinic trials by Chrastil et al in 2013, despite high fusion rates, there may complications associated with BMP such as heterotopic ossification, radiculitis, and endplate osteolysis. While usage of BMP is attractive for avoiding autologous grafting—decreasing operative times, blood loss, avoiding donor site morbidity, and allowing for biologics in older, more morbid patients that may have a limited autograft supply.

Previous reports by Connolly et al. , Gangji et al., Hernigou et al., and Gessmann et al. have also shown that high concentrations of adult stem cells from iliac crest bone marrow can enhance the rate and amount of bone formation. The authors report that technology that quickly and easily concentrates bone marrow stem cells 3 to 6 times harvested baseline concentrations makes practical the use of adult bone marrow stem cells in a spinal fusion. In a study by Gan et al., they found a 95% successful spinal fusion rate when 252 mL BMA harvested from the iliac crest was

concentrated peri-operatively down to 45 mL enriched suspension. In contrast, the historical autograft fusion success rate ranges between 65-95%.

These studies conclude that both BMP and BMAC mimic and supplement the body's natural response to trauma by stimulating vasculogenesis and tissue regeneration. BMAC contains many cell types, while BMP contains only one, the question of superiority between the two methods of bone healing/remodeling stimulation is unanswered. As BMAC is autologous, there are no immuno-rejection side-effects or concerns regarding disease transmission.

Preliminary Data

In an earlier study with unpublished results, 14 BMAC+allograft patients were compared to 3 ICBG. This randomized series determined radiographic fusion in 92.9% of cases among the BMAC+allograft and ICBG cohorts, suggesting no difference in fusion efficacy among these grafts. This study did not identify any difference between lumbar spinal fusion patients receiving ICBG versus BMAC+allograft during surgery, on the basis of patient-reported outcomes up to 1-year follow-up and fusion grading. Only higher SF-12 MCS scores at baseline among ICBG patients were sustained at 6-weeks and 6-months post-operative. These preliminary results are important given the controversy surrounding effective use of interbody grafts, but are not decisive especially when, for many surgeons, the choice is between BMP and BMAC.

Our hypothesis is that:

For patients who undergo lumbar spinal fusion surgery with interbody support, the outcomes in terms of pre-operative measures, intra-operative measures, and post-operative measures in the investigational group (BMAC + allograft) will be similar to the compared BMP group and control group at 24 months postoperatively.

Study Objective

To compare the efficacy of BMAC+allograft versus BMP versus autograft (control), we plan to pursue a prospective, blinded controlled study in which: BMAC+allograft or BMP or autograft will be randomized 1:1:1 ratio, respectively to certain patients undergoing a lumbar fusion by interbody support.

Study Design

This study will be a prospective, randomized clinical study at a single-center, NYU Langone Medical Center. It is intended to compare and evaluate the efficacy of subjects who are either treated with (1) bone marrow aspirate concentrate (BMAC) and allograft or (2) recombinant human bone morphogenetic protein-2 (BMP) or (3) autograft (control) during lumbar spinal fusion with interbody support. The clinical, radiographic, and Health Related Quality of Life (HRQOL) outcomes will be assessed in operatively treated adult spinal degenerative disease patients undergoing lumbar spinal fusion.

Sample Size Analysis

Power Analysis

A power analysis was performed for sample size estimation, based on data from Bishop et al (N=132), comparing arthrodesis rate in autograft vs. allograft fusion groups[31]. In an effort to identify the number of patients needed in the current research project, a power analysis has been investigated with G*Power 3.1.9.2:

- Arthodesis rate one year post-operation (paired t-test):
  The effect size (ES) in this study was 0.4, considered to be low using Cohen's (1988) criteria. With an alpha = .05 and power = 0.80, the projected sample size needed with this effect size is approximately N = 23.

Thus, our proposed sample size of N=60 (with 20 patients per arm; effectively 40 for t-tests between groups) will be more than adequate for the main objective of this study and should also allow for expected attrition

Completion rate of enrolled patients in our protocol is estimated to be 85% based on standard clinical follow up rates for lumbar Spinal Fusion patients at the investigators practices. . Therefore, by enrolling 20, we expect at least 17 in each group.

Age and Gender of Subjects
This prospective study will include both male and female patients over the age of 18 years old.

Racial and Ethnic Origin
For the enrollment of this study, there are no racial or ethnic restrictions.

Vulnerable Subjects:
There will be no vulnerable subjects in study.

Estimated Duration of Study
3 years (1 year for subject enrollment; 2 additional years to complete 2-year follow-up)

Human Subject (Inclusion/Exclusion Criteria)

Inclusion criteria:
1. Must be 18 years old or older
2. Scheduled for elective posterior or anterior and posterior spinal fusion of the lumbar spine with or without anterior interbody support
3. Failed at least 6 weeks of conservative care
4. ODI v2.1 score > 30%
5. No contraindication to BMAC (as per manufacturer)
6. Signed consent form

Exclusion criteria:
1. Prior lumbar fusion surgery at operative level (prior discectomy and/or laminectomy allowed) at any time period, or prior spine surgery at any level 6 months before index recruitment surgery
2. Spondylolisthesis grade 3 or more

3. Excluded patients with myelopathy, history of myelopathy, significant neurological compression, or neurological impairment in the cervical or thoracic spine

4. Incompetent or missing anterior arch at the affected level (e.g. laminectomy, pars defect)
5. Currently requires laminectomy at level of surgery
6. Facet joints at implant level are absent or fractured
7. Post-traumatic vertebral body compromise or acute fracture at implant level
8. Body mass Index (BMI) > 40
9. Known allergy to titanium
10. Paget's disease, osteomalacia, or any other metabolic bone disease
11. Use of medications or any drug known to potentially interfere with bone/soft tissue healing (e.g. chronic systemic steroids)
12. Unlikely to comply with the follow-up evaluation schedule
13. Subject has recent history (less than 3 years) of chemical substance dependency or significant psychosocial disturbance that may impact the outcome or study participation
14. Participation in a clinical trial of another investigational drug or device within the past 30 days
15. Systemic infection such as AIDS, HIV, and active hepatitis
16. Active malignancy defined as history of invasive malignancy, except if the subject has received treatment and displayed no clinical signs and symptoms for at least five years
17. Pregnant or planning to become pregnant during the length of study participation
18. Involvement in active litigation related to back problems at the time of screening (this does not apply to litigation required by no fault states)
19. Direct involvement in the execution of this protocol
20. Patients who have planned spinal surgery intervention after enrollment into study and throughout course of follow up

Intra-operative exclusion

1. Any change in the surgical procedure PRIOR to surgery that violates the inclusion/exclusion criteria.

Randomization Process

The process of randomization will be computerized and completed by an individual not associated with the study. The randomization will be performed at 1:1:1 ratio between the three arms. Sequenced and sealed envelopes or a similar randomization technology approach will be used.
Given posterior, anterior and anterior-posterior surgical techniques will be randomly included in the three study arms, we anticipate equal stratification. However, if study arms show predominance to one surgical approach, attempt will be made to increase enrollment of patients of the unbalanced surgical approach.

Research Design & Methods

Subjects who are candidates for lumbar spinal fusion with interbody support will be screened for inclusion in the study. All procedures are approved by the FDA (see appendix A for approved labeling) and are common practice at NYULMC. If the subject meets all of the eligibility criteria

and agrees to participate in the study after informed consent, they will be enrolled into one of the three arms.

An enrollment ratio of BMAC + allograft to BMP to Autograft with bone marrow aspirate (control) (1:1:1) for a total of 60 subjects to be enrolled in the study. The study will determine and compare differences in fusion rate and health related quality of life parameters at 6 weeks, 3 months, 6 months, 1 year, and 2 years postoperatively.

Intervention

Patients will receive a lumbar fusion with one of the three interbody support grafts listed below:

- **INFUSE rhBMP-2 Bone Graft used according to its approved FDA labels, both the original approval performed from an anterior approach using titanium cages as well as the more recent approvals with the use of PEEK cages from a posterior interbody approach. BMP will be placed in a PEEK cage and to be inserted in a posterior or anterior approach**;

or

- **Allograft infused with adult stem cells from the bone marrow aspirate concentrate harvested from the iliac crest. Harvest® BMAC System delivers high stem cell concentration to the graft site and will be used according to its approved FDA label.**

or

- **Autograft with bone marrow aspirate (control)**

- Enrollment will be 1:1:1
- The study will determine and compare differences in fusion rate and health related quality of life parameters at 6 weeks, 3 months, 6 months, 1 year, and 2 years postoperatively.
- Pre-operative standard care measures include narcotics usage and health-related quality of life measures: Oswestry Disability Index (ODI), Visual Analog Scale (VAS), Euro-Qol 5-dimension (EQ-5D), Health State Scale, PCS, PROMIS Surveys outlined below:
- PROMIS Bank V11 - Pain Interference (Adaptive)
- PROMIS Scale v1.0 - Pain Intensity 3a(Auto-scoring)
- PROMIS Bank v1.2 - Physical Function(Adaptive)
- PROMIS Bank v2.0 - Mobility(Adaptive)PROMIS Bank v2.0 - Upper Extremity
  * While PROMIS will be collected, it will be optional in this study due to limitation of getting patients to collect PROMIS at enrolling surgeon's site. Data will be collected from pre-operative standard-care measures for this study

- Intra-operative standard care measures include intra-operative and peri-operative blood loss, length of stay in hospital, bone marrow quality, and complications. Data will be collected from intra-operative and peri-operative standard care measures for this study.
- Post-operative standard care measures include fusion status at 1 year via CT scan, and health-related quality of life measures previously defined via RedCAP, radiological outcomes, and complications. Data will be collected from post-operative standard care measures for this study
- The radiologist will be blinded to the patient's treatment at the time of postoperative outcomes analysis. The patients will not be blinded to their assigned treatment arm.

- Outcome measures will include:
    1. Pre-operative measures: narcotic usage, and health-related quality of life measures previously definedIntra-operative measures: intra-operative and perioperative blood loss, length of stay, complications
    2. Post-operative measures: fusion status at 1 year via CT scan, and health-related quality of life measures previously defined, length of stay, radiological outcomes, complications
- The patient and reviewer [of the clinical outcomes as well as the radiographic analysis post-operatively] will be blinded to the patient's treatment.

All materials procured from Harvest® BMAC System is FDA approved:

- Collection of Bone Marrow Aspirate Concentration (autologous adult stem cells) for Fusion
    - Bone Marrow Aspirate (BMA) will be aspirated from the anterior iliac crests using an 11 gauge 5 side-hole Jamshidi needle and a 60 mL syringe flushed with heparinized saline. Following a midline incision, the needle will be directed at about 30˚ to the vertical and parallel to the plane of the crest and inserted to a depth of approximately 5 to 8 cm (Figure 1). 1 mL will be sent for cellular analysis.

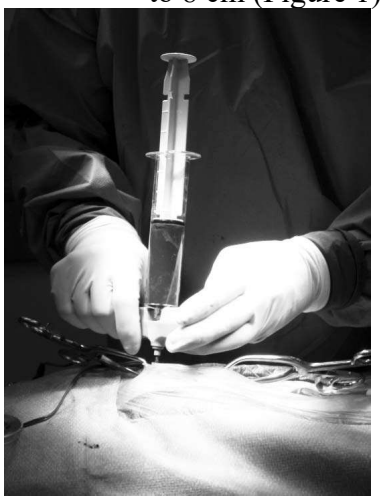

Figure 1

- Sixty mL of BMA will be aspirated while rotating and slowly withdrawing the needle toward the cortex. This step will be repeated on the contralateral ileum for a total of **60, 120, or 180 mL** of BMA. The BMA is then pooled into a blood bag containing Anticoagulant Citrate Dextrose Solution (ACD-A).
- The BMA will then be placed into the SmartPrep® Bone Marrow Concentrate (BMAC™, Harvest Technologies Corp., Plymouth, MA) system and concentrated in 15 minutes to a final volume of **10, 20, or 30 mL**.
- The **BMAC will then be combined with packed allograft cancellous bone chips** using the Graft Delivery Pack (GDP, Harvest Technologies Corp.) **yielding two or three 10 mL surgeon constructed bone logs** (Figure 2). The allograft bone will be obtained routinely from the bone bank in the operating suite.

Figure 2

- The **allograft logs will be placed in the lateral gutter and interbody cages**.

BMAC dosing estimate for the lumbar spine

- If using Harvest Graft Delivery Kit:
  - 1-level fusion: 10 cc of BMAC from 60 cc of BMA (roughly 10 cc of graft)
  - 2-level fusion: 20 cc of BMAC from 120 cc of BMA
  - 3-level fusion: 20 cc of BMAC from 120 cc of BMA
  - 4-level fusion: 180 cc kit
  - 5-level fusion: 240 cc kit
    - BMAC to graft ratio will be 1:1
- If not using Harvest Graft Delivery Kit:
  - Volume of BMAC will be slightly increased (some BMAC will not get directly into hydrating the graft as the BMAC would get lost in the hydration process and left in mixing bowls)

rhBMP-2 Fusion

- Two mL of BMA will be aspirated in identical procedure to the BMAC group for comparison of aspirate quality.
- For patients selected to receive BMP, 12 mL BMP will be applied at the surgical site of the interbody fusion using a collagen sponge following manufacturer's directions.
- BMP kit use per level:
  - 1 Level Fusion: Extra small kit (1.4 cc)
  - 2 Level Fusion: Small Kit (2.8cc)
  - 3 Level Fusion: (4.2 cc)
  - 4 Level Fusion: Medium Kit (5.6cc)
  - 5 Level Fusion: (7.0 cc)

Control Fusion

- As per standard of care, the control group will receive 15cc – 45 cc of allograft with autograft and bone marrow aspirate at each level. The iliac crest is the common donor site

for autograft. Bone marrow aspirate will also be processed for data collection. Both will be harvested and combined in routine fashion to make the bone graft.

- Using the standard technique for anterior lateral fusion, the bone graft will be laid onto the desired site of fusion.

Standard of Care vs. Research Procedures

Standard of care:

All outcome measures are standard of care procedures that are collected at the doctor's office. These procedures are not provided specifically for this research study.

- CT scan to assess fusion status at 1 year post-op
- Cellular analysis of the bone marrow aspirate quality
- and health-related quality of life measures previously defined
- Blood loss
- Length of stay
- Radiological outcomes
- Complications
- Narcotic usage

Research Procedures:

- Collection of Bone marrow aspirate is standard of care but using the Smart Prep Bone Marrow Concentrate system, combining the BMAC with the cancellous bone chips with the Graft Delivery Pack, and dosing as outlined in the Procedures section are unique to the research procedures.

- *Randomization Process:* The process of randomization will be computerized and completed by an individual not associated with the study. The randomization will be performed at 1:1:1 ratio between the three arms. Sequenced and sealed envelopes or a similar randomization technology approach will be used.

Blinding: Patient, Reviewer and Physician

- The patient will not be blinded to his/her treatment assignment.
- The reviewer of the clinical outcomes as well as the radiographic analysis post-operatively will be blinded to the surgery that the patients receive.
- The surgeon performing the surgery will not be blinded.

Data Storage and Confidentiality

Case report forms and all other documentation collected by the investigators and research coordinator will not contain subject names. Each subject will be assigned a subject code. The subject code will consist of 6 characters in an alphanumeric combination (for example nyu-001). The site will maintain the link between the subject code and the names. Primary data collection

will be based on source-documented hospital chart reviews, notes on the source worksheets and subject interviews will be performed by study researchers or investigators at each clinical site. Data will be stored in individual subject binders and locked in a secure office and uploaded onto REDCap for electronic data capture. Only approved research coordinators/investigators will have access to the data.

Investigators Qualifications and Experience

All patients are recruited through the NYU affiliated private office of Dr. Peter Passias at the New York Spine Institute in Long Island, New York. Patients are consented by the investigator, study coordinators and persons completing research fellowships in orthopaedic surgery working exclusively on clinical orthopaedic research projects. These researchers all have experience seeing and consenting patients. These patients will be consented if they meet inclusion criteria. Independent reviewer will be a member of the NYULMC house staff and member of orthopaedic department. Reviewer will be a MD and be experienced in reading and interpreting radiograph outcomes.

Subject Identification, Recruitment and Consent

As part of the standard of care, the subject will have an initial consultation with the PI/MD which includes appropriate physical and radiographic examinations. The subject will be informed of the nature of their spinal disease and treatment options, operative and conservation non operative care. Should the surgeon feel that operative treatment is the best option, they will be eligible for enrollment into this study. Their treatment will not be influenced by the existence of this study.

All study participants will be patients of Dr. Peter Passias. The same care will be provided independent of the patient's willingness to be a part of the study. The 60 subjects to be accrued are based on investigator's caseloads. Only patients who are able to understand the English language will be allowed to participate in the study due to the nature of the validated questionnaires that will be given to them.

PI will identify his clinic patient's eligibility for enrollment into the study using inclusion/exclusion criteria. Should the PI/surgeon feel that operative treatment is the best option, subject will be eligible for enrollment into this study. Their treatment will not be influenced by the existence of this study. PI anticipates to enroll up to 4 patients per month, allowing for completion of enrollment in 15 months, but no longer than 2 years.

Process of Consent: Subject Capacity & Subject Comprehension

Potential participants will be asked to review a copy of the informed consent form prior to enrollment. The investigators will use an informed consent form that has been approved by the Institutional Review Board (IRB) at this institution. Patients will be recruited when meeting all inclusion and exclusion criteria. Once recruited, all subjects will go through the informed consent process. One or more of the research team members will explain, in simple terms, the details about the outcome collection and the subject's involvement.

Patients must have the capacity to comprehend and give informed consent. Patient will be given the opportunity to ask questions prior to signing the informed consent (ICF). Comprehension of

the study will be tested by asking the subject and his/her family follow-up questions about their understanding of the study procedures and follow-up process after informed consent has been given. During this time frame and throughout the time period of the study, the research team will re-educate the patient on the study. Additionally, this will provide the patients with the opportunity to make a fully informed decision about their participation in the outcomes data collection, prior to signing the ICF. This will ensure that all subjects understand the nature of the outcomes data collection, the risks and benefits involved, and their commitment to complete all follow-up visits.

Health information will be collected from participants who are a part of this research study. By signing the consent form, participants will allow the primary investigator and researchers to use health information, but only to use it within this research. Information will only be used as explained in the consent form or when required by law.

Patient participation will require **7 visits as per routine care**: 1 screening visit (15 minutes to determine if patient is qualified for study), 1 pre-operative visit (1-2 hrs to gather preliminary information), and 5 follow up visits at 6 weeks, 3 months, 6 months, 12 months, and 24 months (each requiring about 1 hour per visit).

The patients will be made known that participation in the study will not affect the standard of care delivered by the investigators. The risks of general anesthesia will be explained during the anesthesia consenting process as per standard of care. *The use of BMP during lumbar fusion is currently approved by the FDA. Autograft, Allograft and BMAC have been used at NYULMC in the field of orthopaedics for inducing bone growth for non-unions and osteonecrosis of the extremities and has been used for the spine.*

Document of Consent, Consent Forms

Documentation of ICF process will be completed by IRB approved research staff. Subjects will be provided a copy of the signed ICF. The original ICF with study documentation will be physically stored in a secured location at the NYU HJD Spine Research Center. Participation is entirely voluntary. Participants can withdraw at any time without consequences of any kind. Participation or withdrawal from the study will not affect the patient's treatment in any way.

Potential Benefits

The potential benefits to the subjects in this study are hypothesized to be similar in the 3 groups such as decreased and health-related quality of life measures previously defined, and presence of adequate fusion of spine. Additionally, there may be benefits of not having the high cost or complications associated with the usage of BMP. There may also not be any benefits present at all to the patient. However, from the patient's participation in the study, there will be a better understanding of the efficacy of allograft and BMAC use during lumbar spinal fusions with interbody support.

Adverse Events/Risks

Although BMP is a frequently performed surgical procedure with easy use, complications with BMP, as with all surgeries with and without BMP of this type, are common and well documented in literature including, but not limited to, tumorigenesis, infections, seroma formation, or osteolysis. As the use of BMP to augment spinal instrumentation and fusion is a standard procedure, adverse events will be managed using standard surgical protocols.

The use of allograft as a graft extender has become an acceptable practice especially in fusions employing interbody. The advantages of using of allograft rather than BMP during spinal fusion include decreased cost, similar structural support, and lack of BMP associated complications.
. In general, the use of autograft versus allograft should be balanced with donor site morbidity (pain, bleeding, infection) on the one hand, and the risk of pseudoarthrosis as well as the possibility of revision surgery on the other.

The disadvantages for allograft utilization include a higher potential for transmission of disease or infection, unavailability in some countries, immunogenicity with an inflammatory response, slower incorporation, and possible graft collapse. Allograft cancellous bone invokes a larger inflammatory response when compared to cortical allograft bone due to the larger surface area available for an immune response. In addition, cortical allografts are incorporated more slowly and to a lesser degree prior to remodeling than other allograft bone. In general, allograft is incorporated slower and less completely with decreased vascularization and osteoconduction than its autograft counterpart.

The safety of autologous bone marrow transplantation is quite good. Many surgeons now use bone marrow because of its biological value and low risk. One of the authors in the study by Hernigou et al. (P. Hernigou) has clinical experience with aspiration of bone marrow in more than 1000 patients, in which no complications were encountered. In this study, bone marrow aspirate will be collected in a minimally-invasive manner.

Protection against Risks

Studies involving BMAC and/or allograft have been completed in the past. The study by Robert Johnson, MD has shown positive results of using allograft with BMAC for spinal fusions. The investigators are board certified orthopaedic spine surgeons and are familiar with the protocol and operating procedures. For data collection, the research coordinator is knowledgeable in the field of orthopaedic care and clinical research. All personnel have completed CITI training and the investigators have a dedicated staff and nurse to attend to the patient's medical and psychological needs if needed. If patients require medical monitoring, ancillary care, or equipment, patients will be able to seek care in case of an emergency at the NYU-HJD Immediate Care Center which is open 24/7. The PI and the research coordinator, Mohamed Moawad, MPH, CRCC, will also be available to patients during regular office hours.

Investigation schedule and follow-up

Data will be collected pre-operatively regarding individual patient demographics, radiographic images, laboratory values, and the surgical procedure to be performed. These data will be recorded onto a de-identified data collection sheet by the researchers. The patient data sheets will then be entered into a protected electronic database, while the data sheets will be stored as a back-up until the study is complete. Once the completed database is analyzed and summarized, the results will be presented to the involved participants without any identifiable patient information. A Delegation of Duties log will be prepared and maintained in the study regulatory binder.

A separate surgeon and radiologist will be performing the radiographic analysis and an office medical assistant will have the patients fill out questionnaires and record any complications pertinent to the study. Follow-up will be the investigators' routine follow-up, which is 6 weeks, 3 months, 6 months, 1 year, and 2 years post-op.

Case Report Forms
Pre-op visit
- Informed consent
  - ❖ If informed consent is not obtained at pre-operative visit, the visit will not continue.
- Pre-op investigator form
- Pre-op subject questionnaire

6-week follow-up
- Follow-up investigator form
- Follow-up subject questionnaire

3-month follow-up
- Follow-up investigator form
- Follow-up subject questionnaire

6-month follow-up
- Follow-up investigator form
- Follow-up subject questionnaire

1-year follow-up
- Follow-up investigator form
- Follow-up subject questionnaire

2-year follow-up
- Follow-up investigator form
- Follow-up subject questionnaire

Costs to the Subject

All of the tests (i.e. physical evaluation and imaging components) will be performed as part of the standard of care. The patient may want to discuss this with his insurance carrier in advance. The patient will be responsible for any co-payments and/or deductibles for services rendered.

The patient or his/her insurance company will be responsible for paying for the 1-year follow-up CT scan because it is part of standard care. Patients will have the option to refuse CT scan in which case they will be excluded from the primary data analysis but will be part of the secondary analysis.

Payment for Participation

Subjects will not be compensated for participation in this study.

This clinical trial will be posted on clinicaltrials.gov

Data Analysis

Sample Size Justification

There are no previous studies with exact means in ODI for a BMAC group not the association between clinical outcomes and concentration of MSCs and CFUs. Therefore, assumptions had to be made. If the standard deviation for each group was assumed to be 10 and equivalence as within 12.8 (MCID), given 90% power and alpha=0.05, we would need 14 patients per group. However, if we assume equivalence as within 6 points, we would need 59 patients per group. We understand that assumptions greatly affect sample size, and therefore, our desired sample size of 60 patients is appropriate.

Data analysis plan

Exploratory data analysis will be conducted to examine the distributions of all outcome measurements, demographic and clinical factors. Detection of outliers will be done using histograms, box-plots, normal plots and summary statistics. We will conduct the Kolmogorov-Smirnov or the Shapiro-Wilk test to confirm normality of variables. Where deviated from normality, we will do the suitable transformations such as a box-cox transformation to approximate normality for the subsequent analyses. Missing data will be imputed when appropriate. The Statistical Package for Social Sciences version 17.0 (SPSS Inc, Chicago, IL) will be used for all statistical analysis.

Aim 1: Clinical Study
This study will analyze the clinical and radiographic outcomes in terms of pre-operative measures, intra-operative measures, and post-operative measures followed-up for in the three groups.

Primary Outcome Endpoint: As per the primary outcome measure, fusion status at 1 year will be assessed via CT scan by an independent radiologist. Clinical outcomes will be defined by patient reported and health-related quality of life measures previously defined. Differences from pre-operative visit to post-operative time points will be compared between the 3 groups by Student t-tests. Based on preliminary data, improvements are expected in these outcome measures: ODI from 33.42 (SD:6.22) to 26.75 (SD:8.19); SF-12 PCS from 29.00 (SD:6.05) to 31.42 (SD:6.05); SF-12 MCS from 31.42 (SD: 6.50) to 35.75 (SD: 13.82); NRS from 8.17 (SD: 1.27) to 5.93 (SD: 1.90). Multivariate regression analysis, controlling for age, sex, race, and charlson comorbidity index, will be performed to determine the effect of treatment on reaching MCID values, as defined in Parker et al 2012.[2]

Aim 2: Basic Science Study

Lab analysis of aspirate quality will quantify density of CBC + differential (WBCs, platelets, Hct…), CD34+ cells, cell viability and CFU-f,,Mesenchymal Stem Cells, Colony-Formung Units, CD13, CD 14, CD29, CD34, CD44, CD45, CD73, CD90, and CD105. One-way ANOVA and Student's t-tests will compare significant values between the 3 groups

The lab analysis will be performed as per routine practice Harvest Technology, a Terumo BCT company.

Data Monitoring

1. Types of Data

- Data Accuracy
- Protocol Compliance
- Recruitment of Subjects
- Screen Failures
- Radiological assessment
- Safety Monitoring/Management
- Aspirate quality assays – CBC, CD34+, CFU-F

2. Responsibilities and Roles for Gathering, Evaluating and Monitoring the Data

- Principal Investigator: Themistocles Protopsaltis, MD (orthopaedics faculty)
  - The principal investigator will be the monitoring entity due to the nature of this study – small number of subjects and the study is conducted only at one site
  - Responsible for insuring protocol compliance
  - Responsible for recruiting and consenting patients for study
  - Responsible for collecting and recording all clinical data pre- and post-operatively
  - Responsible for monitoring data collected and evaluating the progress of the study, assessments of data quality, retention, and adverse events
  - Responsible for monitoring safety of research participants from visits with patients
  - Responsible for stopping or modifying protocol if needed
  - Treating surgeon for patients who are enrolled into study
  - Responsible for intraoperative data collection
  - Knowledge of Group assignment

  Research coordinator: Mohamed Moawad, MPH CCRC
  - Knowledge of Group assignment
  - Responsible for monitoring informed consents
  - Responsible for reporting all IRB related matters, storing informed consents, and reporting all adverse events to the IRB
  - Responsible for recruiting and consenting patients for study
  - Responsible intraoperative data collection
  - Evaluates protocol compliance with the above investigators to ensure data protection and patient confidentiality
  - Responsible for maintaining regulatory documents
- Research Assistant: Avery Brown
  - Responsible for ensuring data collection from patients
  - Responsible for ensuring that x-rays and CT-scan are taken of patients at necessary times
  - Monitors and reports to PI and research coordinator the recruitment and retention status as well as adverse events
  - Ensures protocol compliance
  - Responsible for organizing and storing all patient data in a secure location where only authorized personnel have access
  - Responsible for completing informed consent procedural log

- Independent Data Safety Monitoring Board: Dr. Philipp Leucht, MD & John Bendo, M.D
    - Will oversee adverse events and safety of the trial.
    - The board will serve as a consult with the principal investigator when identifying and/or grading adverse events
    - If the Principal Investigator and one of the Data Safety Monitoring Board members reach a mutual conclusion, the second will not be consulted. If there is a discrepancy between conclusions determined by the Principal Investigator and a Data Safety Monitoring Board member the second board member will be used to make the final determination.
    - Philipp Leucht, MD Assistant Professor & Director of Orthopedic Trauma Research at NYU Hospital for Joint Diseases Department of Orthopedic Surgery has extensive experience particularly in prospective bone marrow asparate studies here at NYU and is an ideal candidate for the DSMB
    - John Bendo, M.D, Interim Chief of the Division of Spine Surgery, Director Spine Service - Clinical Affairs, Clinical Professor of Orthopedic Surgery, NYU Langone Orthopedic Department NYU School of Medicine is serving the role Dr. Thomas Errico has held on the DSMB of this study in version prior to April 16th 2018.
- Independent Reviewer / Blinded Clinician / MD - to be named:
    - No knowledge of group assignment
    - Performs radiographic analysis post-operatively
    - Assess Outcomes
    - Outcome adjudicator
- Data analyst:
    - No knowledge of group assignment

3. Reporting Adverse Events and Unanticipated Problems

- Adverse event (AE) grading and attributes
    1. No adverse event or within normal limits
    2. Mild AE, not requiring treatment
    3. Moderate AE, resolved with treatment
    4. Severe AE, resulting in inability to carry on normal activities and required professional medical attention
    5. Life threatening or disabling AE
    6. Fatal AE
- Safety Plan
    - Adverse events related to study will be detected from follow up visits by the patient and during the post-operative period by the principal investigator and co-investigators, through physical exam assessment and reviewing x-rays and CT scans of the subject. The investigators will try to determine if the adverse event is related to the research itself or an isolated event using the above criteria.
    - The research coordinator, Mohamed Moawad, will perform safety reviews (collecting adverse events, reviewing them, and reporting them).
    - Additionally, upon enrollment and treatment of 10th subject, data safety and monitoring will be conducted by PI to ensure the safety and efficacy of the trial.

  - The research assistant will score and review questionnaires to determine if a subject's condition has worsened (adverse event), and if determined by the PI to be related to the surgery, the event will be reported by the research coordinator.
  - All adverse events identified are reported to the PI and the research coordinator
- Plan for periodic or annual reporting of AEs
  - The IRB will be notified of a serious adverse event and unanticipated adverse event within 24 hours. All other adverse events will be reported annually to the IRB at the time of continuation renewal.
  - All unanticipated adverse events related to the study will be reported to the IRB in an expedited manner if they are Grade 2 and above in severity. Unanticipated patient deaths are reportable within 7 days. The expedited report sent to other organizations can be copied to the GCRC. The investigator will continue to follow or obtain documentation of the resolution course of such an event.

4. Privacy and Confidentiality

- Case report forms and all other documentation collected by the investigators and research coordinator/assistant will not contain subject names. Each subject will be assigned a subject code. The subject code will consist of 6 characters in an alphanumeric combination. The site will maintain the link between the subject code and the names. Primary data collection will be based on source-documented hospital chart reviews, notes on the source worksheets and subject interviews will be performed by study coordinators/researchers or investigators at each clinical site. Data will be stored in individual subject binders and locked in a secure office and electronically on the secure REDCap system. Only approved research coordinators/investigators will have access to the data.

5. Assessments

- Safety reviews will be performed monthly by the monitoring entity (the principal investigator). The monitoring entity will be responsible for determining the relationship of an adverse event and the treatment received. Since the PI sees the subjects regularly for follow up visits, he will be familiar with the subjects' outcomes and patient histories, thereby making it easier to detect AEs if they do arise. This plan allows for prompt detection of unanticipated problems involving risks to subjects.
- Monitor the incidents of pseudarthrosis for both graft groups by PI

6. Criteria for Action

- Subject stopping will occur if any adverse events occur that are level 4 or above, or if the subject is unlikely to comply with the follow-up evaluation schedule
- Study stopping will occur if there is a case of mortality. DSMB and IRB review will determine continuation or termination of study.
- Study stopping will occur if there is a greater than normal rate of morbidity as determined by the monitoring entity; the study subject will be un-blinded and the rates of morbidity will be observed for that subject to determine the cause. Acute vs. Subacute vs chronic morbidity complications vary in degree of prevalence, still greater

than 10 – 15% complication rate will deviate from the literature anticipated (Hoffmann 2013, Ajiboye 2016). Study stopping will occur if there is a greater prevalence of pseudarthrosis in the BMAC study group; Lumbar pseudarthrosis rates with use of BMP have been estimated to 6.4% in single center studies. (Kim 2013). Similar percentages can be deduced from reported lumbar arthrodesis rates in larger review studies. Use in lumbar fusions showed a 94% arthrodesis average rate for BMP-2, and 85% average arthrodesis rate using bone marrow aspirate (Chun 2015). For these reasons a pseudarthrosis rate of greater than 10 – 15% would warrant action.

- Study should be stopped if there is a 10% reduction in fusion rates in the studied group relative to the control group which is the current "Gold Standard" of Iliac Crest graft.

7. Communication of Data Safety Monitoring Reports to the IRB

- The IRB will be notified of a serious adverse event and unanticipated adverse event within 24 hours. All other adverse events will be reported annually to the IRB at the time of continuation renewal.

- All unanticipated adverse events related to the study will be reported to the IRB in an expedited manner if they are Grade 2 and above in severity. Unanticipated patient deaths are reportable within 7 days. The expedited report sent to other organizations can be copied to the GCRC. The investigator will continue to follow or obtain documentation of the resolution course of such an event.

Trial Organization

This trial will be conducted at a single institution: Hospital for Joint Diseases at New York University Langone Medical Center. Surgeries will be conducted at NYU-HJD while patient outpatient clinic visits will occur at the New York Spine Institute location in Long Island, NY.

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