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Prospective Study of Thoracolumbar Spinal Fusion Graft Efficacy: Bone marrow aspirate concentrate versus Iliac crest bone graft

Protocol

Purpose of Study

This study is a single-center, prospective randomized clinical study intended to compare and evaluate the efficacy of subjects who are treated with bone marrow aspirate concentrate (BMAC) and allograft to iliac crest bone grafts (ICBG) during posterior lumbar/lumbosacral spinal fusion.

Currently, the ICBG is the gold standard for use as an adjunct in spinal fusions due to its 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, use of ICBG autograft (bone taken from one's own body) has well documented complications such as donor site morbidity, limited supply, and timeliness to harvest a sufficient quantity. 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 ICBG results. In addition, several studies 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 ICBG without including the same complications. This study intends to further investigate and compare the efficacy and long term effects of posterior lumbar/lumbosacral spinal fusions with BMAC and allograft to that of ICBG.

Subjects who are candidates for posterior lumbar or lumbosacral spinal fusion without anterior interbody support will be screened for inclusion in the study. If the subject meets all of the eligibility criteria and agrees to participate in the study after informed consent, they will be enrolled and randomized to either the BMAC + allograft or ICBG group. An enrollment ratio of two BMAC + allograft to one ICBG subject (2:1) for up to a total of 40 subjects will be enrolled in the study which also accounts for failed screening subjects. 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.

The primary hypothesis of this study is that at 24 months postoperatively, 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 control group (ICBG). Pre-operative measures include oswestry disability index (ODI), SF-12, numeric pain rating scale (NRS), and narcotics usage. Intra-operative measures include intra-operative and peri-operative blood loss, length of stay in hospital, and complications. Intra-operative measures include fusion status at 1 year via CT scan, ODI, SF-12, length of stay in hospital, radiological outcomes, and complications. The patient and review of the clinical outcomes as well as the radiographic analysis post-operatively will be blinded to the patient's treatment.

Background

Currently, there are numerous orthopaedic graft adjuncts. These include autograft (iliac crest bone graft), graft substitutes, blood, bone marrow aspirate, platelet rich plasma (PRP), bone morphogenetic proteins (BMP), embryonic culture-expanded stem cells, and bone marrow aspirate concentrate (BMAC). Each graft adjunct involves unique advantages and disadvantages. For example, although autograft is held as the gold standard of orthopedic grafts, disadvantages to its use include donor site morbidity, limited supply, and the time it takes to harvest a sufficient quantity. 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.

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 autograft. Further, BMAC exactly mimics and supplements the body's natural response to trauma by stimulating vasculogenesis and tissue regeneration [1-3].

Conclusions of previous clinical models

Johnson et al. concluded that autologous adult stem cells concentrated from bone marrow harvested from the iliac crest may become a viable alternative to iliac crest bone grafting and its inherent associated morbidity. In the study, an analysis was performed of the spinal fusion rate in a posterior lumbar fusion in which one side of the fusion was randomized to receive ICBG and the contralateral side of the same fusion was randomized to receive concentrated adult stem cells from the bone marrow aspirated from the iliac crest (similar protocol to that of the present study). In the study by Johnson et al. a grade of "fusion" required: less than 3˚ of angulation on lateral flexion and extension radiographs, no loss of fixation, peri-implant lucencies of the pedicle screw constructs, and evidence of trabecular bridging bone from the transverse process to transverse process on reconstructed CT scans on contiguous levels. The patients were followed for 12 months at 3 month intervals. Radiographic images from each follow-up visit and a CT scan at 12 months post-op were read by a blinded radiologist. Radiographic observation demonstrated stable instrumentation and progressive bone formation on *both* sides of the spine (autograft side and BMAC+allograft side)

Previous reports by Connolly et al.[4], Gangji et al.[5], Hernigou et al.[6], and Gessmann et al. [7] 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 BMAC exactly mimics and supplements the body's natural response to trauma by stimulating vasculogenesis and tissue regeneration. BMAC contains many cell types whose combination is superior to any one cell type in the spinal fusion bone healing/remodeling process. As BMAC is autologous, there are no immuno-rejection side-effects or concerns regarding disease transmission.

Significant findings of these clinical models are two-fold: (1) in vivo osteogenesis occurs only if the density of implanted cells at the treated site is sufficiently high, and (2) age, sex, and other comorbidities did not significantly affect the success of the treatment. To achieve a sufficiently high number of implanted cells, either a large amount of concentrated bone marrow should be administered or bone marrow should be administered with a growth factor (Hernigou & Beaujean, 2002).

Study Objective

To compare the efficacy of BMAC+allograft to ICBG, we plan to pursue a prospective randomized controlled study in which: BMAC+allograft or ICBG will be randomized in a 2:1 ratio, respectively to certain patients undergoing a posterior thoracolumbar or lumbar fusion.

Materials & Methods

Trial Organization

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

Investigators

All patients are recruited through the NYU affiliated private office of Dr. Peter Passias and Dr. Alexandre de Moura at the New York Spine Institute in Long Island, New York. Surgeries will occur at New York University - Hospital for Joint Diseases. Patients are consented by the investigator, persons completing research fellowships in orthopaedic surgery and/or persons 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.

Patient Selection

This will be a prospective, randomized, and blinded study. All study participants will be patients of Drs. Peter Passias and Alexandre de Moura. The same care will be provided independent of the patient's willingness to be a part of the study. Patients will be 18 years old or older. There will be no vulnerable subjects in study except for patients older than 65. 40 subjects total will be recruited, which was proposed by the investigators based on their caseloads. This number also accounts for failed screenings. 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.

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. They will be paid $50 for agreeing to participate in the study and $50 for each follow up visit as reimbursement for travel and other expenses. However, the patient or his/her insurance company will have to pay for the 1 year follow-up CT scan because it is part of standard care. Patient participation will require 7 visits: 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 hr 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. No ethnicities will be prohibited from participating in the study. Males and females will participate in the study as close to a 1:1 ratio as possible. Randomization of subjects will be 2 BMAC subjects per 1 ICBG subject (2:1). The use of iliac crest autograft during posterior lumbar/lumbosacral is currently the gold standard procedure at NYU and most other institutions. Allograft and BMAC have been used at NYU in the field of orthopaedics for inducing bone growth for non-unions and osteonecrosis of the extremities but have not been used for the spine.

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 2:1 ratio between the investigational and control arm. Sequenced and sealed envelopes or a similar randomization technology approach will be used.

Standard of Care vs. Research Procedures

- Unique to Research Procedures
    - Questionnaires (Oswestry disability index, Numeric Pain Rating Scale, SF-12)
    - 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
- All other procedures are standard of care for Dr. Passias

- **Inclusion criteria**:
    - Must be 18 years old or older
    - Scheduled for elective posterior spinal fusion of the thoracolumbar spine or lumbar spine with or without anterior interbody support
    - Failed at least 6 weeks of conservative care
    - ODI v2.1 score > 30%
    - No contraindication to BMAC (as per manufacturer)
    - Signed consent form
- **Exclusion criteria**:
    - Spondylolisthesis grade ≥ 3
    - Pagets disease, osteomalacia, or any metabolic bone disease
    - Use of medications that interfere with bone healing (chronic steroids)
    - Patient unlikely to comply with post-op schedule with physician
    - Recent history of chemical dependency
    - Participation in other investigational device trial(s) within past 30 days
    - Active malignancy
    - Pregnancy or planning to become pregnant
    - Direct involvement in execution of this protocol

Patient and Physician Blinding

- The patient will be blinded to the surgery that he/she receives.
- The reviewer of the clinical outcomes as well as the radiographic analysis post-operatively will also be blinded to the surgery that the patients receive.
- The surgeon performing the surgery will not be blinded.

Potential Benefits

The potential benefits to the subjects in this study are hypothesized to be the same as standard of care (iliac crest bone graft) benefits such as decreased ODI, SF-12, and NRP scale, and presence of adequate fusion of spine etc… Additionally, there may be benefits of not having the donor site comorbidities associated with the standard iliac crest bone grafts. 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 posterior lumbar/lumbosacral spinal fusions.

Adverse Events/Risks

Harvested autologous ICBG remains the gold standard to augment spinal instrumentation and fusion because of its osteoconductive, osteoinductive, and osteogenic properties and lack of immunoreactions and transmission of infections. Although iliac crest bone harvesting is a frequently performed surgical procedure with relatively easy access, complications with autologous bone grafts are common and well documented in literature including limited availability of autologous ICBG (if previously harvested),

donor site morbidity (bleeding, infection, chronic pain), haematoma/seroma, fracture, nerve and vascular injuries, and hernias [8]. As the use of ICBG to augment spinal instrumentation and fusion is a standard procedure, adverse events will be managed using standard surgical protocols.

Due to complications such as donor site morbidity, increased operating time, and limited supply, the use of allograft as a graft extender has become an acceptable practice especially in fusions spanning multiple segments. The advantages of using of allograft rather than autograft during spinal fusion include the lack of donor site morbidity, greater supply of graft for the individual, shorter operating time, and in some cases, similar structural strength to autograft. 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. 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 [9].

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[9]. 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 [9].

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 [10].

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 posterior 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 research coordinator, Alexandra Lee, RN, 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, 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 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

Informed Consent Process

A patient of the investigators' will be asked to participate in the study if they both meet the inclusion criteria and not the exclusion criteria. The patients will be given an informed consent form which will also be explained orally by the investigator/research coordinator. Documentation of informed consent will occur by keeping a hard copy of each informed consent form that is signed and initialed by the subject. In addition, the research coordinator will fill out an informed consent documentation process form similar to the one as follows:

"Subject _____ has been enrolled in the study _____ on _____. The study was explained to the subject by research assistant _____. The subject was given a copy of the consent whereby the informed consent was read by the subject and his/her family member. The subject and the family were given an opportunity to ask questions of his surgeon. A signed copy of the consent was given to the subject/family. Consent was obtained prior to the performance of any study procedures."

These will also be kept in a binder that is locked in a secure office that will only be access by study personnel.

Study Design

- A prospective, randomized, blinded control trial.
    - Randomization will be 2:1 favoring BMAC group
- The patient and reviewer [of the clinical outcomes as well as the radiographic analysis post-operatively] will be blinded to the patient's treatment.
- Patients will either receive a posterior lumbar fusion grafted with:
    1. **ICBG**; or
    2. **Allograft infused with adult stem cells from the bone marrow aspirate harvested from the iliac crest**.
- 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.
- The primary goal of this study is to compare the efficacy of BMAC+allograft as an alternative graft material to ICBG in patients undergoing a posterior lumbar/thoracolumbar fusion.
- Outcome measures will include:
    1. Pre-operative measures: narcotic usage, ODI, SF-12, numeric pain rating scale
    2. Intra-operative measures: intra-operative and perioperative blood loss, length of stay, complications
    3. Post-operative measures: fusion status at 1 year via CT scan, ODI, SF-12, length of stay, radiological outcomes, complications

Posterior Lumbar Fusion Procedure: Experimental vs. Control Fusion

All materials procured from Harvest Technologies Corp. is FDA approved

1. Collection of Bone Marrow Aspirate (autologous adult stem cells) for Experimental Fusion
    - Bone Marrow Aspirate (BMA) will be aspirated from the posterior 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).

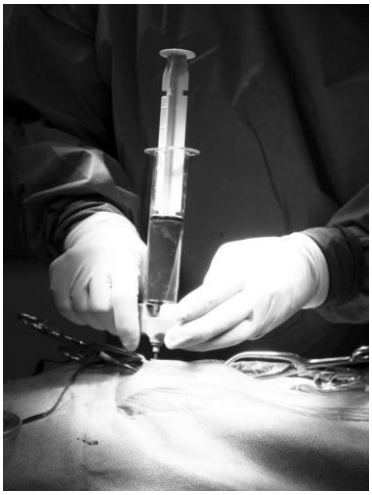

Figure 1

    - 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**.

2. BMAC dosing estimate for the lumbar spine
   - If using Harvest Graft Delivery Kit:
     - 2-level fusion: 10 cc of BMAC from 60 cc of BMA (roughly 10 cc of graft)
     - 3-level fusion: 20 cc of BMAC from 120 cc of BMA
   - 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)

3. Iliac Crest Bone Graft (Control) Fusion

- For patients randomized to receive iliac crest, bone will be harvested in routine fashion.
- Using the standard technique for posterior lateral fusion, the bone graft will be laid onto the decorticated transverse processes, lateral aspects of the facets, par interarticularis, and onto the facets.

Data Analysis and Monitoring

1. Types of Data

- Data Accuracy
- Protocol Compliance
- Recruitment of Subjects
- Screen Failures
- Radiological assessment

- Safety Monitoring/Management

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

- Principal Investigator: Peter Passias, 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 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 and randomized into study
  - Responsible for intraoperative data collection
- Co-investigator: Alexandre de Moura, MD (orthopaedics faculty)
  - Plays large role in recruitment of patients for this study. Most patients will be from Dr. de Moura's private practice office on Long Island, NY.
  - Treating surgeon for patients who are enrolled and randomized into study
- Research coordinator: Alexandra Lee, RN, CCRC
  - 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
  - Evaluates protocol compliance with the above investigators to ensure data protection and patient confidentiality
  - Responsible for maintaining regulatory documents
- Research Assistant: Andy Chang
  - Responsible for recruiting and consenting patients for study
  - 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
  - Facilitates intraoperative data collection and 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

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, Dr. Peter Passias, through physical exam assessment and reviewing x-rays and CT scans of the subject. The investigator 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, Alexandra Lee, will perform safety reviews (collecting adverse events, reviewing them, and reporting them).
- The research assistant, Andy Chang, 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 8 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. 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.

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 greater than normal rate of morbidity or mortality as determined by the monitoring entity; the study subject will be unblinded and the rates of morbidity and mortality will be observed for that subject to determine the cause.

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 8 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 researchers or investigators at each clinical site. Data will be stored in individual subject binders and locked in a secure office. Only approved research coordinators/investigators will have access to the data.

Outcome measures:

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
- ODI
- SF-12
- Numeric Pain Rating Scale
- Blood loss
- Length of stay
- Radiological outcomes
- Complications
- Narcotic usage

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