MEDICAL POLICY

BONE OR SOFT TISSUE HEALING AND FUSION ENHANCEMENT PRODUCTS

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Related Policies:

- Ablative Treatment for Spinal Pain
- Discogenic Pain Treatment
- Surgical Treatment for Spine Pain

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

The 2007 generic Certificate of Coverage (COC) states that devices which are FDA approved under the *Humanitarian Use Device* exemption are not considered to be Experimental or Investigational.

When reviewing for coverage of a Humanitarian Use Device (HUD), the coverage determination on an HUD will be made according to the hierarchy of evidence applied towards the evaluation of any technology, in the same way the evaluation would be applied to a service or technology that is FDA approved without a Humanitarian Device Exemption.

Essential Health Benefits for Individual and Small Group:
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage.

COVERAGE RATIONALE

Bone graft materials used in spinal fusion surgery can be categorized into the following domains:

- Autografts
- Allografts including (cadaver bone graft)
- Amniotic tissue membrane
- Demineralized Bone Matrix (DBM)
- Bone Morphogenetic Proteins (BMP)
- Ceramic-based products
- Cell-based products
- Platelet-Rich Plasma

Autografts
Autografts are proven and medically necessary for bone fusion enhancement:
Autografts harvest bone for grafting from the person undergoing surgery. The harvested bone is typically retrieved from the patient's own tibia, fibula or iliac crest and then placed at the surgery site.

Allografts
Demineralized bone matrix (DBM) is a type of allograft and is proven and medically necessary for bone fusion enhancement.

Allografts are proven and medically necessary for bone fusion enhancement.
Allografts harvest bone for grafting from a person other than the surgical candidate. Cadaver bone is one type of allograft.

Amniotic Tissue Membrane
The use of amniotic membrane products in the treatment of spine disease or in spine surgery is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature. Evidence is limited to animal studies only. No current clinical trials with humans were identified. There is limited evidence that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established.

Bone Morphogenetic Proteins (BMP)
Bone Morphogenetic Protein-2 (rhBMP-2)

Note: As indicated in the Clinical Evidence section below, the use of bone morphogenic protein as an adjunct to spinal fusion surgery may be associated with significant adverse events. Thus, before using bone morphogenic protein, the physician should engage in a shared decision-making process with the patient, discussing the potential advantages, harms and alternatives to the use of bone morphogenic protein as an adjunct to spinal fusion surgery.

When used according to U.S. Food and Drug Administration (FDA) labeled indications, INFUSE Bone Graft is proven and medically necessary for the enhancement of bone healing and/or fusion of the lumbar spine in patients who meet all of the following criteria:

- Implanted via an anterior approach and used in conjunction with an INFUSE Bone Graft fusion device
  INFUSE Bone Graft fusion devices include:
  - InFUSE™ bone graft/LT-Cage
  - InFUSE™ bone graft/Lumbar Tapered Fusion Device
  - InFUSE™ bone graft/InterFix™ threaded fusion device
  - InFUSE™ bone graft/Inter Fix™ RP threaded fusion device
- Skeletally mature patient (18 years of age or older or radiographic evidence of epiphyseal closure) with degenerative disc disease at one level from L4–S1
- No more than Grade I spondylolisthesis at the involved level
- Failure of at least 6 months of non-operative treatment

INFUSE Bone Graft is unproven and not medically necessary for all other indications including but not limited to the following:

- Enhancement of bone healing and/or fusion of the lumbar spine via a posterior approach.
- Treatment of cervical spine or any other area with or without use of other devices including the PEEK device.
- Known contraindications including:
  - hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation
  - Pregnancy
  - Active infection at operative site or patient has an allergy to titanium or titanium alloy
- Planned use of grafting in the vicinity of a resected or extant tumor
- Skeletally immature patient (younger than 18 years of age or 18 years of age or older with no radiographic evidence of epiphyseal closure)

Posterolateral or posterior lumbar interbody fusion utilizing INFUSE Bone Graft has not received FDA approval. Available studies have demonstrated increased adverse events with the posterior approach. The safety and effectiveness of INFUSE Bone Graft in the cervical spine have not been demonstrated. There is insufficient clinical evidence to support the use of INFUSE Bone Graft with devices made of PEEK or other biocompatible materials. In addition, INFUSE Bone Graft has not been approved by the FDA for use with PEEK cages.

When used according to U.S. Food and Drug Administration (FDA) indications, the INFUSE/MASTERGRAFT™ Posterolateral Revision Device system is proven and medically necessary in patients who meet all of the following criteria:

- Implanted via a posterolateral approach
- Presence of symptomatic posterolateral lumbar spine pseudoarthrosis
- Skeletally mature patient (older than 21 years of age or radiographic evidence of epiphyseal closure)
- Treatment of 2 or more levels of the lumbar spine
- Autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion. These patients are diabetics and smokers.

The INFUSE/MASTERGRAFT™ Posterolateral Revision Device system is unproven and not medically necessary for all other indications including the following:

- Known contraindications including:
  - hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation
  - Known active malignancy or patients undergoing treatment for a malignancy
  - Pregnancy

  - Active infection at operative site
- Planned use of grafting in the vicinity of a resected or extant tumor
- Skeletally immature patient (older than 21 years of age or radiographic evidence of epiphyseal closure)
- INFUSE/MASTERGRAFT™ Posterolateral Revision Device system has not received FDA approval for any other indications except those indicated as proven. The safety and effectiveness of INFUSE/MASTERGRAFT™ Posterolateral Revision Device system has not been demonstrated for other conditions in studies published in peer-reviewed literature.

Bone Morphogenetic Protein-7 (BMP-7)
OP-1 Implant and OP-1 Putty are unproven and not medically necessary for the enhancement of bone healing and/or fusion with or without use of other devices (including the PEEK device).
Use of BMP7 has not demonstrated accelerated healing. In one study better results were achieved in patients receiving traditional autograft. Additionally, available studies have been limited by substantial loss of study participants at follow-up as well as by short follow-up times.

Bone graft substitutes have overlapping properties and are made of a variety of materials such as polymers (degradable and nondegradable), ceramics and composites (calcium phosphate, calcium sulfate, and bioactive glass), factor-based techniques (recombinant growth factors) and cell-based techniques (mesenchymal stem cells).

Ceramic-Based Products
Ceramic-based products such as beta tricalcium phosphate (b-TCP) when used alone or with bone marrow aspirate are unproven and not medically necessary for the enhancement of bone healing and/or fusion.
Only very weak conclusions about effectiveness of ceramic-based products may be drawn from studies because of small sample size, lack of control or comparison groups in most studies. The absence of a formal assessment of clinical outcomes in most studies limits the conclusions that can be drawn about the place of b-TCP in bone healing and fusion. Furthermore, definitive patient selection criteria have not been established for the use of b-TCP bone void fillers.

Cell-Based Products
Cell based products such as mesenchymal stem cells, Osteocel, or Trinity Evolution are unproven and not medically necessary for the enhancement of bone healing.

Platelet-Rich Plasma
Platelet-rich plasma (e.g., autologous platelet derived growth factor) is unproven and not medically necessary when used to enhance bone or soft tissue healing.
Evidence in the published scientific literature is inconsistent and does not lend strong support to the clinical utility of using PRP to augment bone or soft tissue healing.

OptiMesh®
The OptiMesh deployable grafting system is unproven and not medically necessary.
There is insufficient evidence that the use of OptiMesh will improve structural support of the vertebrae. Further studies are needed to evaluate safety and efficacy of this grafting system.

DEFINITIONS

Allograft:
An allograft is obtained from a person other than the surgical candidate. It includes cadaveric bone and/or tissue from a bone bank. It may be used alone or in combination with another material. Even when used alone, allograft must be processed to decrease the likelihood of disease transmission and immunogenic response. Examples of allograft-based bone graft substitutes include, but are not limited to Grafton®, OrthoBlast and TruFuse®.

Autografts:
An autograft is taken directly from the patient undergoing surgery. The usual site for an autograft harvest is the posterior iliac crest. When autograft material is of an insufficient volume, of poor quality, or cannot be used for any other reason, then another type of material must be used for the bone graft's.

Amniotic Tissue Membrane:
Amniotic tissue membrane is part of the placenta in a pregnant woman. It can be harvested and stored in tissue banks and used in wound healing, including but not limited to use in spinal surgery.

Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP):
Bone morphogenetic proteins are naturally occurring proteins found in human bone and play an active role in bone formation. There are currently fourteen bone morphogenetic proteins (BMPs) that have been identified. In addition to the fourteen BMPs, there are several recombinant human bone morphogenetic proteins (rhBMPs). Currently there are only two which have been developed for use: - rhBMP-2 and rhBMP-7. An important use of rhBMP is for bone repair, especially in bones that have delayed union or nonunion of a fracture and to promote fusion of. Recombinant human bone morphogenetic protein also plays a role in cartilage formation and repair of other musculoskeletal tissues. Recombinant human bone morphogenetic proteins serve as alternatives or adjuncts to autologous (autografts) bone grafts. They are intended to promote bone formation and enhance fracture healing, and may be used in spinal fusion surgery for degenerative disease to promote bone growth that results in fusion.3 These proteins may also be used for individuals who have up to grade I spondylolisthesis.

Cell-Based Products:
One material proposed for use in combination with allograft is mesenchymal stem cells (MSC), obtained from bone marrow aspirate. This is referred to as a cell-based product. Cell based substitutes use cells to generate new tissue either alone or seeded onto a support matrix. Mesenchymal stem cells (obtained from bone marrow) are multipotent stem cells that can differentiate into a variety of cell types.
The use of mesenchymal and other cell-based products is unproven for use in spinal fusion and for intervertebral disc regeneration. Although currently under investigation, data published in the medical literature evaluating cell-based substitutes is in preliminary stages and mainly in the form of nonhuman trials; data supporting safety and efficacy for these indications are lacking.

Ceramic-Based Products:
Ceramic-based products are synthetically produced. Ceramics are synthetic materials resulting from heating up chemically formed compounds that consequently bond together**.** Ceramic-based products include materials such as calcium phosphate, calcium sulfate and bioactive glass, used alone or in combination with other grafts. Several types of calcium phosphates, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite are available in pastes, putties, solid matrices, and granules. Synthetic hydroxyapatite is brittle, has little tensile strength and is typically used for bone defects with internal fixation.

Combination Bone Graft Substitutes:
A newer practice in the use of bone graft substitutes is to combine different materials, with the theory that each different property working together will work in synergy with another in the healing and grafting process

Demineralized Bone Matrix (DBM):

DBM is a type of allograft; it is produced by acid extraction of allograft bone (known as decalcification). Based on manufacturing techniques, DBM may be a freeze-dried powder, granules, gel, putty, or strips.

Mesh Grafting System:
This is a sterile mesh graft knitted from polyester yarn made of polyethylene terephthale (PET) thread. It is intended to maintain the relative position of autograft or allograft bone graft material.

Xenografts:
A xenograft bone substitute has its origin from a species other than human, such as ebovin. Xenografts are usually only distributed as a calcified matrix.

APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

CPT® Code (Unproven)	Description
0232T	Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed
22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar
22585	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); each additional interspace (List separately in addition to code for primary procedure)
Q4100	Skin substitute, not otherwise specified
Q4131	EpiFix, per sq cm
Q4149	Niox 1K per sq cm

CPT Code (Proven in Certain Circumstances	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20931	Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)
22899	Unlisted procedure, spine

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DESCRIPTION OF SERVICES

The composition of allograft and synthetic bone graft substitutes and their mechanism of action can vary widely. Bone graft materials are often combined to extend graft availability and enhance healing. Used alone or in combination, bone graft substitutes may be utilized for many orthopaedic applications including spinal fusion.

CLINICAL EVIDENCE

Bone Morphogenetic Protein (rhBMP or BMP)
ECRI (2013) reviewed the abstracts of three clinical studies of anterior interbody lumbar fusion, the data from an RCT presented in the premarket approval (PMA) summary of effectiveness. They conclude on the basis of four systematic reviews that Infuse Bone Graft (rhBMP-2) with this surgical approach works as well as autologous bone graft material to promote lumbar spinal fusion, but the potential for adverse events appears high. Based upon this observation, surgeons should use caution when using this product even for its approved indications.

In a prospective, longitudinal cohort study of 688 patients from 3 studies, Burkus et al. (2011) analyzed antibody formation to BMP-2, bovine collagen, and human collagen after three prospective clinical studies investigating rhBMP. Neutralizing antibodies were assessed using a cell bioassay. The incidence of antibodies to bovine and human collagen was determined. Radiographic and clinical outcome data were assessed to determine whether antibodies were correlated to patient outcomes. The authors concluded that formation of anti-BMP-2 antibodies was low and transient. No neutralizing antibodies were observed. Formation of antibodies did not affect fusion success or appear to have clinical sequelae.

Carragee et al. (2011) conducted a comparison review of original publication conclusions to FDA database results. In 13 industry-sponsored studies with 780 patients the authors concluded that "Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications."

A systematic review by Mroz et al. (2010) compared rate of complications after the use of BMP in spine fusion surgery. Incidence rate: 44% resorption, 25% subsidence, and 27% interbody cage migration. The authors concluded that "The complication profile of BMP-2 for [anterior lumbar interbody fusion] ALIF with LT-CAGE is well characterized. Because of the lack of substantive data, the same is not true for other types of lumbar fusions, or for cervical or thoracic fusion applications. BMP has been associated with a variety of unique complications in the ventral cervical and lumbar spines. The published data on BMP fail to precisely profile this product's use in fusion surgery; hence, it should be used only after a careful consideration of the relevant data. Well-designed and executed studies are necessary to completely define the incidence of various complications relative to type of BMP, type and region of fusion, surgical technique, dose, and carrier, and importantly, to define the natural history and management of associated complications."

A systematic review by Agarwal et al. (2009) compared the efficacy and safety of osteoinductive bone graft substitutes using autografts and allografts in lumbar fusion. Of 732 potential studies, 17 studies met the inclusion criteria (nine examined rhBMP-2, three examined rhBMP-7, three examined demineralized bone matrix, and two examined autologous growth factor). Primary outcome measures were nonunion as defined by failure to fuse as demonstrated on CT scans or plain x-rays. Secondary outcome measures were failure to demonstrate improvement on the Oswestry Low-Back Pain Disability Questionnaire (or Oswestry Disability Index [ODI]). When compared with autologous iliac crest bone graft (AIBG), recombinant human BMP-2 significantly increased union as evidenced by radiographic imaging, while rhBMP-7 showed no difference in radiographic nonunion. Neither rhBMP-2 nor rhBMP-7 demonstrated a significant improvement on the Oswestry Disability Index when compared with (AIBG). The controlled trials of demineralized bone matrix or autologous growth factor in comparison with AIBG showed no significant differences in radiographic nonunion. The authors concluded that rhBMP-2 may be an effective alternative to facilitate lumbar fusion in single-level lumbar DJD compared to AIBG. However, the data is limited for rhBMP-7, demineralized bone matrix, and autologous growth factor. The authors note the following limitations: English only published studies were reviewed; there were no double blinded studies; analyses of the efficacy of bone graft substitutes other than rhBMP-2 was limited by the study size and number; and there is a potential for bias because device manufacturers sponsored several studies and more than 1 author reported conflicts of interest.

Bone Morphogenetic Protein-2 (BMP-2) Lumbar Spine

In a systematic review and meta-analysis of randomized, controlled trials and cohort studies by Fu et al. (2013), the clinical effectiveness of BMP-2 in spine fusion was assessed. This review found that in spinal fusion, rhBMP-2 has no proven clinical advantage over bone graft and may be associated with important harms, making it difficult to identify clear indications for rhBMP-2. Earlier disclosure of all relevant data would have better informed clinicians and the public than the initial published trial reports did.

Simmonds et al. (2013) also conducted a systemic review of individual patient data from all of the studies sponsored by the manufacturer, related internal documents, Food and Drug Administration (FDA) documents, and other published research to assess the effectiveness and harms of rhBMP-2 in spinal fusion compared with iliac crest bone graft or other bone grafts. The authors concluded that rhBMP-2 was associated with a small increase in fusion but greater immediate postoperative pain compared with iliac crest bone graft (ICBG). At 2 years, rhBMP-2 offered no clinically important pain reduction and was associated with a possible increased risk for cancer. While rhBMP-2 recipients had nearly double the number of new cancers compared with ICBG recipients, the overall absolute risk for cancer was low in both groups. The investigators could not rule out a bias in pain assessment because participants were not blinded to the treatment received or their fusion status.

Resnick et al. (2005) published guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine regarding bone graft extenders and substitutes. The guideline states that the use of autologous bone or rhBMP-2 bone graft substitute is recommended in the setting of an anterior lumbar interbody fusion (ALIF) in conjunction with a threaded titanium cage.

The California Technology Assessment Forum (CTAF) (Feldman, 2005) concluded that rhBMP-2 carried on a collagen sponge used in conjunction with an FDA approved device meets CTAF criteria for the treatment of patients undergoing single level anterior lumbar interbody spinal fusion for symptomatic single level degenerative disease at L4 to S1 of at least 6 months duration that has not responded to non-operative treatments.

In a systematic review and analysis of randomized controlled trials by Garrison et al. (2007), the clinical effectiveness of BMP for the treatment of spinal fusions and the healing of fractures was compared with the current standards of care. This review found that there was evidence that BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease. No significant difference was found when BMP-7 was compared with autograft for degenerative spondylolisthesis with spinal stenosis and spondylolysis. The use of BMP was associated with reduced operating time, improvement in clinical outcomes and a shorter hospital stay as compared with autograft. The proportion of secondary interventions tended to be lower in the BMP group than the control, but not of statistical significance. The authors concluded that the available evidence indicates that rhBMP-2 may promote healing in patients undergoing single-level lumbar spinal fusion, and may result in higher rates of fusion compared with autogenous bone graft. All selected trials were found to have several methodological weaknesses, including insufficient sample size, such that the statistical power to detect a moderate effect was low.

Burkus et al. (2009) reported 6 year outcomes of 222 patients (112 open; 110 laparoscopic) who received anterior lumbar interbody arthrodesis using interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). Of the 222 enrolled patients, 146 patients (78 open; 68 laparoscopic) completed the 6 year clinical follow-up evaluations with 130 patients having a complete radiographic follow-up at 6 years. Outcomes were measured utilizing the

Oswestry Disability Index (ODI) scores, Short Form-36 health survey physical component summary scores, and back and leg pain scores preoperatively and at 6 weeks and 3, 6, 12, 24,48, and 72 months postoperatively. Plain radiographs and thin-cut computed tomography scans were used to assess fusion status. At follow-up, fusion was confirmed in 128 of the 130 patients undergoing radiographic follow-up. Twenty-five patients required a second surgery. Improvements were achieved by 6 weeks in both the open and laparoscopic groups and were sustained at 6 years in the Oswestry Disability Index scores, Short Form-36 health survey physical component summary scores, and back and leg pain scores. The authors concluded that the use of rhBMP-2 on an absorbable collagen sponge is effective for obtaining anterior intervertebral spinal fusion with use of a stand-alone interbody fusion device. The lack of comparison to iliac crest bone graft or other treatment is a limitation of the study.

In another multi-center study by Burkus et al. (2006), 131 patients were randomized to compare healing and fusion rates after anterior lumbar interbody fusion (ALIF) with either autograft of rhBMP-2. Patients with lumbar spondylosis who were undergoing single-level ALIF with allograft dowels were randomly assigned to either rhBMP-2 (79 patients) as the investigational group or autologous bone graft (52 patients) as the control group. Plain radiographs and computed tomography scans were used to evaluate fusion. At 12 and 24 months, all of the investigational patients had radiographic evidence of new bone formation and incorporation of the allografts into the adjacent vertebral endplates. Radiographic evidence of fusion was documented in 89% of patients in the control group at 12 months. This percentage declined to 81.5% at 24 months with 10% of the patients in the autograft group showing incomplete healing and 11% having no healing of the allograft dowels. On CT scan, 14 (18%) of the patients in the BMP group developed a transient, localized area of bone remodeling within the vertebral body adjacent to the allograft dowel; this disappeared by 24 months.

In 2003, Burkus et al. conducted a prospective randomized study on 42 patients to investigate the radiographic progress of single-level anterior lumbar interbody fusion using cylindrical interbody fusion cages. The patients were randomly divided into two groups. The investigational group underwent interbody fusion using two tapered cylindrical fusion cages (LT-CAGE) and rhBMP-2 on an absorbable collagen sponge, and a control group underwent the procedure, receiving the devices and autogenous iliac crest bone graft. Plain radiographs and computed tomographic scans were used to evaluate the pattern of osteoinduction in the interbody space and the progression of fusion 6, 12, and 24 months after surgery. All the patients in the investigational group showed radiographic evidence of osteoinduction in the interbody cages 6 months after surgery with density in the cages increasing an average of 142 Hounsfield units. At 12 months, the increase had reached 228.7 Hounsfield units. New bone formation occurred in the disc space outside the cages by 6 months in 18 of the patients in the investigational group (18/22; 82%) and by 24 months, all the investigational patients showed new formation outside the cages. In the autograft control group, the density in the cages increased an average of 42 Hounsfield units, and 10 patients (10/20; 50%) showed evidence of bone formation outside the cages. The authors concluded that the use of rhBMP-2 is a promising method for facilitating anterior intervertebral spinal fusion in patients who have undergone anterior lumbar fusion surgery. The conclusions of this study are limited by small sample size.

Glassman et al. (2008) conducted a prospective randomized controlled trial of rhBMP-2/ACS (Infuse bone graft) versus iliac crest bone graft (ICBG) for posterolateral lumbar spine fusion in patients over 60 years of age. Patients were randomized to rhBMP-2/ACS (n = 50) or ICBG (n = 52). Two-year postoperative improvement in Oswestry Disability Index averaged 15.8 in the rhBMP-2/ACS group and 13.0 in the ICBG group. Mean improvement in Short Form-36 physical component score was 6.6 in the rhBMP-2/ACS group and 7.5 in the ICBG group. There were 20 complications in the ICBG group and 8 complications in the rhBMP-2/ACS group. Sixteen ICBG and 10 rhBMP-2/ACS patients required additional treatment for persistent back or leg symptoms. Two rhBMP-2/ACS patients had revision procedures, 1 for nonunion. Eight patients in the ICBG group had revision procedures, 5 for nonunion. Mean fusion grade on computed tomography scan was significantly better in the rhBMP-2/ACS (4.3) compared with the ICBG group (3.8). The investigators concluded that RhBMP-2/ACS is a viable ICBG replacement in older patients in terms of safety, clinical efficacy, and cost-effectiveness. The conclusions of this study are limited by small sample size.

Dimar et al. (2009) conducted a multicenter, prospective, randomized study of 463 patients at 29 sites. Patients had symptomatic single-level lumbosacral degenerative disease with no greater than grade-1 spondylolisthesis treated with single-level instrumented posterolateral arthrodesis through an open midline approach. Patients were randomly assigned to receive either the recombinant human bone morphogenetic protein-2 matrix group (239 patients) or the autogenous iliac crest bone-graft group (224 patients). Outcomes were evaluated with the Oswestry Disability Index, Short Form-36, and back and leg pain scores preoperatively and at 1.5, 3, 6, 12, and 24 months postoperatively. Radiographs and computed tomography scans were made at 6, 12, and 24 months postoperatively to evaluate for fusion. Of the 463 patients who had surgery, 410 (194 iliac crest bone graft group and 216 rhBMP-2 matrix group) were available for assessment at 2 years after surgery. Both groups showed similar improvements in clinical outcomes and reduced pain. Radiographic and computed tomography scans showed a greater incidence of fusion in the rhBMP-2 group. Patients requiring a second surgery was higher in the iliac crest bone graft group (36 patients vs. 20) than the rhBMP-2 group. The authors concluded that the use of recombinant human bone morphogenetic protein-2 in instrumented posterolateral lumbar arthrodesis produces earlier and higher fusion rates than does iliac crest bone graft.

A prospective, randomized trial by Dawson et al. (2009) investigated the use of rhBMP-2 on an absorbable collagen sponge combined with a ceramic-granule bulking agent as a replacement for autogenous iliac crest bone graft in single level posterolateral lumbar arthrodesis with instrumentation. Patients were randomized to receive either a solution of rhBMP-2 on two strips of absorbable collagen sponge combined with ceramic granules (n=25) or iliac crest bone graft (n=21). Outcomes were measured by the Oswestry Disability Index (ODI) and Short Form-36 scores, as well as back and leg pain scores. Radiographs were evaluated to determine fusion. Both groups had similar outcomes in the Oswestry Disability Index (ODI), Short Form-36 scores, back and leg pain scores. Patients in the rhBMP-2 group showed greater incidence of fusion compared to the iliac crest bone graft group (95% vs. 70%). The authors concluded that compared with an iliac crest bone graft, the combination of an absorbable collagen sponge soaked with rhBMP-2 and ceramic granules resulted in greater improvements in clinical outcomes and a higher rate of fusion.

A retrospective review by Rihn et al. (2009) evaluated complications associated with single-level transforaminal lumbar interbody fusion in 119 patients (33 patients with iliac crest autograft and 86 patients with rhBMP-2). Complications occurred in 40 patients. The authors found that the most common complication in the autograft group was related to the donor site while postoperative radiculitis was the most common complication in the rhBMP-2 group.

Singh et al. (2006) compared the use of iliac crest bone graft (ICBG) with INFUSE BMP in 41 patients vs. ICBG alone for lumbar spinal fusion. At 2-year follow-up, the ICBG with INFUSE BMP group achieved an overall fusion rate of 97%. The ICBG alone group achieved a 77% fusion rate. Glassman et al. 2005 randomized patients with single level lumbar degenerative disease in a study of lumbar spine fusion using ICBG (n=36) vs. BMP (n=38). The results of 74 patients at 1-year follow-up were analyzed. Of the ICBG group, 66% achieved grade 4 or 5 fusion and of the BMP group, 89% achieved 4 or 5 fusion. However, because of the small sample size, these differences are not significant.

The intent of using rhBMP-2 in a study by Pradhan et al. (2006) (n=36) was to try to improve fusion rates that were being observed in anterior lumbar interbody fusion (ALIF) using stand-alone femoral ring allografts as the interbody fusion device. These initial procedures (n=27) served as the historical controls and were followed by 9 procedures in which rhBMP-2 rather than autologous ICBG was used to fill the femoral ring allografts. The authors assume that the tight fit of the allograft that was achieved intraoperatively was lost during the resorptive phase of fusion.

The attempt to prevent this with rhBMP-2 failed; there was actually a trend toward less successful fusion in the latter 9 patients. The authors cite the role of BMP-mediated signals in osteoclastic bone resorption as a reason and conclude that the use of rhBMP-2 does not preclude the need for instrumentation for additional stabilization.

The protocols followed in the other four studies of lumbar fusion involved a posterolateral or posterior lumbar interbody fusion (PLIF) approach, neither of which is included in the FDA approval of INFUSE (Boden et al., 2002; Haid et al., 2004; Glassman et al., 2005; Singh et al., 2006). In Boden et al. (n=25), rhBMP-2 was used with or without an internal fixation device, the Texas Scottish Rite Hospital pedicle screw instrumentation (TSRH), and compared with AICBG in conjunction with TSRH. The rhBMP carrier was not collagen but rather granules of hydroxyapatite/tricalcium phosphate (HA/TCP). At 1-year follow-up, there was fusion in 100% of each investigational arm and in only 40% of the control group. The very small number of patients (n=5) in the control group precluded a reliable estimate of fusion success rate. Pain and disability were considered secondary outcomes in this study. However, the rhBMP-2-alone group had consistently and substantially superior clinical outcomes than either the rhBMP-2 with TSRH- or AICBG with TSRH-group. These measures included the Oswestry Low Back Pain Disability Questionnaire score, back and leg pain, the SF-36 Physical Component Summary, and patient assessment of whether the outcome was good to excellent. The authors did not see a clear explanation for the difference in clinical outcomes between the two investigational groups. They speculated that this had to do with the more extensive retraction and prolonged operative time necessitated by internal fixation. There were a few adverse events in the two investigational arms and none in the control group. However, the small size of the control group limits conclusions about safety differences.

Haid et al. (2004) studied single-level posterior lumbar interbody fusion in 67 patients. Patients were randomly assigned to one of two groups: 34 patients received rhBMP-2 on a collagen sponge carrier and 33 patients received an autogenous iliac crest bone graft. The mean operative time and blood loss for the two groups were not significantly different. At 24 months follow-up, the group receiving rhBMP-2 had a fusion rate of 92.3%; the group receiving autogenous iliac crest bone graft had a fusion rate of 77.8%. No significant differences were found in the mean Oswestry Disability Index, back and leg pain scores and physical components of the SF-36. Two adverse events related to the harvesting of the iliac crest graft occurred in two patients.

Glassman et al. (2007) reviewed the outcomes of 91 patients two years after treatment with INFUSE BMP for posterolateral spine fusion. The overall group had a mean of 4.38 computed tomographic (CT) fusion grade and a 6.6% nonunion rate. Primary one-level fusion cases (n=48) had a mean of 4.42 CT fusion grade and a 4.2% nonunion rate. Primary multilevel fusions (n=27) had a mean of 4.65 CT fusion grade. No nonunions were detected. A comparison group of 35 primary one-level patients treated with fusion using iliac crest bone graft had a mean CT fusion grade of 4.35 and a nonunion rate of 11.4%.

Bone Morphogenetic Protein-2 (BMP-2) Cervical Spine

Smucker et al. (2006) examined off-label use of BMP-2 to determine if BMP-2 is associated with an increased incidence of clinically relevant post-operative prevertebral swelling problems in patients undergoing anterior cervical fusions. A total of 234 consecutive patients (aged 12 - 82 years) undergoing anterior cervical fusion with and without BMP-2 over a 2-year period at one institution comprised the study population. The incidence of clinically relevant prevertebral swelling was calculated. The populations were compared and statistical significance was determined. A total of 234 patients met the study criteria, 69 of whom underwent anterior cervical spine fusions using BMP-2; 27.5 % of those patients in the BMP-2 group had a clinically significant swelling event versus only 3.6 % of patients in the non-BMP-2 group. This difference was statistically significant ($p < 0.0001$) and remained so after controlling for other significant predictors of swelling. The authors concluded that off-label use of BMP-2 in the anterior cervical spine is associated with an increased rate of clinically relevant swelling events.

A retrospective review by Yaremchuk et al. (2010) compared the incidence and severity of complications in patients undergoing cervical spinal procedures. A total of 775 patients were included. BMP was utilized in 260 of these patients. The authors found that patients in the BMP group had a higher incidence of acute airway obstruction. This was due to an extensive soft-tissue inflammatory reaction that is most likely to occur 2 to 7 days after surgery.

Several clinical trials have been initiated to study the effect of bone morphogenetic protein for spinal surgery. Additional information is available at: http://clinicaltrials.gov/ct2/results?term=Bone+Morphogenetic+Protein&recr=Open. Accessed August 2012.

Complications of Bone Morphogenetic Proteins

Although early evidence supports safety and efficacy when used according to FDA indications, adverse events have been reported which include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, neck swelling, and painful seroma (Dural tears, bowel/bladder and sexual dysfunction, failure to fuse and paralysis have also been reported as well as carcinogencity and teratogenic effects. Recently there has been concern more specifically safety and efficacy of rhBMP–2 used in spinal fusion surgeries. According to Carragee, et al. (2011), who in a systematic review compared conclusions regarding safety and efficacy published in the original rhBMP–2 industry-sponsored trials when used for spinal fusion to data published following the FDA approval, the risk of adverse events associated with rhBMP–2 for spinal fusion was found to be “10 to 50 times the original estimates calculated from the industry-sponsored peer-reviewed publications.”

Devine et al. (2012) performed a systematic review of the literature of articles published through January 2012. Results: Five published peer-reviewed studies and two FDA safety summaries reported the occurrence of cancer in patients treated with spinal fusion using rhBMP-2 or rhBMP-7. Cancer data for on-label use of rhBMP-2 (InFUSE™) were reported in the FDA data summary but not in one published pivotal study. The risk of cancer was the same in both the rhBMP-2 and control groups, 0.7% after 24 months. Off-label use of rhBMP for posterolateral fusion (PLF) was associated with a slightly higher risk of cancer compared with controls in three randomized controlled trials and one poorly conducted retrospective cohort study at various follow-ups. Conclusions: Cancer risk with BMP-2 may be dose dependent, illustrating the need to continue to study this technology and obtain longer follow-up on patients currently enrolled in the FDA trials. Additionally, refined guidelines regarding the routine use of BMPs should be developed, taking into account the FDA summary data that is not routinely scrutinized by the practicing surgeon.

A review by Epstein (2011) found that complications associated with the use of bone morphogenetic proteins in spinal surgery include excessive or abnormal placement of bone formation, paralysis (cord, nerve damage), dural tears, bowel bladder and sexual dysfunction, airway related complications such as obstruction, dyspnea, dysphagia and respiratory failure, inflammation of adjacent tissues, fetal developmental complications, scar, and excessive bleeding.

Dmitriev et al. (2011) studied the deleterious effects, at the cellular level, of exogenous high-dose rhBMP-2 on the central and peripheral nervous system. They conclude that although rhBMP-2 and similar growth factors may promote bone induction, the relative benefits of rhBMP-2 fusion rates compared with potential and observed complications have not been well reported or analyzed, particularly in off-label indications. The range of negative or adverse effects with the use of this product has only recently become the subject of systematic research. Although this study was performed in a rodent model, the authors raise some very important questions about the true impact of rhBMP-2 when applied around cells of the nervous system. Finally, although rhBMP-2 has certain specific indications, its dosage, delivery route, and carrier materials, and the mechanism of each contributing to observed complications, warrant significant further evaluation.

Carragee et al. (2011) conducted a retrospective review to evaluate the incidence of retrograde ejaculation in 243 male patients undergoing anterior lumbar interbody fusion (ALIF). Sixty nine patients had ALIF with rhBMP-2 while 174 patients underwent ALIF without BMP. Of the 69 patients in the rhBMP group, 6 developed retrograde ejaculation. At 1 year after surgery, 3 of the 6 affected subjects reported resolution of the retrograde ejaculation.

Original industry-supported studies reported positive outcomes with no unanticipated adverse events for the use of rhBMP-2 as a bone graft substitute. However, complications associated with this product are now being reported. Helgeson et al. (2011) retrospectively reviewed the incidence of osteolysis (the gradual disintegration of bone) following the use of rHBMP2 in posterior and transforaminal lumbar interbody fusions in 23 patients. The rate of osteolysis decreased at 1 year compared with 3 to 6 months, but only 24% of the vertebral bodies with evidence of osteolysis at 3 to 6 months completely resolved by 1 year. The area/rate of osteolysis did not appear to significantly affect the rate of fusion or final outcome with an overall union rate of 83%.

Carragee et al. (2011a) completed a comparative review of FDA documents and subsequent publications for originally unpublished adverse events and internal inconsistencies. From this review, an estimate of adverse events associated with rhBMP-2 use in spine fusion varies from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early back pain and leg pain; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy. The authors concluded that Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications.

One potential advantage of use of rHBMP-2 is the reduction of ileac crest pain from the donor site. Howard et al. (2011) studied 112 patients to identify the source of pain after autologous bone graft during fusion. The results of their study highlight the difficulty in differentiating pain originating from the graft site versus residual low back pain. The incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested.

Bone Morphogenetic Protein-7 (BMP-7)
OP-1™ Putty is a recombinant human bone morphogenetic protein-7 (rhBMP-7) and type 1 bovine bone collagen matrix combined with the putty additive carboxymethylcellulose sodium. It is intended to aid in treating lumbar spine pseudoarthrosis. According to the company website, OP-1 Putty is used during revision lumbar spinal fusion procedures. In a typical procedure, after preparing the spine and placing the fixation devices, the surgeon places OP-1 Putty in the lateral gutters on both sides of the spine bridging the dorsal surfaces of the transverse processes.

The FDA approved the OP–1 Implant and the OP–1 Putty for use in specifically-defined patients under a humanitarian device exemption (HDE).

ECRI (2013) reviewed the abstracts of in four abstracts of three studies (two abstracts described one RCT) and results from an RCT described in the product's package insert suggests that OP-1 Putty works as indicated when used to aid lumbar fusion and that it works as well as autologous bone graft material. Evidence from our review of abstracts of three studies and results from an

RCT described in the product's package insert suggests that OP-1 Implant works as indicated when used to aid in the healing of long-bone nonunion fractures and that it works as well as autologous bone graft material.

A prospective, randomized, controlled, multicenter clinical study of 36 patients by Delawi et al. (2010) evaluated the use of OP-1 Putty in single level posterolateral lumbar fusion. Patients were equally divided into 2 treatment groups (OP-1 Putty and autologous iliac crest bone graft) and followed for 1 year. Outcomes were measure by computed tomography scans to evaluate presence or absence of fusion, Oswestry Disability Index (ODI) and Visual Analog Scale (VAS). Eight patients were excluded from the final analysis due to protocol violations (n=4) and failure to complete 1 year follow-up (n=2). Fusion rates at 1 year were similar between the 2 groups (OP-1 group = 63%, bone graft group = 67%). There were no significant differences in ODI scores for both groups. Adverse events were experienced by 17 patients. The authors concluded that OP-1 Putty is as effective as iliac crest bone graft in posterolateral fusion while avoiding the morbidity associated with harvesting autogenous bone grafts from the pelvis. The study is limited by small sample size, short term follow-up, and different levels of fusion between the 2 groups.

Vaccaro et al. (2008) conducted a prospective, randomized, controlled, multicenter clinical pilot study of 36 patients undergoing decompressive laminectomy and single-level uninstrumented fusion for degenerative spondylolisthesis and symptomatic spinal stenosis. The patients were randomized in a 2:1 fashion to receive either OP-1 Putty (24 patients) or autogenous iliac crest bone graft (12 patients). At the 48-month time point, complete radiographic and clinical data were available for 22 of 36 patients (16 OP-1 putty and 6 autograft) and 25 of 36 patients (18 OP-1 putty and 7 autograft). Radiographic evidence of a solid arthrodesis was present in 11 of 16 OP-1 putty patients (68.8%) and 3 of 6 autograft patients (50%). Clinically successful outcomes, defined as at least a 20% improvement in preoperative Oswestry scores, were experienced by 14 of 19 OP-1 putty patients (73.7%) and 4 of 7 autograft patients (57.1%). The investigators concluded that despite the challenges associated with obtaining a solid uninstrumented fusion in patients with degenerative spondylolisthesis, the rates of radiographic fusion, clinical improvement, and overall success associated with the use of OP-1 putty were at least comparable to that of the autograft controls for at least 48 months after surgery.

A multicenter, prospective, 2:1 randomized controlled trial by Vaccaro et al. (2008) compared OP-1 Putty (n=208) with iliac crest autograft (n=87) in patients with symptomatic degenerative spondylolisthesis and spinal stenosis treated with decompression without a device for posterolateral arthrodesis. Patients were followed at 6-weeks, and 3, 6, 9, 12, 24-months. Outcomes were measured by Oswestry Low Back Pain Disability (ODI) questionnaire, Visual Analog Scale (VAS), Short-Form 36 (SF-36) outcomes survey and x-ray studies. In addition, serum samples were examined at regular intervals to assess the presence of antibodies to OP-1. At 24-months, patients were recruited to participate in a 36 month assessment. At 36 months, 202 of the original patients (144 OP-1 Putty patients and 58 autograft patients) underwent CT and flexion/extension x-ray studies to assess fusion success. By 36 months, 74.8% of the OP-1 patients and 77.4% of the autograft patients showed presence of new bone. Improvement from baseline in ODI was seen in 74.5% of OP-1 patients and 75.7% of autograft patients at 24 months and 68.6 % of OP-1 patients and 77.3% of autograft patients at 36 months. While neurologic improvements were noted, there was no difference between the groups by 36 months. Both groups reported significant decreases in pain on VAS; however there were no significant differences between the 2 groups in terms of VAS scores. Patients in the OP-1 Putty group showed early formation of anti-OP-1 antibodies, however this completely resolved in all patients by 24 months. The authors concluded that OP-1 Putty is comparable to iliac crest autograft and is an effective alternative for posterolateral spinal arthrodesis performed without a device for degenerative spondylolisthesis and symptomatic spinal stenosis. However, the study did not compare outcomes between the use of a fusion devices and no device.

Four small trials (total n=88) comparing OP-1 Implant, OP-1 Putty, or OP-1 Putty plus autologous ICBG (intervention groups) with autologous ICBG alone or with local autograft plus a ceramic bone substitute (control groups) showed OP-1 to be safe; however they failed to provide strong evidence of the superiority of OP-1 (Vaccaro et al., 2005a, Kanayama et al., 2006, Vaccaro et al., 2005b, Johnsson et al., 2002). All four protocols were different, and none was consistent with the FDAs HDE for OP-1 Putty. High loss to follow-up or other methodological weaknesses were present.

Technology Assessments

The Agency for Healthcare Research and Quality (AHRQ) in 2010 concluded that the evidence supports the use of rhBMP-2 for fusion of the lumbo-sacral spine. However, there is insufficient evidence to make conclusions regarding the use of BMP-7 to aid fusion in the lumbar spine. There is moderate evidence that the use of rhBMP-2 in cervical spine fusion increases cervical swelling and related complications. The strength of the evidence on clinical outcomes is moderate for on-label use of rhBMP-2 to enhance bony fusion in acute open shaft tibial fractures if the device is applied within 14 days of the initial fracture. BMP-7 may be used as an alternative to autograft in recalcitrant long-bone non-unions where use of an autograft is not feasible and alternative treatments have failed. The strength of the evidence is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone for sinus augmentation.

PEEK (Polyetheretherketone)

Evidence for the use of rhBMP with devices made from polyetheretherketone is limited.

A clinical trial by Viadya et al. (2008) evaluated the use of PEEK cages and recombinant human bone morphogenetic protein (rhBMP)-2 in 59 patients (82 fusion levels) requiring interbody spinal fusion in the cervical (n=23) or lumbar spine (n=36). Patients were followed for an average of 26 months. Plain radiographs were done to assess fusion and 10 of lumbar spine fusion patients were also evaluated with computed tomography scans. Postoperative x-rays confirmed fusion at 6-9 months for cervical patients and 9-12 months for lumbar. End plate resorption was seen on x-ray in all cervical spine fusions and the majority of lumbar fusions. However, 8 of the 24 patients who underwent transforaminal lumbar interbody fusions (TLIF) and 1 of the 2 patients with posterior lumbar interbody fusions (PLIF) showed evidence of migration on x-ray requiring revision surgery in all cases except 1 because of neurologic symptoms. One patient in the cervical group had minimal cage migration with no symptoms. The authors concluded that the use of rhBMP-2 with PEEK cages have good fusion rates; however, the early role of rhBMP in the resorptive phase may cause loosening and cage migration.

A prospective study by Meisel et al. (2008) evaluated the interbody lumbar spinal fusion process in 17 patients with degenerative disc disease. Patients were implanted with rhBMP-2 combined with dorsal fixation with pedicle screws and PEEK interbody cages. All patients showed evidence of vertebral endplate osteoclastic activity on x-ray at 3 months following surgical intervention. The osteoclastic activity was transient and had no impact on the clinical outcomes. All patients had radiographic evidence of fusion at 6 months. Migration was seen in some patients however the rigid posterior fixation prevented slippage that resulted in patient symptoms. The authors note that further studies are warranted to evaluate whether rhBMP-2 can be used as an alternative to bone autograft. Further studies should focus on transient resorption and potential for cage migration.

Ceramic-Based Products

McConnell et al. (2003) randomized 29 patients to coralline hydroxyapatite vs. autograft for cervical interbody fusion. There was no significant difference in clinical outcome or fusion rates between the two groups. However, graft fragmentation occurred in 89% of the coralline hydroxyapatite grafts and 11% of the autografts. One patient in the coralline hydroxyapatite group required revision surgery for graft failure. Follow-up time was not stated in the abstract.

Lerner et al. (2009) conducted a prospective randomized study to compare beta-tricalcium phosphate (b-TCP) with autogenous iliac crest bone graft (ICBG) in 40 consecutive patients with adolescent idiopathic scoliosis. Patients were equally divided and followed for a minimum of 20 months with a mean follow-up of 4 years. Both groups were comparable with respect of the preoperative major curve (b-TCP group: average Cobb angle 59.1 degrees; ICBG group: 60.8 degrees). Standing x-rays were obtained before surgery, after postoperative mobilization, and at all follow-up visits. In 9 patients of the b-TCP group and 8 patients of the ICBG group, thoracoplasty was performed. Average postoperative curve correction was 61.7% (22.9 degrees) in the b-TCP group and 61.2% (23.8 degrees) in the ICBG group and 57.2 (25.5 degrees) and 54.3% (28 degrees), respectively, at follow-up. At last follow-up, all patients in the ICBG group and all but 1 patient in the b-TCP group were considered fused as assessed by conventional x-rays. The authors concluded that these early promising results show that fusion rates are comparable between b-TCP and ICBG in correcting scoliosis. The fact that not all patients had the same procedure, with 17 patients having thoracoplasty with harvested rib bone, is a limitation to the study.

Bansal et al. (2009) prospectively evaluated 30 patients who underwent posterior stabilization and fusion with hydroxyapatite and beta-tricalcium phosphate (b-TCP) mixed with bone marrow aspirate. The mixture was used as a bone graft substitute over one side of spine and autologous bone graft obtained from iliac crest over other side of spine. Patients were followed for a minimum of 12 months. CT scans at 3, 6, and 12 months showed fusion in all patients on the b-TCP side. Fusion on the autologous bone graft side was successful in 29 patients. The authors concluded that hydroxyapatite and beta-tricalcium phosphate mixed with bone marrow aspirate seems to be a promising alternative to conventional autologous iliac bone graft for posterolateral spinal fusion. The study is limited by small sample size.

Four additional small prospective studies showed that beta tricalcium phosphate (b-TCP) was at least as effective as an allograft when used as an autograft extender in surgery for 94 patients with idiopathic scoliosis or reported positive, noncomparison results using b-TCP as an extender in 47 patients with a lumbar fusion. These general results apply to fusion successes, but one study reported positive functional results as well. The two studies comparing b-TCP with allografts in scoliosis surgery combined one of these two extenders with an autograft in each patient group. One study showed little between-group differences in degree of scoliosis improvement, operative time, blood loss, or hospital length of stay (Muschik, 2001). The other study reported fusion success for all patients in both groups but better maintenance of correction in the b-TCP group (Le Huec, 1997). Of the two noncomparison studies involving lumbar fusion, one simply reported that there was fusion success at all treated levels within 6 months (Linovitz and Peppers, 2002). The other reported high (84% to 96%) 1-year fusion success rates (Epstein, 2006).

Four small studies (n=143) provided limited but positive evidence of the safety and efficacy of b-TCP for filling bone voids created by surgical excision of lesions, its superiority over hydroxyapatite (HA) in promoting healing, its ability to prevent postoperative pain in autogenous iliac crest bone graft (ICBG) sites, or its usefulness as a filler when an autograft was obtained from adjacent vertebral bodies in lumbar fusion. The strongest study in this group was a small (n=30) RCT that provided data on pain outcomes (Resnick, 2005). Following cervical discectomy or cervical corpectomy with the use of autogenous ICBG, patients were randomized to either b-TCP or standard treatment for promotion of bone hemostasis at the autogenous ICBG site. Patients were blinded to their treatment assignment and reported pain according to multiple measures. Strong differences were observed at six weeks, but the differences were considerably diminished at 3 months. Furthermore, the 3-month differences did not meet the authors' definition of clinical significance.

Arlet et al. (2006) also used b-TCP to backfill the autograft site in lumbar fusion surgery. In this protocol, the autograft was harvested from an adjacent vertebral body instead of the iliac crest. The overall procedure was successful both radiographically and clinically. However, the contribution of b-TCP to these results cannot be assessed, because there was no control or comparison group. There were no complications attributable to b-TCP; thus, adverse effects associated with autogenous ICBG were avoided without the introduction of new adverse effects. Moreover, use of b-TCP was found not to require special precautions during insertion of posterior pedicle screw fixation in addition to anterior interbody fusion. By contrast, the authors relate that in their experience use of machined cortical allograft, an alternative bone void filler, required careful pedicle screw positioning to avoid extrusion of graft.

Epstein (2008) assessed fusion rates and outcomes in 60 geriatric patients undergoing multilevel lumbar laminectomies and 1- to 2-level noninstrumented fusions using B-TCP/autograft. Odom's criteria and Short-Form 36 (SF-36) outcomes were studied 2 years postoperatively. Pseudarthrosis was documented in nine (15%) patients. Two years postoperatively, Odom's criteria revealed 28 excellent, 23 good, 5 fair, and 4 poor results, whereas SF-36 data revealed improvement on 6 of 8 Health Scales in all patients.

Cell-Based Products

The use of cell based bone graft substitutes (such as Osteocel and Trinity Evolution) has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. The lack of adequate controls, randomization and blinding and the small sample sizes precludes definitive conclusions regarding the net health benefit of MSC therapy.

The American Academy of Orthopaedic Surgeons (2007) provides information on stem cells: At this point, stem cell procedures in orthopaedics are still at an experimental stage. Most procedures are performed at research centers as part of controlled clinical trials. This is the most current position statement of the AAOS.

A prospective, non-randomized multi-center study to compare the use of Osteocel® Plus in Anterior Cervical Discectomy and Fusion (ACDF) surgeries has recently been completed. Subjects will be followed for 24-months following surgery to determine the number of study subjects that are solidly fused at or before 24 months postoperatively, and to determine the mean time to fusion. This data will be compared to published and/or retrospective data for autograft, synthetic ceramics and Bone Morphogenetic Protein (BMP). (NuVasive clinical trial, 2013)

Ammerman et al. (2012) conducted a retrospective chart review to identify all patients who had undergone a minimally invasive instrumented transforaminal lumbar interbody fusion (MITLIF) for degenerative lumbar conditions. 23 patients at 26 spinal levels underwent a MILTLIF. Twenty-one patients went on to achieve radiographic evidence of solid bony arthrodesis by 12 months post-op. The authors concluded that Osteocel plus results in robust and reproducible lumbar interbody fusion. The study is limited by retrospective study design. Additional studies, preferably long-term randomized controlled trials, are needed to further validate these results.

Kerr et al. (2011) conducted a retrospective review to analyze the clinical effectiveness of mesenchymal stem cells allograft (Osteocel") to achieve radiological arthrodesis in adult patients undergoing lumbar interbody fusion surgery for different indications. Fifty-two consecutive patients received lumbar interbody fusion at one (69%) or two contiguous (31%) levels of lumbar spine for various indications. Procedures performed were circumferential fusion (67%), ALIF (17%) and TLIF (16%). Follow-up radiographic data was analyzed to establish arthrodesis versus failure (pseudarthrosis), number of months until achievement of fusion, and possible factors affecting the fusion rate. Followup ranged from 8 to 27 (median, 14) months. Solid arthrodesis was achieved in 92.3% of patients at median follow up time of 5 months (95% CI; range, 3 to 11 months). Kaplan-Meier survival curves and Mantle-Cox test were conducted to assess the effect of various factors on the rate of fusion. Statistics showed that increasing age (older than 50 years) and habitual smoking delayed the fusion time and increased the risk of pseudarthrosis. The use of Osteocel allograft is safe and effective in adult patients undergoing lumbar interbody spinal fusion procedure. Increased age and habitual smoking delays fusion but gender, previous surgery at the index level, type of procedure and number of levels do not affect the fusion rates.

The study is limited by retrospective study design. Additional studies, preferably long-term randomized controlled trials, are needed to further validate these results.

A review of mesenchymal stem cells by Helm and Gazit (2005) found that the use of mesenchymal stem cells has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration.

Clinical Trials

A few clinical trials have been initiated to study the effects of Osteocel in persons who receive artificial cervical disc fusion or eXtreme Lateral Interbody Fusion (XLIF) surgery. Additional information is available at: http://clinicaltrials.gov/ct2/show/NCT00942045 and http://clinicaltrials.gov/ct2/show/NCT00948532. Accessed December 3, 2013.

There are currently 3 clinical trials underway evaluating the use of Trinity Evolution in conjunction with an interbody spacer (NCT00965380 and NCT00951938) and as a graft source in foot/ankle fusions (NCT0098833). Additional information is available at: http://clinicaltrials.gov/ct2/results?term=trinity+Evolution. Accessed December 3, 2013.

Platelet Rich Plasma (PRP)

Bone Healing and Fusion Enhancement

Platelet rich plasma (plasma having a platelet concentration above baseline) is an approach being investigated for the treatment of bone healing. PRP is also referred to as autologous platelet derived growth factor, platelet enriched plasma, platelet-rich concentrate, and autogenous platelet gel or platelet releasate. When activated in the body, platelets release growth factors which accelerate healing, including platelet-derived growth factor, transforming growth factor beta (TGF-β) and insulin-like growth factor to name a few.

Piemontese et al. (2008) conducted a randomized, double-masked, clinical trial to compare platelet-rich plasma (PRP) combined with a demineralized freeze-dried bone allograft (DFDBA) to DFDBA mixed with a saline solution in the treatment of human intrabony defects in 60 patients. Thirty patients each were randomly assigned to the test group (PRP + DFDBA) or the control group (DFDBA + saline). The investigators concluded that treatment with a combination of PRP and DFDBA led to a significantly greater clinical improvement in intrabony periodontal defects compared to DFDBA with saline. No statistically significant differences were observed in the hard tissue response between the two treatment groups, which confirmed that PRP had no effect on hard tissue fill or gain in new hard tissue formation.

Schaaf et al. (2008) conducted a randomized controlled study to evaluate that effectiveness of platelet-rich plasma (PRP). Fifty-three patients who underwent osteoplastic bone grafting for sinus floor elevation were included. The intervention group was treated with defined concentrations of PRP in addition to transplanted bone. Bone biopsies did not indicate superiority of any of the treatments in terms of bone volume. The investigators concluded that topical use of PRP did not improve maxillary bone volume either clinically relevant or statistically significant compared to that in conventionally treated patients. The use of PRP to support bone regeneration cannot be recommended as a standard method for maxillary augmentation.

Carreon et al. (2005) reviewed 76 consecutive patients who underwent lumbar fusion with autologous iliac crest bone graft mixed with autologous growth factor from platelet gel. The investigators randomly selected a control group from patients who underwent lumbar fusion with autologous bone graft alone. Groups were matched for age, sex, smoking history and the number of levels fused. The Fisher exact test was used to compare fusion rates. The difference in the nonunion rate in the two groups was not statistically significant, leading the authors to conclude that platelet gel failed to enhance fusion rates in this setting. Castro (2004) compared 22 consecutive patients who received activated growth factor platelet gel and lumbar interbody fusion with 62 patients who had lumbar interbody fusion alone. Differences in results 34 months post procedure in the first group and 41 months post procedure in the second group were not statistically significant. The author concluded the theoretical benefits of platelet gel were not clinically realized.

Two studies compared bone healing using iliac bone grafts mixed with PRP vs. iliac bone grafts alone. Al-Sukhun et al. (2007) used PRP for reconstruction of the mandible in ten patients. Thor et al., 2005, used PRP for reconstruction of the maxilla in 19 patients. In both studies, statistically significant bone healing was demonstrated by the use of iliac bone grafts mixed with PRP.

Bibbo et al. (2005) studied autologous platelet concentrate to assist bone healing in foot and ankle surgery in 62 high-risk patients who underwent 123 procedures. Overall, a 94% union rate was achieved at a mean of 41 days. There was no control group for comparison.

In two case series of 5 and 19 patients, the authors observed benefits from the use of autologous platelet gel in terms of stable hemostasis, reduced infections, shorter hospital stays, and improved osteoblastic reaction and reconstruction of bone structure (Giannini et al., 2004; Franchini et al., 2005). However, both studies were uncontrolled.

Several clinical trials have been initiated to study the effect of platelet-rich plasma (PRP) for ligament and tendon injuries. Additional information is available at: http://clinicaltrials.gov/ct2/results?term=platelet+rich+plasma. Accessed Accessed December 3, 2013.

Evidence in the published scientific literature is inconsistent and does not support the clinical utility of using PRP to augment bone grafting.

Soft Tissue (Tendon, Joint, and other soft tissue areas of the body)
A systematic review by Rabago et al. (2009) reviewed existing evidence for prolotherapy, polidocanol, autologous whole blood, and platelet-rich plasma (PRP) injection therapies for lateral epicondylosis (LE) and found 5 prospective case series and 4 controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood and 1 PRP) which suggested each of the 4 therapies is effective for LE. The authors concluded that there is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood, and PRP injections in the treatment of LE. However, rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue injury/healing-responsive biomarkers, are needed to determine long-term safety and effectiveness, and whether these techniques can play a definitive role in the management of LE and other tendonopathies.

de Vos et al. (2010) conducted a randomized controlled trial of 54 patients with chronic achilles tendinopathy. Patients were equally divided to receive either an injection of platelet rich plasma or saline. All patients completed a questionnaire consisting of standardized outcome measures for pain and activity levels at 6, 12, and 24 weeks. Upon completion of the study, there were no significant differences in the pain or activity levels between the two groups.

A multi-center randomized controlled trial currently underway by Peerbooms et al. (2010) will evaluate the use of platelet rich plasma in 120 patients with plantar fasciitis. Patients will be randomly allocated to the concentrated autologous platelet group (PRP group) or to the corticosteroid group (control group). Results of the study will be published as soon as they are available. Trial registration number: http://www.clinicaltrials.gov NCT00758641.

In a non-randomized controlled trial by Mishra and Pavelko (2006), 140 patients with elbow epicondylar pain were evaluated to determine if treatment with buffered platelet-rich plasma (PRP) reduces pain and increases function. All patients were initially given a standardized physical therapy protocol and various non-operative treatments. Twenty of these patients had significant persistent pain (mean of 82 of 100; range of 60 to 100 of 100 on visual analog pain scale [VAS]) for a mean of 15 months despite these interventions. All patients were considering surgery. This cohort of patients was then given either a single percutaneous injection of PRP (n = 15) or bupivacaine (n = 5). Eight weeks after the treatment, the PRP-injected patients noted a 60 % improvement in their VAS versus 16 % improvement in bupivacaine-treated patients (p = 0.001). Three of 5 of the control subjects (bupivacaine-treated) withdrew or sought other treatments after the 8-week period, preventing further direct analysis. Thus, only PRP-treated patients were available for continued evaluation. At 6 months, PRP-treated subjects noted 81 % improvement in their VAS (p = 0.0001). At final follow-up (mean of 25.6 months; range of 12 to 38 months), the PRP-treated patients reported a 93 % reduction in pain compared with before the treatment (p < 0.0001). The authors concluded that while treatment of patients with chronic elbow tendinosis with PRP reduced pain significantly, further evaluation of this novel treatment is warranted.

In a study by Moon et al. (2008), 24 patients (26 elbows) with persistent pain from elbow tendinosis for a mean of 15 months, despite of standard rehabilitation protocol and a variety of other non-surgical modalities, were treated arthroscopically with iliac bone marrow plasma injection. The authors hypothesized that injection after arthroscopic debridement of degenerative tissue will bring along biological cure and not only reduce pain but also improve function in patients with resistant elbow tendonitis. Patients were allowed full range of motion exercise after 2 to 3 days. Cytokine analyses for this injective material were done. Outcome was rated by post-operative sonography, VAS and Mayo elbow performance scores (MEPS) at 8 weeks and 6 months follow-up. All patients in this study reported improvement both in their VAS and MEPS; no complication was observed. Evidence of tendon healing was observed in post-operative sonographic examination. Predominant cytokines of this study were interleukin-12, interferon-gamma-inducible protein-10 and RANTES (regulated upon activation, normal T-cell expressed and secreted). The authors concluded that injection of iliac bone marrow plasma after arthroscopic debridement in severe elbow tendinosis demonstrated early recovery of daily activities and clear improvement. This study is limited by lack of a control group and the need to long-term follow-up.

Sanchez et al. (2007) conducted a retrospective, case controlled study of 12 athletes who underwent open suture repair after complete Achilles tendon tear to determine if autologous platelet-rich plasma promotes healing and functional recovery. Participants received either platelet rich growth factors (PRGF) (n=6) or conventional surgery (n=6). Outcomes were evaluated on the basis of range of motion, functional recovery, and complications. Achilles tendons were examined by ultrasound at 50 +/- 11 months in retrospective controls and 32 +/- 10 months in the PRGF group. Athletes receiving PRGF recovered their range of motion earlier (7 +/- 2 weeks vs 11 +/- 3 weeks, P = .025), showed no wound complication, and took less time to take up gentle running (11 +/- 1 weeks vs 18 +/- 3 weeks, P = .042) and to resume training activities (14 +/- 0.8 weeks vs 21 +/- 3 weeks, P = .004). The authors concluded that the operative management of tendons combined with the application of autologous PRGF may present new possibilities for enhanced healing and functional recovery; however, further studies are needed to verify outcomes.

Rompe et al. (2008) stated that the management of Achilles tendinopathy is primarily conservative. Although many non-operative options are available, few have been tested under controlled conditions. Surgical intervention can be successful in refractory cases, however, surgery does not usually completely eliminate symptoms and complications are not rare. The authors conclude that further studies are needed to discern the optimal non-operative and surgical management of mid-portion Achilles tendinopathy.

<u>OptiMesh</u>®
Evidence is limited to a single case study (Inamasu et al. 2008) that utilized OptiMesh for a compression fracture. Long term safety and efficacy have not been established.

Many bone graft substitutes are emerging as new treatments for the repair, restoration or regeneration of bone. Much of the evidence in the peer-reviewed published scientific literature evaluating these materials consists of nonhuman trials, case reports and case series. Materials such as mesenchymal stem cells, human growth factors, and platelet rich plasma, remain under investigation and well designed trials involving human subjects are necessary to support safety and efficacy when used for bone repair.

Amniotic Tissue Membrane

Evidence is limited to animal studies only. No current clinical trials with humans were identified. There is limited evidence that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Bone Morphogenetic Protein-2 (rhBMP-2)

The InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device, approved in 2002, is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease at one level from L4-S1, where the patient has had at least 6 months of non-operative treatment. These patients may also have up to Grade I spondylolisthesis at the involved level. Patients receiving the InFUSE Bone Graft/LT-CAGE are to be implanted via an anterior open or an anterior laparoscopic approach. See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P000058 Accessed September 11, 2013.

In December 2003 the approval was broadened to include additional fusion cages. These devices are to be implanted via an anterior open approach only and are marketed under the following names:

- InFUSE™ bone graft/InterFix™ threaded fusion device
- InFUSE™ bone graft/Inter Fix™ RP threaded fusion device

Additional information (P000058/S004) is available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/ucm111338.htm. Accessed September 11, 2013.

According to the manufacturer, the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human bone morphogenetic protein-2, bovine Type I collagen or to other components of the formulation. This device should not be used in the vicinity of a resected or extant tumor, in patients who are skeletally immature, or in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy. Moreover, the safety and effectiveness of this device during pregnancy or nursing has not been established. See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P000058 Accessed September 11, 2013.

On July 1, 2008, the FDA issued a Public Health Notification regarding life-threatening complications associated with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine. There have been several reports of complications, occurring between 2 and 14 days post-op, such as swelling of neck and throat tissue, resulting in compression of the airway and/or neurological structures in the neck; difficulty swallowing, breathing or speaking; and severe dysphagia following cervical spine fusion with rhBMP due to the anatomical proximity of the cervical spine to airway structures in the body. Safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by FDA for this use. See the following Web site for more information: (Use product code NEK) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm Accessed September 11, 2013.

Additional information is available from the U.S. Food and Drug Administration [Website] - 2008 Safety Alerts for Drugs, Biologics, Medical Devices, and Dietary Supplements available at:

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062000. Accessed September 11, 2013.

The original PMA has multiple supplements and changes to the original labeling. The current indications for use as described on the company website are:
The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level. The INFUSE® Bone Graft/LT-CAGE® Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach. INFUSE® Bone Graft with either the INTER FIX™ or INTER FIX™ RP Threaded Fusion Device is to be implanted via an anterior open approach.
The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device consists of two components containing three parts– a metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. These components must be used as a system for the prescribed indication described above. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.

INFUSE/MASTERGRAFT™
In October 2008, InFUSE® received a humanitarian device exemption (HDE) for the INFUSE/MASTERGRAFT™ Posterolateral Revision Device system. The device uses a three-part component system (InFUSE® bone graft plus Mastergraft Granules plus supplemental posterior fixation system, e.g., the CD HORIZION spinal system). The device is indicated for skeletally mature (≥ 21) patients to repair symptomatic, posterolateral lumbar spine pseudoarthrosis in which autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion, such as diabetics and smokers. The device is indicated to treat 2 or more levels in the lumbar spine. Additional information is available at:
http://www.accessdata.fda.gov/cdrh_docs/pdf4/H040004b.pdf. Accessed September 11, 2013.

Amplify rhBMP-2 Matrix
Amplify™ rhBMP-2 Matrix system is proposed for use in lumbar spinal fusion procedures with a posterolateral surgical approach. The Amplify™ device is to be used in conjunction with a metallic posterior supplemental fixation device that is indicated for temporary stabilization of the spine. On July 27, 2010, an FDA advisory panel voted in favor of approving the Amplify PMA, despite concerns regarding a slightly higher rate of cancer occurrence in patients receiving Amplify. However, on March 10, 2011, the FDA issued a non-approval letter indicating that additional data and information are necessary.

BMP-7 or Osteogenic Protein 1 (OP-1)
Osteogenic Protein 1 or OP-1® consists of rhBMP-7 and bovine collagen, which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms putty.

OP-1 Implant has received 2 Humanitarian Device Exemptions (HDE). In October 2001, OP-1 Implant® received HDE approval for use as an alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/h010002a.pdf. Accessed September 11, 2013.

On April 7, 2004, OP-1 Putty also received HDE approval for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for who autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Additional information is available at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H020008. Accessed September 11, 2013.

Contraindications for OP-1 Putty are:
OP-1 Putty should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen. OP-1 Putty should not be applied at or near the vicinity of a resected tumor or in patients with a history of malignancy. OP-1 Putty should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses). OP-1 Putty should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

Platelet-Rich Plasma
Administration of platelet rich plasma (PRP) is a procedure and is, therefore, not subject to regulation by the FDA.

Devices for the preparation of platelet-poor plasma and PRP (platelet concentration systems) do require FDA approval. Examples of these devices include:

- SmartPReP™ Centrifuge System – 510(k) approval on May 28, 1999
- ACCESS™ System – 510(k) approval on March 26, 2002
- PCCS™ Platelet Concentrate Separation Kit – 510(k) approval July 12, 2002
- Magellan™ Autologous Platelet Separator System – 510(k) approval August 12, 2002

Devices for in the delivery of allograft, autograft, or synthetic bone graft materials to an orthopedic surgical site include:

- SmartJet Bone Grafting Liquid Applicator – 510(k) approval July 3, 2001
- Symphony Graft Delivery System - 510(k) approval November 14, 2001
- Graft Delivery System – 510(k) approval July 1, 2002

Additional information regarding graft delivery systems may be obtained from the U.S. Food and Drug Administration [Website] - Center for Devices and Radiological Health (CDRH) under product code FMF at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/listing.cfm Accessed September 11, 2013.

Ceramic-Based Products
Bone Void Fillers under product code MQV include Vitoss® Scaffold Synthetic Cancellous Bone Void Filler (Orthovita Inc.) which was approved on December 14, 2000 (K032130) for use as a bone void filler for voids or gaps that are not intrinsic to the stability of the bony structure. It is indicated for use in the treatment of surgically created osseous defects or osseous defects resulting from traumatic injury to the bone. Vitoss should not be used to treat large defects that in the surgeon's opinion would fail to heal spontaneously. This product is intended to be packed into bony voids or gaps of the skeletal system (i.e., the extremities, spine, and pelvis). The bone filler product and the IMBIBE™ II Syringe (K030208) have since been combined to create the Vitoss-Filled Cartridge (K032130) approved November 3, 2003. The syringe is prefilled with Vitoss Bone Void Filler. A secondary syringe, the Meric Piston Syringe (K875196), and an adapter valve for the vacuum line in the surgical suite, are also included in the kit. The surgeon can use either the secondary syringe or the vacuum line to aspirate blood or marrow into the Vitoss-Filled Cartridge. Lastly, a mixture of b-TCP and Type 1 bovine collagen in a hydroxyapatite carrier, Vitoss® Scaffold Foam™ (K032288), was approved December 19, 2003.

Biosorb® Resorbable Bone Filler (Science for Biomaterials) was approved January 28, 2003 (K021963); and chronOS™ (Synthes-Stratec Inc.) was approved November 26, 2002 (K013072). These products are very similar to Vitoss, although less porous, and are approved for the same indications. The FDA has approved other b-TCP products as well.

Cross-Bone Bone Filler received 510(k) approval on December 17, 2007 as a bone filler and for bone reconstruction. Similar to other b-TCP, Cross Bone is a resorbable, biphasic ceramic implant composed of 60% hydroxyapatite and 40% P-tricalcium phosphate in the form of granules.

Additional information regarding b-TCP devices may be obtained from the U.S. Food and Drug Administration [Website] - Center for Devices and Radiological Health (CDRH) under product code MQV at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/listing.cfm. Accessed September 11, 2013.

Cell-Based Products
Osteocel by NuVasive Inc. is registered with the FDA's *Human Cell, Tissues and Cellular and Tissue-Based Products (HCT/P) List of Registered Establishments*. Additional information is available at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/FindaTissueEstablishment/ucm110270.htm. Accessed September 11, 2013.

OptiMesh®
OptiMesh received 510(k) approval in November, 2003 as a class II device. The device is intended to maintain bone graft material within a vertebral defect. This device is contraindicated for patients with instability and does not provide structural support. The safety and effectiveness of OptiMesh used for fusion of the interbody space has not been established. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/K014200.pdf. Accessed September 11, 2013.

Additional Products
Accell 100, Actifuse, Allomatrix, Grafton DBM, Hydroxyapatite, NovaBone and NovaBone-C/M, Optefil, Origen DBM, PerioGlas, Plasmax, ProOsteon 200™, TRUFIT

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover blood-derived products such as platelet rich plasma for the healing of soft tissue and bone. See the National Coverage Determination (NCD) for Blood-Derived Products for Chronic Non-Healing Wounds. Local Coverage Determinations do exist. Refer to the LCDs for Services That Are Not Reasonable and Necessary, Non-Covered Services, Noncovered Services, Non-Covered Category III CPT Codes and Category III CPT Codes.

Medicare does not have a National Coverage Determination (NCD) for the growth factor-mediated lumbar spinal fusion, bone morphogenetic protein, or bone void fillers for enhancement of bone healing and/or fusion. Local Coverage Determinations (LCDs) do not exist at this time.

InFUSE™ (effective for discharges on or after October 1, 2003) and OP-1 (effective for discharges on or after October 1, 2004) are recognized by CMS for new technology add-on payments. An add-on payment is made for discharges involving approved new technologies, if the total covered costs of the discharge exceed the diagnosis-related group (DRG) payment for the case. Cases eligible for the new technology add-on payment are identified by assignment to DRG 497 or 498 as a lumbar spinal fusion with the combination of ICD-9-CM procedure codes 84.51 and 84.52.

Effective October 1, 2005, OP-1 and InFUSE™ are no longer eligible for the new technology add-on payment. See CMS Medicare Claims Processing Manual Transmittal 692 Fiscal Year (FY) 2006 IPPS and LTCH PPS Changes dated September 30, 2005 at http://www.cms.hhs.gov/transmittals/downloads/R692CP.pdf.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2014	• Reorganized policy content • Updated benefit considerations; added language for *Essential Health Benefits for Individual and Small Group* plans to indicate: o For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and

	outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs") o Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs; however, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans o The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee's specific plan document to determine benefit coverage • Revised coverage rationale: o **Amniotic Tissue Membrane**: Added language to indicate the use of amniotic membrane products in the treatment of spine disease or in spine surgery is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature (**e**vidence is limited to animal studies only;no current clinical trials with humans were identified) o **Bone Morphogenetic Proteins (BMP)**: Added language to indicate the use of bone morphogenic protein as an adjunct to spinal fusion surgery may be associated with significant adverse events. Thus, before using bone morphogenic protein, the physician should engage in a shared decision-making process with the patient, discussing the potential advantages, harms and alternatives to the use of bone morphogenic protein as an adjunct to spinal fusion surgery o Reformatted and relocated information pertaining to medical necessity review (when applicable); added language to identify if service is "medically necessary" or "not medically necessary" to applicable proven/unproven statement • Revised definitions: o Added definition of *amniotic tissue membrane* and *mesh grafting system* o Removed definition of *OptiMesh*® o Removed proprietary names of specific mesenchymal stem cell products • Revised list of unproven CPT codes for amniotic (tissue) membrane products; added Q4100, Q4131 and Q4149 • Updated supporting information to reflect the most current clinical evidence, FDA and CMS information, and references • Archived previous policy version 2013T0410M