BONE OR SOFT TISSUE HEALING AND FUSION ENHANCEMENT PRODUCTS

Policy Number: SURGERY 056.14 T2
Effective Date: March 1, 2016

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CONDITIONS OF COVERAGE

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Benefit Type

General benefits package

Referral Required

(Does not apply to non-gatekeeper products)

No

Authorization Required

(Precertification always required for inpatient admission)

Yes

Precertification with Medical Director Review Required

Yes

Applicable Site(s) of Service

(If site of service is not listed, Medical Director review is required)

Outpatient, Inpatient

Special Considerations

1Review by a Medical Director or their designee is required - EXCEPT for CPT Codes 20930 and 20931
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 HUD 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 member specific benefit 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. DBM is human bone processed with hydrochloric acid to remove mineral content.

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.

**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)

**Note:** The Infuse Bone Graft is also known as bone morphogenic, or morphogenetic protein-2, BMP-2.

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 (younger than 21 years of age or no 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. Available studies have been limited by substantial loss of study participants at follow-up as well as by short follow-up times.

**Ceramic-Based Products**

Ceramic-based products such as beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate and bioactive glass, used alone or in combination with other grafts including 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.

**Note:** For additional information on ceramic-based products please see definition section.

**Cell-Based Products**

Cell-based products such as mesenchymal stem cells (MSC), are unproven and not medically necessary for the enhancement of bone healing.

Evidence in the published scientific literature has not demonstrated an improved health outcome benefit over standard therapies. Well-designed, large randomized comparative clinical trials are needed to demonstrate the efficacy and safety of MSC therapy for orthopedic indications.
**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

**Overview**
Orthobiologics are designed to substitute for real bone, but they can also enhance bone-fracture healing or bone fusion by providing substances that are either osteoconductive or osteoinductive (described in further detail below). Some products may have both properties. Orthobiologics require an invasive surgical procedure to place the material in the bone void site or at the site of bone fusion.

- **Osteoconductive matrix materials**: Osteoconductive materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone. This material acts only as a scaffold into which the new bone cells grow.

- **Osteoinductive bone graft substitutes**: Osteoinduction means that the product induces osteoblast formation from the patient’s own osteogenic stem cells that are already present at the fusion site. The osteoinductive properties of bone tissue are attributed to bone morphogenetic proteins (BMPs).

**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).**

**Allograft**: An allograft is obtained from a person other than the surgical candidate. Harvested through a minimally invasive procedure, this allograft provides a population of osteoprogenitor cells and critical growth factors that help cell differentiation, leading to bone healing. It can include 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.

More recently, processing methods used for preparation of some allografts have been refined and products are now available that manufacturers claim retain higher concentrations of naturally occurring growth factors and/or stem cells. Human growth factors such as fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, transforming growth factor-beta, and microglobulin-B, are examples of osteogenic growth factors that are naturally found within the matrix of bone.

**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.

**Anorganic Bone Graft Materials**: Anorganic bone graft materials are a type of xenograft bone graft substitute made from other than human material, such as cow (i.e., bovine) or coral, and is typically used in combination with other types of bone graft materials, for example with collagen or a calcified matrix. The animal bone is processed to remove any organic components (i.e., anorganic bone material) reducing concerns of disease transmission or immunogenic reactions.
Some of the anorganic type xenograft materials may be used as stand-alone graft material to enhance healing.

**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 grafts.

**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 fifteen bone morphogenetic proteins (BMPs) that have been identified. In addition to the fifteen BMPs, there are several recombinant human bone morphogenetic proteins (rhBMPs). 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. These proteins may also be used for individuals who have up to grade I spondylolisthesis.

Infuse Bone Graft (Medtronic, Inc., Minneapolis, MN, USA) is a bone graft substitute intended to aid in fusing lumbar vertebrae using an anterior lumbar interbody fusion (ALIF) procedure, in combination with a titanium threaded cage implant to treat degenerative disc disease. The primary reason for using Infuse Bone Graft is to avoid the adverse events (AEs) (e.g., pain, infection) associated with harvesting autologous bone graft material from the patient. Infuse Bone Graft contains recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge.

Carrier systems, which are absorbed over time, function to maintain the concentration of the rhBMP at the treatment site, provide temporary scaffolding for osteogenesis and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymer, natural polymers and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also function to provide mechanical support. The carrier and delivery system are important variables in the clinical use of rhBMPs. For example, different clinical applications will require different dosages of rhBMP with different carriers and delivery systems. Therefore, the results of one clinical application cannot be extrapolated to others.

At the present time, two rhBMPs and associated carrier/delivery systems have received FDA approval. OP-1TM consists of rhBMP-7 and bovine collagen which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms a putty. The Infuse system consists in part of rhBMP-2 on an absorbable collagen sponge carrier.

**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 not medically necessary 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. (They may also be referred to as synthetic bone grafts.) 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. Because each of these components has different binding, biodegradability, and adhesion characteristics, there is variability seen among carriers depending on composition.

Note: Bone void fillers are most commonly used in orthopedic surgery for filling defects; their use as such is considered a medically necessary part of the surgical procedure.

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. After processing, the material contains 90% type I collagen and 10% noncollagen protein containing a variety of bone growth stimulators such as bone morphogenetic protein (BMPs). The bone growth stimulators induce osteoblast formation (osteoiduction) from the patient’s osteogenic stem cells. Added materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone (osseoaduction). DBM is commonly used as a bone graft extender for posterolateral spinal fusion surgery.

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

Platelet-Rich Plasma: Platelet concentrate products are derived from platelet-rich plasma (PRP), which involves concentrating whole blood through a centrifugation process. However, variability in processing methods, classification systems, and terminology has led to wide inconsistency in the results of its use in many orthopedic conditions, including bone healing.

### 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.

#### Applicable CPT Codes

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<tr>
<th>CPT®/HCPCS Codes (Unproven/Not Medically Necessary)</th>
<th>Description</th>
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<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed</td>
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<tr>
<td>22558</td>
<td>Arthrodesis, anterior interbody technique, including minimal disectomy to prepare interspace (other than for decompression); lumbar</td>
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CPT®/HCPCS Codes
(Unproven/Not Medically Necessary)

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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>22585</td>
<td>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)</td>
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<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
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<tr>
<td>Q4149</td>
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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.

Many bone graft substitute products are available in the U.S. marketplace. The American Academy of Orthopedic Surgeons has created a list of these products available in 2010 that provides the company name, composition, commercially available forms, claimed mechanism of action, burdens of proof, and FDA status of the products.

CLINICAL EVIDENCE

Bone Morphogenetic Protein (rhBMP or BMP)

Hayes (2015) reviewed a total of 19 randomized controlled trials and 4 cohort studies evaluating bone morphogenetic proteins for lumbar and cervical spinal fusion, published from 2002 to 2014. The available studies suggest that, compared with autograft, use of rhBMP-2 for lumbar spinal fusion provides minor, short-term benefits, and poses some risk. For most patients, use of rhBMP-2 does not seem to provide greater long-term benefit than autograft, and it has not been possible to rule out certain serious long-term risks. The small number of available studies for cervical spinal fusion precludes conclusions for this indication.

ECRI (2014) 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.

Adams et al. (2014) conducted a retrospective cohort study to compare clinical outcomes, fusion rates, and rates of complications in posterior lumbar interbody fusions (PLIFs) and transfemoral lumbar interbody fusion procedures with either recombinant human bone morphogenetic protein-2 (rhBMP-2) and local bone graft (LBG) or LBG alone used as graft material. All patients who underwent primary interbody fusions under a single surgeon were identified from the surgeon's records. A retrospective review of prospectively collected data preoperatively and up to 12
months postoperatively was performed. Data collected included visual analogue scale, pain scores for back and leg, Oswestry Disability Index scores, Short-Form 36 (SF-36), standing lumbar radiographs, and clinical notes. Seventy-seven patients met the study criteria and 70 consented to be part of the study. Fifty-one were treated with rhBMP-2 and 19 with LBG. At 12-month follow-up, no significant differences were seen in visual analogue scale score, Oswestry Disability Index score, or SF-36 scores. A total of 89.5% of the LBG group and 94.1% of the rhBMP-2 group went on to show radiographic evidence of fusion by 12-month follow-up. The rhBMP-2 group had a higher complication rate (41.2% vs. 10.5%). The authors concluded that there was no difference in clinical outcomes, comparable rates of fusion and a significant increase in complication rates with rhBMP-2. Using rhBMP-2 may unnecessarily increase the risk of complication in routine PLIF and transformaminal lumbar interbody fusion procedures.

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**

Rodgers et al. (2013) investigated published results of industry funded trials of recombinant human bone morphogenetic protein 2 (rhBMP-2) in spinal fusion matching underlying trial data by comparing three different data sources: individual participant data, internal industry reports, and publicly available journal publications and conference abstracts. Outcomes from 11 of the 17 manufacturer-sponsored studies were reported in 32 publications. The authors concluded that the published literature only partially represents the total data known to have been collected on the effects of rhBMP-2. This did not lead to substantially different results for meta-analysis of effectiveness outcomes. In contrast, reporting of adverse event data in trial publications was inadequate and inconsistent to the extent that any systematic review based solely on the publicly available data would not be able to properly evaluate the safety of rhBMP-2. Analysis of individual participant data enabled the most complete, detailed, and in-depth analysis and was not more resource intensive than extracting, collating, and analyzing aggregate data from multiple trial publications and conference abstracts. Confidential internal reports presented considerably more adverse event data than publications, and in the absence of individual participant data access to these reports would support more accurate and reliable investigation, with less time and effort than relying on incomplete published data.

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.

The U.S. Food and Drug Administration reported a higher incidence of cancer in patients who had spinal arthrodesis and were exposed to a high dose of recombinant human bone morphogenetic protein-2 (rhBMP-2). The purpose of this study was to determine the risk of cancer after spinal arthrodesis with BMP. Kelly et al. (2014) performed a retrospective analysis of the incidence of cancer in 467,916 Medicare patients undergoing spinal arthrodesis from 2005 to 2010. Patients with a preexisting diagnosis of cancer were excluded. The main outcome measure was the relative risk of developing new malignant lesions after spinal arthrodesis with or without exposure to BMP. The relative risk of developing cancer after BMP exposure was 0.938. In the BMP group, 5.9% of the patients developed an invasive cancer compared with 6.5% of the patients in the control group. The relative risk of developing cancer after BMP exposure was 0.98 in males and 0.93 in females. The control group showed a higher incidence of each type of cancer except pancreatic cancer. The authors concluded that recent clinical use of BMP was not associated with a detectable increase in the risk of cancer within a mean 2.9-year time window.

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 spondyloysis. 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 spondylolisthesis 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 by 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/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**

Cole et al. (2014) performed a retrospective database study from 2006 to 2010. The authors identify 91,543 patients who underwent anterior cervical discectomy and fusion (ACDF) with or without cervical corpectomy. A total of 3197 patients were treated with rhBMP intraoperatively. Mean follow-up was 588 days in the non-treated cohort and 591 days in the rhBMP-treated cohort. Multivariate logistic regression as well as propensity score analysis were used to evaluate the association of rhBMP usage with postoperative complications. Authors reported an overall rate of postoperative complications in patients receiving rhBMP for cervical spinal fusion procedures compared with patients not receiving rhBMP. Hematoma or seroma, pulmonary complications, and dysphagia were also more common in the rhBMP cohort.

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.


**Complications of the Use 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 carcinogenicity and teratogenic effects. Recently there has been concern more specifically safety and efficacy of rhBMP-2 used in spinal fusion surgeries. In mid-2013 two major meta-analyses were published based on individual subject data supplied by Medtronic, Inc. through Yale University Open Data Access (YODA) Project. This has prompted surgeons to reassess their use of the rhBMP-2 in spine fusion procedures. Two groups were selected by YODA in an open competition to synthesize evidence regarding the safety of rhBMP-2 (Fu, 2013; Simmonds, 2013). The analyses used de-identified data from industry-sponsored RCTs of rhBMP-2 vs. iliac crest bone graft when used during spinal fusion surgery for
degenerative disc disease and related conditions. Additional data of similar populations from observational studies were also used for investigation of adverse events.

The meta-analysis conducted by the group led by Simmonds included subject-level data from 11 RCTs, regardless of spinal level or surgical approach. Adverse event data was also collected from an additional 35 observational studies. The authors reported that at 24 months, rhBMP-2 increased the rate of radiographic fusion by 12%, and improved mean scores on the ODI by 3.5%. The improvement in ODI did not reach the previously defined threshold for a clinically significant effect. Subjects who received rhBMP were reported to have a clearly higher incidence of leg and back pain in the immediate postoperative period. This contrasts with the data for 3 months postoperatively, where recipients of rhBMP had less pain than subjects who had allograft treatment. There was an almost 2-fold increased risk of cancer reported in subjects treated with rhBMP-2. However, due to the small number of events recorded, confidence intervals were large and definite conclusions could not be drawn. The overall risk of cancer was low with either rhBMP or autograft procedures. With regard to adverse events analysis from the observational studies, the risk of heterotopic bone formation, leg pain and radiculitis, retrograde ejaculation, and osteolysis were all more frequent in subjects receiving rhBMP during lumbar spinal fusion. Among subjects undergoing cervical spine procedures, dysphagia was more common in rhBMP subjects. The authors note that there was weak correlation between spinal fusion rates and reduction in pain scores.

The meta-analysis by Fu and colleagues included individual subject data from 13 RCTs and 31 cohort studies. They found that rhBMP-2 and iliac bone crest autograft resulted in similar effectiveness outcomes for both lumbar and cervical fusion. An increased risk of cancer was found, but data were not sufficient to determine if risk was related to dose, and increased risk was no longer significant at 48 months. Event rates were low, and the types of cancers recorded were heterogeneous. Pain was more common shortly after surgery with rhBMP-2. The authors concluded that the use of rhBMP provides no additional advantage over autologous bone grafting and may be associated with significant risk of harm. In their analysis on the quality of available data, they reported that there was significant reporting bias in the journal publications and they state, "Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and under-reporting."

A report by Glassman and colleagues describes a retrospective case review of 1037 subjects who underwent posterolateral spine fusion using rhBMP-2, with a focus on complication rates (2011). They reported that medical and surgical complications were observed in 190 of 1037 subjects, with 81 major complications and 110 minor complications. New or more severe postoperative radicular symptoms were noted in 7 subjects. Complications directly related to rhBMP-2 were observed in at least 1 and in a worst case analysis, in as many as 6 subjects. The authors concluded that, "there were extremely few complications directly attributed to rhBMP-2/ACS, and the overall complication rates were consistent with established norms."

Chrastil and others (2013) published a systematic review of the spectrum of complications reported in the literature after posterior interbody fusions of the lumbar spine augmented with BMP. Seventeen articles were identified and reviewed that addressed the use and complications of BMP use during PLIF and TLIF procedures. The studies ranged from level I prospective randomized trial to case reports of complications. The authors reported appreciable rates of BMP-specific complications, including heterotopic ossification within the epidural space or neuroforamina, postoperative radiculitis, and endplate osteolysis with interbody device subsidence. They conclude by stating, "High-quality clinical trials should be initiated to develop appropriate paradigms to maximize the safety and efficacy of BMP for posterior interbody fusions."

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 transforminal 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 iliac 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.

At this time there are no clinical trials available describing the use of rhBMP during thoracic spinal fusion procedures.

**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 measured 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. The conclusions of this study are limited by small sample size.

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, Johansson 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
Technology assessments evaluating the safety and efficacy of bone graft substitutes in general were not found in the medical literature. Although the American Academy of Orthopaedic Surgeons does not have a formal position statement, the Orthopaedic Device Forum initially published a document addressing the use of bone graft substitutes in 2001 (Greenwald, et al., 2001). The forum noted at that time, and again in 2006 and 2008, that the currently marketed products vary in their composition and their claimed mechanisms of action—not all substitutes perform the same. Selection should be based on reasoned burdens of proof which include the examination of the product claims and whether or not they are supported by preclinical and human studies in site specific locations, where they are to be utilized in surgery. The AAOS noted it is imperative to appreciate the level of evidence claimed in the latter studies.

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 polyetheretherketone (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 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.

Several preclinical studies have been conducted to evaluate the effectiveness of MSCs in tissue regeneration. Caudwell and colleagues (2014) conducted a systematic review of preclinical studies using MSC and scaffolds in the treatment of knee ligament regeneration. The authors concluded, based on their investigation of 21 articles, that preclinical evidence of ligamentous regeneration with MSC and scaffold use was established, but limited clinical evidence exists to support recently developed scaffolds.

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 MITLIF. 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. Follow-up 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
There is currently one clinical trial underway evaluating the use of Trinity Evolution in conjunction with an interbody spacer (NCT00965380).

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.

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 epicondylitis (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: https://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 tendinosis. 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.

**OptiMesh**
Zheng et al. (2010) evaluated the biomechanics of lumbar motion segments instrumented with stand-alone OptiMesh system augmented with posterior fixation using facet or pedicle screws and the efficacy of discectomy and disc distraction. The filled mesh bag serves as the interbody device providing structural support to the motion segment being fused. Twenty-four fresh human cadaveric lumbar motion segments were divided into two groups. In the control group, multidirectional flexibility testing was conducted after an intact condition and standard transforaminal lumbar interbody fusion (TLIF) procedure. In the OptiMesh group, testing was performed following intact, stand-alone OptiMesh procedure, OptiMesh with facet screws (placed using the transfacet approach), and OptiMesh with pedicle screws and rods. Range of motion (ROM) was calculated for each surgical treatment. The lordosis and disc height change of intact and instrumented specimens were measured in the lateral radiographs to evaluate the disc space distraction. The OptiMesh system offers large volume of bone graft in the disc space with small access portals. The OptiMesh system had similar construct stability to that of standard TLIF procedure when posterior fixation was applied. However, the amount of distraction was limited without additional distraction tools. With the anterior support provided by the expandable meshed bag, facet screws had comparable construct stability to that of pedicle screws.

Inamasu et al (2008) reported a patient with a flexion-distraction injury of the L1 vertebra treated with a combination of short-segment posterior fixation and Optimesh (Spineology Inc., St. Paul, MN), a flexible balloon-shaped mesh that is deployed into the fractured vertebra together with allograft. The role of minimally invasive procedures for reconstruction of the vertebral column height, including the OptiMesh system, in patients with thoracolumbar compression fracture seems promising. However, the long-term effectiveness of these new techniques is unknown. It also remains to be seen how the delivery of allograft into the fractured vertebra via OptiMesh affects remodeling, and whether the restored vertebral height is maintained.

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**
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.

No professional guidelines offered recommendations regarding the use of amniotic-derived tissues for the treatment of orthopedic conditions.

**Clinical Practice Guidelines**
American Association of Neurological Surgeons, Congress of Neurological Surgeons (2014) recommendations:

The use of demineralized bond matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions.
The use of b-tricalcium phosphate (b-TCP)/local autograft as a substitute for autologous iliac crest bone (AICB) is an option for single-level instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.

The use of calcium sulfate preparations mixed with local autograft, as a substitute for autologous iliac crest bone, (AICB), is an option for instrumented posterolateral fusions.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Allografts are considered tissues for transplantation. FDA: “Minimally manipulated human bone for transplantation: Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P.” If combined with other materials, the resulting product is considered a device and regulated by the FDA as a medical device.

**Examples of Bone Growth and Bone Graft Products**

Actifuse synthetic bone graft—Actifuse (ApaTech, Ltd., Hertfordshire, UK) is a silicate-substituted calcium phosphate bone filler designed to provide an osteoconductive scaffold. According to the company, the interconnected and open porous structure of the hydroxyapatite phase of Actifuse is similar to human cancellous bone.

Actifuse received U.S. Food and Drug Administration (FDA) 510(k) clearance for marketing and is indicated to be packed gently into bony voids or gaps of the skeletal system (i.e., extremities, spine, pelvis) that are not intrinsic to the stability of the bony structure. These voids or defects may be surgically created or may result from traumatic injury to the bone. After placement, the product is resorbed and replaced by bone during the healing process.

Bioglass - This osteoconductive material is sold under the brand names PerioGlas®, NovaBone®, and NovaBone-C/M® (NovaBone Products, LLC, Alachua, FL, USA) and consists of synthetic calcium phosphosilicate, which offers a scaffold for new bone growth. The manufacturer claims that the material is also osteoinductive, although it contains no biologic growth factors (see links to the manufacturer website in section 7 of the Search Summary).

NovaBone has received FDA 510(k) clearance for marketing as a resorbable bone graft substitute intended only for bony voids or gaps that are not intrinsic to the stability of the bony structure. PerioGlas has received 510(k) clearance for marketing for use in dental intraosseous, oral, and cranio-/maxillofacial bony defects.

Infuse Bone Graft (Medtronic, Inc., Minneapolis, MN, USA) contains rhBMP-2 combined with a bovine-derived absorbable collagen sponge carrier.

Infuse Bone Graft received FDA marketing approval in April 2004 through the PMA process. The current indications for use as described on the company website are as follows: The Infuse Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. Infuse Bone Graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature.

The Infuse Bone Graft 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 and should not be used in the vicinity of a resected or extant tumor, in patients with an active malignancy or patients undergoing treatment for a malignancy. The Infuse Bone Graft should also not be used in patients who are skeletally immature, in patients with an inadequate neurovascular status, in patients with compartment syndrome of the affected limb, in pregnant women, or in patients with an active infection at the operative site.

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. The Infuse™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of two components containing three parts – a tapered metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. The Infuse™ Bone Graft component is inserted into the LT-Cage™ Lumbar Tapered Fusion Device component to form the complete Infuse™ Bone Graft/LT-Cage™ Lumbar Tapered Fusion Device. See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P000058

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

**Note:** The INTER FIX™ Threaded Fusion Device and the INTER FIX™ RP Threaded Fusion Device may be used together to treat a spinal level. LT-CAGE® Lumbar Tapered Fusion Device implants are not to be used in conjunction with either the INTER FIX™ or INTER FIX™ RP implants to treat a spinal level.

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

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 November 17, 2015.

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

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](http://www.accessdata.fda.gov/cdrh_docs/pdf4/H040004b.pdf). Accessed November 17, 2015.

**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.

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.

**Contraindications for OP-1 Putty**

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.

**Demineralized Bone Matrix**

Grafton® DBM-Grafton DBM (originally produced by Osteotech, Inc., Eatontown, NJ, USA, and acquired by Medtronic in 2010) is a human-bone allograft product containing human DBM and an inert additive for intraoperative handling. According to the company, the product has both osteoconductive and osteoinductive properties. Grafton DBM received FDA 510(k) clearance for marketing and is intended for use as a bone graft extender, bone graft substitute, and bone void filler in bony voids or gaps of the skeletal system (i.e., spine, pelvis and extremities) not intrinsic to the stability of the bony structure. The voids or gaps may be surgically created defects or defects created by traumatic injury to the bone. GRAFTON® DBM is resorbed/remodeled and is replaced by host bone during the healing process.
**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.

**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). The ChronOS™ consists of pure β-tricalcium phosphate (β-TCP). Putty form is mixed with a non-animal-derived sodium hyaluronate. 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.


**Bone Marrow Aspirate**

The use of concentrated bone marrow aspirate in spinal fusion surgeries is a procedure and therefore not subject to FDA regulation. However any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.
In addition, the FDA has a comprehensive regulatory system for human cell, tissue, and cellular and tissue-based (HCT/P) products, which are defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

**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](http://www.accessdata.fda.gov/cdrh_docs/pdf/K014200.pdf). Accessed November 17, 2015.

**REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2016T0410P]


Humanitarian Device Exemption (HDE). OP-1 Putty H020008. [approved 2004 Apr 7].


POLICY HISTORY/REVISION INFORMATION

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| 03/01/2016 | • Updated benefit considerations; added language to indicate:  
  o 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  
  o 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 HUD exemption  
• Updated coverage rationale; added language pertaining to clinical evidence/study findings for cell-based products to indicate:  
  o Evidence in the published scientific literature has not demonstrated an improved health outcome benefit over standard therapies  
  o Well-designed, large randomized comparative clinical trials are needed to demonstrate the efficacy and safety of MSC therapy for orthopedic indications  
• Reorganized and revised definitions:  
  o Updated definition of “allograft”  
  o Added definition of “anorganic bone graft materials”  
  o Removed definition of “xenografts”  
• Updated lists of applicable codes:  
  o Reorganized list of applicable CPT/HCPCS codes by coverage status (“proven/medically necessary” vs. “unproven/not medically necessary”)  
  o Removed coding clarification statement indicating most bone healing and fusion enhancement products are not represented by a specific CPT/HCPCS code; it may be necessary to use the most closely appropriate code and supplement with specific comments in the precertification documentation  
• Updated supporting information to reflect the most current clinical evidence, FDA information and references  
• Archived previous policy version SURGERY 056.13 T2 |