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**Name of Policy:****Bone Morphogenetic Protein**

Policy #: 189  
Category: Surgery

Latest Review Date: November 2013  
Policy Grade: A

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**Background/Definitions:**

*As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.*

*The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:*

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

*Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:*

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

### **Description of Procedure or Service:**

Two recombinant human bone morphogenetic proteins (rhBMP) are now commercially available, rhBMP-2 applied with an absorbable collagen sponge (InFUSE®) and rhBMP-7 applied in putty (OP-1®). These products have been investigated as an alternative to bone autografting in a variety of clinical situations, including spinal fusions, internal fixation of fractures, treatment of bone defects, and reconstruction of maxillofacial conditions.

Bone morphogenetic proteins (BMPs) are members of the family of transforming growth factors. At present, some 20 different BMPs have been identified, all with varying degrees of tissue stimulating properties. rhBMPs are delivered to the bone grafting site as part of a surgical procedure; a variety of carrier and delivery systems has been investigated. 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, and different clinical applications, such as long-bone nonunion, or interbody or intertransverse fusion, have been evaluated with different carriers and delivery systems. For example, rhBMP putty with pedicle and screw devices are used for instrumented intertransverse fusion (posterolateral fusion; PLF), while rhBMP in a collagen sponge with bone dowels or interbody cages are used for interbody spinal fusion. In addition, interbody fusion of the lumbar spine can be approached from an anterior (anterior lumbar interbody fusion; ALIF), lateral (XLIF), or posterior direction (PLIF or TLIF). Surgical procedures may include decompression of the spinal canal and insertion of pedicle screws and rods to increase stability of the spine.

Posterior approaches (PLIF and TLIF) allow decompression (via laminotomies and facetectomies) for treatment of spinal canal pathology (e.g., spinal stenosis, lateral recess and foraminal stenosis, synovial cysts, hypertrophic ligamentum flavum) along with stabilization of the spine and are differentiated from instrumented or noninstrumented posterolateral intertransverse fusion (PLF), which involves the transverse processes. Due to the proximity of these procedures to the spinal canal, risks associated with ectopic bone formation are increased (e.g., radiculopathies). Increased risk of bone resorption around rhBMP grafts, heterotopic bone formation, epidural cyst formation, and seromas has also been postulated.

### **Policy:**

#### **Effective for dates of service on or after January 31, 2014:**

**Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in skeletally mature patients:**

- For anterior lumbar interbody fusion procedures when use of autograft is unfeasible; or
- For instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is unfeasible\*; or

- For the treatment of acute, open fracture of the tibial shaft, when use of autograft is unfeasible.

**Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:**

- As an alternative to autograft in compromised patients (e.g., osteoporosis, tobacco use, or diabetes) requiring noninstrumented revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible\* or are not expected to promote fusion.
- For recalcitrant\*\* long-bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed.\*\*\*

**Bone morphogenetic protein (rhBMP-2 or rhBMP-7) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other indications, including but not limited to spinal fusion when use of autograft is feasible.**

\*Use of iliac crest bone graft (ICBG) may be considered unfeasible due to situations that may include, but are not limited to, prior harvesting of ICBG or need for a greater quantity of ICBGH than available (e.g., for multi-level fusion).

\*\*A recalcitrant nonunion would thus be considered to be a non-union with a larger fracture gap (e.g., greater than 1 cm) or a non-union that has persisted for a longer duration of time with no response to conservative treatment (e.g., 3 months of ultrasound or electrical stimulation).

\*\*\*FDA approved under a Humanitarian Device Exemption (HDE)

**Effective for dates of service on or after December 1, 2013 through January 30, 2014:**

**Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:**

- For anterior lumbar interbody fusion procedures when use of \*autograft is unfeasible.
- For instrumented posterolateral intertransverse spinal fusion procedures when use of \*autograft is unfeasible.

**Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:**

- For revision posterolateral intertransverse lumbar spinal fusion, when use of \*autograft is unfeasible.
- For recalcitrant long-bone nonunions where\*use of autograft is unfeasible and alternative conservative treatments have failed.

\*Use of iliac crest bone graft (ICBG) may be considered unfeasible due to situations that may include, but are not limited to, prior harvesting of ICBG or need for a greater quantity of ICBGH than available (e.g., for multi-level fusion).

**Bone morphogenetic protein (rhBMP-2 or rhBMP-7) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other indications, including but not limited to spinal fusion when use of autograft is feasible.**

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**Effective for dates of service on or after April 7, 2013 through November 30, 2013:**

**Use of recombinant human bone morphogenetic protein-2 (rhBMP, InFUSE) meets** Blue Cross and Blue Shield of Alabama's medical criteria for the following indications:

- For anterior spinal interbody fusion procedures, in conjunction with an FDA-approved interbody fusion device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1. Patients should have failed at least 6-months of conservative treatment\*;
- For instrumented posterolateral intertransverse spinal fusion procedures, in conjunction with an FDA-approved device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1. Patients should have failed at least six months of conservative treatment;
- For the treatment of acute, open fracture of the tibial shaft\*\*.

**Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications:

- As an alternative to autograft in compromised patients (e.g., osteoporosis, tobacco use, or diabetes) requiring noninstrumented revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion\*\*\*;
- As an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed\*\*\*.

**Bone morphogenetic protein (rhBMP-2 or RhBMP-7) does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered investigational for all other indications, including but not limited to:

- Cervical spinal fusion;
- Posterior or transforaminal lumbar interbody spinal fusion;
- As initial treatment or revision of noninstrumented posterolateral intertransverse spinal fusion that does not meet the criteria listed above;
- As an alternative or adjunct to bone grafting in other locations, including craniomaxillofacial\*\* surgeries.

Both OP-1 and InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion device are contraindicated in patients who:

- Are pregnant;
- May be allergic to any of the materials contained in the devices;
- Have an infection near the area of the surgical incision;
- Have had a tumor removed from the area of the implantation site or currently have a tumor in that area;
- Are skeletally immature.

\*FDA approved for one level

\*\*FDA approved indication

\*\*\*FDA approved under a Humanitarian Device Exemption (HDE)

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**Effective for dates of service on or after July 1, 2009 through April 6, 2013:**

**Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications:

- Anterior spinal interbody fusion procedures, in conjunction with an FDA-approved interbody fusion device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1 when the patients have had at least six months of conservative treatment\*;
- Instrumented posterolateral intertransverse spinal fusion procedures, in conjunction with an FDA-approved device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1 when patients have failed at least six months of conservative treatment;
- Treatment of acute, open fracture of the tibial shaft\*\*.

**Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications:

- As an alternative to autograft in compromised patients (e.g., osteoporosis, tobacco use, or diabetes) requiring non-instrumented revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion\*\*\*;
- As an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed\*\*\*.

**Use of recombinant human bone morphogenetic protein (rhBMP-2 or rhBMP-7) does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered investigational for all other indications, including but not limited to:

- Posterior or transforaminal interbody spinal fusion;
- Initial treatment or revision of non-instrumented posterolateral intertransverse spinal fusion that does not meet the criteria listed above;
- An alternative or adjunct to bone grafting in other locations, including craniomaxillofacial\*\* surgeries.

Both OP-1 and InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion device are contraindicated in patients who:

- Are pregnant;
- May be allergic to any of the materials contained in the devices;
- Have an infection near the area of the surgical incision;
- Have had a tumor removed from the area of the implantation site or currently have a tumor in that area;
- Are skeletally immature.

\*FDA approved for one level

\*\*FDA approved indication

\*\*\*FDA approved under a Humanitarian Device Exemption (HDE)

***Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.***

### **Key Points:**

The most recent literature update was through October 2013.

At the time this policy was created, randomized clinical trials supported the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in the treatment of anterior interbody spinal fusion when used in conjunction with a tapered cage and also in the treatment of open tibial fractures. In addition, a randomized study supported the use of rhBMP-7 in the treatment of recalcitrant nonunions of the long bones. It should be noted that the majority of trials were designed to show that use of rhBMP is equivalent (not superior) to autologous bone grafting. Although the proposed advantage of rhBMP is the elimination of a separate incision site required for harvesting of autologous bone graft and the associated pain and morbidity secondary to this procedure, a 2011 study by Howard and colleagues raises questions about the magnitude of pain observed with iliac crest bone graft (ICBG) harvesting. In this study, 112 patients who had an instrumented posterolateral lumbar fusion at one or two levels were seen at a tertiary spine center for a routine postoperative visit. ICBG was harvested in 53 patients (47.3%) through the midline incision used for lumbar fusion and rhBMP-2 was used in 59 patients (52.7%) with no graft harvest. An independent investigator who was not directly involved in the care of the patient and was unaware of the type of bone graft used in the fusion examined the patient for tenderness over the surgical site, as well as the left and right posterior iliac crest. At a mean follow-up of 41 months (range 6 to 211 months), there was no significant difference between the groups in the proportion of patients complaining of tenderness over either iliac crest (3.8 vs. 3.6 on a 10-point scale). While 54% of patients complained of tenderness over one or both iliac crests, only 10 patients (9% of 112) had pain over the same crest from which the graft was harvested (mean pain score of 4.4).

### **Spinal Fusion**

In 2013, two systematic reviews on the effectiveness and harms of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spine fusion were published. These two systematic reviews of patient-level data followed a 2011 U.S. Senate investigation of industry influence on Infuse clinical studies and a systematic review by Carragee and colleagues of emerging safety

concerns with rhBMP-2. The systematic review by Carragee et al compared conclusions regarding safety and efficacy from the 13 published rhBMP-2 industry-sponsored trials with available U.S. Food and Drug Administration (FDA) data summaries, subsequent studies, and databases. Evaluation of the original trials suggested methodologic bias against the control group in the study design (discarding local bone graft and failure to prepare facets for arthrodesis) and potential bias (overestimation of harm) in the reporting of iliac crest donor site pain. Comparison between the published studies and FDA documents revealed internal inconsistencies and adverse events that were not reported in the published articles.

Both of the 2013 studies conducted meta-analyses on individual patient data, both published and unpublished, that was provided by the manufacturer through the Yale University Open Data Access (YODA) Project. One meta-analysis was conducted by Simmonds and colleagues from the University of York in the United Kingdom; the other was by Fu and colleagues from the Oregon Health and Science University.

The meta-analysis by Simmonds et al included patient-level data from 12 randomized controlled trials (RCTs, n=1,408), regardless of spinal level or surgical approach, and adverse event data from an additional 35 observational studies. rhBMP-2 increased the rate of radiographic fusion by 12% compared to ICBG, with substantial heterogeneity across trials. A small improvement in the Oswestry Disability Index (ODI, 3.5 percentage points) did not reach the previously defined threshold for a clinically significant effect. The review also found a small improvement in back pain (one point on a 20-point scale) and SF-36 physical component score (PCS, 1.9 percentage points). There was no significant difference between the groups for leg pain. There was a potential for bias in the pain and functional outcomes since outcomes were patient-reported and patients were not blinded to the treatment received. Overall, the increase in successful fusion at up to 24 months did not appear to be associated with a clinically significant reduction in pain.

The meta-analysis by Fu et al included individual-patient data from 13 RCTs (n=1,981) and 31 cohort studies. The review found moderate evidence of no consistent differences between rhBMP-2 and ICBG in overall success, fusion rates, or other effectiveness measures for anterior lumbar interbody fusion (ALIF) or posterolateral fusion (PLF). A small RCT and three cohort studies revealed no difference in effectiveness outcomes between rhBMP and ICBG for anterior cervical fusion. Reporting in the original published trials was found to be biased, with journal publications selecting analyses and results that favored rhBMP over ICBG.

Both studies found that cancer risk may be increased with rhBMP-2, although the number of events was low and there was heterogeneity in the types of cancer. In the Simmonds analysis, combined analysis revealed a relative risk of 1.84 for cancer in the BMP group, but this increased rate did not reach statistical significance (95% CI: 0.81 to 4.16). Fu et al performed a combined analysis of cancer incidence at 24 months and 48 months post-treatment. At 24 months, there was a significant increase in cancer for the BMP group (risk ratio [RR]: 3.45, 95% CI: 1.98 to 6.0), and at 48 months, there was a smaller increase that did not reach statistical significance (RR: 1.82, 95% CI: 0.84 to 3.95).

Other adverse events were also increased for the BMP group. Simmonds et al found a higher incidence of early back and leg pain with rhBMP-2 in the analysis of patient-level data. The

studies consistently reported increased rates of heterotopic bone formation, leg pain/radiculitis, osteolysis and dysphagia, but combined analysis for these outcomes was not performed. The Fu study reported that BMP-2 was associated with a non-significantly increased risk for urogenital problems when used for anterior lumbar fusion and an increased risk for wound complications and dysphagia when used for anterior cervical spine fusion. Fu et al documented that the information on adverse events in the published literature was incomplete in comparison to the total amount of information available.

Off-label use of BMP can include multiple levels and dosages greater than the FDA-approved dose of rhBMP-2 for single level fusion. In 2013, Carragee et al assessed cancer risk after high dose rhBMP-2 (40 mg) using publicly available data from the pivotal, multi-center, randomized controlled trial of AMPLIFY (n=463). The study found an increase in the incidence of cancer, a reduction in the time to first cancer, and a greater number of patients with multiple cancers. For example, at two years there were 15 new cancer events in 11 patients in the rhBMP-2 group compared with two new cancer events in two patients treated with autogenous bone graft, with an incidence rate ratio of 6.75. When calculated in terms of the number of patients with one or more cancer events two years after surgery, the incidence rate per 100 person-years was 2.54 in the rhBMP-2 group compared with 0.50 in the control group and the incidence rate ratio was 5.04. The mean time to development of cancer was 17.5 months after use of rhBMP-2 compared with 31.8 months in the controls. Three patients in the rhBMP-2 group and none in the control group developed multiple new cancers.

### **Long-Bone Fractures and Nonunions**

A 2010 Cochrane review evaluated the effectiveness and costs of rhBMP on fracture healing in acute fractures and nonunions compared with standards of care. The literature was searched to October 2008, and 11 RCTs (976 participants) and four economic evaluations were included in the review. The times to fracture healing were comparable between the rhBMP and control groups. There was some evidence for increased healing rates, mainly for open tibial fractures without secondary procedures (risk ratio [RR]: 1.19). Three trials indicated that fewer secondary procedures were required for acute fractures treated with rhBMP (RR: 0.65). The authors concluded that limited evidence suggests that rhBMP may be more effective than standard of care for acute tibial fracture healing; however, the use of rhBMP for treating nonunion remains unclear (RR: 1.02).

### **Oral and Maxillofacial Procedures**

A 2010 AHRQ technology assessment on the state of the evidence of on-label and off-label use of rhBMP included the following conclusions:

- The strength of the body of evidence on clinical outcomes is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone.
- There is moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Through April 30, 2011, the FDA's Manufacturer and User Facility Device Experience (MAUDE) received 83 reports of adverse events involving rhBMP-2 in oral and maxillofacial operations. rhBMP-2 was used off-label in 66.3% of these cases and included reconstruction of



the mandible after fracture or cancer and alveolar cleft repair. The most frequently reported adverse events were local edema/pain, surgical site infections/wound complications, and graft failure.

Overall, the evidence does not support a health benefit of rhBMP in oral and maxillofacial procedures.

### **Additional Applications**

There has been research interest in the following applications: management of early stages of osteonecrosis of the vascular head, as an adjunct to hip arthroplasty to restore bone defects in the acetabulum or femoral shaft, and as an adjunct to distraction osteogenesis (i.e., Ilizarov procedure). The literature regarding these applications consists of small case series; no controlled trials have been identified.

### **Summary**

In 2013, two systematic reviews on recombinant human bone morphogenetic protein-2 (rhBMP-2) that used manufacturer-provided individual patient data were published. Overall, these systematic reviews found little to no benefit of rhBMP-2 over iliac crest bone graft for spinal fusion, with an uncertain risk of harm. The small benefits reported do not support the widespread use of rhBMP-2, but do leave the possibility that rhBMP-2 may lead to clinically significant improvements in selected subgroups, such as patients in whom use of iliac crest bone graft (ICBG) is unfeasible and have a high risk of fusion failure. While there was a low adverse event rate overall, concerns remain about the possibility of increased adverse event rates with rhBMP-2, including cancer. Based on this new evidence, it is not possible to conclude that the small benefits of rhBMP-2 outweigh the risks. In cases where use of ICBG is not feasible, such as when previous bone harvest has been performed, the benefit of rhBMP in promoting fusion will likely outweigh the adverse effects.

The U.S. Food and Drug Administration's humanitarian device exemptions (HDE) for rhBMP-7 state that use is restricted to patients in whom autologous bone and bone marrow harvest are not feasible or are not expected to promote to promote fusion. Therefore, the policy on rhBMP-7 remains unchanged.

Use of rhBMP has not been shown to be as beneficial as the established alternative (ICBG) and evidence is insufficient to permit conclusions concerning the effect of rhBMP for other indications, including but not limited to:

- Cervical spinal fusion;
- Posterior or transforaminal lumbar interbody spinal fusion (this is considered investigational because of safety concerns related to ectopic bone formation in the spinal canal);
- Treatment of noninstrumented posterolateral intertransverse spinal fusion when autograft is feasible and expected to promote fusion;
- As an alternative or adjunct to bone grafting in other locations, including craniomaxillofacial surgeries.

**Key Words:**

Bone morphogenetic protein, BMP, InFUSE<sup>®</sup>, OP-1, bone morphogenetic protein-2, rhBMP-2, bone morphogenetic protein-7, rhBMP-7, InFUSE<sup>™</sup> Bone Graft/LT-CAGE<sup>™</sup>, InFUSE<sup>™</sup> Bone Graft/INTER FIX<sup>™</sup> Threaded Fusion Device, OP-1 Implant, OP-1 Putty, osteobiologics, BMP-7, BMP, Recombinant human bone morphogenetic protein

**Approved by Governing Bodies:**

Two rhBMPs and associated carrier/delivery systems have received approval from the U.S. Food and Drug Administration (FDA). The InFUSE<sup>®</sup> system consists of rhBMP-2 on an absorbable collagen sponge carrier. OP-1<sup>®</sup> consists of rhBMP-7 and bovine collagen, which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms putty.

1. InFUSE<sup>®</sup> Bone Graft in conjunction with one of two interbody fusion devices, i.e., either the LT-Cage Lumbar Tapered Fusion Device or the Inter Fix RP Threaded Fusion device. This device received FDA approval through the premarket approval (PMA) process:
  - a. The device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit, and/or neurologic deficit and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level or retrolisthesis. The InFUSE<sup>®</sup> Bone Graft/LT-CAGE<sup>™</sup> devices are to be implanted via an anterior open or a laparoscopic approach. The InFUSE<sup>®</sup> Bone Graft/INTER FIX<sup>™</sup> Threaded Fusion Device; and InFUSE<sup>®</sup> Bone Graft/INTER FIX<sup>™</sup> RP Threaded Fusion Device are to be implanted via an anterior open approach only. Patients receiving the InFUSE<sup>®</sup> Bone Graft/Interbody Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE<sup>™</sup> Bone Graft/Interbody Fusion Device. (Note: A collagen sponge consists of the carrier, while the interbody fusion device is a delivery system. Use with posterior or transforaminal lumbar interbody fusion is considered off-label.)
  - b. For the treatment of acute, open fractures of the tibial shaft.
  - c. For sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. (P050053, March 2007)
2. OP-1<sup>®</sup> (Stryker Biotech, Hopkinton, MA) has received two FDA approvals through the Humanitarian Device Exemption (HDE) process. HDE is available to devices intended for fewer than 4,000 patients per year; as part of this process, the manufacturer is not required to demonstrate unequivocal benefit but only “probable” benefit. OP-1 received the following labeled indications:
  - a. “OP-1<sup>®</sup> Implant is indicated for use as an alternative to autograft in recalcitrant long-bone nonunions where use of autograft is unfeasible and alternative treatments have failed.”
  - b. “OP-1<sup>®</sup> Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for which autologous bone and bone marrow harvest are not feasible or are not

expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.”

Stryker Biotech recently sought FDA permission to expand use of OP-1 Putty to include use in uninstrumented posterolateral lumbar spinal fusion for the treatment of lumbar spondylolisthesis. In March 2009, an FDA advisory committee voted 6 to 1 against recommending the expanded approval.

Both OP-1<sup>®</sup> and InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion device are contraindicated in patients who are pregnant, may be allergic to any of the materials contained in the devices, have an infection near the area of the surgical incision, have had a tumor removed from the area of the implantation site or currently have a tumor in that area, or who are skeletally immature.

In July 2008, the FDA issued a public health notification regarding life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. The FDA has received reports of complications with the use of rhBMP in cervical spine fusion. These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurologic structures in the neck. Some reports describe difficulty swallowing, breathing, or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature. As stated in the public health notification, the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated, and these products are not approved by the FDA for this use.

In 2011, Medtronic received a “nonapprovable letter” from the FDA for AMPLIFY. The AMPLIFY rhBMP-2 Matrix utilizes a higher dose of rhBMP (2.0 mg/mL) with a compression-resistant carrier and is being evaluated for posterolateral fusion of single level lumbar (L2–S1) degenerative disc disease.

### **Benefit Application:**

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.

### **Current Coding:**

There is not CPT or HCPCS code for bone morphogenetic protein. In 2011, CPT code 20930 was revised to include BMP-type materials used in spine surgery.

<b>CPT:</b>	<b>20930</b>	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
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In the setting of spinal fusion, bone morphogenetic proteins may be used primarily as an alternative to autologous bone grafting. Since harvesting of autologous bone graft is coded separately from the fusion procedure (i.e., CPT codes 20936-20938), when bone morphogenetic protein is used as an alternative to the bone graft, these codes should no longer be reported. In contrast, the CPT code for treating tibial fracture nonunions with autograft (i.e., CPT code 27724) includes the harvesting component, and, therefore, when bone morphogenetic protein is used as an alternative in this setting, presumably the associated physician's work would be decreased, since no autologous harvest is required.

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### **Policy History:**

Medical Policy Group, July 2004 (2)

Medical Policy Administration Committee, August 2004

Available for comment August 11-September 24, 2004

Medical Policy Group, July 2006 (1)

Medical Policy Group, July 2008 (1)  
 Medical Policy Panel, June 2009  
 Medical Policy Group, June 2009 (2)  
 Medical Policy Administration Committee, July 2009  
 Available for comment July 2-August 15, 2009  
 Medical Policy Group, August 2010 (2)  
 Medical Policy Administration Committee, September 2010  
 Available for comment September 4-October 18, 2010  
 Medical Policy Group, October 2010  
 Medical Policy Panel, November 2012  
 Medical Policy Group, January 2013 (2): Policy statement excluding coverage for cervical fusion added. Key Points, Approved by Governing Bodies, References updated to reflect changes. Information regarding high-risk patients for fusion added to Key Points  
 Medical Policy Administration Committee, February 2013  
 Available for comment February 21 through April 7, 2013  
 Medical Policy Panel, September 2013  
 Medical Policy Group, September 2013 (2): Policy statement changed to coverage when harvesting of iliac crest bone graft bone is unfeasible. Description, Key Points, References updated to support policy changes. CPT code added. ICD-10-PC code added. Deleted coverage statements prior to 2009.  
 Medical Policy Group, October 2013 (2): Removed ICD-9 Procedure codes; no change to policy statement.  
 Medical Policy Administration Committee, October 2013  
 Available for comment October 16 through November 30, 2013  
Medical Policy Panel, November 2013  
Medical Policy Group, November 2013 (2): Policy updated with literature review through October 2013. Added coverage for treatment of tibial shaft with BMP-2 (when autograft is unfeasible). Returned to use of FDA language regarding treatment of noninstrumented revision posterolateral intertransverse lumbar spinal fusion with BMP-7 where use of autograft is unfeasible. Additional instructions added to Coding section. Key Points and References updated to support policy changes.  
Medical Policy Administration Committee, December 2013  
Available for comment December 17, 2013 through January 30, 2014

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*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*