Policy Statement

Use of recombinant human bone morphogenetic protein-2 (rhBMP-2; Infuse®) may be considered **medically necessary** in skeletally mature patients for **any** of the following:

- Anterior lumbar interbody fusion procedures when the use of autograft is not feasible
- Instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible
- The treatment of acute, open fracture of the tibial shaft, when the use of autograft is not feasible

Use of recombinant human bone morphogenetic protein (rhBMP-2) is considered **not medically necessary** for all other indications, including but not limited to:

- Craniomaxillofacial surgery
- Spinal fusion when the use of autograft is feasible

Policy Guidelines

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

Coding

There is no specific CPT or HCPCS code for bone morphogenetic protein (BMP). In 2011, CPT code 20930 was revised to include BMP-type materials used in spine surgery:

- **20930**: Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)

For spinal fusion, BMPs may be used primarily as an alternative to autologous bone grafting. Because harvesting of autologous bone graft is coded separately from the fusion procedure (i.e., CPT codes 20936-20938), when BMP 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 BMP is used as an alternative in this setting, presumably the associated physician’s work would be decreased because no autologous harvest is required. Finally, for treatment of acute, open tibial fractures, BMP is not used as an alternative to autologous bone graft, but in addition to standard treatment with an intramedullary nail.

ICD-10-PCS procedure codes 3E0U0GB, 3E0U3GB, 3E0V0GB, and 3E0V3GB explicitly identify the use of BMP in open or percutaneous procedures on joints and bones.

Description

Two recombinant human bone morphogenetic proteins (rhBMPs) have been extensively studied: rhBMP-2, applied with an absorbable collagen sponge (Infuse®), and rhBMP-7, applied in putty (OP-1). These protein products have been investigated as alternatives 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.
Related Policies

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Electrical Bone Growth Stimulation of the Appendicular Skeleton
- Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures
- Ultrasound Accelerated Fracture Healing Device

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The INFUSE® Bone Graft product (Medtronic) consists of rhBMP-2 on an absorbable collagen sponge carrier; it is used in conjunction with several carrier and delivery systems. The INFUSE® line of products has been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process (see summary of key approvals in Table 1). FDA product code: NEK.

In 2008, the FDA issued a public health notification on life-threatening complications associated with rhBMP in cervical spine fusion, based on reports of complications with use of rhBMP in cervical spine fusion.1 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 described 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 efficacy of rhBMP in the cervical spine have not been demonstrated. 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 uses a higher dose of rhBMP (2.0 mg/mL) with a compression-resistant carrier.

OP-1® Putty (Stryker Biotech), which consists of rhBMP-7 and bovine collagen and carboxymethylcellulose, forms a paste or putty when reconstituted with saline. OP-1® Putty was initially approved by the FDA through the humanitarian device exemption process (H020008) for 2 indications:

“OP-1 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.”

FDA product code: MPW.

“OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom 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.”

FDA product code: MPY.
Stryker Biotech sought the FDA permission to expand the use of OP-1® Putty to include uninstrumented posterolateral lumbar spinal fusion for the treatment of lumbar spondylolisthesis.

In 2009, the FDA Advisory Committee voted against the expanded approval. Olympus Biotech (a subsidiary of Olympus Corp.) acquired OP-1® assets in 2010. In 2014, Olympus closed Olympus Biotech operations in the United States and discontinued domestic sales of Olympus Biotech products. The rhBMP-7 product is no longer marketed in the U.S.

Table 1. rhBMP Products and Associated Carrier and Delivery Systems Approved by the FDA

<table>
<thead>
<tr>
<th>Systems</th>
<th>Manufacturer</th>
<th>Approved</th>
<th>PMA No.</th>
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<tbody>
<tr>
<td>INFUSE® Bone Graft</td>
<td>Medtronic</td>
<td>03/07</td>
<td>P050053</td>
</tr>
<tr>
<td>• Alternative to autogenous bone graft for sinus augmentations</td>
<td></td>
<td></td>
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<tr>
<td>• For localized alveolar ridge augmentations in extraction socket defects</td>
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<tr>
<td>INFUSE® Bone Graft</td>
<td>Medtronic</td>
<td>10/09</td>
<td>P050053/S012</td>
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<tr>
<td>• Expanded indication for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Expanded indication for acute, open tibial shaft fractures stabilized with nail fixation</td>
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<tr>
<td>INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device</td>
<td>Medtronic Sofamor Danek USA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>07/02</td>
<td>P000058</td>
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<tr>
<td>• Indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Up to grade 1 spondylolisthesis at involved level</td>
<td></td>
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<tr>
<td>• Implantation via anterior open or anterior laparoscopic approach</td>
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<tr>
<td>INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device</td>
<td></td>
<td>07/04</td>
<td>P000058/S002</td>
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<tr>
<td>• Extension of device use from L2 to S1</td>
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<td></td>
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<tr>
<td>• May be used with retrololisthesis</td>
<td></td>
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<tr>
<td>INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device</td>
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<td>10/09</td>
<td>P000058/S033</td>
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<tr>
<td>• Indicated for acute, open tibial shaft fractures stabilized with nail fixation</td>
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<tr>
<td>• Alternative to autogenous bone graft for sinus augmentations</td>
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<tr>
<td>• For localized alveolar ridge augmentations in extraction socket defects</td>
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<td></td>
<td></td>
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<tr>
<td>INFUSE™ Bone Graft/Medtronic Interbody Fusion Device (Marketing name change)</td>
<td></td>
<td>12/15</td>
<td>P000058/S059</td>
</tr>
<tr>
<td>• Expanded indication for 2 additional interbody fusion devices</td>
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<td></td>
<td></td>
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<tr>
<td>• Perimeter Interbody Fusion Device implanted via retroperitoneal ALIF L2 to S1 or OLIF L5 to S1</td>
<td></td>
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<tr>
<td>• Clydesdale Spinal System implanted via OLIF at single level from L2-S5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>INFUSE™ Bone Graft/Medtronic Interbody Fusion Device</td>
<td></td>
<td>09/17</td>
<td>P000058/S065</td>
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<tr>
<td>• Expanded indication for 2 additional interbody fusion devices:</td>
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<tr>
<td>o Divergence-L Anterior/Oblique Lumbar Fusion System</td>
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<tr>
<td>o Pivox™ Oblique Lateral Spinal System</td>
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</table>

ALIF: anterior lumbar interbody fusion; FDA: Food and Drug Administration; OLIF: oblique lateral interbody fusion; PMA: premarket approval; rhBMP: recombinant human bone morphogenetic protein; S: supplement.

<sup>a</sup> Medtronic is the manufacturer for all of the INFUSE bone graft and carrier systems.

Rationale

Background

Bone Morphogenetic Protein and Carrier and Delivery Systems

Bone morphogenetic proteins are members of the transforming growth factors family. At present, some 20 bone morphogenetic proteins have been identified, all with varying degrees of tissue-stimulating properties.
The recombinant human bone morphogenetic proteins (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, 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 provide mechanical support.

Applications
The carrier and delivery system are important variables in the clinical use of rhBMPs, and different clinical applications (e.g., long-bone nonunion, 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), while rhBMP in a collagen sponge with bone dowels or interbody cages are used for interbody spinal fusion. Also, interbody fusion of the lumbar spine can be approached from an anterior (anterior lumbar interbody fusion), lateral, or posterior direction (posterior lumbar interbody fusion or transforminal lumbar interbody fusion; see Appendix). Surgical procedures may include decompression of the spinal canal and insertion of pedicle screws and rods to increase the stability of the spine.

Posterior approaches (posterior lumbar interbody fusion, transforminal lumbar interbody fusion) 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 spine stabilization. Such approaches are differentiated from instrumented or noninstrumented posterolateral fusion, 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.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function— including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

When this evidence review was created, RCTs supported the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in the treatment of anterior interbody spinal fusion when used with a tapered cage and in the treatment of open tibial fractures. A randomized study reported by Govender et al (2002) supported the use of rhBMP-7 in the treatment of recalcitrant nonunions of the long bones. It should be noted that most of these trials were designed to show...
that use of rhBMP was equivalent (not superior) to autologous bone grafting. The proposed advantage of rhBMP is the elimination of a separate incision site to harvest autologous bone graft and the associated pain and morbidity. However, Howard et al (2011) raised 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 1 or 2 levels were seen at a tertiary spine center for a routine postoperative visit. ICBG was harvested in 53 (47.3%) patients through the midline incision used for lumbar fusion, and rhBMP-2 was used in 59 (52.7%) patients with no graft harvest. An independent investigator, not directly involved in patient care and was unaware of the type of bone graft used in the fusion, examined each 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, 6-211 months), there was no significant difference between the groups in the proportion of patients complaining of tenderness over either iliac crest (mean pain score, 3.8 vs 3.6 on a 10-point scale). While 54% of patients complained of tenderness over 1 or both iliac crests, only 10 (9%) of 112 patients had pain over the crest from which the graft was harvested (mean pain score, 4.4).

Lumbar Spinal Fusion
Clinical Context and Therapy Purpose
The purpose of rhBMP is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as allograft bone or synthetic bone substitute, in patients with who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible.

The question addressed in this evidence review is: does the use of BMP improve the net health outcome in individuals who are undergoing spinal fusion when an autograft is not feasible?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible.

Interventions
The therapy being considered is rhBMP. Two rhBMPs have been extensively studied: rhBMP-2, applied with an absorbable collagen sponge (Infuse), and rhBMP-7, applied in putty (OP-1). These protein products have been investigated as alternatives to bone autografting.

Comparators
Comparators of interest include allograft bone or synthetic bone substitute. Allograft bone is obtained from a donor for use in grafting procedures, such as a spine fusion surgery. The donor bone graft acts as a temporary calcium deposit on which a patient's own bone eventually grows and replaces in the bone-fusing process called "creeping substitution." This is managed by an orthopedic surgeon and primary care providers in an inpatient surgical setting.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, and treatment-related morbidity. Negative outcomes of interest the potential for heterotopic bone formation, leg pain/radiculitis and, osteolysis.

Timing
The existing literature evaluating rhBMP as a treatment for patients who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible has varying lengths of follow-up. At least one year of follow-up is desirable to adequately evaluate outcomes.

Setting
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Patients with who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible are actively managed by neurosurgeons, orthopedic surgeons, physical therapists and primary care providers in an outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
- **Methodologically credible studies** were selected using the following principles:
  - To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
  - In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
  - To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
  - Studies with duplicative or overlapping populations were excluded.

**Food and Drug Administration-Approved Uses of rhBMP-2**

**Systematic Reviews**
Two meta-analyses, assessing the effectiveness and harms of rhBMP-2 in spine fusion were published following a 2011 U.S. Senate investigation of industry influence on the INFUSE clinical studies and a systematic review by Carragee et al (2011) of emerging safety concerns with rhBMP-2. The systematic review by Carragee et al (2011) compared conclusions about safety and efficacy from the 13 published rhBMP-2 industry-sponsored trials with available 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 the FDA documents revealed internal inconsistencies and adverse events not reported in the published articles.

Both meta-analyses assessed individual patient-level data, published and unpublished, provided by the manufacturer through the Yale University Open Data Access Project. One meta-analysis was conducted by Simmonds et al (2013) and the other by Fu et al (2013).

**Simmonds et al (2013)** included patient-level data from 12 RCTs (total n=1408 patients), regardless of spinal level or surgical approach, and adverse event data from an additional 35 observational studies. Use of rhBMP-2 increased the rate of radiographic fusion by 12% compared with ICBG, with substantial heterogeneity across trials. A small improvement in the Oswestry Disability Index score (3.5 percentage points) fell below the previously defined threshold for a clinically significant effect. Reviewers also found a small improvement in back pain (1 point on a 20-point scale) and 36-Item Short-Form Health Survey Physical Component Summary score (1.9 percentage points). There was no significant difference between groups for leg pain. There was a potential for bias in the pain and functional outcomes because outcomes were patient-reported and patients were not blinded to the treatment received. Overall, the increase in successful fusion rate at up to 24 months did not appear to be associated with a clinically significant reduction in pain.

The systematic review by Fu et al (2013) included individual patient-level data from 13 RCTs (total n=1981 patients) and 31 cohort studies. Reviewers 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 or posterolateral fusion. A small RCT and three cohort studies revealed no difference in effectiveness outcomes between rhBMP and ICBG for anterior cervical fusion. Reporting in the originally published trials was found to be biased with the publications selecting analyses and results that favored rhBMP over ICBG.

Both meta-analyses suggested that cancer risk might be increased with rhBMP-2, although the number of events was low and there was heterogeneity in the types of cancer. In the Simmonds et al (2013) trial, the combined analysis revealed a relative risk (RR) of 1.84 (95%
confidence interval, 0.81 to 4.16) for cancer in the BMP group but this increased rate was not statistically significant. Fu et al (2013) performed a combined analysis of cancer incidence at 24 and 48 months posttreatment. At 24 months, there was a statistically significant increase in cancer for the BMP group (RR=3.45; 95% confidence interval, 1.98 to 6.0); at 48 months, the increase was not statistically significant (RR=1.82; 95% confidence interval, 0.84 to 3.95).

Other adverse events were increased for the BMP group. Simmonds et al (2013) found a higher incidence of early back and leg pain with rhBMP-2. The individual publications consistently reported higher rates of heterotopic bone formation, leg pain/radiculitis, osteolysis, and dysphagia but combined analysis for these outcomes was not performed. Fu et al (2013) reported that rhBMP-2 was associated with a statistically nonsignificant increase in the risk for urogenital problems when used for anterior lumbar fusion and an increase in the risk for wound complications and dysphagia when used for anterior cervical spine fusion. Fu et al (2013) also noted that the data on adverse events in the published literature was incomplete compared with the total amount of data available.

Off-Label Use of BMP in Lumbar Spinal Fusion
Off-label use of BMP can include multiple levels and dosages greater than the FDA-approved dose of rhBMP-2 for single-level fusion. Carragee et al (2013) assessed cancer risk after high-dose rhBMP-2 (40 mg) using publicly available data from the pivotal, multicenter RCT 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 2 years, there were 15 new cancer events in 11 patients in the rhBMP-2 group compared with 2 new cancer events in 2 patients treated with autogenous bone graft (incidence rate ratio, 6.75). When calculated in terms of the number of patients with 1 or more cancer events 2 years after surgery, the incidence rate per 100 person-years was 2.54 in the rhBMP-2 group and 0.50 in the control group (incidence rate ratio, 5.04). The mean time to development of cancer was 17.5 months after use of rhBMP-2 and 31.8 months in the controls. Three patients, all in the rhBMP-2 group, developed multiple new cancers.

Zadegan et al (2017) conducted a systematic review and meta-analysis investigating the off-label uses of rhBMP. Reviewers evaluated the evidence for rhBMP-2 and rhBMP-7 in anterior cervical spine fusions. A literature search returned 18 articles (total n=4782 patients). Reviewers specifically assessed rhBMP for fusion rates, adverse events and complication rates. The fusion rate was higher in rhBMP than in alternative treatments such as bone grafting. However, serious complications (e.g., cervical swelling, dysphagia/dysphonia, ossification) occurred more frequently in rhBMP procedures than in any other treatment alternative.

Observational Studies
In a retrospective cohort study, Khan et al (2018) investigated the effectiveness and safety of using rhBMP-2 in transformaminal lumbar interbody fusions. The authors compared rhBMP-2 with bone autograft by reviewing data on 191 patients undergoing anteroposterior instrumented spinal fusion with transformaminal lumbar interbody fusion from 1997 to 2014 at a single institution. Patients were separated into 2 treatment groups: 83 patients were treated with rhBMP-2 (BMP group) and 104 patients were treated with bone grafting (non-BMP group. Results were similar between groups; fusion rates were 92.7% and 92.3% for BMP and non-BMP patients, respectively. Seven patients in the BMP group and two patients in the non-BMP group experienced radiculitis. Seroma was observed in two patients in the BMP group; it was not observed in any patients in the non-BMP group. Given these very small differences, the authors concluded that rhBMP-2 is a comparable treatment option to bone grafting in transformaminal lumbar interbody fusion procedures.

Section Summary: Lumbar Spinal Fusion
The evidence on the effectiveness and potential harms of rhBMP-2 and rhBMP-7 in spinal fusion consists of RCTs, systematic reviews, meta-analyses, and observational studies. The fusion rates
with the use of rhBMP are comparable to bone autograft. There is evidence that specific complication rates are higher with rhBMP.

**Tibial Fractures and Nonunions**

**Clinical Context and Therapy Purpose**
The purpose of rhBMP is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as plate or intramedullary nail, in patients who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible.

The question addressed in this evidence review is: does the use of BMP improve the net health outcome in individuals who are undergoing surgery for acute tibial shaft fracture when an autograft is not feasible?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals who are undergoing surgery for a acute tibial shaft fracture and in whom autograft is not feasible.

**Interventions**
The therapy being considered is rhBMP. Two rhBMPs have been extensively studied: rhBMP-2, applied with an absorbable collagen sponge (Infuse), and rhBMP-7, applied in putty (OP-1). These protein products have been investigated as alternatives to bone autografting in internal fixation of fractures.

**Comparators**
Comparators of interest include plate or intramedullary nail. An intramedullary rod, also known as an intramedullary nail or inter-locking nail or Küntscher nail (without proximal or distal fixation), is a metal rod forced into the medullary cavity of a bone. Intramedullary nails have long been used to treat fractures of long bones of the body. This is managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are symptoms, morbid events, functional outcomes, and treatment-related morbidity.

**Timing**
The existing literature evaluating rhBMP as a treatment for patients who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible has varying lengths of follow-up. At least six months of follow-up is desirable to adequately evaluate outcomes.

**Setting**
Patients who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible are actively managed by orthopedic surgeons or general surgeons.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.
Dai et al (2015) published a meta-analysis on rhBMP for the healing of acute tibial fractures (4 RCTs; n=868 patients) and nonunions (4 RCTs; n=245 patients). For acute tibial fractures, three RCTs were conducted with rhBMP-2 and one with rhBMP-7. All included studies were conducted over a decade ago. Use of rhBMP was associated with a higher rate of union (RR=1.16) and a lower rate of revision (RR=0.68) than controls (3 trials with soft-tissue management, 1 with intramedullary nail plus autograft). There was no significant difference between the BMP and control groups for hardware failure or infection. For tibial fracture nonunions, three trials used rhBMP-7 and the fourth trial did not state which formulation. The RR was nearly 1 (0.98), and there was no significant difference between the BMP and intramedullary nail plus autograft groups in the rates of revision or infection. Interpreting these results is difficult given the variations in control groups and formulations of rhBMP used, one of which is no longer marketed in the U.S.

A Cochrane review by Garrison et al (2010) evaluated the comparative effectiveness and costs of rhBMP for healing of acute fractures and nonunions vs standard of care. The literature search was conducted to 2008; 11 RCTs (total n=976 participants) and 4 economic evaluations selected for inclusion. The times to fracture healing were comparable between the rhBMP and control groups. There was some evidence for faster healing rates, mainly for open tibial fractures without secondary procedures (RR=1.19). Three trials indicated that fewer secondary procedures were required for acute fractures treated with rhBMP (RR=0.65). Reviewers concluded that limited evidence suggested rhBMP may be more effective than standard of care for acute tibial fracture healing; however, the efficacy of rhBMP for treating nonunion remains uncertain (RR=1.02).

Lyon et al (2013) reported on a manufacturer-funded, randomized, double-blind trial of injectable rhBMP-2 in a calcium phosphate matrix for closed tibial diaphyseal fractures. The trial had a target enrollment of 600 patients but was stopped after interim analysis with 387 patients enrolled. Addition of the injectable rhBMP-2 paste to the standard of reamed intramedullary nail fixation did not shorten the time to fracture healing, resulting in study termination due to futility.

Section Summary: Tibial Fractures and Nonunions
The evidence for the use of rhBMP in long-bone fractures and nonunions consists of RCTs, systematic reviews, and meta-analyses. Two systematic reviews have concluded that rhBMP can reduce reoperations rates compared with soft-tissue management with or without intramedullary nailing.

Miscellaneous Surgical Procedures
Clinical Context and Therapy Purpose
The purpose of rhBMP is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as autograft plus allograft bone, in patients who are undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis).

The question addressed in this evidence review is: does the use of BMP improve the net health outcome in individuals who are undergoing surgery for miscellaneous conditions such as oral and maxillofacial fracture when an autograft is not feasible?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals who are undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis).

Interventions
The therapy being considered is rhBMP. Two rhBMPs have been extensively studied: rhBMP-2, applied with an absorbable collagen sponge (Infuse), and rhBMP-7, applied in putty (OP-1).
These protein products have been investigated as alternatives to bone autografting in a variety of surgical procedures such as treatment of bone defects, and reconstruction of maxillofacial conditions.

**Comparators**
Comparators of interest include autograft bone or synthetic bone substitute. Oral sensory loss may be associated with autograft bone harvest in maxillofacial procedures.

**Outcomes**
The general outcomes of interest are symptoms, morbidity events, functional outcomes, and treatment-related morbidity.

**Timing**
The existing literature evaluating rhBMP as a treatment for patients who are undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis) has varying lengths of follow-up. At least one year of follow-up is desirable to adequately evaluate outcomes.

**Setting**
Patients who are undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis) are actively managed by orthopedic surgeons and oral and maxillofacial surgeons.

Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

An Agency for Healthcare Research and Quality (2010) technology assessment on the state of the evidence for on-label and off-label use of rhBMP13, 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 with autograft plus allograft bone.
- There is moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP-2.

**Additional Applications**
Limited research has evaluated the use of rhBMP for 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).14,15 The literature on these applications consists of small case series; no controlled trials have been identified.

**Section Summary: Other Surgical Procedures**
There is little evidence supporting the use of rhBMP in surgical procedures or interventions other than spinal fusion and acute long fractures. Conclusions cannot be drawn on the utility of rhBMP for other surgical indications.

**Summary of Evidence**
For individuals who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible who receive rhBMP, the evidence includes RCTs, systematic reviews, and meta-analyses. The relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. In 2013, 2 systematic reviews of rhBMP-2 trials using
manufacturer-provided individual patient-level data were published. Overall, these reviews found little to no benefit of rhBMP-2 over iliac crest bone graft for all patients undergoing spinal fusion, with an uncertain risk of harm. The small benefits reported do not support the widespread use of rhBMP-2 as an alternative to iliac crest autograft. However, the studies do establish that rhBMP-2 has efficacy in promoting bone fusion and will improve outcomes for patients for whom use of iliac crest bone graft is not feasible. The overall adverse event rate was low, though concerns remain about increased adverse event rates with rhBMP-2, including cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible who receive rhBMP, the evidence includes RCTs and systematic reviews of the RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. Two systematic reviews have concluded that rhBMP can reduce reoperations rates compared with soft-tissue management with or without intramedullary nailing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis) who receive rhBMP, the evidence includes a health technology assessment and small case series. The relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. The evidence does not permit conclusions about the effect of rhBMP for craniomaxillofacial surgery or tibial shaft fracture nonunion. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

Joint guidelines on lumbar spinal fusion from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (2014) were updated. Both groups gave a grade B recommendation (multiple level II studies) for the use of recombinant human bone morphogenetic protein-2 as a substitute for autologous iliac crest bone for anterior lumbar interbody fusion and single-level posterolateral instrumented fusion. Grade C recommendations were made for recombinant human bone morphogenetic protein-2 as an option for posterior lumbar interbody fusion and transforminal lumbar interbody fusion, posterolateral fusion in patients older than 60 years, and as a graft extender for either instrumented or noninstrumented posterolateral fusions. The societies also gave a grade C recommendation (based on multiple level IV and V studies) that the use of recombinant human bone morphogenetic protein-2 as a graft option has been associated with a unique constellation of complications of which surgeons should be aware when considering this graft extender/substitute.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There are no national coverage determinations specifically related to bone morphogenetic proteins.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 2.
Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00984672</td>
<td>Evaluation of Radiculitis Following Use of Bone Morphogenetic Protein-2 for Interbody Arthrodesis in Spinal Surgery</td>
<td>240</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02718131</td>
<td>A Study of INFUSE Bone Graft (BMP-2) in the Treatment of Tibial Pseudarthrosis in Neurofibromatosis Type 1 (NF1)</td>
<td>54</td>
<td>Dec 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

Appendix

Lumbar Interbody Fusion Procedures

Procedures used for lumbar interbody fusion differ primarily by the direction of approach to the spine, i.e., from the front (anterior), from the back (posterior or transforaminal), or from the side (lateral) (see Appendix Table 1). An alternative approach to interbody fusion is arthrodesis of the transverse processes alone (posterolateral), which does not fuse the adjoining vertebral bodies. Circumferential fusion fuses both the adjacent vertebral bodies and the transverse processes, typically using both an anterior and posterior approach to the spine.

Appendix Table 1. Open and Minimally Invasive Approaches to Lumbar Interbody Fusion

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Access</th>
<th>Approach</th>
<th>Visualization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior lumbar interbody fusion</td>
<td>Open, MI, or</td>
<td>Transperitoneal or</td>
<td>Direct, endoscopic or laparoscopic with fluoroscopic guidance</td>
</tr>
<tr>
<td></td>
<td>laparoscopic</td>
<td>retroperitoneal</td>
<td></td>
</tr>
<tr>
<td>Posterior lumbar interbody fusion</td>
<td>Open or MI</td>
<td>Incision centered on spine</td>
<td>Direct, endoscopic or microscopic, with fluoroscopic guidance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with laminectomy/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>laminotomy and retraction of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>nerve</td>
<td></td>
</tr>
<tr>
<td>Transforaminal lumbar</td>
<td>Open or MI</td>
<td>Offset from spine, through the</td>
<td>Direct, endoscopic or microscopic, with fluoroscopic guidance</td>
</tr>
<tr>
<td>interbody fusion</td>
<td></td>
<td>intervertebral foramen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>via unilateral facetectomy</td>
<td></td>
</tr>
<tr>
<td>Lateral interbody fusion</td>
<td>MI</td>
<td>Retropertoneal through</td>
<td>Direct, with neurologic monitoring and fluoroscopic guidance</td>
</tr>
<tr>
<td>Extreme lateral interbody fusion</td>
<td></td>
<td>transpsoas</td>
<td></td>
</tr>
<tr>
<td>Direct lateral interbody fusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MI: minimally invasive.

Anterior Lumbar Interbody Fusion

Anterior lumbar interbody fusion access provides direct visualization of the disc space, potentially allowing a more complete discectomy and better fusion than lateral or posterior approaches. An anterior approach avoids trauma to the paraspinal musculature, epidural scarring, traction on nerve roots, and dural tears. However, the retraction of the great vessels, peritoneal contents, and superior hypogastric sympathetic plexus with a peritoneal or retroperitoneal approach place these structures at risk of iatrogenic injury. Access to the posterior space for the treatment of nerve compression is also limited. Laparoscopic anterior lumbar interbody fusion has also been investigated.

Posterior Lumbar Interbody Fusion

Posterior lumbar interbody fusion (PLIF) can be performed using a traditional open procedure with a midline incision or using a minimally invasive approach with bilateral paramedian incisions. In the open procedure, the midline muscle attachments are divided along the central incision to facilitate wide muscle retraction and laminectomy. In minimally invasive PLIF, tubular retractors may be used to open smaller central bilateral working channels to access the pedicles and foramen. Minimally invasive PLIF typically involves partial laminotomies and facetectomies. The decompression allows treatment of spinal canal pathology (e.g., spinal...
stenosis, lateral recess and foraminal stenosis, synovial cysts, hypertrophic ligamentum flavum), as well as stabilization of the spine through interbody fusion.

**Transforaminal Lumbar Interbody Fusion**

Transforaminal lumbar interbody fusion (TLIF) differs from the more traditional bilateral PLIF because TLIF uses a unilateral approach to the disc space through the intervertebral foramen. In minimally invasive TLIF, a single incision about 2 to 3 cm in length is made approximately 3 cm lateral to the midline. A tubular retractor is docked on the facet joint complex and a facetectomy with partial laminectomy is performed. Less dural retraction is needed with access through the foramen via unilateral facetectomy, and contralateral scar formation is eliminated. TLIF provides access to the posterior elements along with the intervertebral disc space.

**Lateral Interbody Fusion**

Lateral interbody fusion (e.g., extreme lateral interbody fusion or direct lateral interbody fusion) uses specialized retractors in a minimally invasive, lateral approach to the anterior spine through the psoas. Compared with anterior lumbar interbody fusion, the lateral approach does not risk injury to the peritoneum or great vessels. However, exposure to the spine may be more limited, and dissection of the psoas major places the nerves of the lumbar plexus at risk. Electromyographic monitoring and dissection predominantly within the anterior psoas major may be used to reduce the risk of nerve root injury. These various factors restrict the ability to perform a complete discectomy and address pathology of the posterior elements.

**Circumferential Fusion**

Circumferential fusion is 360° fusion that joins vertebrae by their entire bodies and transverse processes, typically through an anterior and posterior approach.

**Posterolateral Fusion**

Posterolateral fusion is a procedure where the transverse processes of the involved segments are decorticated and covered with a mixture of bone autograft or allograft.

**References**


Documentation for Clinical Review

Please provide the following documentation (if/when requested):
- History and physical and/or consultation report(s) including:
  - Description of the patient’s current condition and treatment plan
  - Duration and degree of illness or injury
  - Progress notes pertaining to request (if applicable)
  - Proposed procedure(s), type of rhBMP product, medical device/implants (if applicable) and rationale for treatment
  - Summary of past failed treatments and treatment duration (conservative (non-operative) treatments or other surgical interventions)

Post Service
- Operative report(s)
- Product (rhBMP etc.) invoice

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/NMN

The following services may be considered medically necessary when policy criteria are met. Services may be considered not medically necessary when policy criteria are not met.
### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2005</td>
<td>New policy MPC reviewed and accepted CTAFebruary 2005 technology review.</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/15/2007</td>
<td>Policy revision without position change Policy updated BCBSA MPP (07/07).</td>
<td>Medical Policy Committee</td>
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<tr>
<td>04/03/2009</td>
<td>Policy Title Revision, criteria revised Policy title changed from Recombinant Human Bone Morphogenic Protein-2(rhBMP-2) to Bone Morphogenic Protein</td>
<td>Medical Policy Committee</td>
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<td>03/30/2011</td>
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<tr>
<td>04/13/2011</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<tr>
<td>03/30/2012</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/13/2012</td>
<td>Coding Update</td>
<td>Administrative Review</td>
</tr>
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<td>03/28/2014</td>
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<td>Coding update</td>
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</tr>
<tr>
<td>06/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.
**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.