| 7.01.100 | Bone Morphogenetic Protein | | |
|---|---|---|---|
| **Original Policy Date:** | March 1, 2005 | **Effective Date:** | June 1, 2024 |
| **Section:** | 7.0 Surgery | **Page:** | Page 1 of 23 |

## Policy Statement

I. Use of recombinant human bone morphogenetic protein-2 (Infuse™) may be considered **medically necessary** in skeletally mature individuals:
   A. For anterior lumbar interbody fusion procedures when the use of autograft is not feasible;
   B. For instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible;
   C. For the treatment of acute, open fracture of the tibial shaft, when the use of autograft is not feasible.

II. Use of recombinant human bone morphogenetic protein-2 is considered **investigational** for all other indications, including but not limited to spinal fusion when the use of autograft is feasible and craniomaxillofacial surgery.

**NOTE**: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

## 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**
See the Codes table for details.

## Description

Two recombinant human bone morphogenetic proteins (rhBMPs) have been extensively studied: recombinant human bone morphogenetic protein-2 (rhBMP-2), applied with an absorbable collagen sponge (Infuse), and recombinant human bone morphogenetic protein-7 (rhBMP-7), applied in putty (OP-1; not currently available in the U.S.). 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
- Low Intensity Pulsed Ultrasound 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 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 United States.

**Table 1. Recombinant Human Bone Morphogenetic Protein Products and Associated Carrier and Delivery Systems Approved by U.S. Food and Drug Administration**

| Systems | Manufacturer | Approved | PMA No. |
|---|---|---|---|
| **INFUSE™ Bone Graft** | Medtronic | 03/07 | P050053 |

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

ALIF: anterior lumbar interbody fusion; OLIF: oblique lateral interbody fusion; PMA: premarket approval; rhBMP: recombinant human bone morphogenetic protein; S: supplement.
[a]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 polymers, 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 transforaminal 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 (e.g., posterior lumbar interbody fusion, transforaminal 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 have 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA

(Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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.[2,] A randomized study reported by Govender et al (2002) supported the use of recombinant human bone morphogenetic protein-7 (rhBMP-7) in the treatment of recalcitrant nonunions of the long bones.[3,] 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 harvesting.[4,] 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. Iliac crest bone graft 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 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 to 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 individuals with who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible.

The following PICO was used to select literature to inform this review.

##### *Populations*

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

##### *Interventions*

The therapy being considered is rhBMP. One rhBMP is currently available: rhBMP-2, applied with an absorbable collagen sponge (Infuse). This protein product has been investigated as an alternative 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."

##### *Outcomes*

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

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 1 year of follow-up is desirable to adequately evaluate outcomes.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## U.S. Food and Drug Administration-Approved Uses of Recombinant Human Bone Morphogenetic Protein-2

### Systematic Reviews

Two meta-analyses[5,6,] assessing the effectiveness and harms of rhBMP-2 in spine fusion were published following a 2011 U.S. Senate investigation[7,] of industry influence on the INFUSE clinical studies and a systematic review by Carragee et al (2011)[8,] 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 U.S. Food and Drug Administration (FDA) data summaries, subsequent studies, and databases.[8,] 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).[5,6,]

Simmonds et al (2013) included patient-level data from 12 RCTs (N=1408), regardless of spinal level or surgical approach, and adverse event data from an additional 35 observational studies.[5,] Use of rhBMP-2 increased the rate of radiographic fusion by 12% compared with illiac crest bone graft, 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 (N=1981) and 31 cohort studies.[6,] Reviewers found moderate evidence of no consistent differences between rhBMP-2 and iliac crest bone graft in overall success, fusion rates, or other effectiveness measures for anterior lumbar interbody fusion or posterolateral fusion. A small RCT and 3 cohort studies revealed no difference in effectiveness outcomes between rhBMP and iliac crest bone graft 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 iliac crest bone graft. 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 [CI], 0.81 to 4.16) for cancer in the bone morphogenetic protein group but this increased rate was not statistically significant.[5,] 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 bone morphogenetic protein group (RR, 3.45; 95% CI, 1.98 to 6.0); at 48 months, the increase was not statistically significant (RR, 1.82; 95% CI, 0.84 to 3.95).[6,]

Other adverse events were increased for the bone morphogenetic protein group. Simmonds et al (2013) found a higher incidence of early back and leg pain with rhBMP-2.[5,] The individual publications consistently reported higher rates of heterotopic bone formation, leg pain/radiculitis, osteolysis, and dysphagia but a 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.[6,] Fu et al (2013) also noted that the data on adverse events in the published literature were incomplete compared with the total amount of data available.

The following systematic reviews and meta-analyses are described in Tables 2 and 3, with results described in Table 4.

A systematic review and meta-analysis assessing the safety and efficacy of bone substitutes in lumbar spinal fusion was published by Feng et al (2019).[9,] The study identified 27 RCTs involving 2488 patients utilizing various bone grafts for lumbar arthrodesis. Use of rhBMP-2 provided the highest fusion rate and was found to be significantly superior to iliac crest bone graft (odds ratio [OR], 0.21; 95% CI, 0.11 to 0.36; p<.001), autograft local bone (OR, 0.18; 95% CI, 0.04 to 0.78; p=.022), and allograft (OR, 0.13; 95% CI, 0.03 to 0.60; p=.009). However, both iliac crest bone graft and rhBMP-2 demonstrated an increased incidence of adverse events. A systematic review and meta-analysis of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion was reported by Liu et al (2020).[10,] A total of 20 RCTs involving 2185 patients were identified. A higher fusion success rate (OR, 3.79; 95% CI, 1.88 to 7.63; p=.0002; $I^2$ = 58%), enhanced improvement in Oswetry disability index scores (mean difference, 1.54; 95% CI, 0.18 to 2.89; p=.03), and a lower re-operation rate (OR, 0.59; 95% CI, 0.43 to 0.80; p=.0007) was demonstrated in the rhBMP group. No statistically significant difference in the incidence of adverse events was reported between rhBMP and iliac crest bone graft (OR, 0.91; 95% CI, 0.70 to 1.18; p=.47).

Mariscal et al (2019) conducted a meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for posterolateral fusion of the lumbar spine.[11,] Six RCTs evaluating 908 patients (446 bone morphogenetic protein-2; 462 iliac crest bone graft) were identified. The fusion success rate was significantly higher at 86% versus 60% at 6 months (n=687; OR, 3.75; 95% CI, 2.58 to 5.44; p<.00001; $I^2$=86%) and 88% versus 80% at 12 months (n=448; OR, 1.76; 95% CI, 1.06 to 2.92; p=.03; $I^2$=43%) in the bone morphogenetic protein versus iliac crest bone graft groups. Moderate to high statistical heterogeneity was determined. Administration of osteoinductive materials (bone morphogenetic protein-2 or iliac crest bone graft) used variable vehicles, doses, and concentrations. Surgery time (p<.00001; $I^2$=83%) and hospitalization duration (p=.003; $I^2$=83%) were both found to be significantly longer in the iliac crest bone graft group. Differences in quality of life measures including Oswetry Disability Index, 36-Item Short Form Health Survey, and Back Pain Score were not significantly different between the 2 groups. No significant differences in adverse events (e.g., respiratory effects, infection, malignancy, and additional surgical procedures) were noted between groups except for the non-unions subgroup (OR, 0.28; 95% CI, 0.11 to 0.68; p=.005; $I^2$=0%), which demonstrated a higher incidence of adverse events with iliac crest bone graft.

Wu et al (2020) conducted a meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for posterolateral fusion of the lumbar spine.[12,] Fourteen RCTs including 1516 patients (789 bone morphogenetic protein-2; 727 iliac crest bone graft) were identified. Patients who received bone morphogenetic protein-2 had a significantly higher fusion rate, lower surgery time, lower additional surgical procedures, and higher Oswestry Disability Index score compared to patients who received iliac crest bone graft. No significant difference was found between bone morphogenetic protein-2 and iliac crest bone graft in non-union rates, hospitalization days, and adverse events. Tables 2 and 3 describe study characteristics and Table 4 describes study results.

**Table 2. Comparison of Trials/Studies Included in SR & M-A**

| Study | Feng et al (2019)[9,] | Mariscal et al (2019)[11,] | Liu et al (2020)[10,] | Wu et al (2020)[12,] |
|---|---|---|---|---|
| **Boden et al (2000)** | | | | |

| Study | Feng et al (2019)[9], | Mariscal et al (2019)[11], | Liu et al (2020)[10], | Wu et al (2020)[12], |
|---|---|---|---|---|
| Coughlan et al (2018) | | | | |

| Study | Spinal fusion rates (rhBMP vs. ICBG) | Spinal fusion rates at 6 months (rhBMP vs. ICBG) | Spinal fusion rates at 12 months (rhBMP vs. ICBG) | Oswetry disability index score (rhBMP vs. ICBG) | Surgery time (rhBMP vs. ICBG) | Reoperation rates (rhBMP vs. ICBG) | Rate of AEs (rhBMP vs. ICBG) |
|---|---|---|---|---|---|---|---|
| $I^2$ (p) | *0.12* (95% CrI, 0.00 to 1.135) | | | | | | *0.65* (95% CrI, 0.150 to 2.332) |
| **Mariscal et al (2019)[11,]** | | | | | | | |
| **Total N** | | 687 | 448 | 195 | 824 | 799 | 611[1] |
| **Pooled effect (95% CI)** | | OR, 3.75 (2.58 to 5.44) | OR, 1.76 (1.06 to 2.92) | MD, 2.57 (-3.51 to 8.66) | MD, -17.56 (-23.98 to -11.14) | OR, 0.49 (0.30 to 0.79) | OR, 0.28 (0.11 to 0.68) |
| **p-value** | | <.00001 | .03 | .83 | <.00001 | .004 | .005 |
| $I^2$ (p) | | *0.86* (<.0001) | *0.43* (.17) | *0* | *.83* (.0001) | *0* | *0* |
| **Liu et al (2020)[10,]** | | | | | | | |
| **Total N** | 1386 | | | 1252 | | 2113 | 1644 |
| **Pooled effect (95% CI)** | OR, 3.79 (1.88 to 7.63) | | | MD, 1.54 (0.18 to 2.89) | | OR, 0.59 (0.43 to 0.80) | OR, 0.91 (0.70 to 1.18) |
| **p-value** | .0002 | | | .03 | | .0007 | .47 |
| $I^2$ (p) | *0.58* (.004) | | | *0.59* (.007) | | *0.22* (.21) | *0.37* (.08) |
| **Wu et al (2020)[12,]** | | | | | | | |
| **Total N** | 1301 | | | 1004 | 1069 | 1231 | 930 |
| **Pooled effect (95% CI)** | OR, 4.19 (2.86 to 6.20) | | | OR, 1.49 (0.02 to 2.97) | OR, -26.64 (-38.71 to -14.57) | OR, 0.46 (0.31 to 0.69) | OR, 0.78 (0.52 to 1.16) |
| **p-value** | <.001 | | | .05 | <.0001 | .0002 | .22 |
| $I^2$ (p) | *0.16* (.29) | | | *0.62* (.008) | *0.66* (.003) | *0* | *0* |

AE: adverse events; CI: confidence interval; CrI: credibility interval; ICBG: iliac crest bone graft; M-A: meta-analysis; MD: mean difference; NR: not reported; OR: odds ratio; rhBMP: recombinant human bone morphogenetic protein; SR: systematic review.
[1]Non-union rates were the only significant difference between groups; all other differences between AEs (respiratory, malignancy, wound/surgical infection) were not significant.

### Off-Label Use of Bone Morphogenetic Protein in Lumbar Spinal Fusion

Off-label use of bone morphogenetic protein 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-AMPLIFY (N=463).[13,] 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.[14,] Reviewers evaluated the evidence for rhBMP-2 and rhBMP-7 in anterior cervical spine fusions. A literature search returned 18 articles (N=4782). 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 transforaminal lumbar interbody fusions.[15] The authors compared rhBMP-2 with bone autograft by reviewing data on 191 patients undergoing anteroposterior instrumented spinal fusion with transforaminal 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 (bone morphogenetic protein group) and 104 patients were treated with bone grafting (non-bone morphogenetic protein group). Results were similar between groups; fusion rates were 92.7% and 92.3% for bone morphogenetic protein and non-bone morphogenetic protein patients, respectively. Seven patients in the bone morphogenetic protein group and 2 patients in the non-bone morphogenetic protein group experienced radiculitis. Seroma was observed in 2 patients in the bone morphogenetic protein group; it was not observed in any patients in the non-bone morphogenetic protein group. Given these very small differences, the authors concluded that rhBMP-2 is a comparable treatment option to bone grafting in transforaminal lumbar interbody fusion procedures.

Retrospective analyses of data from Medicare[16] and from a commercial insurer database[17] failed to confirm a higher risk of cancer in rhBMP-2 patients. The results probably reflect decreased off-label use and indicate that, in doses and vehicles approved for lumbar surgery, cancer risk is negligible. Long-term follow-up data from patients treated with elective spinal fusion continue to reveal no increased risk of cancer with the use of rhBMP.[18]

### Section Summary: Lumbar Spinal Fusion

The evidence on the effectiveness and potential harms of rhBMP 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 individuals who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible.

The following PICO was used to select literature to inform this review.

#### *Populations*

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

#### *Interventions*

The therapy being considered is rhBMP. One rhBMP is currently available: rhBMP-2, applied with an absorbable collagen sponge (Infuse). This protein product has been investigated as an alternative to bone autografting.

#### *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.

*Outcomes*

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

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 6 months of follow-up is desirable to adequately evaluate outcomes.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Systematic Reviews

Dai et al (2015) published a meta-analysis on rhBMP for the healing of acute tibial fractures (4 RCTs; n=868) and nonunions (4 RCTs; n=245).[19,] For acute tibial fractures, 3 RCTs were conducted with rhBMP-2 and 1 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 bone morphogenetic protein and control groups for hardware failure or infection. For tibial fracture nonunions, 3 trials used rhBMP-7 and the fourth trial did not state which formulation was used. The RR was nearly 1 (0.98), and there was no significant difference between the bone morphogenetic protein 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, 1 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 versus standard of care.[20,] The literature search was conducted to 2008; 11 RCTs (N=976 participants) and 4 economic evaluations were 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).

### Randomized Controlled Trials

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.[21,] The trial had a target enrollment of 600 patients but was stopped after an 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.

The Major Extremity Trauma Research Consortium (2019) published the results of a multicenter RCT comparing rhBMP-2 and absorbable collagen sponge (INFUSE Bone Graft) against iliac crest bone graft for the treatment of open tibia fractures with critical size defects.[22,] The study enrolled 30 adult patients with Type II, IIIA, or IIIB open tibia fractures and bone defects treated with an intramedullary nail and critical size defects 1 to 5 cm in length and at least 50% circumference on orthogonal

radiograph. Patients with bone defects exceeding the size of 1 large INFUSE kit were excluded. Sixteen patients were randomized to rhBMP-2 and 14 patients were randomized to iliac crest bone graft. The primary outcome measure was radiographic union within 52 weeks without the need for a secondary intervention as assessed by a panel of experienced orthopedic trauma surgeons blinded to patient treatment assignment. Secondary outcome measures included clinical healing, patient-reported measures, and major complications. Union data were available for 23 patients at 52 weeks; 7/12 (58.3%) in the rhBMP-2 group achieved radiographic union compared to 9/11 (81.8%) in the iliac crest bone graft group (mean difference, -0.23; 90% CI, -0.55 to 0.10). Patients in the rhBMP-2 also exhibited lower rates of clinical healing at 52 weeks (27% vs. 54%), poorer mean Short Musculoskeletal Function assessment scores, and experienced more major complications (5 vs. 3). The authors concluded that there was not enough evidence to conclude that iliac crest bone graft and rhBMP-2 are equivalent for radiographic union in patients with open tibial fractures. Target enrollment in this study was not met due to a low incidence of eligible bone defects in the civilian trauma population. After 5 years, trial enrollment was discontinued.

### 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. An RCT evaluating patients with open tibia fractures with critical size defects concluded that there was not enough evidence to support equivalence between iliac crest bone graft and rhBMP-2 for radiographic union.

## 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 individuals who are undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis).

The following PICO was used to select literature to inform this review.

#### *Populations*

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

#### *Interventions*

The therapy being considered is rhBMP. One rhBMP is currently available: rhBMP-2, applied with an absorbable collagen sponge (Infuse) This protein product has been investigated as an alternative to bone autografting.

#### *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, morbid events, functional outcomes, and treatment-related morbidity.

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 1 year of follow-up is desirable to adequately evaluate outcomes.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Technology Assessment

An Agency for Healthcare Research and Quality (2010) technology assessment on the state of the evidence for on-label and off-label use of rhBMP included the following conclusions:[23,]

- 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.

### Systematic Reviews

Ramly et al (2019) published a systematic review assessing the safety and efficacy of rhBMP-2 in craniofacial surgery.[24,] A total of 17 RCTs were identified evaluating the use of rhBMP-2 in the maxillary sinus, alveolar ridge, alveolar cleft, or for cranial defect reconstruction. Study follow-up durations were variable (range, 3 to 36 months) and outcome assessments were based on clinical exam, radiology, and/or histology. There was also wide variation in concentrations, carriers, and controls. Five RCTs evaluating rhBMP-2 in maxillary sinus floor augmentation were identified. Two RCTs comparing rhBMP-2 to bone graft controls found the control group to be superior. Three RCTs comparing rhBMP-2 to xenografts reported variable outcomes. Seven RCTs evaluated rhBMP-2 in alveolar ridge augmentation. Three studies found no significant difference versus control whereas 4 studies favored rhBMP-2 over various controls. Only 1 of 4 RCTs comparing rhBMP-2 to iliac crest bone graft in alveolar cleft reconstruction favored rhBMP-2 and reflected the only trial in this subgroup that enrolled skeletally mature patients. The authors concluded that the safety profile of rhBMP-2 and the quality of evidence supporting its use in craniofacial surgery is still in development.

### Clinical Trials

In the premarket approval application for rhBMP-2 (INFUSE Bone Graft) as an alternative to autogenous bone graft for sinus augmentation, and for localized alveolar ridge augmentations for defects associated with extraction sockets, data from 5 clinical studies were submitted (3 for sinus floor augmentation and 2 for extraction socket augmentation).[25,] All 5 studies had a similar protocol with the treatment course consisting of study device implantation followed by an osteoinduction phase, dental implant placement followed by an osseointegration phase, and prosthesis placement (functional loading) followed by functional restoration. A total of 312 patients were enrolled across the 5 studies with varying rhBMP-2 doses and control groups utilized. In the pivotal sinus augmentation study, results revealed that 79% (95% CI, 68.5% to 87.3%) of patients in the rhBMP-2 group successfully received dental implants without additional augmentation, received a prosthesis, and maintained functional loading for at least 6 months. The success rate at 6 months post-loading in the autogenous bone graft group was higher by 11.8% (95% CI, 0.8% to 22.8%); however, the graft group had a significantly increased rate of adverse events as compared to rhBMP-2. The FDA concluded that the "benefits (despite success rates being lower than that reported for bone graft) outweigh the risks." With regard to the clinical data for extraction socket augmentation, the functional loading success rate for rhBMP-2 ranged from 48% to 66% across all postoperative evaluation time points; however, the patient population was too small to determine statistical significance. Similarly to the sinus augmentation data, fewer adverse events were noted with rhBMP-2 as compared to the autogenous bone graft group, which may offset any concerns regarding reduced effectiveness.

### Additional Applications

#### Case Series

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 (ie, Ilizarov procedure).[26,27,] The literature on these applications consists of small case series; no controlled trials have been identified.

### Section Summary: Other Surgical Procedures

For patients undergoing certain craniofacial surgeries, results from systematic reviews and clinical trials have generally shown that bone morphogenetic protein administration may not be as effective as a bone graft approach; however, it is associated with fewer adverse events. Conclusions cannot be drawn on the utility of rhBMP for other surgical indications.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### American Association of Neurological Surgeons et al

Joint guidelines on lumbar spinal fusion from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (2014) were updated.[28,] Both groups gave a grade B recommendation (multiple level II studies) for the use of recombinant human bone morphogenetic protein-2 (rhBMP-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 rhBMP-2 as an option for posterior lumbar interbody fusion and transforaminal 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 rhBMP-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.

#### North American Spine Society

In 2014, the North American Spine Society (NASS) issued coverage policy recommendations outlining the clinical indications for the adjunct use of rhBMP-2 in spinal fusion surgeries based on the strength of the available evidence (level I to level IV).[29,] NASS recommends adjunct use of rhBMP-2 in spinal fusion surgeries for the following clinical scenarios and qualifying criteria, as appropriate:

1. "Stand-alone anterior lumbar interbody fusion : in all patient groups except males with a strong reproductive priority"
2. "Posterolateral lumbar fusion : in all patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor quality autogenous bone available"
3. "Posterior lumbar interbody fusion and transforaminal lumbar interbody fusion in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor quality autogenous bone available"
4. "Posterior cervical or thoracic fusions "

   a. "in pediatric patients at very high risk for fusion failure (e.g., neuromuscular scoliosis, occipitocervical pathology)"
   b. "in adult patients at high risk for nonunion, for example, revision surgery"
5. "Anterior cervical fusion : in patients at high risk for nonunion, for example, revision surgery"

The NASS emphasizes that rhBMP-2 is not indicated in the following scenarios:

1. "Routine anterior and posterior cervical fusion procedures"
2. "Single level posterior/posterolateral fusions in healthy adults"
3. "Routine pediatric spine fusion procedures (e.g., adolescent idiopathic scoliosis)"

### 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 ongoing and unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Ongoing and Unpublished Clinical Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| *Ongoing* | | | |
| NCT02924571 | Prospective, Blinded, Non-randomized Study of Thoracolumbar Spinal Fusion Graft Efficacy: Bone Marrow Aspirate Concentrate and Allograft Versus Recombinant Bone Morphogenetic Protein-2 (BMP) | 48 | Jan 2025 |
| NCT04073563[a] | Prospective, Randomized, Controlled, Blinded Pivotal Study In Subjects Undergoing A Transforaminal Lumbar Interbody Fusion At One Or Two Levels Using Infuse™ Bone Graft and The Capstone™ Spinal System With Posterior Supplemental Fixation For The Treatment Of Symptomatic Degenerative Disease Of The Lumbosacral Spine | 1017 | Apr 2028 |
| NCT05238740[a] | Comparison of Radiographic Fusion Rate & Clinical Outcome of Standalone ALIF L5/S1 Performed With Either rhBMP-2 or ViviGen® Cellular Bone Matrix, a Prospective Randomized Single Blind, Monocentric Trial | 168 | Nov 2026 |
| *Unpublished* | | | |
| NCT00984672 | Prospective Evaluation of Radiculitis Following Use of Bone Morphogenetic Protein-2 for Interbody Arthrodesis in Spinal Surgery | 103 | April 2016 |

NCT: national clinical trial; BMP: bone morphogenetic protein.
[a] Denotes industry-sponsored or cosponsored trial.

## Appendix 1

### 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**

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

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 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 posterior lumbar interbody fusion, tubular retractors may be used to open smaller central bilateral working channels to access the pedicles and foramen. Minimally invasive posterior lumbar interbody fusion 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 differs from the more traditional bilateral posterior lumbar interbody fusion because transforaminal lumbar interbody fusion uses a unilateral approach to the disc space through the intervertebral foramen. In minimally invasive transforaminal lumbar interbody fusion, 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. Transforaminal lumbar interbody fusion 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.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- **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 (in addition to the above, please include the following):**

- 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.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

| Type | Code | Description |
|---|---|---|
| CPT® | 20930 | Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure) |
| HCPCS | None | |

## Policy History

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

| Effective Date | Action |
|---|---|
| 03/01/2005 | New policy MPC reviewed and accepted CTAF February 2005 technology review. |
| 10/15/2007 | Policy revision without position change Policy updated BCBSA MPP (07/07). |
| 04/03/2009 | Policy Title Revision, criteria revised Policy title changed from Recombinant Human Bone Morphogenic Protein-2(rhBMP-2) to Bone Morphogenic Protein |
| 03/30/2011 | Policy revision with position change |
| 04/13/2011 | Coding Update |
| 03/30/2012 | Policy revision with position change |
| 06/13/2012 | Coding Update |
| 03/28/2014 | Policy revision with position change |
| 01/30/2015 | Policy revision without position change |
| 10/30/2015 | Coding update |

| Effective Date | Action |
|---|---|
| 07/01/2016 | Policy revision without position change |
| 09/01/2017 | Policy revision without position change |
| 12/01/2017 | Policy revision without position change |
| 06/01/2018 | Policy revision without position change |
| 06/01/2019 | Policy revision without position change |
| 06/01/2023 | Policy reactivated. Previously archived from 06/01/2020 to 05/31/2023. |
| 06/01/2024 | Annual review. No change to policy statement. Policy guidelines and literature review updated. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

**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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

*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.*

## Appendix A

| POLICY STATEMENT (No changes) | |
|---|---|
| **BEFORE** | **AFTER** |
| **Bone Morphogenetic Protein 7.01.100**<br><br>**Policy Statement:**<br>I. Use of recombinant human bone morphogenetic protein-2 (Infuse™) may be considered **medically necessary** in skeletally mature individuals:<br>A. For anterior lumbar interbody fusion procedures when the use of autograft is not feasible;<br>B. For instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible;<br>C. For the treatment of acute, open fracture of the tibial shaft, when the use of autograft is not feasible.<br><br>II. Use of recombinant human bone morphogenetic protein-2 is considered **investigational** for all other indications, including but not limited to spinal fusion when the use of autograft is feasible and craniomaxillofacial surgery. | **Bone Morphogenetic Protein 7.01.100**<br><br>**Policy Statement:**<br>I. Use of recombinant human bone morphogenetic protein-2 (Infuse™) may be considered **medically necessary** in skeletally mature individuals:<br>D. For anterior lumbar interbody fusion procedures when the use of autograft is not feasible;<br>E. For instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible;<br>F. For the treatment of acute, open fracture of the tibial shaft, when the use of autograft is not feasible.<br><br>II. Use of recombinant human bone morphogenetic protein-2 is considered **investigational** for all other indications, including but not limited to spinal fusion when the use of autograft is feasible and craniomaxillofacial surgery. |