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Bone Morphogenetic Protein

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Related Policies (if applicable)
None

Disclaimer

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Coverage

Use of recombinant human bone morphogenetic protein-2 (rhBMP-2; Infuse™) **may be considered medically necessary** in skeletally mature individuals:

- For anterior lumbar interbody fusion procedures when the use of autograft is not feasible;
- For instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible;
- For the treatment of acute, open fracture of the tibial shaft, when ALL the following criterion are met:
    - The use of autograft is not feasible; AND
    - The INFUSE Bone Graft is applied within 14 days after the initial fracture; AND
    - The fracture is stabilized with intramedullary nail fixation after appropriate wound management.

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

NOTE: 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).

Policy Guidelines

None.

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.

Background

Bone Morphogenetic Protein and Carrier and Delivery Systems

Bone Morphogenetic Proteins are members of the transforming growth factors family. At present, some 20 morphogenetic proteins have been identified, all with varying degrees of tissue-stimulating properties.

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

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 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.

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 Extreme lateral interbody fusion 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 (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 a 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 process of the involved segments are decorticated and covered with a mixture of bone autograft or allograft.

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 United States (U.S.) Food and Drug Administration (FDA) through the premarket approval process (PMA) (see summary of key approvals in Table 2). 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 U.S. and discontinued domestic sales of Olympus Biotech products. The rhBMP-7 product is no longer marketed in the U.S.

Table 2. rhBMP Products and Associated Carrier and Delivery Systems Approved by the U.S. FDA

Systems	Manufacturer	Approved	PMA No.
INFUSE™ Bone Graft: • Alternative to autogenous bone graft for sinus augmentations. • For localized alveolar ridge augmentations in extraction socket defects.	Medtronic	03/07	P050053
INFUSE™ Bone Graft: • Expanded indication for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1. • 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: • Indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1. • Up to grade 1 spondylolisthesis at involved level. • 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: • Extension of device use from L2 to S1. • May be used with retrolisthesis.		07/04	P000058/S002
INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device: • Indicated for acute, open tibial shaft fractures stabilized with nail fixation. • Alternative to autogenous bone graft for sinus augmentations. • For localized alveolar ridge augmentations in extraction socket defects.		10/09	P000058/S033
INFUSE™ Bone Graft/Medtronic Interbody Fusion Device (Marketing name change): • Expanded indication for 2 additional interbody fusion devices.		12/15	P000058/S059

• Perimeter Interbody Fusion Device implanted via retroperitoneal ALIF L2 to S1 or OLIF L5 to S1. • Clydesdale Spinal System implanted via OLIF at single level from L2-S5.			
INFUSE™ Bone Graft/Medtronic Interbody Fusion Device: • Expanded indication for 2 additional interbody fusion devices: ○ Divergence-L Anterior/Oblique Lumbar Fusion System. ○ Pivox™ Oblique Lateral Spinal System.		09/17	P000058/S065

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

[a] Medtronic is the manufacturer for all of the INFUSE bone graft and carrier systems.

Rationale

This medical policy was created in January 2017 with searches of the PubMed database. The most recent literature update was performed through July 2023.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 (AEs) 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.

The objective of this medical policy is to determine whether the use of bone morphogenetic protein (BMP) improves the net health outcome in individuals who are undergoing surgery for spinal fusion or acute tibial shaft fracture when an autograft is not feasible or when used in other surgical procedures (e.g., oral and maxillofacial).

When this medical policy 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 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 (ICBG) 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 (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 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 policy.

Populations

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. 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 who 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 AEs, 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.

United States (U.S.) Food and Drug Administration (FDA) Approved Uses of rhBMP-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. (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 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 AEs 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 patients), regardless of spinal level or surgical approach, and AE 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 (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 (N=1981 patients) and 31 cohort studies. (6) 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 3 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. 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 BMP group, but this increased rate was not statistically significant. (5) Fu et al. 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% 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 AEs were increased for the BMP 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 combined analysis for these outcomes was not performed. Fu et al. (2013) reported that rhBMP-2 was associated with a statistically nonsignificant increased 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 AEs in the published literature was incomplete compared with the total amount of data available.

The following systematic reviews and meta-analyses are described in Tables 3 and 4, with results described in Table 5.

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 ICBG (odds ratio [OR] 0.21; 95% CI, 0.11 to 0.36; p<0.001), autograft local bone (OR 0.18; 95% CI, 0.04 to 0.78); p=0.022), and allograft (OR 0.13; 95% CI, 0.03 to 0.60; p=0.009). However, both iliac crest bone graft and rhBMP-2 demonstrated an increased incidence of AEs.

A systematic review and meta-analysis of BMP versus autologous ICBG 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=0.0002; I^2=58%), enhanced improvement in Oswetry disability index scores (mean difference 1.54; 95% CI, 0.18 to 2.89; p=0.03), and a lower re-operation rate (OR 0.59; 95% CI, 0.43 to 0.80; p=0.0007) was demonstrated in the rhBMP group. No statistically significant difference in the incidence of AEs was reported between rhBMP and ICBG (OR 0.91; 95% CI, 0.70 to 1.18; p=0.47).

Mariscal et al. (2019) conducted a meta-analysis of BMP-2 versus ICBG for posterolateral fusion of the lumbar spine. (11) Six RCTs evaluating 908 patients (446 BMP-2; 462 ICBG) 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<0.00001; I^2=86%) and 88% versus 80% at 12 months (n=448; OR 1.76; 95% CI, 1.06 to 2.92; p=0.03; I^2=43%) in the BMP versus ICBG groups. Moderate to high statistical heterogeneity was determined. Administration of osteoinductive materials (BMP-2 or ICBG) used variable vehicles, doses, and concentrations. Surgery time (p<0.00001; I^2=83%) and hospitalization duration (p=0.003; I^2=78%) were both found to be significantly longer in the ICBG 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 AEs (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=0.005; I^2=0%), which demonstrated a higher incidence of AEs with ICBG.

Wu et al. (2020) conducted a meta-analysis of BMP-2 versus iliac crest bone graft for posterolateral fusion of the lumbar spine. (12) Fourteen RCTs including 1516 patients (789 BMP-2; 727 ICBG) were identified. Patients who received BMP-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 ICBG. No significant difference was found between BMP-2 and ICBG in non-union rates, hospitalization days, and adverse events. Tables 3 and 4 describe study characteristics and Table 4 describes study results.

Table 3. 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)				
Burkus, Gornet et al. *(*2002)			●	●
Butkus, Transfeldt, et al. (2002)			●	
Boden et al. (2002)		●	●	●
Johnsson et al. (2002)	●		●	
Burkus et al. (2003)			●	●
Vaccaro et al. (2004)	●			
Haid et al. (2004)	●		●	●
Glassman et al. (2005)	●		●	●
Korovessis et al. (2005)	●			
Burkus et al. (2005)			●	●
Vaccaro et al. (2005)	●		●	
Dimar et al. (2006)	●	●	●	●
Kanayama et al. (2006)	●		●	
Burkus et al. (2006)	●			
Glassman et al. (2008)	●	●	●	●
Dai et al. (2008)	●			
Vaccaro et al. (2008)	●		●	
Dimar et al. (2009)	●	●	●	●
Dawson et al. (2009)	●	●	●	●

Putzier et al. (2009)	●			
Carreon et al. (2009)				●
Delawi et al. (2010)	●		●	
Ohtori et al. (2011)	●			
Sys et al. (2011)	●			
Kang et al. (2012)	●			
Michielsen et al. (2013)			●	●
Pimenta et al. (2013)	●			
Hurlbert et al. (2013)	●	●	●	●
Hart et al. (2014)	●			
Nandyala et al (2014)	. ●			
Huang et al. (2014)	●			
Delawi et al. (2016)	●		●	
Cho et al. (2017)	●	●		●
VonderHoeh et al. (2017)	●			

M-A: meta-analysis; SR: systematic review.

Table 4. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration (Range)
Feng et al. (2019) (9)	2002-2018	27	Patients diagnosed with lumbar degenerative disease undergoing spinal fusion with bone graft	2488 (10 to239)	RCTs	mean,19.8 + 8.5 months (6 to 36)

			materials (rhBMP vs. ICBG)			
Mariscal et al. (2019) (11)	2002-2017	6	Patients undergoing posterolateral spinal fusion (rhBMP-2 vs. ICBG)	908 (16 to 463)	RCTs	mean, 24 months (5.6 to 48)
Liu et al. (2020) (10)	2000-2016	20	Adult patients with lumbar degenerative diseases requiring lumbar fusion (rhBMP vs. ICBG)	2185 (14 to 63)	RCTs	mean, 2 months (12 to >48)
Wu et al. (2020) (12)	2000-2017	14	Adults undergoing posterolateral fusion of the spine and receiving rhBMP or ICBG	1516 (14 to 372)	RCTs	NR

ICBG: iliac crest bone graft; M-A: meta-analysis; NR: not reported; RCT: randomized controlled trial; rhBMP: recombinant human bone morphogenetic protein; SR: systematic review; vs: versus.

Table 5. SR &M-A Results

Study	Spinal fusion rates (rhBMP vs.ICBG)	Spinal fusion rates at 6 months (rhBMP vs. ICBG)	Spinal fusion rates at 12 months (rhBM 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)
Feng et al. (2019) (9)							
Total N	1708						1708
Pooled effect (95% CI)	OR, 0.21 (95% CrI, 0.11 to 0.36)						OR, 0.71 (95% CrI, 0.32 to 1.44)

p-value	<.001						NR
I^2 (p)	0.12 (95% CrI, 0.00 to1.135)						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 to5.44)	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	
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 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). (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 use 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 patients). Reviewers specifically assessed rhBMP for fusion rates, AEs 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 (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 2 patients in the non-BMP group experienced radiculitis. Seroma was observed in 2 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 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)

<u>Section Summary: Lumbar Spinal Fusion</u>

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 patients 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 policy.

Populations

The relevant population of interest are 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: rhBMP2, applied with an absorbable collagen sponge (Infuse). These protein products have 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 AEs, 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.

Systematic Reviews

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). (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 BMP 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 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 versus standard of care. (20) The literature search was conducted to 2008; 11 RCTs (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).

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 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 was 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.

The current FDA label states the INFUSE Bone Graft is indicated for skeletally mature patients with acute, open tibial shaft fractures that have been stabilized with intramedullary nail fixation after appropriate wound management. INFUSE Bone Graft must be applied within 14 days after the initial fracture. (2)

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 patients 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 policy.

Populations

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. One rhBMP is currently available: rhBMP2, 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 AEs, 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.

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 (23), included the following conclusions:
- The strength of the body of evidence on clinical outcomes is moderate that rhBMP2 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 rhBMP2.

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, 3-36 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%-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%-22.8%); however, the graft group had a significantly increased rate of AEs 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 AEs 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 (i.e., 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 BMP administration may not be as effective as a bone graft approach; however, it is associated with fewer AEs. 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 recombinant human bone morphogenetic protein (rhBMP), the evidence includes randomized controlled trials (RCTs), systematic reviews, and meta-analyses. 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 (ICBG) 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 ICBG. However, the studies do establish that rhBMP-2 has efficacy in promoting bone fusion and will improve outcomes for patients for whom use of ICBG 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. 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, systematic review, clinical trials, and small case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. The evidence generally shows that rhBMP may not be as effective as a bone graft approach in craniomaxillofacial surgery; however, its use is associated with fewer adverse events (AEs). The evidence does not permit conclusions about the effect of rhBMP for tibial shaft fracture nonunion. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

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 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)"

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this medical policy are listed in Table 6.

Table 6. 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)	30	Jan 2023 (active, not recruiting)
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 (recruiting)

NCT05238740	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	Jan 2025 (recruiting)
Unpublished			
NCT00984672	Prospective Evaluation of Radiculitis Following Use of Bone Morphogenetic Protein-2 for Interbody Arthrodesis in Spinal Surgery	103	Apr 2022

BMP: bone morphogenetic protein; NCT: national clinical trial. No: number.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20930, 20931, 20999
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Schultz DG. Center for Devices and Radiological Health, Food and Drug Administration (FDA). FDA public health notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion [letter] (Jul 1 2008). Available at <https://www.wayback.archive-it.org> (accessed July 13, 2023).
2. U.S. Food and Drug Administration (FDA). Summary of safety and effectiveness: InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion Device [P000058] (2002). Available at <https://www.accessdata.fda.gov> (accessed July 13, 2023).
3. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am. Dec 2002; 84(12):2123-2134. PMID 12473698
4. Howard JM, Glassman SD, Carreon LY. Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest. Spine J. Jun 2011; 11(6):534-537. PMID 20947439

5. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med. Jun 18 2013; 158(12):877-889. PMID 23778905
6. Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med. Jun 18 2013; 158(12):890-902. PMID 23778906
7. United States Senate Finance Committee. Staff report on Medtronic's influence on INFUSE clinical studies. Int J Occup Environ Health. Apr-Jun 2013; 19(2):67-76. PMID 23684264
8. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. Jun 2011; 11(6):471-491. PMID 21729796
9. Feng JT, Yang XG, Wang F, et al. Efficacy and safety of bone substitutes in lumbar spinal fusion: a systematic review and network meta-analysis of randomized controlled trials. Eur Spine J. Jun 2020; 29(6):1261-1276. PMID 31872300
10. Liu S, Wang Y, Liang Z, et al. Comparative clinical effectiveness and safety of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion: A meta-analysis and systematic review. Spine (Phila Pa 1976). Jun 15 2020; 45(12):E729-E741. PMID 31923133
11. Mariscal G, Nunez JH, Barrios C, et al. A meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for the posterolateral fusion of the lumbar spine. J Bone Miner Metab. Jan 2020; 38(1):54-62. PMID 31292724
12. Wu Z, Zhou B, Chen L, et al. Bone morphogenetic protein-2 against iliac crest bone graft for the osterolateral fusion of the lumbar spine: A meta-analysis. Int J Clin Pract. Apr 2021; 75(4):e13911. PMID 33277737
13. Carragee EJ, Chu G, Rohatgi R, et al. Cancer risk after use of recombinant bone morphogenetic protein-2 for spinal arthrodesis. J Bone Joint Surg Am. Sep 4 2013; 95(17):1537-1545. PMID 24005193
14. Zadegan SA, Abedi A, Jazayeri SB, et al. Bone morphogenetic proteins in anterior cervical fusion: a systematic review and meta-analysis. World Neurosurg. Aug 2017; 104:752-787. PMID 28315798
15. Khan TR, Pearce KR, McAnany SJ, et al. Comparison of transforaminal lumbar interbody fusion outcomes in patients receiving rhBMP-2 versus autograft. Spine J. Mar 2018; 18(3):439-446. PMID 28822825
16. Cooper GS, Kou TD. Risk of cancer after lumbar fusion surgery with recombinant human bone morphogenic protein-2 (rh-BMP-2). Spine (Phila Pa 1976). Oct 01 2013; 38(21):1862-1868. PMID 23883824
17. Cooper GS, Kou TD. Risk of cancer following lumbar fusion surgery with recombinant human bone morphogenic protein-2 (rhBMP-2): An analysis using a commercially insured patient population. Int J Spine Surg. Apr 2018; 12(2):260-268. PMID 30276083
18. Dettori JR, Chapman JR, DeVine JG, et al. Longer follow-up continues to reveal no increased risk of cancer with the use of recombinant human bone morphogenetic protein in spine fusion. Spine J. Oct 2019; 19(10):1640-1647. PMID 31108234

19. Dai J, Li L, Jiang C, et al. Bone morphogenetic protein for the healing of tibial fracture: a meta-analysis of randomized controlled trials. PLoS One. Oct 2015; 10(10):e0141670. PMID 26509264
20. Garrison KR, Shemilt I, Donell S, et al. Bone morphogenetic protein (BMP) for fracture healing in adults. Cochrane Database Syst Rev. Jun 16 2010(6):CD006950. PMID 20556771
21. Lyon T, Scheele W, Bhandari M, et al. Efficacy and safety of recombinant human bone morphogenetic protein-2/calcium phosphate matrix for closed tibial diaphyseal fracture: a double-blind, randomized, controlled phase- II/III trial. J Bone Joint Surg Am. Dec 4 2013; 95(23):2088-2096. PMID 24306695
22. Cannada LK, Tornetta P, Obremskey WT, et al. A randomized controlled trial comparing rhBMP-2/absorbable collagen sponge versus autograft for the treatment of tibia fractures with critical size defects. J Orthop Trauma. Aug 2019; 33(8):384-391. PMID 31022069
23. Ratko TA, Belinson SE, Samson DJ, et al. Bone Morphogenetic Protein: The State of the Evidence of On-Label and Off-Label Use (AHRQ Technology Assessment Report). Rockville, MD: Agency for Healthcare Research and Quality; 2010. PMID 25855840
24. Ramly EP, Alfonso AR, Kantar RS, et al. Safety and efficacy of recombinant human bone morphogenetic protein-2 (rhBMP-2) in craniofacial surgery. Plast Reconstr Surg Glob Open. Aug 2019; 7(8):e2347. PMID 31592029
25. U.S. Food and Drug Administration (FDA). Infuse Bone Graft. Summary of safety and effectiveness data (Mar 2007). Available at <https://www.accessdata.fda.gov> (accessed July 13, 2023).
26. Valentin-Opran A, Wozney J, Csimma C, et al. Clinical evaluation of recombinant human bone morphogenetic protein-2. Clin Orthop Relat Res. Feb 2002; 395:110-120. PMID 11937870
27. Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future development. J Bone Joint Surg Am. 2003; 85-A(Suppl 3):82-88. PMID 12925614
28. Kaiser MG, Groff MW, Watters WC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. J Neurosurg Spine. Jul 2014; 21(1):106-132. PMID 24980593
29. North American Spine Society (NASS). NASS Coverage Policy Recommendations: Recombinant Human Bone Morphogenetic Protein (rhBMP-2) (2014). Available at <https://www.spine.org> (accessed February 27, 2023).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
09/15/2024	Reviewed. No changes.
10/01/2023	Document updated with literature review. The following changes were made in Coverage 1) Editorial: the term “patients” changed to “individuals”; 2) the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) changed from not medically necessary to experimental, investigational, and/or unproven for all other indications, including but not limited to spinal fusion when the use of autograft is feasible, and craniomaxillofacial surgery. Added reference 12, others updated.
07/15/2022	Reviewed. No changes.
09/15/2021	Document updated with literature review. Coverage unchanged. Added references 2, 3, 9-11, 15-17, 21, 23, 28; others updated.
07/15/2020	Reviewed. No changes.
10/01/2019	Document updated with literature review. The following changes were made in Coverage: 1) Term changed from “unfeasible” to “not feasible” 2) Added additional criteria for acute, open fracture of the tibial shaft to include: a) The INFUSE Bone Graft is applied within 14 days after the initial fracture; and b) The fracture is stabilized with intramedullary nail fixation after appropriate wound management. No new references.
07/15/2017	Reviewed. No changes.
01/01/2017	New medical document. Coverage states: 1) Use of recombinant human bone morphogenetic protein-2 (rhBMP-2; Infuse®) may be considered medically necessary in skeletally mature patients for anterior lumbar interbody fusion procedures when use of autograft is unfeasible, for instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is unfeasible and for the treatment of acute, open fracture of the tibial shaft, when use of autograft is unfeasible. 2) Bone morphogenetic protein (rhBMP-2) is considered not medically necessary for all other indications, including but not limited to spinal fusion when use of autograft is feasible. 3) added NOTE: Use of iliac crest bone graft (ICBG) may be considered unfeasible due to situations that may include, but are not limited to, prior harvesting of ICBG or need for a greater quantity of ICBG than available (e.g., for multilevel fusion).