
Medical Policy



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***Current Policy Effective Date: 9/1/26**
(See policy history boxes for previous effective dates)

Title: Bone Morphogenetic Protein

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.

Medical Policy Statement

The use of recombinant human bone morphogenetic protein-2 (Infuse™) is established when inclusionary criteria have been met.

Inclusionary and Exclusionary Guidelines

INCLUSIONS:

The use of **recombinant human bone morphogenetic protein-2 (Infuse™)** (osteoinductive) is indicated in skeletally mature patients when used as described per FDA approval when **ONE** of the following are met:

1. For spinal indications when **ALL** of the following criteria are met:

- a. For treatment of degenerative disc disease
- b. The graft is used with the appropriate FDA-approved cage
- c. Surgery is planned for one level from L2-S1 via anterior, oblique, or direct lateral approach; OR, one or two adjacent levels from L2-S1 via transforaminal interbody approach (TLIF)
- d. There is a high risk of failure of fusion (prior failed spinal fusion, recent history of smoking, presence of diabetes or renal disease, alcoholism, long-term steroid use, or osteoporosis)
- e. Autologous bone and/or marrow are not available or not expected to promote fusion

OR

2. For use in tibia trauma indications when the following is met:

- a. For the treatment of acute, open fracture of the tibial shaft when the use of autograft is not feasible*.

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

EXCLUSIONS:

The following are considered contraindications in the use of bone morphogenetic protein:

1. Planned posterior approach fusion other than indicated above.
2. Cervical or thoracic indications or any other indications (i.e., craniomaxillofacial surgery) not listed above.
3. Known sensitivity to implant material or bovine type II collagen, or with an allergy to titanium (including alloys) or polyetheretherketone (PEEK)
4. Use near the site of extant or resected tumor, or for patients with active malignancy or receiving treatment for cancer
5. Infection at the planned operative site
6. Individuals under 18, or skeletal immaturity
7. Female individuals who are pregnant
8. In combination with another allograft (see Bone Graft Substitutes policy)

CPT/HCPCS Level II Codes

Established codes:

20930*	22533	22558
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Other codes (investigational, not medically necessary, etc.):

N/A

Notes:

- *Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*

- *Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*

*Note: 20930 can also be used for other bone allografts aside for BMP. Product name is required to determine approval for other allografts. 20930 may only be requested at a quantity of 1 per procedure for the same operative session regardless of how many allografts are planned.

Background

Bone Morphogenetic Protein and Carrier and Delivery Systems

Bone morphogenetic proteins (BMP) 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 have 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 allografts. The rhBMP and carrier may be inserted via a delivery system, which may also provide mechanical support.

Currently the only BMP that has received FDA approval for certain clinical indications is produced by Medtronic under the brand name Infuse.

The objective of this evidence review is to determine whether the use of bone morphogenetic protein 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).

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). 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 non-instrumented 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.

Summary of Evidence

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

Rationale

Evidence reviews assess 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 individuals 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. The following is a summary of the key literature to date.

Lumbar Spinal Fusion

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 investigation⁷ 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 iliac 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 more recent systematic reviews and meta-analyses are described in Tables 1 and 2, with results described in Table 3.

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 Oswestry 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 Oswestry 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 1 and 2 describe study characteristics and Table 3 describes study results.

Table 1. 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)	●			
Coughlan et al (2018)	●			

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

Table 2. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration (Range)
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Feng et al (2019) ⁹	2002-2018	27	Patients diagnosed with lumbar degenerative disease undergoing spinal fusion with bone graft materials (rhBMP vs. ICBG)	2488 (10 to 239)	RCTs	mean, 19.8±8.5 months (6 to 36)
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, 24 months (12 to >48)
Wu et al (2020) ¹²	2000-2017	14	Adults undergoing posterolateral fusion of the spine and receiving rhBMP-2 or ICBG	1516 (14 to 372)	RCTs	NR

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

Table 3. 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 (rhBMP vs. ICBG)	Oswestry 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 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.
¹Non-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 Medicare¹⁶ and from a commercial insurer database¹⁷, 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

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).

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.

Chen et al (2025) conducted a large multicenter randomized controlled trial evaluating the efficacy and complications of low-dose rhBMP-2 compared with iliac crest bone graft in anterior cervical discectomy and fusion (ACDF) for degenerative cervical spine disease.²⁶ A total of 1100 patients undergoing 1- or 2-level ACDF in China between 2013 and 2018 were enrolled and randomized to receive either 0.5 mg rhBMP-2 per level with a hydroxyapatite/gelatin/lecithin carrier or iliac crest autograft. All procedures used a zero-profile polyetheretherketone anchored spacer, and patients were followed for a minimum of 5 years. The primary outcomes included radiographic fusion at predefined intervals (3, 6, and 12 months) and key clinical measures (visual analog scale [VAS] and Japanese Orthopedic Association [JOA] questionnaire scores). Early fusion outcomes favored rhBMP-2: at 3 months, 83% of rhBMP-2 patients demonstrated radiographic fusion vs 74% in the iliac crest autograft group ($p < .05$). By 6 months and 1 year, fusion rates were equivalent (98% and 100%, respectively) in both groups. Both VAS and JOA improvements were similar across groups at all postoperative time points.

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 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 to review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they are 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.³ 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).⁴ NASS recommends adjunct use of rhBMP-2 in spinal fusion surgeries for the following clinical scenarios and qualifying criteria, as appropriate: (A draft update to the NASS coverage position is being developed, therefore an updated coverage position is not currently available.)

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 unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Ongoing and Unpublished Clinical Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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	600	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	Dec 2027
Unpublished			
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)	59 (actual)	June 2024 (actual)

NCT: national clinical trial; BMP: bone morphogenetic protein.

^a Denotes industry-sponsored or cosponsored trial.

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 5). 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-2Matrix 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 5. Recombinant Human Bone Morphogenetic Protein Products and Associated Carrier and Delivery Systems Approved by U.S. Food and Drug Administration

Systems	Manufacturer	Approved	PMA/HDE 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 • 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		12/15	P000058/S059
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; OLIF: oblique lateral interbody fusion; PMA: premarket approval; rhBMP: recombinant human bone morphogenetic protein; S: supplement; HDE: humanitarian device exemption.

^aMedtronic is the manufacturer for all of the INFUSE bone graft and carrier systems.

Government Regulations

National:

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

Local:

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

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Low Intensity Pulsed Ultrasound Fracture Healing Device
- Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Electric Bone Growth Stimulation of the Appendicular Skeleton

- Lumbar Spinal Fusion
 - Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/2023	6/13/23		Joint policy established Vendor: TurningPoint 8/28/23: When a policy include add-on codes, generally included is a list of appropriate primary procedure codes that it can be billed with. This is because the payability of the service depends on whether the primary procedure is covered. Added the below codes to the policy: 22533 and 22558 (ky)
9/1/24	6/11/24		• Routine maintenance • Vendor: TurningPoint (TP) - JUMP policy aligns with TP policy: OR-1005, Bone Morphogenetic Protein 4/2023. • Updated Inclusions – added coverage for InFUSE/MASTERGRAFT™ Posterolateral Revision Device System (or InFUSE BMP used with MASTERGRAFT) • Updated Exclusions within combination with another allograft (See Bone Graft Substitutes policy) Post JUMP changes: • Updated MPS and exclusions section based on discussion at JUMP. (ky)
9/1/25	6/17/25		Routine policy maintenance, minor changes to exclusion section for clarity, no change in status. Vendor: TurningPoint (ds)
9/1/26	6/16/26		Vendor: TurningPoint Annual review InFUSE/Mastergraft information removed to align with TurningPoint policy TLIF added to inclusions for Infuse (rh/mk)

Next Review Date: 2nd Qtr., 2027

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MORPHOGENETIC PROTEIN

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered criteria applied.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.