Subject: Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion

Background: Bone morphogenetic proteins (BMPs) are members of the larger transforming growth factors-beta (TGF-beta), and they play an important role in the stimulation of bone formation. Recombinant human bone morphogenetic proteins (rhBMPs) are delivered to the bone grafting site as part of a surgical procedure through carrier systems, which are absorbed over time and function to maintain the concentration of rhBMPs at the treatment site.

Policy and Coverage Criteria:
Harvard Pilgrim Health Care (HPHC) considers recombinant human bone morphogenetic protein-2 (e.g. rhBMP-2, InFUSE) as reasonable and medically necessary when members reach skeletal maturity and for ANY of the following:
- As an alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed; OR
- For intertransverse spinal fusion procedures at one or more levels in members with at least 6 months’ duration of degenerative disc disease from L2-S1 when autograft is unfeasible; OR
- For the treatment of acute, open fracture of the tibial shaft when autograft is unfeasible

Exclusions: Harvard Pilgrim Health Care (HPHC) considers rhBMP-2 as experimental/investigational for all other indications. In addition, HPHC does not cover:
- rhBMP-7 (OP-1)
- When autograft is feasible

Supporting Information:
BMPs belong to a family of growth factors and play an important role in bone and cartilage formation, fracture healing, and repair of other musculoskeletal tissues. The function of this osteoinductive protein is to attract and promote differentiation of pluripotent mesenchymal cells into chondrocytes and osteoblasts, promote differentiation of osteoprogenitors into osteoblasts, and influence skeletal pattern formation. BMPs can positively influence bone formation at several points along the developmental and healing pathway. BMP overcomes many disadvantages of both autografts and bone allografts. In order to remain confined within the region of repair, rhBMP must be used in conjunction with a suitable carrier. Collagen is currently the most common carrier. The approved technique for using INFUSE involves reconstituting the powdered rhBMP-2 with sterile water, drawing it into a syringe, and distributing it on an absorbable bovine tendon type I collagen sponge, which is placed in a cage that serves as the fusion device. OP-1 Putty is composed of rhBMP-7, bovine collagen, and a putty additive that is mixed with sterile saline solution to form a paste, which is applied directly to bone at the fusion site. Marketed in the U.S. as INFUSE® Bone Graft (Medtronic Sofamor Danek) as an alternative to autogenous bone graft in certain types of spinal surgery, acute tibia fracture treatment, and some oral maxillofacial procedures. Marketed in the U.S. as OP-1® Putty (Stryker Biotech) it is aimed at an alternative to autogenous bone graft in some spinal and trauma procedures.
Pimenta et al. (2013) published results of an RCT comparing rhBMP-2 with synthetic silicate calcium phosphate as bone graft substitutes and their effect of fusion rates and clinical outcomes in patients undergoing single-level lumbar stand-alone extreme lateral interbody fusion. 15 patients underwent the procedure with rhBMP-2 and 15 with the silicate material. Clinical and radiographic results were compared between the two groups. Clinical outcomes were similar improved between the two groups from baseline to 36 months postoperatively. Complication rates between the two were similar, though with slightly more instances of subsidence in the silicate group and high rates of excessive bone formation and adjacent segment disease in the rhBMP-2 group. Additional studies have evaluated complications related to the use of rhBMP-2 used in posterior lumbar spinal fusion and did not identify a significant increase in complication rates (Cahill et al. 2011; Williams et al. 2011; Glassman et al. 2011).

A 2011 retrospective study by Tressler et al. investigated the results of rhBMP-2 compared to autologous iliac crest bone graft in the treatment of long-bone non-union. 19 patients with non-union received rhBMP-2 and 74 non-union patients received autologous iliac crest bone graft. Results showed no statistical difference in the rate of healing between the two groups. rhBMP-2 patients had a lower incidence of postoperative infection and a shorter intraoperative time. The authors concluded the outcomes suggest rhBMP-2 may be a suitable alternative to iliac bone graft for long bone non-unions.

Protocols followed by four studies of lumbar fusion involved a posterolateral or PLIF approach, neither of which is included in the FDA approval of INFUSE (Boden et al., 2002; Haid et al., 2004; Glassman et al., 2005; Singh et al., 2006). In Boden et al. (n=25), rhBMP-2 was used with or without an internal fixation device, the Texas Scottish Rite Hospital pedicle screw instrumentation (TSRH), and compared with autogenous iliac crest bone graft (AICBG) in conjunction with TSRH. The rhBMP carrier was not collagen but rather granules of hydroxyapatite/tricalcium phosphate (HA/TCP). At 1-year follow-up, there was fusion in 100% of each investigational arm and in only 40% of the control group. The very small number of patients (n=5) in the control group precluded a reliable estimate of fusion success rate. Pain and disability were considered secondary outcomes in this study. However, the rhBMP-2-alone group had consistently and substantially superior clinical outcomes than either the rhBMP-2 with TSRH- or AICBG with TSRH-group. These measures included the OLBPDQ, back and leg pain, the SF-36 PCS, and patient assessment of whether the outcome was good/excellent. The authors did not see a clear explanation for the difference in clinical outcomes between the two investigational groups. They speculated that this had to do with the more extensive retraction and prolonged operative time necessitated by internal fixation. There were a few adverse events in the two investigational arms and none in the control group, but again, the size of the control group limits conclusions about safety differences.

Haid et al. (2004) (n=67) used Inter Fix cages for PLIF and randomized patients to the INFUSE product or AICBG within the cages. They found that the fusion rate was much higher in the rhBMP-2 group (97.3% patients) than in the control group (77.8%). However, a more clinically relevant measure of fusion success comparable with that used by Burkus et al. (2002 and 2005) was nearly identical in the two groups (82.4% and 81.8%). The use of rhBMP-2 appeared to result in substantially greater improvement of neurological symptoms, although the differences were statistically significant only for back pain. Patients in the rhBMP-2 group had somewhat better functional improvement, as measured by the OLBPDQ and the SF-36 PCS, but differences were not tested statistically. rhBMP-2 appeared to be more successful in enabling patients to work (an increase of 8.8% working at 2 years compared with a decrease of 3.1% of patients in the control group) or return to work (at 43 versus 137 days). However, patient satisfaction was slightly higher (nonsignificant) in the control group. There were no safety differences other than a significantly greater incidence of bone formation outside the disc space in the rhBMP-2 group (70% versus 12%). The study was suspended due to this finding, but it did not appear to have any relationship to increased leg pain. A limitation of this study was a 10.4% loss to follow-up or dropout rate at 24 months in the rhBMP group; there was no loss to follow-up after this interval in the control group.

**HPHC Clinical Medical Policy**

**Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion**

HPHC policies are based on medical science, and written for the majority of people with a given condition.

Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.
Dimar et al. (2009) reported on a multi-center RCT comparing results of patients with degenerative disc disease treated with either AICBG or rhBMP-2. 224 control patients underwent AICBG and 239 underwent rhBMP. The ODI, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12, and 24 months postoperatively. Radiographs and computed tomography scans were made at 6, 12, and 24 months postoperatively to evaluate for fusion. Results found both groups had similar improvements in pain and disability scores. At 24 months, results suggested rhBMP-2 patients had more successful fusion than those in the control group.

Vaccaro et al. (2008) published the results of a randomized controlled multicenter trial comparing the safety and clinical radiographic efficacy of OP-1 (rhBMP-7) Putty with an iliac crest bone autograft control in uninstrumented, single-level posterolateral spinal arthrodesis. 335 patients were randomized 2:1 to receive either OP-1 Putty or autograft. Radiographs, clinical examinations, and appropriate clinical indicators, including ODI, SF-36 and VAS scores were observed serially. Serum samples were also measured at regular intervals to assess the presence of antibodies to OP-1. Overall success was evaluated at 24 months. The study was then extended to include additional imaging data and long-term clinical follow-up at 36+ months. Results found OP-1 Putty demonstrated statistical equivalency to autograft with respect to the primary end point of overall success. OP-1 Putty has statistically lower intraoperative blood loss and shorter operative times. Vaccaro et al. concluded OP-1 to be a safe and effective alternative to autograft in the setting of uninstrumented posterolateral spinal arthrodesis performed for degenerative spondylolisthesis and symptomatic spinal stenosis.

Singh et al. (2006) (n=52) designed a study to test the osteoconductivity of a reduced dose of rhBMP-2 on absorbable collagen sponge combined with autogenous bone as a bulking agent. Patients enrolled for the study underwent instrumented posterolateral lumbar fusion. rhBMP-2 was used as an adjunct to AICBG, with laminectomy bone added to the collagen sponge; all three graft materials were placed on either side of the spine at each affected level. Results were compared with those of 11 sex-matched patients who had undergone the same procedure without the addition of rhBMP-2 (AICBG, with laminectomy bone plus collagen sponge). No serious adverse events were observed. The rhBMP-2 group exhibited more probable fusion, higher quality fusion, and earlier fusion according to interpretation of computed tomography (CT) scans. Differences were substantial. Glassman et al. (2005) (n=74) reported interim fusion results at one of multiple sites participating in a randomized controlled trial approved by the FDA as an investigational device exemption (IDE) protocol (G00137) to evaluate the CD Horizon® Spinal System (Medtronic Sofamor Danek) for instrumented posterolateral fusion. This fusion system applies rhBMP-2 to a bovine collagen/HA-TCP compression resistant matrix (CRM). Patients were randomized to the CD-Horizon system or AICBG. A significant difference in fusion grade was observed as early as 6 months. After 1 year, the mean fusion grade (on a scale of 1 for no fusion to 5 for solid bilateral fusion) was 4.62 for the rhBMP-2 group and only 3.77 (P<0.0023) for the control group. The proportions of patients with grade 4 or 5 were 89% and 66%, respectively. The authors' scheme for grading fusion was not part of the IDE protocol, and no clinical outcomes were presented.

Swiontkowski et al. (2006) combined results from the randomized controlled trial reported by Govender et al. (2002) with a smaller trial (n=60) in U.S. centers only. The U.S. study followed a design identical to that of the BESTT trial. Data for the 0.75 mg/mL treatment group in the BESTT trial were excluded. This analysis was published partly in response to criticisms of the earlier study, including the claim that the study group was not representative of the U.S. population due to differences in the use of reaming, which was left up to the discretion of the surgeon. The U.S.-only study group did, indeed, have a higher rate of reaming (50% and 53% in interventional and control groups) than the BESTT trial study group (40% and 26%). Since reaming had been shown by Govender et al. to have an independent effect in preventing the need for secondary procedure, the results from that study would not be entirely generalizable to the U.S. Swiontkowski et al. also intended to further explore the earlier finding that the effect of rhBMP-2 on infection rates was stronger in patients with severe
fractures. Raw data from the two studies were combined for two subgroup analyses: (1) severe (Gustilo-Anderson type IIIA-IIIb) fractures and (2) reamed nailing. The severe fracture subgroup analysis showed that rhBMP-2 reduced the risk of secondary procedure by 68% (compared with 44% in the entire BESTT trial study group), improved time to full weight bearing from 126 to 95 days, and reduced infection by 47% (about the same as in the severe fracture subgroup of the BESTT trial). In the reamed nailing subgroup of the combined analysis, these outcomes were only modestly and non-significantly superior in the rhBMP-2 treatment group compared with standard treatment. Thus, the greater benefit of rhBMP-2 for severe fractures than for mild-to-moderate fractures and the confounding effect of reamed nailing were corroborated.

Vaccaro et al. (2005) prospectively enrolled 12 patients for a trial of OP-1 Putty plus AICBG. At 24 months, fusion success was observed in 50% of patients and clinical success (20% improvement in OLBPDQ score) was observed in 89% of patients. These rates were reduced to 42% and 67% when patients who were lost to follow-up, dropped out, or had poor film quality were included in the analysis and counted as failures. A group of historical controls exhibited a 50% fusion success rate.

Clinical studies evaluating the use of rhBMP-2 in patients with tibial fractures have supported safety and efficacy. Govender et al., (2002); Jones et al., (2006); Swiontkowski et al., (2006) reviewed the use of BMP-2 in patients with tibial fractures. In order to partially compensate for the lack of surgeon blinding, overall treatment success was defined in terms of both blinded radiographic assessment and unblinded clinical assessment. Govender et al. (2002) conducted a multicenter randomized controlled trial involving 49 centers in 11 countries, referred to as the BMP-2 Evaluation in Surgery for Tibial Trauma (BESST) Trial. The study group consisted of 450 patients with open tibial fractures. Both treatment groups underwent standard primary treatment (intramedullary nail fixation). The trial compared the addition of an rhBMP-2 implant (rhBMP-2 on collagen sponge) at two different concentrations (0.75 mg/mL and the approved concentration of 1.5 mg/mL) with standard treatment alone, based on earlier evidence that the osteoinductive effect of rhBMP-2 is driven by concentration rather than dose. The primary outcome measure was the proportion of patients requiring secondary interventions due to delayed union or nonunion within 12 months post surgery. Patients with rhBMP implants were substantially less likely to require secondary intervention (37% at 0.75 mg/mL and 26% at 1.5 mg/mL) than patients receiving nail fixation alone (46%), and a statistically significant dose-response relationship was demonstrated ($P=0.0004$). This difference, however, did not meet the authors’ a priori definition of clinical significance (difference of 30%). Compared with standard treatment alone, rhBMP-2 at 1.5 mg/mL reduced the risk of secondary procedure by 44%. rhBMP-2 implants also reduced the invasiveness of procedures, promoted faster healing, and resulted in greater overall treatment success (54% and 65% for the lower-dose and higher-dose rhBMP-2 implants, 47% for nail fixation alone; $P=0.0028$). The authors did not offer an explanation for the modest treatment success observed in all groups. Adverse events were substantially less frequent in patients who received the rhBMP-2 implants; differences in infection rates were observed only in the more severe fractures. Multivariate analysis of potential predictors of the need for secondary procedure revealed rhBMP-2 implant and the use of reaming to be independent predictors. Reaming involves enlargement of the intramedullary canal to facilitate the insertion of a nail larger than the intramedullary canal. Differences in use of reaming (used more frequently in the two rhBMP-2 groups) do not fully explain outcome differences since both rhBMP-2 and reaming had independent effects in multivariate analysis. However, the role that reaming played in this study is difficult to assess since the authors do not report the values of the relative risks associated with rhBMP-2 and reaming in multivariate analysis; they also do not identify the other variables included in the model.

There are few studies that have assessed rhBMP-7 in tibial fractures. Two randomized controlled trials evaluated rhBMP-7 as an aid to promoting bone repair in tibial fracture with nonunion (Friedlaender et al., 2001) or fresh tibial fracture (Maniscalco et al., 2002). Friedlaender et al. (n=122) followed a protocol consistent with the HDE for OP-1 Implant. Inclusion criteria included nonunion of a tibial fracture at $\geq$ 9 months following injury. The

**HPHC Clinical Medical Policy**

Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion

*HPHC policies are based on medical science, and written for the majority of people with a given condition.*

*Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.*
control was IM fixation with fresh bone autograft, and the intervention was IM fixation with implantation of rhBMP-7 in a type I collagen carrier. At 9-month follow-up (after treatment of nonunion), clinical success, physician satisfaction, and bone bridging were slightly better in the control group. Most adverse events were similar in the two groups, except for a much higher incidence of osteomyelitis in the control group. The advantage of using rhBMP-7 was that it gave similar results without the need for bone-harvesting surgery. The limitation to this study was the short follow-up (primary endpoint was 9 months). However, the clinical success rate at 2 years was 82% of patients in each group, nearly as high as at 9-month follow-up. Substantial loss to 2-year follow-up (38% of the control group and 26% of the investigational group) limits long-term conclusions. The other study (Maniscalco et al., 2002) (n=14) was designed to standardize the surgical procedure, to evaluate tolerance and toxicity to rhBMP-7, and to evaluate its potential to accelerate bone healing and functional recovery. It differed from both the study by Friedlaender et al. (2001) and the parameters defined by the HDE for OP-1 Implant in that treatment was for a recent fracture (mean time from injury < 1 week) rather than for nonunion. The study protocol involved randomizing patients with closed fractures of the tibial shaft to monolateral external fixation with rhBMP-7 applied at the fracture site (investigational group) or monolateral external fixation with fresh bone autograft (control group). The rhBMP-7 was well tolerated, and there were no adverse events associated with its use. However, there was no accelerated healing advantage conferred by the rhBMP-7, and its application required an extra incision. The authors concluded that rhBMP-7 is not indicated for fresh shaft fractures of the tibia. This study was limited by the small number of patients and short follow-up period (5 months).

Based on the available evidence, the North American Spine Society states rhBMP is indicated as an adjunct to spinal fusion in cases in which other alternatives are either not available or are not likely to lead to successful fusion.

**Guidelines:**
The U.S. Food and Drug Administration (FDA) approval process consisted of individuals undergoing single-level laparoscopic lumbar interbody fusion with rhBMP-2. Although there were no differences in fusion success rates, there was significantly less blood loss and pain in those receiving rhBMP-2.

The Institute for Clinical and Economic Review recommended that rhBMP-2 be used in conjunction with a FDA approved device for the treatment of individuals undergoing single level anterior lumbar interbody spinal fusion for symptomatic single level degenerative disc disease of at least six months’ duration that has not responded to non-operative treatment.

**Coding:**
Codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible.

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20930</td>
<td>Allograft, morselized, or placement of osteopromotive material, for spine surgery only (list separate in addition to code for primary procedure)</td>
</tr>
<tr>
<td>20999</td>
<td>Unlisted procedure, musculoskeletal system, general</td>
</tr>
</tbody>
</table>

**Billing Guidelines:**
Member’s medical records must document that services are medically necessary for the care provided. Harvard Pilgrim Health Care maintains the right to audit the services provided to our members, regardless of the

**HPHC Clinical Medical Policy**

Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion

HPHC policies are based on medical science, and written for the majority of people with a given condition.

Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.
participation status of the provider. All documentation must be available to HPHC upon request. Failure to produce the requested information may result in denial or retraction of payment.

References:

HPHC Clinical Medical Policy

Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion

HPHC policies are based on medical science, and written for the majority of people with a given condition.

Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.

HPHC Clinical Medical Policy

Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion Page 7 of 8

HPHC policies are based on medical science, and written for the majority of people with a given condition.

Coverage described in this policy is standard under most HPHC plans. Specific benefits may vary by product and/or employer group. Please reference appropriate member materials (e.g., Benefit Handbook, Certificate of Coverage) for member-specific benefit information.
## Summary of Changes

<table>
<thead>
<tr>
<th>Date</th>
<th>Changes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/18</td>
<td>Policy coverage criteria refined, background, coding and references updated</td>
</tr>
<tr>
<td>4/17</td>
<td>Removed Benchmarks</td>
</tr>
</tbody>
</table>

Approved by Medical Policy Review Committee: 1/23/18  
Initiated: 6/07