Two recombinant human bone morphogenetic proteins (rhBMPs) are now commercially available, rhBMP-2, applied with an absorbable collagen sponge (InFUSE, Medtronic, Memphis, TN) and rhBMP-7, applied in putty (OP-1). These products have been investigated as an alternative 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.

Bone morphogenetic proteins (BMPs) are members of the family of transforming growth factors. At present, some 15 different BMPs have been identified, all with varying degrees of cartilage and/or bone inductive properties. 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, function to maintain the concentration of the rhBMP at the treatment site; provide temporary scaffolding for osteogenesis; and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymer, natural polymers, and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also function to provide mechanical support.

The carrier and delivery system are important variables in the clinical use of rhBMPs, and different clinical applications, such as long bone nonunion, or interbody or intertransverse fusion, may require different dosages of rhBMP along with different carriers and delivery systems. For example, rhBMP with pedicle and screw devices are commonly used for instrumented intertransverse fusion, while rhBMP with interbody cages are used for interbody spinal fusion. In addition, interbody fusion of the lumbar spine can be approached from an anterior, lateral, or posterior direction. Surgical procedures may include decompression of the spinal canal and insertion of pedicle screws and rods to increase stability of the spine.
Anterior lumbar interbody fusion (ALIF) provides direct visualization of the disc space through a peritoneal or retroperitoneal approach.

Extreme lateral interbody fusion (XLIF) and direct lateral interbody fusion (DLIF) use a lateral (retroperitoneal) approach through the psoas.

An axial approach to lumbar interbody fusion (AxiaLIF) is performed perpendicular to the long axis of the spine with access through the sacrum.

Posterior lumbar interbody fusion (PLIF) is performed through either a traditional open procedure with a long midline incision and wide muscle retraction, with laminotomy or with a minimally invasive approach using bilateral paramedian incisions.

Transforaminal interbody fusion (TLIF) provides posterior access to the spine with a unilateral approach to the disc space (facetectomy) through the intervertebral foramen. In minimally invasive TLIF, a single incision approximately 2-3 cm in length is made approximately 3 cm lateral to the midline, and a tubular retractor is docked on the facet joint complex to provide a working channel for facetectomy with partial laminectomy.

Posterior approaches (PLIF and 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 stabilization of the spine and are differentiated from instrumented or noninstrumented posterolateral intertransverse fusion, which involves the transverse processes. Due to the proximity of these procedures to the spinal canal, risks associated with ectopic bone formation are increased (e.g., radiculopathies). Increased risk of bone resorption around rhBMP grafts, heterotopic bone formation, epidural cyst formation, and seromas has also been postulated.

**Regulatory Status**

At the present time, two rhBMPs and associated carrier/delivery systems have received approval from the U.S. Food and Drug Administration (FDA). The InFUSE system consists of rhBMP-2 on an absorbable collagen sponge carrier. The labeled indications for these devices are summarized here. OP-1 consists of rhBMP-7 and bovine collagen, which is reconstituted with saline to form a putty.

1. **InFUSE Bone Graft in conjunction with 1 of 2 interbody fusion devices, i.e., either the LT-Cage Lumbar Tapered Fusion Device or the Inter Fix RP Threaded Fusion device.** This device received FDA approval through the premarket approval (PMA) process:
   - The device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at 1 level from L2-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit, and/or neurologic deficit and radiographic studies. These DDD patients may also have up to grade I spondylolisthesis at the involved level or retrolisthesis. The InFUSE™ Bone Graft/LT-CAGE™ devices are to be implanted via an anterior open or a laparoscopic approach. The InFUSE™ Bone Graft/INTER FIX™ Threaded Fusion Device; and InFUSE™ Bone Graft/INTER FIX™ RP Threaded Fusion Device are to be implanted via an anterior open approach only. Patients receiving the InFUSE™ Bone Graft/Interbody Fusion Device should have had at least 6 months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/Interbody Fusion Device. (Note: A
collagen sponge consists of the carrier, while the interbody fusion device is a delivery system. Use with posterior or transforaminal lumbar interbody fusion is considered off-label.)

- For the treatment of acute, open fractures of the tibial shaft
- For sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets (P050053, March 2007)

2. OP-1 (Stryker Biotech, Hopkinton, MA) has received 2 FDA approvals through the Humanitarian Device Exemption (HDE) process. HDE is available to devices intended for fewer than 4,000 patients per year; as part of this process, the manufacturer is not required to demonstrate unequivocal benefit but only “probable” benefit. OP-1 received the following labeled 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.”
- “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.”

Stryker Biotech recently sought FDA permission to expand use of OP-1 Putty to include use in uninstrumented posterolateral lumbar spinal fusion for the treatment of lumbar spondylolisthesis. In March 2009, an FDA advisory committee voted 6-1 against recommending the expanded approval.

Both OP-1 and InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion device are contraindicated in patients who are pregnant, may be allergic to any of the materials contained in the devices, have an infection near the area of the surgical incision, have had a tumor removed from the area of the implantation site or currently have a tumor in that area, or who are skeletally immature.

In July 2008, the FDA issued a public health notification regarding life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. The FDA has received reports of complications with the use of rhBMP in cervical spine fusion. These 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 describe 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 effectiveness of rhBMP in the cervical spine have not been demonstrated, and these products are not approved by the FDA for this use.

On July 27, 2010, the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee voted to endorse FDA approval of a PMA application for the AMPLIFY rhBMP-2 Matrix, sponsored by Medtronic. The AMPLIFY rhBMP-2 Matrix utilizes a higher dose of rhBMP (2.0 mg/mL) with a compression-resistant carrier and is being evaluated for posterolateral fusion treatment of single level lumbar (L2–S1) degenerative disc disease. The executive summary of the meeting is available online.
Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) may be considered **medically necessary** for the following indications:

- For anterior spinal interbody fusion procedures, in conjunction with an FDA-approved interbody fusion device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1. Patients should have failed at least 6 months of conservative treatment*;
- For instrumented posterolateral intertransverse spinal fusion procedures, in conjunction with an FDA-approved device, at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1. Patients should have failed at least 6 months of conservative treatment;
- For the treatment of acute, open fracture of the tibial shaft**.

Use of rhBMP-2 should be restricted to cases where there is a high risk of fusion failure. High risk for fusion failure can be defined by the presence of one or more of the following criteria:

- one or more previous failed spinal fusion(s);
- grade III or worse spondylolisthesis;
- fusion to be performed at more than one level;
- current tobacco use;
- diabetes;
- renal disease;
- alcoholism;
- steroid use.

Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) may be considered **medically necessary** for the following indications:

- As an alternative to autograft in compromised patients (e.g., osteoporosis, tobacco use, or diabetes) requiring noninstrumented revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion***;
- As an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed***.

* It has been reported that, in March 2011, Medtronic received a “nonapprovable letter” from the FDA for AMPLIFY.
Bone morphogenetic protein (rhBMP-2 or rhBMP-7) is considered investigational for all other indications, including but not limited to:

- Cervical spinal fusion;
- Posterior or transforaminal lumbar interbody spinal fusion;
- As initial treatment or revision of noninstrumented posterolateral intertransverse spinal fusion that does not meet the criteria listed above;
- As an alternative or adjunct to bone grafting in other locations, including craniomaxillofacial** surgeries.

*FDA approved for one level

**FDA-approved indication

***FDA approved under a Humanitarian Device Exemption (HDE)

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Policy Guidelines

Because of the differing benefits and risks of iliac crest bone graft harvest and bone morphogenetic protein, patients should make an informed choice between the procedures.

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

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

In the setting of spinal fusion, bone morphogenetic proteins may be used primarily as an alternative to autologous bone grafting. Since harvesting of autologous bone graft is coded separately from the fusion procedure (i.e., CPT codes 20936-20938), when bone morphogenetic protein is used as an alternative to the bone graft, these codes should no longer be reported. In contrast, the CPT code for treating tibial fracture nonunions with autograft (i.e., CPT code 27724) includes the harvesting component, and, therefore, when bone morphogenetic protein is used as an alternative in this setting, presumably the associated physician’s work would be decreased since no autologous harvest is required. Finally, for treatment of acute, open tibial fractures, bone morphogenetic protein is not used as an alternative to autologous bone graft, but in addition to standard treatment with an intramedullary nail.

ICD-9 procedure code 84.52 explicitly identifies the use of bone morphogenetic protein:

84.52: Insertion of recombinant bone morphogenetic protein rhBMP (via collagen sponge, coral, ceramic, or other carriers)

This ICD-9 code notes that the code 84.52 should be used in conjunction with the primary procedure performed:
79.00-79.99: Fracture repair
81.00-81.08: Spinal fusion
81.30-81.39: Spinal refusion

Note that the code ranges of the above ICD-9 codes include any type of fracture repair or spinal fusion.

Rationale

At the time this policy was created, randomized clinical trials supported the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in the treatment of interbody spinal fusion when used in conjunction with a tapered cage and also in the treatment of open tibial fractures. (2) In addition, a randomized study supported the use of rhBMP-7 in the treatment of recalcitrant nonunions of the long bones. (3) There were inadequate data to document efficacy in other clinical applications. Specifically, approval by the U.S. Food and Drug Administration (FDA) through the Humanitarian Device Exemption of rhBMP-7 in the treatment of revision posterolateral spinal fusion was based on a small trial of 48 patients. While the largest clinical trials and randomized studies demonstrated that rhBMP can be an alternative to an autologous bone graft for interbody spinal fusion, treatment of tibial fractures, and fracture nonunions, these results could not be extrapolated to other clinical indications for autologous bone graft because of the variable of the carrier and delivery systems. Use of these devices as part of a posterior interbody lumbar fusion was an off-label indication.

Since the policy was created, the literature has been updated periodically using the MEDLINE database. Studies published in 2005 supported the conclusion that rhBMP is an effective component of multilevel fusion procedures, and the policy statement no longer limited its use to a single level. In 2006, the policy statement was revised to exclude the limitation of rhBMP carrier systems. In 2009, the policy was revised to consider use of rhBMP-2 in instrumented posterolateral intertransverse fusion and selected use of rhBMP-7 in noninstrumented posterolateral intertransverse fusion, as medically necessary. The most recent literature review was for the period July 2011 through July 2012.

The following summarizes the results of key clinical trials involving either OP-1 or the InFUSE product for different indications. It should be noted that the majority of trials were designed to show that use of rhBMP is equivalent (not superior) to autologous bone grafting for bone grafting. Although the proposed advantage of rhBMP is the elimination of a separate incision site required for harvesting of autologous bone graft and the associated pain and morbidity secondary to this procedure, a 2011 study by Howard and colleagues raises questions about the magnitude of pain observed with iliac crest bone graft harvesting. (4) In this study, 112 patients who had an instrumented posterolateral lumbar fusion at 1 or 2 levels were seen at a tertiary spine center for a routine postoperative visit. Iliac crest bone graft was harvested in 53 patients (47.3%) through the midline incision used for lumbar fusion and recombinant human
bone morphogenetic protein (rhBMP-2) was used in 59 patients (52.7%) with no graft harvest. An independent investigator who was not directly involved in the care of the patient and was unaware of the type of bone graft used in the fusion examined the 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 (3.8 vs. 3.6 on a 10-point scale). While 54% of patients complained of tenderness over one or both iliac crests, only 10 patients (9% of 112) had pain over the same crest from which the graft was harvested (mean pain score of 4.4).

Spinal Fusion

A 2008 meta-analysis evaluated 2 randomized controlled trials (RCTs) (plus a follow-up report), 4 quasi-randomized trials, and 1 prospective comparative study (total of 383 patients) on posterolateral fusion (interbody or intertransverse) of the lumbar spine. (5) Reoperation rates were not significantly different between the rhBMP and autograft groups. Data from 2 of the trials showed that patients treated with rhBMPs had a shorter hospitalization (by 1 day) compared with patients treated with iliac crest bone graft. The overall fusion failure rate was 14.5% for the rhBMP group and 39% for the autograft group. Number-needed-to-treat analysis indicated that 4 posterolateral fusion procedures with the use of autologous bone graft would result in one additional case of fusion failure. Subgroup analysis indicated that rhBMP-2 was more efficacious than iliac crest bone graft in promoting fusion (relative risk [RR]: 0.29), whereas rhBMP-7 was equivalent to autograft (RR: 1.17). As discussed, the carrier and delivery system are important variables in the clinical use of rhBMPs. The relative contribution of instrumentation, carrier (absorbable sponge or putty), dose, and type of rhBMP are addressed in further detail below.

In 2009, Agarwal and colleagues published a meta-analysis of osteoinductive bone graft (stimulate new bone formation) substitutes for lumbar fusion in patients with degenerative disc disease (DDD). (6) The interventions examined were rhBMP-2, rhBMP-7, demineralized bone matrix, and platelet gel. Seventeen studies (1,342 patients) met the inclusion criteria, including 9 RCTs and 5 prospective controlled trials. Procedures included anterior lumbar interbody fusion (ALIF; 5 studies), posterolateral or posterior lumbar interbody fusion (PLF/PLIF; 11 studies), and anterior-posterior lumbar fusion (1 study). Four studies used rhBMP-2 for posterior fusion, which is not currently an FDA-approved indication. BMPs were combined with an osteoconductive material (scaffolding to support bone growth) in 9 of the 17 studies, and the comparison group was autologous iliac crest bone graft in all but 2 of the 17 studies. Meta-analysis of the 3 RCTs that compared rhBMP-7 with autologous bone graft showed no significant improvement in radiographic nonunion or Oswestry Disability Index (ODI). Meta-analysis of the 6 RCTs that compared rhBMP-2 with autologous bone graft showed a decrease in the risk of radiographic nonunion with rhBMP-2 following either ALIF or PLF/PLIF at 12-24 months. When the radiographic results were corrected for publication bias, the effect of rhBMP-2 remained clinically significant. It was calculated that 8 patients would be needed to treat to avoid 1 radiographic nonunion. Four RCTs on rhBMP-2 reported dichotomous data from the ODI. The ODI was not significantly improved by rhBMP-2 at 12-24 months’ follow-up; however, there was a trend toward benefit, and the studies were not powered to detect differences in clinical outcomes. Results were mixed regarding operating time, blood loss, and length of hospital stay.
The Agency for Healthcare Research and Quality (AHRQ) published a 2010 technology assessment on the state of the evidence of on-label and off-label use of rhBMP. (7) The assessment, which was prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, included the following conclusions:

- The evidence gives moderate support to clinical benefit from the on-label use of rhBMP-2 for fusion of the lumbar-sacral spine as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events. No significant adverse events were attributed to rhBMP-2 in any study. However, the size and duration of the trials were not sufficient to precisely determine the frequency and severity of adverse events. The strength of the evidence that off label use of rhBMP-2 in the lumbar-sacral spine improves radiographic fusion success is moderate. The strength of evidence that rhBMP-2 improves other outcomes is low.

- The strength of evidence is insufficient for the on-label use of rhBMP-7 in the lumbar spine. The evidence is insufficient to draw conclusions on the off-label use of rhBMP-7 in fusion of the lumbar-sacral spine.

- There is moderate evidence that off-label use of rhBMP-2 in anterior cervical spinal fusion increases cervical swelling and related complications. There is insufficient evidence to draw conclusions about radiographic fusion success or associated changes in neck disability scores.

- The quality of adverse event reporting in publications is variable and inconsistent, in particular with respect to attribution of harms to BMP use and the use of standardized or validated instruments to collect harms. It is also not clear that the absence of reported harms in many studies reflects true absence, or that the investigators did not seek such data or did not report it.

Mroz and colleagues published a 2010 systematic review of complications related to use of rhBMP. (8) The most commonly reported complications associated with rhBMP use in spine surgery include resorption/osteolysis, extradiscal/ectopic/heterotopic bone formation, graft subsidence, graft or cage migration, and elevated antibody response, and hematoma. The reported rate of rhBMP-related complications is highly variable (ranging from 0% to 100%), and there is a lack of data on rates of complications without rhBMP for comparative purposes. However, given the potential complications related to the use of rhBMP-2 in ventral cervical spine surgery, its use was not recommended. Data were considered insufficient to validate the use of rhBMP-2 for posterior cervical or thoracic fusion, and the potential complications related to the use of rhBMP-2 in posterior lumbar Interbody fusion raised concerns regarding its routine use in this application.

In 2011, Carragee and colleagues published a systematic review of emerging safety concerns with rhBMP-2. (9) The review compared conclusions regarding 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. 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 (overestimating of harm) in the reporting of iliac crest donor site pain. In addition, even though there were no rhBMP-2-associated adverse events reported in the original 13 trials (0 events in 780 patients), comparison between the published studies and FDA documents revealed internal inconsistencies and adverse events that were not reported in the published articles. Based on
the FDA data and subsequent studies, the systematic review estimated that adverse events with use of rhBMP-2 ranged from 10% to 50%, depending on the approach to spinal fusion.

- With anterior interbody lumbar fusion, there was a 10% to 15% risk of rhBMP-2-associated adverse events including osteolysis, subsidence, graft migration, cyst formation, neuritis, urinary retention, and retrograde ejaculation. A non-industry supported prospective cohort study of rhBMP-2 found more than 10% graft subsidence with a mean collapse of 27%. A controlled cohort study found greater subsidence and need for reoperation with rhBMP-2 compared with allograft alone. Infection and neurologic events (urogenital and retrograde ejaculation) were also higher with rhBMP-2 than controls. In one comparative study, the rate of retrograde ejaculation was 7.9% with rhBMP-2 and 1.4% with iliac crest bone graft. Another cohort controlled study found a risk ratio of 12.6 for retrograde ejaculation with rhBMP-2 and a number needed to harm of 15. FDA documents show a higher rate of urogenital events (7.9% vs. 3.6%) and delayed infections in the first year after surgery (4.2% vs. 1.4%).

- Posterior lumbar interbody fusion was associated with a 25% to 50% risk of adverse events including osteolysis, subsidence, graft migration, cyst formation, neuritis, and other events. Computed tomography (CT) scan found new bone formation in the spinal canal or neuroforamina in 70.1% of rhBMP-2 patients compared with 12.9% of controls. Although the investigators stated that these findings were not associated with adverse outcomes, FDA documents indicated that 2 patients had significant posterior bony overgrowth impinging on their nerve roots that required additional surgery. In addition, global outcomes at 2 years showed a trend for patients to be less satisfied with the surgery when rhBMP was used, which was possibly due to inflammation.

- In posterolateral fusions, there was strong, level 1 evidence (more than one randomized controlled trial [RCT]) suggesting that rhBMP-2 causes equivalent or greater pain and functional impairment (early back pain and leg pain) than iliac crest bone graft harvesting in the early postoperative period. In one study, early back and leg pain events occurred in 12.1% of rhBMP-2 cases compared with 5.4% of controls. There was also a higher rate of wound complications, and higher doses of rhBMP-2 (AMPLIFY) were associated with a greater apparent risk of new malignancy (3.8% vs. 0.9%).

- In the cervical spine, use of rhBMP-2 has been associated with a 40% greater risk of adverse events in the acute postoperative period including potentially life-threatening swelling of neck and throat tissue. One study reported a 1.5% rate of percutaneous endoscopic gastrostomy feeding, 3% reintubation, 4% emergency incision; drainage; and decompression of the prevertebral space, and 12% prolonged hospitalization. A 57% moderate or severe osteolysis rate and end-plate resorption with implant migration and loss of sagittal alignment has also been reported with rhBMP-2 in the cervical spine.

- Overall, this retrospective review of complications and adverse events as reported in FDA and other documents suggests the true risk to patients receiving rhBMP-2 may be 10 to 50 times the original estimates calculated from industry-sponsored publications (described below). A number of editorials and commentaries on these findings have been published in the same issue of the journal.

**Anterior Interbody Fusion of Lumbar Vertebrae**

The pivotal clinical trial of InFUSE (rhBMP-2) as part of the FDA approval process consisted of 279 patients undergoing single-level lumbar fusion via an open anterior approach who were
randomly assigned to receive either the LT (i.e., lumbar tapered)-cage with rhBMP-2 or the same cage filled with iliac crest autograft. (2) In a nonrandomized portion of the trial, an additional 136 patients underwent a single-level laparoscopic lumbar interbody fusion with rhBMP-2. There were no differences in fusion success rates, ODI, or back pain between the randomized groups. The group treated laparoscopically also had similar fusion rates. The operative time and blood loss were significantly lower in those receiving rhBMP-2, and these patients did not have to experience the pain and morbidity associated with the harvesting of autologous bone from the iliac crest.

A report by Burkus et al. in 2002 focused on the use of allograft bone dowels filled with rhBMP-2 on a collagen sponge. (10) A total of 46 patients undergoing a single-level open anterior lumbar discectomy and interbody fusion were randomly assigned to receive an allograft dowel filled with either rhBMP or autologous bone harvested from the iliac crest. At 12 and 24 months, the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. In 2005, Burkus and colleagues reported on rhBMP delivered with a threaded cortical allograft dowel, (11) a continuation of their 2002 study. (10) This study included 131 patients undergoing anterior interbody fusion who were randomly assigned to receive rhBMP on a threaded allograft or conventional fusion using autologous bone graft. Fusion rates were superior in the rhBMP group, as well as the subjective outcomes of pain and disability.

Additional studies published in 2005 reported on the outcomes of patients undergoing multiple levels of fusion with rhBMP-2. For example, Luhmann and colleagues reported on a case series of 70 patients undergoing multilevel fusions with both anterior and posterior surgical approaches. (12) The fusion rate was 93–100%, depending on the type of surgery, similar to that reported in the pivotal trials of the InFUSE product.

An increase in the rate of retrograde ejaculation following use of rhBMP-2 was reported by Carragee et al. in 2011. (13) This was a retrospective analysis of prospectively collected data from consecutive patients who had ALIF of L5/S1 with (n=69) and without (n=174) the use of rhBMP-2. Pre-operative clinical data along with operative details, post-operative outcomes, and complications (including retrograde ejaculation) had been recorded by independent research assistants in a de-identified database. Analysis of the 2 cohorts showed a significant increase in the rate of retrograde ejaculation in the rhBMP-2 group (7.2%) in comparison with the control group (0.6%).

**Posterior Interbody Fusion or Transforaminal Interbody Fusion of Lumbar Vertebrae**

Transforaminal interbody spinal fusion with rhBMP-2 was reported by Villavicencio et al. in 2005 in a consecutive case series of 74 patients, wherein some patients underwent multiple fusions and others underwent a minimally invasive approach in which the rhBMP was delivered on an absorbable collagen sponge. (14) The authors did not identify any differences in short-term outcomes and concluded that the use of an absorbable collagen sponge as a carrier permits a minimally invasive approach.

Results of PLIF in 2 similarly designed trials are comparable to anterior fusion. (15, 16) In one trial with 77 patients, the group receiving rhBMP-2 had a hospital stay of 3.4 days compared to 5.1 days for the control group. (15) Radiographic fusion success was observed in 92% versus 78% of patients, respectively, and success on the ODI was reported in 69% versus 56% of patients, respectively; these were not statistically significant. (16) New bone formation adjacent
to the interbody fusion cages, extending outside the disc space and into the spinal canal or neuroforamina, was found in 24 investigational and 4 control patients. However, the posterior bone formation was not correlated to a recurrence or increase in leg pain.

Neurologic impairment from ectopic bone in the lumbar canal following this off-label use of rhBMP-2 was reported by Wong et al. (17) Five patients had been referred to a tertiary spine institute with complications following use of rhBMP-2 for PLIF and transforaminal lumbar interbody fusion (TLIF). Retrospective review was performed for patient demographics, operating room notes from the index rhBMP surgery, imaging studies, and current clinical status. The authors concluded from their review that ectopic bone in the spinal canal associated with posterolateral rhBMP-2 application may, in rare cases, contribute to symptomatic neurologic findings requiring difficult revision surgery. It was also noted that the FDA trial of PLIF with rhBMP-2 had been halted because of a high incidence (75%) of ectopic bone forming in the neural canal. In 2010, Chen and colleagues reported 4 cases of delayed symptomatic ectopic bone formation after minimally invasive transforaminal lumbar interbody fusion, in which bone fusion was augmented with rhBMP-2 applied to an absorbable collagen sponge. (18)

In 2011, Mannion and colleagues reported fusion and adverse event rates following use of low-dose rhBMP-2 (1.4 mg) with local bone graft in a series of 30 patients who underwent minimally invasive posterior or TLIF. (19) Computed tomography (CT) scan showed complete fusion in 33 of 36 spinal levels at the first postoperative scan (mean of 7.1 months). There was one case of nonunion at 12 months, with vertebral body osteolysis and cage subsidence into the end plate. In addition, despite very low dose rhBMP-2, there were 2 cases (6.7%) of asymptomatic heterotopic ossification in the neural foramen and 2 cases (6.7%) of inflammatory perineural cyst formation, one of which was symptomatic and required revision. Another retrospective review of 23 patients who had a complete set of CT scans after TLIF found the incidence of osteolysis in the adjacent vertebral bodies to be 54% at 3-6 months and 41% at 1-2 years. (20)

Radiculopathy due to an inflammatory response induced by rhBMP-2 after TLIF has also been reported. (21) This retrospective review found that 4 of 35 patients (11.4%) who had received rhBMP-2 with minimally invasive TLIF had new onset of radicular symptoms after surgery (without structural etiology) compared with 0 of 8 patients who had not received BMP. (22) Symptoms included pain along the involved dermatomal distribution and subjective paresthesias in the absence of lower extremity paresis and were ipsilateral to the side on which the procedure was performed.

Another retrospective review compared complications in 86 patients who had received rhBMP-2 and 33 patients who received iliac crest autograft after TLIF. (23) Complications specific to the autograft group included persistent donor-site pain (30.3%) and donor-site infection (3.1%). Complications specific to the rhBMP-2 group included vertebral osteolysis (5.8%) and ectopic bone formation (2.3%). Postoperative radiculitis was observed in 3.0% of the autograft group and 14% of the rhBMP-2 group (p=0.08). Use of a hydrogel sealant posterior to the interbody cage and over the exposed dura and nerve root decreased the rate of postoperative radiculitis in the rhBMP-2 group from 20.4% to 5.4%. The radiographic non-union rate was similar for the 2 groups (3.0% for iliac crest autograft and 3.5% for rhBMP-2).

A 2010 systematic review of complications related to use of rhBMP in spine surgery indicates considerable uncertainty regarding the rate of complications following off-label use (e.g., posterior and transforaminal) in the lumbar spine. (8)
A search of online site clinicaltrials.gov in October 2011 identified a prospective observational case-control study from Mayo Clinic that will evaluate the incidence and etiology of radiculitis with use of rhBMP-2 in transfomaminal interbody arthrodesis (NCT00984672). Patients who have undergone TLIF with rhBMP within an interbody cage will be compared with patients undergoing other bone grafting techniques (iliac crest autograft, allograft, local autograft). This study began in March 2009, has an estimated enrollment of 240 patients, and lists an estimated completion of the primary outcome measure in 2011.

Based on safety concerns, use of BMP in interbody fusion using a posterior or transfomaminal approach is considered investigational.

**Instrumented Posterolateral Intertransverse Lumbar Spinal Fusion**

In 2006, Dimar and colleagues reported an FDA-regulated investigational protocol that compared rhBMP-2 (bovine collagen and tricalcium hydroxyapatite compression-resistant matrix) with iliac crest autograft for single-level lumbar degenerative disease with instrumented (pedicle screw/rod) posterolateral fusion. (24) Similar improvements were observed in the 2 groups for back pain (score change from 16.4 to 9.0 and from 16.1 to 9.5, respectively) and leg pain (score change from 14.2 to 8.5 and from 14.5 to 9.3, respectively) at 24-month follow-up. Solid fusion was observed by blinded observers in 48 of 53 (91%) of the rhBMP-2 patients and 33 of 45 (73%) of the autograft patients. This study is limited by loss to follow-up; only 98 of 150 patients (65%) enrolled in the randomized trial were available for 24-month follow-up. These investigators also reported a retrospective subgroup analysis based on smoking status. (25) Of 148 radiographs reviewed, successful fusion was seen in 20 of 21 smokers (95%) in the rhBMP-2 group and 16 of 21 smokers (76%) in the autograft group.

In 2008, Glassman and colleagues reported instrumented posterolateral intertransverse fusion using rhBMP-2 with an absorbable collagen sponge (InFUSE) compared with iliac crest autograft in patients older than 60 years of age. (26) A total of 106 patients with a diagnosis of disc pathology, spondylolisthesis, stenosis, deformity, instability, postdecompression revision, or adjacent level fusion were randomly assigned to rhBMP-2 (n=50) or autograft (n = 52). All patients underwent decompression and instrumented lumbar fusion; none of the patients had an interbody fusion. Two-year follow-up in 100 patients showed similar improvements for the 2 groups in the ODI, Short Form (SF)-36, and back pain and leg pain scores. Four patients in the rhBMP-2 group and 11 in the autograft group had additional surgical procedures during the 2-year follow-up. In the rhBMP group, the 4 additional surgeries (1 each) were for wound infection, adjacent compression fracture, nonunion, and adjacent level degeneration. The 11 additional procedures in the autograft group were due to wound infection (n=2), nonunion (n=5), and (1 each) reposition of the pedicle screw, late screw removal, pain pump insertion, and adjacent level degeneration. Two-year postoperative CT scans showed an average CT grade that was higher in the rhBMP-2 group (4.3) than the autograft group (3.8). Blinded analysis of fusion rate based on bridging bone (CT grades 4 and 5) was 86% in the rhBMP-2 group and 71% in the autograft group.

Efficacy of rhBMP-2 for the treatment of multilevel adult spinal deformity was investigated in a prospective, single center, nonblinded radiographic analysis for anterior and posterior intertransverse (off-label) fusion with 98 patients (308 levels) with a mean age of 51.4 years. (27) For all groups, the posterior instrumentation consisted of bilateral pedicle screw/rod constructs with 5.5-mm stainless steel rods. Routine radiographic and clinical follow-up was performed at 6 weeks, 3 months, 6 months, 1 year, and 2 years, with a minimum radiographic
follow-up of 2 years. Anterior spinal fusion was performed in 47 patients (109 levels) with rhBMP-2 (8–12 mg/level) placed on an absorbable collagen sponge within a titanium mesh cage. The anterior reconstructions were in the distal lumbar spine and were protected with posterior instrumented fusion. Two surgeons not involved in the operative procedure independently reviewed and graded each fusion level. At a mean 2.5 years of follow-up, fusion was observed in 91% of the levels (average 2.3 levels per patient). Posterolateral intertransverse fusion was performed in 43 patients (156 levels) with rhBMP-2 (19.8 mg/level) applied to the posterolateral spine with local bone graft and extender. At a mean 2.6 years of follow-up, 97% of the levels (average 3.6 levels per patient) were graded as fused. A third group was composed of 8 patients (43 levels) who received FDA-approved posterolateral “compassionate use” surgeries on the basis of multiple prior fusion failures with past harvesting of iliac bone. Five of these patients had preoperative pseudarthrosis. High-dose rhBMP (40 mg/level) without any autogenous bone resulted in a 100% fusion rate with a mean number of levels fused of 5.4 per patient. The average fusion rate with rhBMP-2 for the 3 groups was 95% of levels, and the overall pseudarthrosis rate after multilevel spinal deformity fusion was 5% (13 levels).

With the addition of these 2 studies to the literature in 2008, evidence is sufficient for rhBMP-2 to be considered medically necessary for instrumented posterolateral intertransverse fusion.

In 2009, Dimar and colleagues reported results from an ongoing Investigational Device Exemption (IDE) trial of a new rhBMP-2 formulation (higher dose of 2.0 mg/mL with a compression resistant carrier) compared with autograft for single-level posterolateral fusion combined with pedicle screw and rod instrumentation. (28) Of the 463 patients who were randomized and had surgery, 410 (89%) were available for per-protocol assessment 2 years after surgery. Blinded radiographic assessment showed greater fusion success at 6 months (79% vs. 65%, respectively), 12 months (88% vs. 83%, respectively), and 24 months (96% vs. 89%, respectively). There was a modest reduction in operative time (2.5 vs. 2.9 hours, respectively) and blood loss (343 vs. 449 mL, respectively), and no difference in hospital stay (4.1 vs. 4.0 days, respectively). There was no difference in functional status (ODI, SF-36, back pain, or leg pain) between the rhBMP-2 and autograft groups throughout the 24-month follow-up. The percentage of patients having second surgery (revision, removal, or supplemental fixation) was lower in the rhBMP-2 group than the autograft group (8% vs. 16%, respectively). Sixty percent of patients in the iliac crest bone-graft group reported persistent donor-site pain, with a mean pain score of 5.1 at 24 months after surgery. (For comparison, back pain scores were near 16 at baseline, decreasing to around 7-8 points after surgery.)

Noninstrumented Posterolateral Intertransverse Lumbar Spinal Fusion

Non-instrumented posterolateral intertransverse process fusion is another common type of spinal fusion procedure as a treatment of spondylolysis but with distinct mechanical and biologic demands compared to instrumented interbody or intertransverse fusion and thus requires a distinct approach to carrier/delivery systems. At the time this policy was created, preclinical studies indicated that a carrier sponge was inadequate, and the structural support of an interbody back cage (i.e., the delivery system) was not available for this setting. Boden and colleagues investigated rhBMP-2 in this clinical situation. (29) In this study, the carrier system consisted of hydroxyapatite and tricalcium phosphate. One randomized study was identified that focused on the use of rhBMP-7 for posterolateral lumbar fusion. (30) The delivery system for rhBMP-7 consisted of bovine collagen mixed with saline, creating a paste that was applied to the decorticated surface. The trial included 20 patients who were randomly assigned to receive
rhBMP-7 or autologous bone. There were no significant differences in fusion outcomes between the 2 groups.

Subsequently, rhBMP-7 (OP-1) in a putty carrier (i.e., OP-1 Putty) received FDA approval through the Humanitarian Device Exemption (HDE) as an alternative to autologous bone graft in “compromised” patients undergoing revision of a prior fusion. Compromised patients include those with osteoporosis, those who smoke, and those with diabetes. The data presented to the FDA are provided in “Summary of Safety and Probable Benefit” and consist of a randomized trial of 48 patients with single-level degenerative lumbar spondylolisthesis and spinal stenosis who underwent treatment with rhBMP-7 alone, in combination with an autograft, or autograft alone. (31) The data were reported only for those receiving rhBMP-7 alone or autograft alone, constituting 24 and 12 patients, respectively. The summary provided minimal details regarding the compromised nature of these patients, stating only that 7 of the 24 patients receiving rhBMP-7 alone had compromising factors. In addition, unlike the labeled indication, which limits the use of this product to those undergoing revision surgery, patients in this trial were undergoing primary fusion. Effectiveness was based on radiographic success and improvement in the ODI. The clinical and radiographic success rate was superior in those receiving rhBMP-7. The FDA summary concludes: “Based on a pilot clinical study, OP-1 Putty has demonstrated probable benefit as an alternative to autograft in patients who required a primary uninstrumented fusion for the treatment of degenerative spondylolisthesis. While these data cannot be extrapolated directly to the expected performance of OP-Putty in revision posterolateral spinal fusions in the compromised population, there is reason to believe that OP-Putty could have a probable benefit in this population. When revision of a failed fusion is required, most patients are limited to either living with pain and altered function or repeating the original procedure with additional autologous bone, which may result in depletion of the bone stock and further risk to the patient. Allograft bone and bone graft substitutes are not considered feasible alternatives to autografts in revision surgery due to their lack of osteogenic potential. For certain patients, for example those with implanted leads, bone growth stimulators would not be considered as feasible options. OP-1 Putty has the potential to eliminate the risk and complications associated with these treatment alternatives while providing a feasible and beneficial alternative treatment. The preclinical and clinical data suggest that it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits or currently available alternative treatments.”

In 2008, Vaccaro and colleagues published an FDA trial on use of rhBMP-7 (OP-1) in patients with symptomatic degenerative spondylolisthesis and spinal stenosis. (32) None of the patients had undergone previous lumbar surgery, and all had failed at least 6 months of nonoperative treatment (including physical therapy, lumbar epidural injections, anti-inflammatory medications, and activity modifications). Excluded were patients with current or history of smoking, morbid obesity, or a known sensitivity to collagen. After enrollment, 335 patients were randomly assigned in a 2:1 ratio to receive OP-1 Putty or iliac crest autograft; 295 were treated (208 OP-1 and 87 autograft). Following treatment, patients were fitted with a lumbosacral orthosis and instructed to wear the brace when out of bed for 3 months. Follow-up visits were scheduled at 6 weeks, and 3, 6, 9, 12, and 24 months after surgery. Patients who were still alive and had not been categorized as a retreatment failure were invited to participate in the 36+ month follow-up. Approximately 70% of patients from both groups were available at the 36+ month follow-up, which was reported to be 80% of the eligible patients (i.e., not failures and still alive). The number of treatment failures prior to 24 months was not reported. The primary endpoint at 24 months, as designed for FDA submission, was a composite measure of a 20% improvement in
the ODI, absence of serious adverse events, absence of a decrease in neurologic status, and radiographic fusion success. Overall success at 24 months did not achieve noninferiority, primarily due to a decrease in bridging bone in the OP-1 Putty group (62%) compared with the autograft group (83%), as evaluated by radiologists who were blinded to the treatment condition. The 36+ month Modified Overall Success composite outcome was found to be similar between the 2 treatment groups, having replaced the measure of radiologic success with simple presence of bone on CT scan. The percentage of patients showing a greater than 20% improvement on the ODI was 69% for OP-1 and 77% for autograft. These scores were not significantly different. A visual analogue scale (VAS) score for donor site pain in the autograft patient group averaged 2.1 of 10 at 6 weeks, 1.6 at 12 months, 1.2 at 24 months, and 1.1 at 36 months. Following review of the study results, an FDA panel voted 6-1 against expanding the indications for OP-1. This study supports the FDA’s HDE for use of OP-1 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, but results are insufficient to support use of OP-1 Putty (rhBMP-7) in primary posterolateral intertransverse lumbar spinal fusion when autograft is feasible.

A retrospective analysis described posterolateral fusion without instrumentation using rhBMP-2 and morselized autologous spinous process elements. (33) The study included 55 patients (mean of 68 years of age) who were moderately to severely disabled; 44 (80%) were diagnosed with degenerative spondylolisthesis with disabling pain and radiculopathy. Fusion was performed in all patients to prevent instability after significant medial facet joint resection. At an average 6 months after surgery (range, 3–36 months), 80% of patients showed significant fusion. Two patients (4%) showed no fusion. Follow-up evaluation by telephone or mail was conducted on 47 patients (85%) using an SF-12 Health Survey and a Modified Oswestry Low Back Pain Disability Questionnaire. Patients were asked to recall both their pre- and postoperative low back pain and their overall health status. Prior to surgery, 11 patients were bed bound and 30 experienced very severe pain that impacted all aspects of daily living and work. At an average of 34 months of follow-up (range, 29–36 months), no patients were bedridden, 1 reported very severe pain, 12 reported moderate to severe pain, and 34 reported none to minimal pain. Prospective controlled studies are needed to evaluate rhBMP-2 on an absorbable collagen sponge for posterolateral intertransverse fusion without instrumentation.

**Fusion of Cervical Vertebrae**

rhBMP-2 has been used as an alternative to autologous bone graft in fusion of the cervical spine. In one study the carrier/delivery system consisted of machined fibular rings. (34) The trial consisted of 33 patients undergoing single or 2-level discectomy and fusion randomly assigned to receive fibular rings filled either with rhBMP-2 or autologous bone graft. Fusion was recorded in all patients at 6 months after surgery. Another study (with 77 consecutive patients undergoing either cervical or lumbar interbody fusion) found greater end plate resorption and subsidence following treatment with rhBMP-2 (49% of levels) in comparison with allograft/demineralized bone matrix (6% of levels). (35)

There have been reports of adverse events with rhBMP in cervical fusion. Vaidya et al. reported that use of rhBMP-2 (1 mg/level) for cervical interbody fusion (22 consecutive patients) resulted in greater swelling (8 vs. 6 mm, respectively) and dysphagia (65% vs. 22%, respectively) at up to 6 weeks after surgery in comparison with 24 consecutive patients treated with demineralized bone matrix. (36) A 2006 study that compared swelling in patients treated with (n=69) and
without (n=165) rhBMP-2 for anterior cervical fusion found an odds ratio of 10.1 (95% confidence interval [CI]: 3.8 - 26.6) for swelling after controlling for confounding variables. (37)

Stachniak and colleagues retrospectively reviewed the incidence of prevertebral soft tissue swelling and dysphagia in 30 patients who underwent multi-level anterior cervical discectomy and fusion with rhBMP-2 (0.6 mg/level). (38) Most patients were treated with a standardized dexamethasone taper postoperatively to reduce clinical complications. Soft tissue swelling was assessed by an independent radiologist using cervical spine radiographs on postoperative day 1 and at 2, 6, and 10 weeks and 6 months after surgery. Soft tissue swelling peaked at 2 weeks and decreased to near preoperative levels by 6 months. At 2 weeks, the Cervical Spine Research Society Swallowing-Quality of Life tool showed 19% of patients frequently choking on food, 4.8% frequently choking when drinking, and 47.6% with frequent food sticking in the throat. By 6 months, 0% had frequent choking on food, 6.7% had frequent difficulty drinking, and 6.7% had frequent food sticking in the throat. No patients required reoperation or hospitalization for soft tissue swelling. The Neck Disability Index, neck pain, and arm pain scores all improved progressively over 6 months. Incidence of fusion, measured by cervical CT scans, was 95% at 6 months and 100% at 9 months. A number of questions were raised by this report, including what is the appropriate dose of rhBMP-2, whether the rhBMP-2-soaked sponges should be contained solely within the grafts, whether the grafts should be vented or unvented, and whether tissue glue should be used in conjunction with rhBMP-2 to shield the tissue. Financial support for this study was received from Medtronic Spinal and Biologics.

In July 2008, the FDA issued a public health notification regarding life-threatening complications associated with recombinant human BMP in cervical spine fusion. (1) The FDA recommended that practitioners either use approved alternative treatments or consider enrolling as investigators in approved clinical studies.

Complications, including seroma formation and heterotopic bone formation, have also been reported with the use of rhBMP-2 in pediatric craniocervical arthrodesis. (39) In a retrospective review of 48 pediatric patients who underwent dorsal occipitocervical fusion, there were 6 complications (12.5%). Two of the 5 patients who developed postoperative seroma required emergency reoperation for symptoms suggesting brainstem compression and obstructive hydrocephalus. A sixth patient required reoperation for heterotopic bone formation causing cervicomedullary compression. The authors conclude that use of rhBMP during occipitocervical fusion in this population can create life-threatening complications and should be avoided whenever possible.

**Long-Bone Fractures and Nonunions**

A 2010 Cochrane review evaluated the effectiveness and costs of rhBMP on fracture healing in acute fractures and nonunions compared with standards of care. (40) The literature was searched to October 2008, and 11 RCTs (976 participants) and 4 economic evaluations were included in the review. The times to fracture healing were comparable between the rhBMP and control groups. There was some evidence for increased healing rates, mainly for open tibial fractures without secondary procedures (risk ratio [RR]: 1.19). Three trials indicated that fewer secondary procedures were required for acute fractures treated with rhBMP (RR: 0.65). The authors concluded that limited evidence suggests that rhBMP may be more effective than standard of care for acute tibial fracture healing; however, the use of rhBMP for treating nonunion remains unclear (RR: 1.02). Limited evidence suggests that the direct medical costs associated with rhBMP could be offset by faster healing and reduced time off work for patients.
with the most severe open tibia fractures. The authors noted that there was a high level of industry involvement and a high risk of bias in the evidence. A limitation of this review is that the authors did not distinguish results obtained from rhBMP-2 versus rhBMP-7. Relevant studies, along with trials published after October 2008, are described below.

The 2010 AHRQ technology assessment on the state of the evidence of on-label and off-label use of rhBMP (7) included the following conclusions:

- For on-label use of rhBMP-7 in recalcitrant long bone non-unions, the strength of the evidence on radiographic fusion, pain, and function outcomes is low.
- The strength of the body of evidence on clinical outcomes is moderate for on-label use of rhBMP-2 to enhance bony fusion in acute open shaft fractures.

Open Tibial Fractures

Govender and colleagues reported on the results of a trial that randomly assigned 450 patients with open tibial shaft fractures to receive initial irrigation and debridement followed by treatment with a locked intramedullary nail either alone or with additional rhBMP-2 on a absorbable collagen sponge placed over the fracture at the time of definitive wound closure. (3) The primary outcome measure was the proportion of patients requiring secondary intervention due to delayed union or nonunion at 12 months. A total of 58% of patients treated with rhBMP-2 were healed compared with only 38% in the control group. The rhBMP-2 group also had fewer hardware failures, fewer infections, and showed faster wound healing.

A subgroup analysis from combined European (n=450) and American (n=60) multicenter trials assessed the interaction of rhBMP-2 and reaming in the treatment of type-III open tibial fractures. (41) From the total group of patients (n=131) who presented with a type-III open tibial fracture, the rhBMP-2-treated group was found to have fewer bone grafting procedures, fewer secondary interventions, and a lower rate of infection compared with intramedullary nail fixation alone. However, examination of the subgroup treated with reamed intramedullary nailing (n=113; rhBMP-2: 65, control: 48) revealed no significant differences between the 2 groups. The uneven distribution of intramedullary preparation between the groups raises questions about the relative contribution of reaming to the overall results.

In a 2011 study, Aro and colleagues found no significant benefit of rhBMP-2 on the rate of healing in open tibial fractures treated with reamed nail fixation. (42) A total of 277 patients were randomized to standard of care (SOC) consisting of reamed intramedullary nail fixation and routine soft tissue management or SOC plus an absorbable collagen sponge implant containing rhBMP-2. The fractured tibia and the surrounding tissues were assessed at 6, 10, 13, 16, 20, 24, 32, 41, and 52 weeks in this single-blind study. The primary efficacy outcome was the proportion of subjects with a healed fracture at 13 and 20 weeks by intent-to-treat analysis, and a 20% difference in healing rates was considered to be clinically meaningful. At week 13, the proportions of patients with a healed fracture were 60% for rhBMP-2 and 48% for SOC (p=0.054). At week 20, the proportions of patients with a healed fracture were 68% and 67% for rhBMP-2 and SOC, respectively. Twelve percent of the subjects in each group underwent secondary procedures. Infection was seen in 27 (19%) of the patients in the rhBMP-2 group and 15 (11%) in the SOC group (p=0.065). Deep infections involving bone were more common in the rhBMP-2 group (9% vs. 2%). There was also a higher rate of serious adverse events (requiring hospitalization) in the rhBMP-2 group (3% vs. 0%) due primarily to the difference in
infections. The adverse event incidence (i.e., hardware failures, peripheral edema, heterotopic ossification, and pain) was otherwise similar between the treatment groups.

Fracture Nonunions

rhBMP-7 has received FDA approval through the HDE process as an alternative to bone autograft in recalcitrant long bone nonunions, and the data presented to the FDA have been published in the medical literature. (43) The study included 122 skeletally mature patients with 124 tibial nonunions. Each patient was treated by intramedullary rod fixation, either accompanied by rhBMP-7 or fresh bone autograft. The rhBMP-7 was applied as a paste to the fracture ends. At 9 months after the procedure, 81% of the rhBMP-treated nonunions and 84% of the control group reported clinical success compared to a radiologic success of 75% and 84%, respectively. Because both treatment groups received an intramedullary rod, this study was not designed to determine if either the rhBMP-7 or autologous grafting improved outcomes compared to intramedullary rod fixation alone. However, approximately half of the patients had undergone a prior fusion attempt with an intramedullary rod, and between 30% and 40% had undergone a prior autograft. In its Summary of Safety and Probable Benefit, the FDA concluded: “…the OP-1 implant has demonstrated probable benefit as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed, thus providing patients with a treatment for nonunion where the alternative is either amputation or no treatment. This should allow the patients to regain some mobility and may decrease their pain on ambulation.” (44)

Ekrol et al. randomly assigned 30 patients undergoing corrective osteotomy for symptomatic malunion after distal radial fractures to receive either rhBMP-7 or autogenous bone graft harvested from the ipsilateral iliac crest. (45) The first 10 patients (4 rhBMP-7 and 6 autogenous bone grafts) were treated with nonbridging external fixation, the next 20 with internal fixation with a dorsal pi-plate to improve stability. All patients who had been treated with autogenous bone graft had complete filling of the metaphyseal defect, with healing at an average of 7 weeks. The 14 patients treated with rhBMP-7 exhibited slower (13–18 weeks) and incomplete healing. Two of the 4 patients treated with external fixation and rhBMP-7 developed excessive osteolysis around the osteotomy site, resulting in loss of the corrected position and nonunion of the osteotomy. Of the 10 patients treated with internal fixation with a dorsal pi-plate, 5 healed at the volar cortex, with a dorsal defect remaining at 1 year. Two of the 10 developed nonunion. The authors concluded that rhBMP-7 does not confer the same stability as bone graft and heals at a slower rate than autogenous bone graft.

A 2008 study by Calori et al. randomly assigned 120 patients with long bone nonunions (tibial, femoral, humeral, ulnar, or radial) to application of rhBMP-7 or platelet-rich plasma (PRP). (46) Autologous bone graft had been previously used in 45 patients. Union was observed in 87% of the rhBMP-7 group, with radiological union occurring at a median of 8 months. In the PRP group, union was observed in 68% of cases with a median healing time of 9 months. Interpretation of this study is limited by the lack of an autograft control group.

Results from 68 consecutive cases of rhBMP-7 for tibial nonunions (minimum follow-up of 12 months) were reported from 6 orthopedic centers in Europe, using a specialized rhBMP data registry. (47) The median time between the initial injury and treatment with rhBMP-7 was 23 months (range, 9 to 317). In 24 cases (35%), previous treatment with autologous bone graft had been unsuccessful. In 25 cases (14 of which had previously been treated with rhBMP-7), rhBMP-7 was combined with autologous bone graft. Thus, 37% of the 68 patients received both
rhBMP-7 and autologous bone graft. At a mean 21-month follow-up (range, 12–30 months), the union rate was reported to be 90%, with a median time to union of 6.5 months (range, 3–15 months). The number of patients who were lost to follow-up before 12 months was not reported, and no comparison was conducted with use of autologous bone graft alone. No systemic allergic reactions or adverse effects were observed and/or reported.

Oral and Maxillofacial Procedures

The 2010 AHRQ technology assessment on the state of the evidence of on-label and off-label use of rhBMP (7) included the following conclusions:

- The strength of the body of evidence on clinical outcomes is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone. There is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

In 2009, Triplett and colleagues reported a pivotal multicenter RCT (160 patients) comparing rhBMP-2 (1.5 mg/mL) to autograft for 2-stage maxillary sinus augmentation. (48) Among those subjects available for follow-up, the mean change in bone height was 7.8 mm for rhBMP-2 versus 9.5 mm for the bone graft patients. At 6-month follow-up, a dental prosthesis had been successfully implanted into a lower percentage of rhBMP-2 treated patients compared to autograft (82% vs. 95%, respectively), and successful functional loading was reduced compared to autograft (76% vs. 91%, respectively). The percentage of patients available for follow-up at 24 months was 70% in the BMP-2 group and 88% in the autograft group. The primary complications of autografts were sensory loss, pain, and gait disturbance, while patients treated with rhBMP-2 reported greater facial edema. Based on these results, rhBMP-2 does not appear to provide an advantage compared to autograft bone for maxillary sinus floor augmentation.

A 2011 systematic review of rhBMP-2 for reconstruction of the alveolar cleft identified 3 studies with a total of 49 patients that compared rhBMP-2 with iliac crest bone grafting (ICBG) and had radiographic quantification of bone in the reconstructed cleft. (49) One small randomized controlled trial (n=16) reconstructed the alveolar clefs in children with mixed dentition and found comparable bone quantity (difference of 5.8%) but lower bone height (10.2 mm vs. 13.9 mm) for patients treated with rhBMP-2 compared to ICBG. Local postoperative swelling was observed in 37.5% of the rhBMP-2 group, while significant donor site pain was reported in 87.5% of patients in the control group. In another small randomized controlled trial in skeletally mature patients (n=21), bone quantity (95% vs. 63%) and bone height (85% vs. 70%) were superior following use of rhBMP-2. The control group showed significant donor site pain, more wound healing problems and a longer hospital stay. The third study included in the review was a retrospective analysis with only 2 children in the control group.

Use of rhBMP-2 delivered by hydrogel was associated with severe swelling when used in children with cleft lip and palate. (50) A low rhBMP-2 concentration (50 mcg/mL) did not induce bone formation in the first 2 patients randomized to rhBMP-2. The study was terminated when treatment of the next 2 patients with a higher dose of rhBMP-2 (250 mcg/mL) resulted in severe gingival swelling.

Through April 30, 2011, the FDA’s Manufacturer and User Facility Device Experience (MAUDE) received 83 reports of adverse events involving rhBMP-2 in oral and maxillofacial operations. (51) rhBMP-2 was used off-label in 66.3% of these cases and included reconstruction of the
mandible after fracture or cancer and alveolar cleft repair. The most frequently reported adverse events were local edema/pain, surgical site infections/wound complications, and graft failure.

Overall, the evidence does not support a health benefit of rhBMP in oral and maxillofacial procedures.

**Additional Applications**

There has been research interest in 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). (52, 53) Craniofacial applications have included periodontal defect regeneration, cleft palate repair, cranial defect repair, restoration, and maintenance of the alveolar dental ridge. However, the literature regarding these applications consists of small case series; no controlled trials have been identified.

**Ongoing Clinical Trials**

A search of the online site clinicaltrials.gov in September 2012 identified several ongoing studies. Of particular interest is an industry-sponsored Phase II randomized controlled dose-finding study of intra-articular BMP-7 for osteoarthritis of the knee (NCT01111045). The study lists an enrollment of 355 subjects and is described as completed as of January 2012. As of September 2012, no publications from this study have been identified.

NCT00984672 is a prospective observational study of radiculitis following use of rhBMP-2 in spinal fusion. The study will evaluate the incidence of this complication and use postoperative imaging studies to help determine whether bony overgrowth occurs adjacent to the effected spinal nerves. The study has an estimated enrollment of 240 patients with completion in February 2013.

**Summary**

Evidence reviewed here is sufficient to consider use of rhBMP-2 on a collagen sponge (InFUSE) medically necessary for the following indications:

- Anterior lumbar spinal interbody fusion when used with an FDA-approved interbody fusion device. rhBMP-2 is FDA-approved for single level anterior fusion from L2–S1. Fusion of more than one level is considered off-label use.
- Posterolateral intertransverse spinal fusion, when used with an FDA-approved fusion device. This is an off-label indication.
- Treatment of acute, open fracture of the tibial shaft. This is an FDA-approved indication.

Due to emerging safety concerns, the risk/benefit ratio for use of rhBMP is uncertain, especially for patients who are at average risk for fusion failure. As a result, use of rhBMP should be restricted to cases where there is a high risk of fusion failure, pending the results of ongoing secondary analysis of the data on adverse effects.

Current evidence supports the use of rhBMP-7 in putty (OP-1 Putty) in the following FDA Humanitarian Device Exemption-approved indications only when autograft is not feasible or expected to promote fusion:
• Revision noninstrumented posterolateral intertransverse lumbar spinal fusion
• Recalcitrant long bone nonunions

Use of rhBMP either has not been shown to be as beneficial as the established alternative (iliac crest autograft) and/or evidence is insufficient to permit conclusions concerning the effect of rhBMP for other indications, including but not limited to:

• Cervical spinal fusion
• Posterior or transforaminal lumbar interbody spinal fusion (this is considered investigational because of safety concerns related to ectopic bone formation in the spinal canal);
• Treatment of noninstrumented posterolateral intertransverse spinal fusion when autograft is feasible and expected to promote fusion;
• As an alternative or adjunct to bone grafting in other locations, including craniomaxillofacial surgeries.

Practice Guidelines and Position Statements
None identified.

Medicare National Coverage
The Centers for Medicare and Medicaid Services (CMS) has established an add-on to the diagnosis-related group (DRG) payment to cover a portion of the cost of new technologies during the 2-year period before charge data for the technologies are incorporated into the DRG weights. To qualify, a technology must be new, must provide verifiable improvement in the treatment or diagnosis of beneficiaries, and the mean standardized charge for treatment using the new technology must be at least 1 standard deviation above the mean standardized charge for treating the same case without the new technology. In 2004, CMS concluded that the InFuse™ Bone Graft/LT-CAGE met these criteria and will receive an add-on payment to DRGs 497 or 498. Medtronic, the manufacturer of the InFuse device, has applied for a new technology add-on payment for the FDA-approved indication of treatment of open acute fractures of the tibial shaft.

References:


30. Johnsson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented


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<td>84.52</td>
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<tr>
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<td>M51.16</td>
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