Technology Assessment

Technology Assessment Program

Bone Morphogenetic Protein: The State of the Evidence of On-Label and Off-Label Use

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Peer Reviewers

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Executive Summary

Background. Bone morphogenetic proteins (BMP) are key factors necessary for bone regeneration and healing. Recombinant DNA techniques have been used to produce BMP2 and BMP7 as alternatives to autograft bone to enhance healing of bony defects and fractures in patients where autograft bone harvest is unfeasible or contraindicated.

Currently, two rhBMPs and four associated carrier/delivery systems (one of which has been voluntarily withdrawn from the U.S. market) have received approval as devices from the U.S. Food and Drug Administration (FDA). The InFUSE® system (Medtronic Sofamor Danek, Inc.) consists of rhBMP2 on an absorbable collagen sponge carrier. OP-1® (Stryker Biotech) consists of rhBMP7 and bovine collagen, which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms putty.

Methods. This assessment is based on an electronic search of the literature as follows:

- MEDLINE® (January 1, 1998, through July 28, 2009)
- EMBASE® (January 1, 1998, through July 28, 2009)
- Cochrane Controlled Trials Register (no date restriction)

The searches were updated in February 2010.

The interventions of interest for all Key Questions (see table, following) are the use of either of the two commercially available BMP products in the U.S. Interventions were considered to be delivered on-label when administered according to the indication specified in the FDA-approved marketing label. All other uses and applications of BMP products were considered off-label.

Studies were selected to address 10 Key Questions identified for this technology assessment. In general, we abstracted data from full-length randomized, controlled trials (RCTs) and nonrandomized, comparative trials that utilized BMP therapy in patients with a bony defect that required intervention and reported at least one outcome of interest.

The quality of included studies was assessed using the general approach to grading evidence developed by the U.S. Preventive Services Task Force (USPSTF). The strength of the overall body of evidence was assessed using a framework developed by AHRQ for the EPC Methods Guide, based on a system developed by the GRADE Working Group.

Results. The electronic literature search yielded 1,992 records. Among those, 1,738 were excluded at initial title and abstract review and 254 were retrieved for full text examination. Forty-one articles describing results of comparative studies were abstracted. The conclusions of this assessment are summarized in the following table.

Executive Summary Table. Conclusions According to Key Questions

Key Questions	Conclusion
1. What is the evidence supporting improved outcomes with on-label* use of rhBMP2 (InFUSE®) for fusion of the lumbar-sacral spine? * Spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at 1 level from L2-S1	The strength of the body of evidence for improved outcomes with on-label use of rhBMP2 (InFUSE®) was graded as moderate. Two RCTs reported radiographic fusion outcomes to be similar to that of autograft bone. No significant adverse events were attributed to rhBMP2 in any study. However, the size and duration of the RCTs are not sufficient to precisely determine the frequency and severity of adverse events. Thus, the evidence gives moderate support to clinical benefit from the use of rhBMP2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.
2. What is the evidence supporting improved outcomes with on-label* use of rhBMP7 (OP-1®) for fusion in the lumbar spine? * Revision posterolateral lumbar spinal fusion	No comparative studies were identified for this Key Question. The strength of evidence is insufficient, thus no conclusions can be reached.
3. What is the evidence supporting improved outcomes with on-label* use of rhBMP7 (OP-1®) in recalcitrant long bone non-unions? ***** Alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed	There are two RCTs and one retrospective cohort study. The risk of bias in this evidence is high. In one RCT, the intervention arm was confounded by use of a mix of bone graft extenders, and it was unclear if radiographic outcomes were assessed independently. In the second RCT the BMP arm had higher risk for poor outcomes, and thus the effect of BMP could be underestimated. The third study was nonrandomized and thus had high risk of bias. Device-related harms are inconsistently reported in this literature. The strength of the body of evidence on radiographic fusion, pain, and function outcomes is low.
4. What is the evidence supporting improved outcomes with on-label* use of rhBMP2 (InFUSE®) for the treatment of acute, open shaft tibial fractures? ***** Acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. The device must be applied within 14 days after the initial fracture.	The main evidence is in one RCT (n=450) (BESTT) that compared two different doses of rhBMP2 versus standard of care. The RCT is supported by a combined subgroup analysis that pooled data from patients with Gustilo-Anderson type III fractures in BESTT with data from a second smaller unpublished RCT (n=60) with identical design. The strength of the body of evidence on clinical outcomes is moderate for on-label use of rhBMP2 to enhance bony fusion in acute open shaft fractures.
5. What is the level of evidence and summary of evidence for the on-label* use of rhBMP2 (InFUSE) for sinus augmentation? ***** Sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets	Three RCTs were identified in which rhBMP2 was used according to the FDA-approved marketing label in patients undergoing staged bilateral or unilateral maxillary sinus floor augmentation and extraction socket alveolar ridge augmentation procedures. The strength of the body of evidence is moderate that rhBMP2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone. However, there is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Key Questions	Conclusion
6. For which indications are there clinical studies in which BMP is used off-label? In such studies, what is the evidence of the effectiveness of BMP?	The strength of evidence for off-label uses was graded only for settings that had more than one comparative trial involving patients with bony defects sufficiently similar to allow synthesis. **Lumbar-Sacral Spine** **rhBMP2** There are six randomized and five nonrandomized comparative studies of off-label use of rhBMP2 in fusion of the lumbar-sacral spine. The two largest RCTs were rated "fair" and are given greatest weight in this review of evidence. Among all six RCTs, interstudy variables included rhBMP2 dose, surgical approach, carrier matrix formulation, and interbody devices. Despite the use of different surgical approaches and unapproved formulations and instrumentation, the strength of evidence that rhBMP2 improves radiographic fusion success is moderate. No conclusions can be drawn regarding the potential impact of the off-label components on radiographic fusion success. The strength of evidence that rhBMP2 improves other outcomes is low. **rhBMP7** The best available evidence for the efficacy of rhBMP7 used off-label for lumbar spinal fusion comes from one randomized trial. There are three additional small, poor quality trials. The evidence is insufficient to draw conclusions on the off-label use of rhBMP7 in fusion of the lumbar-sacral spine. **Cervical Spine** **rhBMP2** The evidence consists of one randomized trial and four nonrandomized comparative studies of off-label use of rhBMP2 for cervical spinal fusion. Two small studies, a randomized trial and a nonrandomized comparative study, reported on radiographic fusion success and changes in mean neck disability scores. The other 3 nonrandomized studies focused mainly on complications. There is moderate evidence that off-label use of rhBMP2 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. There are 10 additional off-label uses, each with a single small study, most rated as poor quality. There is insufficient evidence to draw conclusions about any of these off-label uses.

Key Questions	Conclusion
7. What is the evidence of adverse events with (a) on-label use of BMP and (b) off-label use of BMP? And, at what dosage and administration do such adverse events occur?	Overall the evidence on BMP-specific harms is insufficient to draw conclusions in most settings. There is moderate evidence that off-label use of rhBMP2 in cervical spinal fusion increases cervical swelling and related complications. The body of evidence suggests that autograft bone harvest is associated with pain at the harvest site, but it is not possible to systematically assess the frequency, duration, and clinical significance. Overall, autograft harms were inconsistently reported. It is not clear that the absence of reported harms in many studies reflects true absence, or whether the investigators did not seek such data or did not report it.
8. What is the quality of reporting of adverse events in publications? Provide summary to support conclusion.	BMP-specific harms in comparative studies were assessed using a modification of the McHarms survey. The quality of reporting in the 41 comparative studies reviewed in this assessment 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 also is 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.

Key Questions	Conclusion
9. What is the incremental cost effectiveness of the use of BMP for spinal fusion and tibial fracture?	When base case analyses assume identical initial hospitalization costs within the Medicare diagnosis-related group payment system, use of rhBMP-2 dominates the alternative strategy for both open tibial fracture ands spinal fusion. In sensitivity analyses, the incremental cost-effectiveness ratios (ICERs) for both open tibial fracture and spinal fusion are highly influenced by the assumed added cost of rhBMP2. **Open Tibial Fracture** Assuming rhBMP-2 to be an added cost of $3,000, the ICER when all other variables were at mean or middle values was $49,204 per quality-adjusted life year (QALY) gained. Excluding the lowest and highest values for one influential variable, ICERs ranged between $24,471 and $64,181 per QALY gained. Assuming the cost of rhBMP2 to be $1,000 yields a mean ICER of $7,960 per QALY gained and a restricted range between $5,201 and $16,771 per QALY gained. When rhBMP2 is assumed to cost $5,000, rhBMP2 becomes much less cost-effective, with a mean ICER of $90,449 per QALY gained and a range of $59,101 to $190,491 per QALY gained. At a cost for rhBMP2 of $8,000, the mean ICER is $152,317 per QALY gained, with a range of $99,525 to $198,677 per QALY gained. As concluded in Key Question 4, of the effects of rhBMP2 in on-label treatment of acute open tibial shaft fracture, evidence is moderate that healing is enhanced and need for secondary intervention is reduced. These outcomes are reflected in QALY differences captured in the Markov model. **Spinal Fusion** Assuming that rhBMP2 was an added cost of $3,000, the ICER for all other variables at mean or middle value was $121,160 per QALY gained. Excluding the lower and upper values of one influential variable, the restricted range of ICERs was between $56,959 and $162,714 per QALY gained. At a cost of $1,000, the mean ICER is $37,785 per QALY gained and the range is between $17,763 and $50,557. If rhBMP2 is assumed to cost $5,000, the mean ICER is $204,536, and range is from $96,155 to $274,870 per QALY gained. When the cost of rhBMP2 is assumed to be $8,000, the mean ICER is $329,599 per QALY gained and the range is from $154,948 to $443,385 per QALY gained. As concluded in Key Question 1, of the effects of on-label lumbar spinal fusion, evidence is moderate, consistently showing similar and possibly better frequency of fusion and avoidance of bone graft harvest adverse events. The spinal fusion cost-effectiveness analysis relies primarily in the effectiveness component results on the avoidance of bone graft donor site pain.

Key Questions	Conclusion
10. What is the age distribution of study patients compared to the Medicare population (age 65 and older)? What are the considerations in generalizing evidence from trials to the age 65 and older Medicare populations (such as comorbid conditions in the Medicare population and this population's susceptibility to adverse events).	Among all studies the mean reported age was typically in the mid- to upper-50-years range. A randomized trial performed by Glassman and colleagues is the study identified as most relevant to the age 65 years and older Medicare population. The Glassman study does not specifically relate outcomes to age or comorbidities. The considerations relevant to generalizing from studies in the non-Medicare population include patient age, presence of comorbidities such as osteoporosis or diabetes. However, in generalizing from available studies to the Medicare population, BMP dose and surgical methods should also be considered.

INTRODUCTION

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report regarding on-label and off-label uses of bone morphogenetic protein from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center (EPC): Blue Cross and Blue Shield Association Technology Evaluation Center (via Duke EPC Sub-Contract Number: HHSA 290 2007 10066 I). The specific questions to be addressed are described at the end of the Introduction.

Biology of Bone Repair

Bone remodeling is a complex process by which old bone is continuously replaced by new tissue, requiring the interaction of various cell phenotypes and regulation by a variety of factors. Remodeling allows bone to maintain its shape, quality and size of the skeleton through the repair of microfractures and modifications of structure in response to stress and other biomechanical forces.[1,2]

Types and Composition of Bone

Two types of bone are found in the normal mature human skeleton: cortical and trabecular. Cortical bone is dense and compact and comprises 80 percent of the human skeleton. It has a slow turn over rate, a high resistance to bending and torsion, and constitutes the outer portion of all skeletal structures. Cortical bone provides mechanical strength and protection, but can participate in metabolic responses, especially during prolonged mineral deficit.

Trabecular bone is 20 percent of the skeletal mass, but 80 percent of the bone surfaces. It is less dense, more elastic and has a higher turnover rate than cortical bone. Trabecular bone provides mechanical support to the vertebrae and provides mineral supplies during acute deficiency states.[1,2]

Bone is composed of cells and an extracellular matrix. The extracellular matrix is comprised of type I collagen fibers and noncollagenous proteins, and it represents approximately 90% of the organic bone tissue. Cells, osteoblasts, osteocytes and osteoclasts work within the matrix to perform their functions.

Osteoblasts are derived from mesenchymal stem cells and occupy spaces called lacunae. They are responsible for bone formation. Upon cell activation, they secrete extracellular matrix around themselves forming new bone matrix called osteoid. These are nondividing cells and connect to other cells via gap junctions. Upon termination of bone matrix synthesis, osteoblasts either undergo cell death by apoptosis or differentiate into osteocytes or bone-lining cells, which are inactive osteoblasts. Osteocytes form a network of thin canaliculi, permeating the entire bone matrix. The exact function of these cells remains unclear. It is likely that osteocytes respond to bone tissue strain and enhance bone-remodeling activity by recruiting osteoclasts to sites where bone remodeling is required,[3] but there is no direct evidence for osteocytes signaling to other cells. Bone formation begins with irregular-shaped pieces of bone called a spicule. These form into trabeculae when osteoblasts deposit additional matrix onto the surface of the spicule. Eventually, a network of trabeculae forms a spongy bone (cancellous bone). Osteoblasts on the surface of the trabeculae continue to add new layers of bone. Compact bones

are formed in a process called bone remodeling, which involves the concerted action of osteoblasts and osteoclasts that have the capacity to erode bone surfaces (bone resorption).

Osteoclasts are the bone-lining cells derived from hematopoietic stem cells; they are multinucleated cells whose function is bone resorption. They reside in bone resorption pits (Howship's lacunae). Osteoclasts resorb bone by acidification and proteolysis of the bone matrix and the hydroxyapatite crystals encapsulated within the sealing zone. Osteoclast function is regulated by locally acting cytokines and by systemic hormones. Parathyroid hormone stimulates receptors on osteoblasts that activate osteoclastic bone resorption.

Fracture Healing

A fracture is a broken bone. The rate of fracture healing (union) depends on many factors, including the presence of an adequate blood supply and achieving mechanical stability of the fracture. While immobilization and surgery may facilitate healing, a fracture ultimately heals through physiological processes occurring in three distinct but overlapping stages: 1) the early inflammatory stage; 2) the repair stage; and 3) the late remodeling stage.[4,5]

In the inflammatory stage, a hematoma develops within the fracture site during the first few hours and days. Inflammatory cells (macrophages, monocytes, lymphocytes, and polymorphonuclear cells) and fibroblasts infiltrate the bone under prostaglandin mediation. This results in the formation of granulation tissue, ingrowth of vascular tissue, and migration of mesenchymal cells. Cancellous bone and muscle provide the primary nutrient and oxygen supply of this early process. The use of anti-inflammatory or cytotoxic medication during this first week may alter the inflammatory response and inhibit bone healing.

Repair begins as fibroblasts lay down a stroma that helps support vascular ingrowth. As vascular ingrowth progresses, a collagen matrix is laid down while osteoid is secreted and subsequently mineralized, which leads to the formation of a soft callus around the repair site. This callus is very weak in the first four to six weeks of the healing process and requires adequate protection in the form of bracing or internal fixation. Eventually, the callus ossifies, forming a bridge of woven bone between the fracture fragments. Failing to provide proper immobilization, ossification of the callus may not occur, and an unstable fibrous union may develop instead.

The healing process is completed during the remodeling stage in which the healing bone is restored to its original shape, structure, and mechanical strength. Remodeling of the bone occurs slowly over months to years and is facilitated by mechanical stress placed on the bone. As the fracture site is exposed to an axial loading force, bone is generally laid down where it is needed and resorbed from where it is not needed. Adequate strength is typically achieved in three to six months.

Regulation of Bone Healing

When a fracture occurs, fracture healing restores tissue to its original physical and mechanical properties influenced by both systemic and local factors. Bone integrity seems to be controlled by hormones and other proteins secreted by hemopoietic bone marrow cells and bone cells.[1,2] Parathyroid hormone (PTH) is the most important regulator of calcium homeostasis. Intermittent PTH stimulates bone formation and bone resorption when secreted continuously.[6] Thyroid hormones stimulate both bone formation and resorption. Calcitriol by enhancing

intestinal calcium and phosphorus absorption promotes bone mineralization. Growth hormones IGF-1 and IGF-2 are important for skeletal growth, specifically at the cartilaginous end plates and are among the major determinates of adult mass through their effect on regulation of bone formation and resorption. Glucocorticoids are essential for osteoblasts maturation and they sensitize bone cells to regulators of bone remodeling. Gonadal steroids (estrogen and testosterone) play key roles in maintaining skeletal mass. They suppress the production of signals promoting osteoclastogenesis, and stimulate fracture healing through a receptor mediated mechanism.

The molecular control of bone remodeling has been studied extensively and is well understood. On the other hand, local signaling in bones is far less understood and recent studies have indicated that signals directly between bone cells are highly important for the control of bone remodeling.[7–9] In addition to these local signals, other cellular systems, such as the sympathetic nervous system, hematopoietic stem cells, the immune system, the vasculature and even articular cartilage, also appear to exert control over bone turnover.[10]

Factors Affecting Bone Healing

Local anatomic factors such as soft tissue injury, interruption of the local blood supply, and interposition of soft tissue at the fracture site can have a dramatic effect on the ability of bone to heal. Likewise, bone death from radiation, thermal, or chemical burns can affect healing. Infection causes necrosis and edema, taking energy away from fracture healing.

Systemic factors such as nutrition, smoking, diabetes, and older age can all interfere with the fracture healing response. Nutritional deficiencies have an impact on bone healing due to the increase in metabolism requirements during fracture healing. The influence of malnutrition seems to be seen on the later phase of callus formation. The lack of nutritional contribution does not cause significant delay in union, but in the mechanical strength of the boney callus thus requiring a longer period before mineralization is completed.[11] A significantly decreased union rate has been consistently demonstrated among tobacco users.[12–14] During the repair stage the presence of nicotine can inhibit capillary ingrowth,[15–18] decreasing the vascularization of the fracture site. Diabetes mellitus is often associated with delayed fracture union, due to both vascular and neuropathy problems. In diabetic patients, a clear reduction in the formation of collagen in the bone callus and a marked reduction of the cells involved in the repair process have been noted.[19]

Potentially, the largest influence on a person's ability to heal a fracture is age.[20] The aging process and osteoporosis have a profound impact and while not all elderly are osteoporotic, it is generally accepted that if one lives long enough, one will become osteoporotic.[20] Osteoporosis is the result of progressive catabolic changes, mainly but not exclusively, occurring in the skeleton, that alter the balance of bone remodeling. Bone strength depends on bone size and density; bone density is a function of the amount of calcium, phosphorus and other minerals that are contained within bone. Depletion of these minerals below normal levels reduces bone strength, so they eventually lose their internal supporting structure. Other factors, such as hormone levels, also affect bone density. In women, when estrogen levels drop at menopause, bone loss increases dramatically. In men, low estrogen and testosterone levels can cause a loss of bone mass.

Osteoporosis increases the risk of fracture.[21,22] Fractures of the femoral neck, vertebrae, and distal radius as a result of falls and low-energy trauma occur almost exclusively in the geriatric population, being hallmarks of osteoporosis.[23,24] Histological and radiological measures show

that age-related decreases in bone quality can at least partially explain the high fracture incidence in those with osteoporosis.[25] Additionally, the repair mechanisms are compromised with age. As a consequence with increasing age there is an increase in fracture incidence and a compromised ability to heal those fractures.[20]

Bone Grafts

The choice of bone material for enhancing bony union has important clinical implications. Currently, autogenous iliac crest bone graft is considered the gold standard graft for bone induction.[26] Since the bone is taken from the patient, it is both histocompatible and non-immunogenic,[27] and it has the three properties required for bone formation: osteogenicity, osteoinductivity, and osteoconductivity. A material is osteogenic if it causes bone formation due to the implantation of viable cells, osteoinductive if it induces bone to form in an extraskeletal site, such as within skeletal muscle, and osteoconductive if due to its composition, shape or surface texture, it promotes bone formation along its surface when it is placed in bone.[28] These properties are relative and understanding the bioactive properties of a material is essential in determining its appropriateness for a given clinical application.

While it represents the current gold standard, the use of autograft bone has potentially substantial morbidities at the harvest site, generally the iliac crest.[13] These morbidities include moderate-to-severe, sometimes prolonged pain; deep infection; adjacent nerve and artery damage; and increased risk of stress fracture. Although there may be slight differences between autograft and allograft sources in the postoperative rate of union, clinical studies demonstrate similar rates of postoperative fusion (90–100 percent) and satisfactory outcomes for single-level, anterior-plated anterior cervical discectomy and fusion, using either bone source.[14,29–31] There is a limited supply of autogenous bone, which usually becomes important if the patient has had previous bone grafts and therefore no longer has an adequate quantity requiring bone to be harvested from sites other than the iliac crest or supplemented with bone graft substitutes.[32] Morbidity at the donor site has been commonly reported and seems to be enduring. Complication rates are variable but have been reported to occur anywhere from 9–49 percent of the time,[26,33–41] with pain at the harvest site still present in 26 percent of patients at 48 months post-harvest.[42] In the case of anterior cervical fusion surgery, pain at the donor site often overshadows the pain at the primary surgical site.[42] The high rates of donor site pain have been a major force behind the search for alternatives to autograft.

Allograft bone, bone from another person, represents approximately one-third of all bone grafts used in North America.[43] Allograft bone has osteoconductive and weak osteoinductive properties representing an attractive alternative to the morbidity associated with an autograft. There are several drawbacks, including a small (albeit, unproven) risk of infectious disease transmission; possible immunological reaction to the allograft, and possible limited commercial availability of appropriate graft material.[12] Demineralized bone matrix (DBM) is made from allograft bone and is a composite of collagen, noncollagenous proteins and growth factors.[26] The extensive processing required makes this the least immunogenic of all types of allograft bone.

Thus, the choice of graft material involves a trade-off between the risks specific to autograft harvest versus those specific to use of allograft material. This choice is usually left to the patient, based on thorough explanation and discussion of the relative risks and benefits with the surgeon.

Bone Morphogenetic Proteins (BMP)

Bone morphogenetic proteins (BMP) were discovered in 1965 by Urist; he also was the first to describe osteoinduction.[44] Urist observed new local bone formation in rodents after they were given intramuscular implantation of bone cylinders decalcified with hydrochloric acid. This phenomenon was attributed to BMP, a protein in the bone matrix. Having realized the osteoinductive properties of BMPs and having identified their genetic sequences, recombinant gene technology has been used to produce BMPs for clinical application—most commonly, as alternatives or adjuncts in the treatment of cases in which fracture healing is compromised.

BMPs are members of the family of the larger transforming growth factors-beta (TGF-beta) and play an important role in embryonic development including brain[45] and bone formation.[46,47] At present, some 20 different BMPs have been identified, but only BMPs 2, 4, 6, and 7 have been shown to have significant osteoinductive properties. BMP signal transduction is induced via interaction with the heterodimeric complex of two transmembrane serine/threonine kinase receptors.[48,49] BMPs encourage bone production through two pathways. They recruit mesenchymal cells from surrounding tissue and differentiate the cells into either osteoblasts that make bone directly or cartilage cells which subsequently change to bone cells.[26]

Recombinant human bone morphogenetic proteins (rhBMP) 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. For interbody spinal fusion, delivery systems include interbody fusion cages, whereas pedicle and screw devices are more commonly used for intertransverse fusion. Therefore, the carrier and delivery system are important variables in the clinical use of rhBMPs. For example, different clinical applications, such as long bone non-union, or interbody or intertransverse fusion, may require different dosages of rhBMP with different carriers and delivery systems. Therefore, the results of one clinical application cannot always be extrapolated to others.

Currently, two rhBMPs and four associated carrier/delivery systems (one of which has been voluntarily withdrawn from the U.S. market) have received approval as devices from the U.S. Food and Drug Administration (FDA). The InFUSE® system (Medtronic Sofamor Danek, Inc.) consists of rhBMP2 on an absorbable collagen sponge carrier.[50–53] Osteogenic Protein 1 or OP-1® (Stryker Biotech) consists of rhBMP-7 and bovine collagen, which is reconstituted with saline to form a paste.[54,55] The addition of carboxymethylcellulose forms putty.

Clinical Applications of BMP

Clinical applications of BMP2 (InFUSE®) and BMP7 (OP-1®) products according to FDA-approved marketing labels are presented in Table 1 by device.

Table 1. Indications in FDA-Approved Marketing Labels for BMP Devices

Product/FDA Approval Mechanism	Carrier/scaffold	Indication(s)	Comments
InFUSE® (50, 51) PMA (P000054; tibial) (P050053; dental)	Collagen sponge	1) Treating acute, open tibial shaft fractures that have been stabilized with [intramedullary] nail fixation after appropriate wound management. The device must be applied within 14 days after the initial fracture. 2) An alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets	
InFUSE® (52) PMA (P00058)	LT-Cage or Inter Fix Threaded Fusion devices	Spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level.	Patients receiving the InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE Bone Graft/LT-Cage device. The InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach.
InFUSE® (53) HDE (H040004)	Mastergraft/CD HORIZON	Revision/repair of symptomatic, posterolateral lumbar spine pseudarthrosis Note: The HDE approval for this product was voluntarily withdrawn by Medtronic in early 2010.	This device is intended to "address a small subset of patients for whom autologous bone and/or bone marrow harvest are not feasible or are not expected to promote fusion" (i.e., patients who smoke or have diabetes). This device is indicated to treat two or more levels of the lumbar spine. Must be used with a posterior fixation device such as CD HORIZON spinal system.
OP-1 Implant® HDE (H010002)	N/A	Indicated for use as an alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed	Must be used with fixation including cast, external fixation, IM rod and internal plate
OP-1 Putty® HDE (H020008)	N/A	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.

Abbreviations: FDA: U.S. Food and Drug Administration; HDE: Humanitarian Device Exemption; N/A: not applicable; PMA: Premarket Application

InFUSE®

InFUSE® (rhBMP-2) is available as a lyophilized powder in vials containing either 4.2 mg or 12 mg of protein. After reconstitution, both configurations result in the same concentration (1.5 mg/mL). After reconstitution, the solution should then be applied to the collagen sponge ("carrier") provided, and should be used immediately.

In July 2002, the FDA approved via its Premarket Application (PMA) device approval process, the InFUSE® bone graft in conjunction with the LT-Cage Lumbar Tapered Fusion device for spinal fusion procedures via an anterior approach; the Agency has subsequently approved other interbody devices (e.g., Inter Fix RP Threaded Fusion device) for this use. The current specific indication is for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit, and/or neurological 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 should have had at least six months of nonoperative treatment prior to treatment with the InFUSE® Bone Graft/Interbody Fusion Device.

In April 2004, InFUSE® received PMA approval for treatment of acute, open fractures of the tibial shaft that have been stabilized with intramedullary (IM) nail fixation following appropriate wound management. In March 2007, the device received PMA approval as an alternative to autogenous bone grafts for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. In both cases, the device must be used with the absorbable collagen sponge carrier.

In October 2008, InFUSE® received FDA device approval via a special approval process called a humanitarian device exemption (HDE) for use as part of a three-part component system (InFUSE® bone graft plus Mastergraft Granules plus supplemental posterior fixation system, e.g., the CD HORIZON spinal system) for:

> Symptomatic, posterolateral lumbar spine pseudoarthrosis among patients for whom autologous bone and/or bone marrow harvest are not feasible or are not expected to promote fusion, such as diabetics and smokers. The device is indicated to treat two or more levels in the lumbar spine. Patients receiving the InFUSE®/Mastergraft should be skeletally mature (≥ 21).

The HDE process is available to devices intended for fewer than 4,000 patients per year in the U.S.; as part of this process, the manufacturer is not required to demonstrate unequivocal benefit, but only "probable" benefit. It should be noted that the HDE approval was voluntarily withdrawn by Medtronic in early 2010 (Jason E. Kemner, Medtronic Inc. Spinal and Biologics, personal communication, May 7, 2010).

OP-1®

OP-1 Implant® is supplied as a vial containing one gram of the device as a dry powder comprised of rhBMP-7 and bovine bone collagen. OP-1 Putty® is provided as 2 units. Each unit is comprised of one 20-mL vial of OP-1® Implant containing one gram of a sterile dry powder consisting of bovine collagen and OP-1® and a 10 mL vial of putty additive containing 230 mg of sterile carboxymethylcellulose. One vial of OP-1® Implant and one vial of putty additive must be combined with sterile saline to produce one unit of OP-1® Putty. One unit of OP-1 Putty is used for each side of the spine.[55]

OP-1® has received two FDA approvals through the HDE approval process. In October 2001, OP-1 Implant® received HDE approval for "…use as an alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed." In April 2004, OP-1 Putty® received HDE approval 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.[56]

Safety

OP-1® and InFUSE® Bone Graft are contraindicated in patients who are pregnant, who may be allergic to any of the materials contained in the devices, who have an infection near the area of the surgical incision, who 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.[57] 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 neurological 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 FDA for this use.

Few documented adverse events can be attributed to BMP. Nonetheless, certain complications and safety issues are of concern. Adverse events that have been reported include but are not limited to inflammation, ectopic bone formation, infection, immune responses, vertebral osteolysis and vertebral edema.[50–54]

Clinical Guidelines

The literature search conducted for this technology assessment did not identify any evidence-based guidelines for the use of any BMP device.

Summary

Bone remodeling is a complex process by which old bone is continuously replaced by new tissue. Remodeling allows bone to maintain its shape, quality and size of the skeleton through the repair of microfractures and modifications of structure in response to stress and other biomechanical forces.[1,2] After a fracture both local and systemic factors affect bone healing or fusion. Age may be the factor exerting the largest influence on bone fusion.

Under certain circumstances it may be necessary to enhance the likelihood of fusion. Currently, autogenous iliac crest bone graft is considered the gold standard graft for bone induction.[26] However, the use of autograft bone has potentially substantial morbidities at the harvest site, generally the iliac crest.[13] Allograft bone, bone from another person, represents approximately one-third of all bone grafts used in North America.[43] Allograft bone has osteoconductive and weak osteoinductive properties representing an attractive alternative to the morbidity associated with an autograft, but this is not without some risk including a small (albeit, unproven) risk of infectious disease transmission; possible immunological reaction to the allograft, and possible limited commercial availability of appropriate graft material of infection.

BMPs are members of the family of the larger transforming growth factors-beta (TGF-beta). At present, some 20 different BMPs have been identified, but only BMPs 2, 4, 6, and 7 have been shown to have significant osteogenic properties. Currently, two rhBMPs and four associated carrier/delivery systems have received approval via different approval mechanisms from the. FDA. The InFUSE® system consists of rhBMP2 on an absorbable collagen sponge carrier and was approved for marketing via the PMA process for acute, open shaft fractures, lumbar spinal fusion (used with specific approved cage devices) or sinus or alveolar ridge augmentation; the product was approved for use via HDE for lumbar spine pseudarthrosis (with Mastergraft/CD HORIZON spinal system). OP-1® products consist of rhBMP7 and bovine collagen, which is reconstituted with saline to form a paste or with the addition of carboxymethylcellulose forms putty. These products were approved for use via HDE for long bone non-union and revision lumbar spinal fusion.

Few documented adverse events can be directly attributed to BMP. Adverse events that have been reported include but are not limited to inflammation, ectopic bone formation, infection, immune responses, vertebral osteolysis and vertebral edema.

Key Questions to be Addressed by this Technology Assessment

Key Question 1. What evidence of improved outcomes is associated with the on-label use of InFUSE for fusion of the lumbar-sacral spine?

Key Question 2. What evidence of improved outcomes is associated with the on-label use of OP-1 for fusion in the lumbar spine?

Key Question 3. What evidence of improved outcomes is associated with the on-label use of OP-1 in recalcitrant long bone non-unions?

Key Question 4. What evidence of improved outcomes is associated with the on-label use of InFUSE for the treatment of acute, open shaft fractures?

Key Question 5. What is the level of evidence and summary of evidence for the on-label use of InFUSE for sinus augmentation?

Key Question 6. For which indications are there clinical studies in which BMP is used off-label? In such studies, what is the evidence of the effectiveness of BMP?

Key Question 7. What evidence of adverse events is associated with (a) the on-label use of BMP and (b) the off-label use of BMP? And, at what dosage and administration do such adverse events occur?

Key Question 8. What is the quality of reporting of adverse events in publications? Provide summary to support conclusion.

Key Question 9. What is the incremental cost effectiveness of the use of BMP for spinal fusion and open tibial fracture?

Key Question 10. What is the age distribution of study patients compared to the Medicare population (age 65 and older)? What are the issues associated with generalizing evidence from trials to the age 65+ Medicare populations (such as co-morbid conditions in the Medicare population and this population's susceptibility to adverse events).

METHODS

As detailed below, certain aspects of Methods and Materials may vary to satisfy requirements of each question. However, the Methods are generally applicable to all Key Questions, including Methods of the Review, Evidence Tables, Identifying Additional Studies, and Assessing Study Quality.

Database Search Strategies

The following electronic databases were searched for citations (search strategy can be found in Appendix 6).

- MEDLINE® (January 1, 1998, through July 28, 2009)
- EMBASE® (January 1, 1998, through July 28, 2009)
- Cochrane Controlled Trials Register (no date restriction)

The searches were updated in February 2010. At that time, we became aware of a report of 6-years results from two earlier trials of rhBMP2 (InFUSE®) in lumbar-sacral spinal fusion.* These data do not change the conclusions of this technology assessment.

The search was not limited to English-language references, but because the non-English articles that were identified did not add to the analysis or conclusions, they were excluded . Because the review of on-label uses primarily focused on RCTs, the Cochrane Handbook search strategy for controlled trials[58] was applied.

The MEDLINE® search resulted in 1,606 unique citations (2 duplicates were found within the 1,608 citations total). The EMBASE search resulted in 499 citations and the Cochrane search resulted in 54 citations. The total number of citations, due to overlap between the searches, was 1,992 citations.

In addition to the electronic database searches, we examined the bibliographies of all retrieved articles for citations to any RCT that was missed in the database searches. We did not seek or include studies published in conference proceedings and abstracts.

Patient Populations

The populations of interest for all key questions comprise patients with a skeletal bone defect or bone-related condition for which intervention is undertaken to effect or augment correction of such a defect.

Interventions

The interventions of interest for all Key Questions are the use of either of two BMP products, rhBMP2 (InFUSE®) and rhBMP7 (OP-1®) that are licensed for marketing and use in the U.S.

Interventions will be considered to be delivered on-label only when administered alone (without additional entities such as autograft bone, allograft bone, other osteoconductive or

* Burkus JK, Gornet MF, Schuler TC, et al. Six-year outcomes of anterior lumbar interbody arthrodesis with use of interbody fusion cages and recombinant human bone morphogenetic protein-2. J Bone Joint Surg Am. 2009;91:1181-1189.

osteoinductive agents such as platelet-rich plasma (PRP), demineralized bone matrix or other such carriers) according to the indication specified in the FDA-approved marketing label. Dose will only be addressed if it is a primary objective in a study, but will be abstracted from primary studies.

All other uses and applications of BMP products will be considered off-label.

Comparators

Comparators may include other osteoconductive, osteoblastic, or osteoinductive agents, (including, but not limited to, autologous bone, allogeneic bone, bone marrow, demineralized bone matrix, stem cells, or others that are used to augment bone remodeling and healing processes), a placebo (e.g., BMP or bovine collagen placebo), or standard surgical care.

Outcomes of Interest

Outcome measures should be standard, valid, reliable, and clinically meaningful, with defined minimally detectable change (in a statistical sense) and minimally important clinical difference (a change patients perceive as beneficial). Durability and outcomes (short- and long-term effects) will be examined according to the time frame of study reporting.

The primary outcomes of interest are subdivided according to type of skeletal bone defect, but because the technology assessment sought to assess off-label uses, not all were prespecified in the workplan.

Fractures

A consistent definition of fracture healing that is clinically and biologically accurate has been difficult to develop.[59] A wide range of clinical and radiographic criteria have been used to assess fracture non-union, for example tibial fractures, with non-union defined as ranging from 2 to 12 months. Available methods include radiographic technologies, mechanical property assessment, and patient-centered and health-related quality-of-life (QoL) outcomes.

Several radiographic measures can be used to assess fracture healing, including conventional radiography, absorptiometry, and photodensitometry, bone scintigraphy, ultrasound, and computed tomography. The oldest and most common is conventional radiography, which allows qualitative assessment of callus formation, cortical bridging, loss of the fracture line, and trabecular crossing at the fracture site. This method is widely available, relatively inexpensive, and delivers a low dose of radiation to the patient. However, the relationship between radiographic features and mechanical strength is not well established. Furthermore, it is unclear how any radiographic measures correspond to outcomes that are important to the patient, such as pain, function, or QoL.

Mechanical property testing to assess fracture healing includes vibrational analysis and biomechanical testing to determine true measures of stiffness and strength. These have been introduced for bedside use, but neither is commonly used or well-validated clinically in typical settings.

Patient-Reported and Health-Related Outcomes

Several classes of health-related QoL measurement instruments are available. General health instruments, such as the Short Form-36 (SF-36) address a broad spectrum of domains surrounding physical and mental health. The SF-36 survey is widely validated in a variety of conditions; however, it may not be sufficiently responsive to detect smaller functional changes secondary to orthopedics procedures.

Changes in disability, pain, or function of an extremity or body region may be assessed using specific instruments, such as the Disability of the Arm, Shoulder and Hand (DASH[60]), which can be more responsive than general health instruments.

Pain severity or intensity (typically measured by either visual analog scale (VAS) or a numeric rating scale (NRS) at the site of a fracture, in conjunction with the ability to bear weight, walk, or perform activities of daily living are commonly used criteria to assess fracture healing. A combination of conventional radiography and clinical questions on pain and weight-bearing was the most commonly used approach to assessing fracture healing in a recent survey of published articles.[59] The need for subsequent surgical interventions secondary to treatment failure also may be considered a clinical outcome.

Spinal Fusion

As outlined above, radiographic methods are used to evaluate bone healing in spinal fusion procedures. In addition, clinical outcomes of treatments for back pain are compared using a variety of techniques. Most common are pain scales measured on a visual analog scale. Various questionnaires have been developed to additionally capture measures of physical functioning. These types of clinical findings may be combined with radiographic assessment in composite measures, often referred to as overall success.

One of the more common measurement scales in use specific to patients with back pain is the Oswestry Disability Index (ODI), originally developed in 1976. The validity, consistency, and reproducibility of the ODI were extensively reviewed by Roland and Fairbank.[61] This review cites an article by Meade and co-workers,[62] which suggests that a 4-point difference in the ODI is the minimum clinically significant difference. The Roland and Fairbank article also cites a personal communication from the FDA, which states that the FDA has chosen a minimum 15-point change in spinal surgery patients as a clinically meaningful difference in the ODI.

Three primary outcome variables used to assess outcomes of cervical spinal fusion include the Neck Disability Index (NDI), neurological status, and functional spinal unit height (FSU). The NDI is a validated multidimensional instrument that measures the effects of pain and disability on a patient's ability to manage everyday life.[63] It is a modification of the Oswestry Low Back Pain Index, based on the response to 10 questions that focus on neck pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. The response to each question ranges from 1 to 5, with a lower numeric score representing a better pain and disability status for that variable. A total NDI score is obtained by adding individual question scores and dividing by the maximum total of 50 if all questions are answered. Therefore, NDI scores range from 0 percent to 100 percent, with a lower percentage indicating less pain and disability.

The neurological status is a composite measure of motor function, sensory function, and deep tendon reflexes. It is used to judge if patients are within normal parameters for those categories

based on physiological measurement. Neurological success may be based on postoperative maintenance or improvement of condition as compared to preoperative status for each component.

The anterior FSU height is a radiographic measure of interdiscal space. Comparison of the immediate postoperative FSU height with the 6-week postoperative value shows whether or not the disc space has decreased, which indicates graft or device subsidence has occurred.

Secondary outcome measures include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) mental (MCS) and physical (PCS) component summaries, neck and arm pain status, patient satisfaction, patient global perceived effect, gait assessment, foraminal compression test, adjacent level stability and measurements, return to work, and physician's perception. In addition to disability and QoL instruments, the need for subsequent surgical interventions secondary to treatment failure also may be considered a clinical health outcome in spinal fusion patients.

Alveolar Ridge and Sinus Augmentation

Outcomes in these studies will be as defined in the FDA-approved marketing label, based on the pivotal trials for these uses. Thus, a successful outcome of sinus augmentation is defined as successful dental implant borne restoration after 6 months of functional loading. A secondary outcome would be the achievement of clinical osseointegration and maintained functional restoration after 6, 12, 18, and 24 months of functional loading

Off-label Uses

Because the results of this analysis could not be predicted a priori, it was not possible to specify outcomes to be compiled. However, whenever possible, we compiled outcomes deemed to be clinically relevant to the patient, ideally based on validated criteria for each use.

Harms

Specific harms secondary to the use of BMP products have been reported (e.g., excessive or ectopic bone formation, antibody response to BMP or bovine collagen, neck swelling, etc). We will use the FDA-approved marketing labels for rhBMP2 (InFUSE®) and rhBMP-7 (OP-1®) as guidance for collection of information on harms (including dose information) reported in the primary literature. While the absence of information on harms is not construed as evidence that none occurred in any particular study, we are unaware of any established method to efficiently systematically review and compile this type of information.

There are no validated standard tools to assess either reporting bias or completeness for harms. Consequently, reporting was assessed using an empirically derived set of questions informed by the McMaster Quality Assessment Scale for Harms (McHarm[64]) and the Agency for Healthcare Research and Quality (AHRQ) draft Methods Manual guidance.[65]

- Is there an explanation of how harms were identified?
- Was a standardized or validated instrument or scale used?
- Was ascertainment similar and complete in all study groups?
- Was a measure of severity reported?

- Were harms attributed to the study intervention likely causally associated?
- Were the number and type of harmful events reported separately for study groups?

Practice Settings

Interventions relevant to all key questions are used in hospitals or outpatient surgical centers.

Study Selection Criteria

Studies were selected to address the following 10 Key Questions identified for this technology assessment (see Introduction). One reviewer screened titles and abstracts of identified studies using the following eligibility criteria. If this could not be done satisfactorily from the title and abstract, we obtained a full text version for assessment. Articles published in a language other than English were not included in this technology assessment.

Key Questions 1–6

We abstracted data from full-length RCTs that utilized BMP therapy in patients with a bony defect that required intervention and reported at least one health benefit of interest. If RCT evidence was unavailable, data from nonrandomized comparative studies (quasi-experimental) was sought to assess clinical efficacy.

Key Questions 7 and 8

We retrieved studies and abstracted data on harms from full-length reports with English-language abstracts, including all RCTs and nonrandomized comparative studies, and other observational studies with more than 50 patients in which the specified aim of the study was to evaluate harms attributable to BMP use.

Key Question 9

Economic evaluation was addressed by: 1) identifying and appraising published economic evaluations and 2) developing economic decision models for spinal fusion and tibia fractures. To identify economic evaluations, the search strategy was modified using economics as a keyword. Databases of economic evaluations were also searched, including:

CEA Registry at Tufts (https://research.tufts-nemc.org/cear/default.aspx),
National Health Service Economic Evaluation Database (http://www.crd.york.ac.uk/crdweb/Home.aspx?DB=NHS%20EED)
Health Economic Evaluations Database (http://www3.interscience.wiley.com/cgi-bin/mrwhome/114130635/HOME? CRETRY=1&SRETRY=0)

Quality of economic evaluations was assessed using the checklist developed by Drummond et al.[66]:

- Was a well-defined question posed in answerable form?

- Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?
- Was the effectiveness of the program or services established?
- Were all the important and relevant costs and consequences for each alternative identified?
- Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?
- Were the cost and consequences valued credibly?
- Were costs and consequences adjusted for differential timing?
- Was an incremental analysis of costs and consequences of alternatives performed?
- Was allowance made for uncertainty in the estimates of costs and consequences?
- Did the presentation and discussion of study results include all issues of concern to users?

Economic decision models were developed for spinal fusion and tibia fractures relevant to the Medicare population. Evidence used to inform the cost-effectiveness analyses were derived from two sources. Outcome probabilities came from this technology assessment, published systematic reviews, and meta-analyses. Cost estimates came from payor databases and published sources. Utilities used in the systematic review by Garrison et al.[26] were to be employed if more recent values could not be identified.

Key Question 10

We abstracted and compiled data on the age distribution of patients included in studies selected for inclusion in this technology assessment.

Data Analysis and Presentation

Electronic search results were stored in a ProCite® database and the number of references retrieved and included in the technology assessment was documented. Using the final study selection criteria for screening titles and abstracts, a single reviewer marked each citation as 1) eligible for review as a full-text article, 2) ineligible for full-text review, or 3) uncertain. A second reviewer reviewed all citations marked as uncertain by the first reviewer, and the two reviewers formed a consensus opinion.

Detailed records of the results of this evaluation were kept for each paper retrieved in full text, including the reason for exclusion of each excluded study. A listing of excluded studies with reasons for exclusion is available in Appendix 6. Any disagreement about the inclusion or exclusion of a particular article was resolved by consultation with a third reviewer to achieve a consensus.

The following data elements of primary studies were abstracted as available from the articles meeting all selection criteria.

a. General information: title, authors, source, year of publication, duplicate publications, setting, funding.

b. Trial characteristics: method of randomization, concealment of allocation, blinding of patients and clinicians.
c. Patients: sampling, exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, withdrawals, losses to follow up.
d. Interventions: dose, dosing regimen, duration, route, co-medications with dose, timing.
e. Analytical methods
f. Outcomes: outcomes as specified above
g. Data on costs (if applicable)

Evidence Tables

We created templates for evidence tables in Microsoft Excel® and Microsoft Word®. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer performed accuracy checks on the evidence tables.

Assessment of Study Quality

The quality (internal validity) of included studies (RCTs and other comparative designs) was assessed on the basis of the general approach to grading evidence developed by the U.S. Preventive Services Task Force (USPSTF[67]). The quality of the abstracted studies was assessed by two independent reviewers. Discordant quality assessments were resolved with input from a third reviewer, if necessary. Quality criteria were as follows:

a. Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
b. Maintenance of comparable groups (includes attrition, crossovers, adherence contamination)
c. Important differential loss to follow-up or overall high loss to follow-up
d. Measurements: equal, reliable, and valid (includes masking of outcome assessment)
e. Clear definition of interventions
f. All important outcomes considered
g. Analysis: adjustment for potential confounders, intention-to-treat analysis
h. The rating of intervention studies encompasses the three quality categories described here:

Studies were rated as "good" if they met all criteria: Comparable groups were assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments were used and applied equally to the groups; interventions were spelled out clearly; all important outcomes are considered; and appropriate attention was given to confounders in analysis. In addition, for RCTs, intention-to-treat analysis was used.

Studies were rated as "fair" if any or all of the following problems occurred, without the fatal flaws noted in the "poor" category below: In general, comparable groups were assembled

initially but some question remained as to whether some (although not major) differences occurred with follow-up; measurement instruments were acceptable (although not the best) and generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were accounted for. In addition, for RCTs, intention-to-treat analysis was used.

Studies were graded "poor" if any of the following fatal flaws existed: Groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments was used or not applied at all equally among groups (including not masking outcome assessment); and key confounders were given little or no attention. For RCTs, intention-to-treat analysis was lacking.

Assessment of Applicability

Applicability of findings in this review will be assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, Time stamp[68]). Selected studies were assessed for relevance against target populations, interventions of interest and outcomes of interest.

Data Synthesis

This evidence review did not incorporate quantitative data synthesis using meta-analysis. Rather, the synthesis emphasized comparative studies sorted by interventions, specific patient characteristics, specific outcomes and status relative to the evidence hierarchy/study quality assessment.

Rating the Body of Evidence

The system used for rating the strength of the overall body of evidence was developed by AHRQ[69] for the EPC Methods Guide, based on a system developed by the GRADE Working Group.[70] This system explicitly addresses the following domains: risk of bias, consistency, directness and precision. Grade of evidence strength was classified into the following four categories:

- High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit estimation of an effect.

RESULTS

Search Results

The electronic literature search yielded 1,992 records, of which 1,738 were excluded at initial title and abstract review and 254 were retrieved for full text examination. Based on the study selection criteria, 140 of 254 retrieved articles were excluded, while 114 met inclusion criteria. Examination of abstracts of non-English language articles revealed no information that could alter the results of the assessment based on English articles, so all were excluded.

Forty-one articles describing results of comparative studies were abstracted, as summarized in Table 2. This technology assessment will focus on the comparative studies, but we also abstracted and compiled data from noncomparative studies in off-label indications to further gather evidence of possible harms associated with clinical use of bone morphogenetic protein (BMP) devices (see Table 3). The key questions addressed in this technology assessment are listed in the Introduction.

Organization of the Results Chapter

- Assessment of power and sample size in comparative BMP studies
- Synthesis and summary of evidence for each Key Question organized by setting and U.S. Food and Drug Administration (FDA) label status (i.e., indication included as part of the approved label [“on-label”] or not [“off-label”)

Table 2. Distribution of Comparative Studies of rhBMP2 and rhBMP7 According to U.S. Food and Drug Administration (FDA) Label Status

FDA Label Status	rhBMP2 RCT (reference numbers)	rhBMP7 RCT (reference numbers)	rhBMP2 non-RCT (reference numbers)	rhBMP7 non-RCT (reference numbers)
On-label	6 studies (71, 72, 74, 75, 76, 77)	2 studies (78, 79)	2 studies (80, 81)	2 studies (82, 83)
Off-label	9 studies (73, 84, 85, 86, 87, 88,89, 90, 91)	7 studies (92, 93, 94, 95, 96, 97, 98)	11 studies (99, 100, 101,102, 103, 104, 105, 106, 107, 108, 109)	2 studies (110, 111)

Abbreviations: RCT: randomized, controlled trial

Table 3. Distribution of Off-Label Noncomparative Studies of rhBMP2 and rhBMP7

Surgical Setting	rhBMP2 case series (reference numbers)	rhBMP7 case series (reference numbers)	rhBMP2 case report (reference numbers)	rhBMP7 case report (reference numbers)
Cervical spine	10 reports (112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122)	2 reports (123, 124)	2 reports (125, 126)	0
Lumbar spine	19 reports (116, 118, 120,127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142)	5 reports (123, 124, 136 143, 144,)	5 reports (145, 146, 147, 148, 149, 150)	1 report (151)
Arm	0	2 reports (152, 153)	1 report (154)	1 report (155)
Wrist (2 case reports; rhBMP type not reported)				
Femur	1 report (156)	1 report (156)	1 report (157)	1 report (158)
Tibia	0	1 report (159)	0	2 reports (160, 161)
Foot and ankle	2 reports (162, 163)	0	1 report (164)	1 report (165)
Oral-facial cleft	4 reports (166, 167, 168, 169)	0	1 report (167)	0
Mandibular defects	3 reports (170, 171, 172)	1 report (170)	2 (173, 174)	0
Other	3 reports (175, 176, 177)	2 reports (178, 179)	2 reports (180, 181)	0

Assessment of Power and Sample Size

Detailed results from this evaluation are presented in Appendix 3, Table A (on-label comparative studies) and Appendix 3, Table B (off-label comparative studies).

Among on-label studies, 4 of 13 (31 percent) had some level of reporting of power and/or sample size. Two trials appear to report these numbers retrospectively.[76,78] Two performed the

calculations prior to participant enrollment.[74,77] Of those, only one enrolled enough participants and followed a sufficient number to assess their primary outcome at the prespecified level.[74]

Among off-label studies 2 of 28 (7 percent) had some level of reporting of power and/or sample size. These numbers were calculated retrospectively in one trial.[90] In the other trial, power calculations were performed prior to participant enrollment; however the investigators did not recruit or follow a sufficient number of participants to assess their primary outcome measures.[94]

Overall, the frequency of reporting of power calculations and/or the adequacy of sample size in this literature is low. This finding is consistent with the generally poor to fair quality of individual comparative studies that comprise the evidence base for BMP efficacy and safety.

Synthesis of Evidence According to Key Questions

We have synthesized the body of evidence available for on- and off-label use of rhBMP2 and rhBMP7 for Key Questions 1-6 using the modified AHRQ/GRADE framework.[69] This analysis was applied only if at least two studies were available involving a single rhBMP device and patients with similar bone defects.

Key Question 1

What is the evidence supporting improved outcomes with on-label use of rhBMP2 (InFUSE®) for fusion of the lumbar-sacral spine?

As shown in Table 4, the strength of the body of evidence for improved outcomes with on-label use of rhBMP2 (InFUSE®) was graded as moderate. Two RCTs reported fusion outcomes to be similar to that of autograft bone.[71, 72] No significant adverse events were attributed to rhBMP2 in any study. However, the size and duration of the RCTs are not sufficient to precisely determine the frequency and severity of adverse events. Thus, the evidence gives moderate support to clinical benefit from the use of rhBMP2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.

Table 4. Overall Grade of Strength of Comparative Study Evidence for On-Label Use of rhBMP2 for Fusion of the Lumbar-Sacral Spine

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What evidence of improved outcomes is associated with the on-label use of InFUSE for fusion of the lumbar-sacral spine? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	There are two RCTs. The largest included 279 patients, the other included 14 patients. Both used independent assessment of radiographic outcomes. Neither reported statistically significant results or power and sample size calculations.	Risk of bias is medium in these studies. Both were RCTs, but all did not clearly report randomization methods. Intent-to-treat analysis was not consistently reported but loss to follow-up was relatively low. Standardized clinical outcomes measures were used. Only radiological fusion was independently assessed. Device-related harms are inconsistently reported in this literature. Therefore there is a high risk of bias with respect to adverse events.	Consistent results were seen in the sense that no study or scale within a study reported numerically worse results for rhBMP2 versus iliac crest bone graft (ICBG). No quantitation of effect size is possible because no statistical significance was reported. Radiographic fusion outcomes were qualitatively similar with rhBMP2 and ICBG. The most numerically favorable results were reported in the smaller RCT. The frequency of adverse events associated with autograft bone harvest varied in these reports.	Direct evidence was available for all outcomes considered under this Key Question.	The body of evidence is imprecise.	The strength of the body of evidence for this indication is moderate. The results are consistent in that frequency of fusion was similar, and may possibly be better, for rhBMP2 compared to autograft bone. Among the two RCTs, no device-related adverse events were reported. However, the size and duration of RCTs are not sufficient to precisely determine the frequency and severity of adverse events. Thus, the evidence gives moderate support to clinical benefit from the use of rhBMP2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.

Key Question 1 Evidence Summary

Table 5 summarizes two RCTs that compared rhBMP2 (total N=154) and autograft bone (AGB) (total n=139) for fusion within the lumbar spine.[71, 72] Both studies were rated as "fair" according to the USPSTF study quality evaluation system (see Appendixes 1 and 2 for full details on study characteristics and USPSTF quality ratings). These trials reflect on-label use according to the PMA for InFUSE®. The literature search did not identify any trials deemed on-label for the product initially approved via the HDE process (InFUSE®/Mastergraft).

Table 5. On-Label Randomized Trials of rhBMP2 for Lumbar-Sacral Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Degenerative disc disease of the lumbar spine (71, 72)	2	rhBMP2	154	24	4.2–8.4	2 FAIR
		AGB	139	24	0	

Abbreviations: AGB: autograft bone; mos.: months; no.: number; pts: patients; ref: reference; USPSTF: U.S. Preventive Services Task Force

All patients had symptomatic (low back pain, leg pain, functional impairment) single-level DDD that had not responded to noninvasive therapies for a minimum of 6 months.

Spinal fusion was performed using an anterior approach in both studies[71,72] with follow-up of 24 months. Autograft bone was harvested from the iliac crest in all cases that received this treatment.

In both studies,[71,72] rhBMP was used at a dose of 4.2-8.4 mg per patient; The BMP product was administered via absorbable collagen sponge (ACS), inside interbody fusion cages according to the approved marketing label (InFUSE®). [71,72] Patient demographics were similar in each study, with no statistically significant intergroup differences (see Appendix 1 Table C for detailed patient characteristics). Tobacco use was reported in about 33 percent[72] of all patients in one study, but was uneven in the third[71] (0 percent in the BMP group versus 33 percent in the control group), although this difference was not statistically significant and likely due to a very small number of cases (n=3) in the control group

Table 6 shows key results from the two RCTs of the use of rhBMP2 in lumbar spinal fusion.[71, 72]

Table 6. Clinical Outcomes in On-Label Randomized Trials of rhBMP2 for Lumbar-Sacral Spinal Fusion

Study (ref no.)	Group	No. of Pts.	BMP dose range (mg/pt)	Radiographic fusion success, 24 mos., %	ODI success, 24 mos., %	Leg pain mn point score ↑ 24 mos.	Work status 24 mos. , %	Patient satisfaction 24 mos., %	USPSTF study quality
Burkus et al., 2002 (72)	BMP2	143	4.2-8.4 (InFUSE®)	94	84	6.2	66	81	FAIR
	ICBG	136	0	89	82	6.2	56	80	
Boden et al., 2000 (71)	BMP2	11	4.2-8.4 (InFUSE®)	100	91	NR	91	100	FAIR
	ICBG	3	0	67	67	NR	67	100	

Abbreviations: ICBG: iliac crest bone graft; mn: mean; mos.: months; no.: number; ODI: Oswestry Disability Index; pt(s): patient(s); USPSTF: U.S. Preventive Services Task Force

In both studies,[71, 72] radiographic fusion success reflected the presence of continuous trabecular bone growing through both interbody fusion cages. ODI success was defined explicitly as a 15 percent or greater improvement over the preoperative score in one study.[71] The second study[72] alluded to a 15% improvement as important, but did not specify it as significant. Leg pain visual analog scores (VAS) improved significantly from baseline in both groups, but no significant intergroup differences were reported.[71, 72] Work status reflected the proportion of patients who were working prior to surgery and resumed work postsurgery. [71,72]

In one study,[71] the mean operating room time was significantly longer in the iliac crest bone graft (ICBG) group than in the BMP2 group (3.3 vs. 1.9 hours, respectively, p=0.006). Mean operating room time was 1.6 and 2.0 hours, respectively, in the second trial,[72] which were not statistically significant differences. No other significant intergroup differences in perioperative outcomes were reported in any of the trials, including the need for second procedures, blood loss, or procedural complications (see Appendix 1 for details).

Iliac crest harvest site pain was reported in 100% of patients in one study,[72] with a mean VAS of 12.7 (of a 20-point scale) immediately following surgery; 32 percent of patients still experienced pain at 24 months' follow-up, with an average score of 1.8. In that study, seven adverse events related to bone graft harvest (three injuries to the lateral femoral cutaneous nerve, two avulsion fractures of the anterior superior iliac crest, one infection, one hematoma) were identified in eight (5.9 percent) patients. No adverse events related to graft harvest were reported in the other trial.[71]

Evidence is available from two randomized trials of rhBMP2 to enhance fusion in the lumbar spine.[71, 72] Both studies used InFUSE® at a dose of 4.2–8.4 mg per patient. [71,72] Both report results numerically favoring or identical to rhBMP2, but results are not statistically significant. No device-related complications (biological or mechanical) were reported in these studies. Pain and complications were reported secondary to autograft bone harvest in 1 study.[72]

Table 7 notes a pooled analysis that has been widely cited in the review literature of BMP for lumbar-sacral spinal fusion.[182] The authors state this report includes data from four prospective multicenter clinical trials. These include the largest of the RCTs reviewed above[72] (n=279), a partial dataset (n=22) published from a prospective RCT,[183] and the balance (n=378) from unpublished sources. The literature search identified no on-label studies that used InFUSE®/Mastergraft approved under the HDE.

Table 7. Pooled Comparative Analysis of On-Label Use of rhBMP2 for Lumbar-Sacral Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
DDD of the lumbar spine (182)	1	rhBMP2	277	24	4.2-8.4	POOR
		ICBG	402	24	0	

Abbreviations: AGB: autograft bone; mos.: months; no.: number; pts: patients; ref: reference; USPSTF: U.S. Preventive Services Task Force

This pooled analysis does not add substantively to the evidence reviewed above. Concerns include inability to access more than half the primary data, which precludes appraisal of its quality, methods, population, and outcomes. Nor does the report clearly outline statistical methods used to combine data from these disparate sources.

Key Question 2

What is the evidence supporting improved outcomes with on-label use of rhBMP7 (OP-1®) for fusion in the lumbar spine?

As shown in Table 8, no comparative studies were identified for this Key Question.

Table 8. Overall Grade of Strength of Comparative Study Evidence for On-Label Use of rhBMP7 for Fusion of the Lumbar-Sacral Spine

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What evidence of improved outcomes is associated with the on-label use of OP-1 for fusion of the lumbar-sacral spine?	No comparative studies addressed this Key Question	Not applicable (NA)	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.

Key Question 2 Evidence Summary

OP-1® Putty received FDA Humanitarian Device Exemption (HDE) approval for use in revision posterolateral lumbar spinal fusion based on several lines of data. A primary source of data was the results of a pilot study conducted in 36 patients (n=24 OP-1, n=12 ICBG) undergoing primary fusion to treat symptomatic single-level degenerative lumbar spondylolisthesis and spinal stenosis.[184] Patients included those for whom autograft bone harvest

was not feasible or not expected to promote fusion because of tobacco use, osteoporosis, or diabetes. Clinical success reflected improvement in pain and function as assessed by at least 20 percent improvement over the baseline ODI score. Radiographic success was defined as lack of motion of flexion/extension radiographs manifested as not more than 5 degrees angulation or 2 mm translation and evidence of bridging trabecular bone. Outcomes at 12 months of follow-up are summarized in Table 9.

Table 9. Pilot Study Outcomes for OP-1 Putty in Lumbar Spinal Fusion

Outcome*	OP-1 Putty (%) (n=24)	ICBG (%) (n=12)
Clinical Success	83	67
Radiographic Success	62	50
Overall Success	50	33

* no significant differences reported in any outcome

Abbreviations: ICBG: iliac crest bone graft

Subsequent publications reported follow-up data at two[185] and four years.[95] Data from the four-year follow-up study are contained in Appendix 1 Table B and in Table 28 (Key Question 6), with results consistent with the pilot study.

This study evaluated the use of OP-1® Putty in primary posterolateral spinal fusions. However, the basis for using these data to support the probable benefit of using OP-1® Putty for revision posterolateral spinal fusion surgery was based on a risk/benefit judgment, adopted as follows from the FDA summary (http://www.accessdata.fda.gov/cdrh_docs/pdf2/H020008b.pdf):

> Preclinical studies in animals demonstrate that OP-1 Putty is osteoinductive and:
> - is capable of inducing solid fusion in the posterolateral spine following primary treatment or revision of nicotine induced pseudarthrosis
> - induces bone formation in a variety of animal species and
> - generates bone that is mechanically and histologically normal.

The FDA noted that results from the pilot clinical study suggested probable benefit as an alternative to autograft in patients who require primary uninstrumented fusion for the treatment of degenerative spondylolisthesis. These data cannot be directly extrapolated to the expected performance of OP-1® Putty in revision posterolateral spinal fusions in the compromised population, but there is reason to believe that OP-1 Putty could have a probable benefit in this population, as follows.

The FDA emphasized that 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 autograft 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 risks and complications associated with these treatment alternatives while providing a feasible and beneficial alternative treatment.

The FDA concluded that the body of preclinical and clinical evidence available at the time was reasonably sufficient 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. Accordingly, the FDA's Center for Devices and Radiological Health (CDRH) determined that, based on the data submitted in the HDE application, the use of OP-1® Putty will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an HDE approval order on April 7, 2004.

Key Question 3

What is the evidence supporting improved outcomes with on-label use of rhBMP7 (OP-1®) in recalcitrant long bone non-unions?

The evidence for this indication consists of two RCTs, one of fair quality[79] and one of poor quality,[78] as well as a poor quality nonrandomized cohort study.[83] Appraisal and synthesis of the randomized trial evidence is complicated by the choice of different comparators, platelet-rich plasma (PRP) in one[78] and autograft bone in the other.[79] Radiographic fusion rates with rhBMP7 in both studies were similar to the comparator rates, with a statistically significant (p=0.016) advantage for rhBMP7 in one trial.[78] However, in the other trial, the relative efficacy of rhBMP7, in fact, may have been underestimated because statistical adjustments were not made to account for group demographic differences predisposing to a poor fusion outcome.[79]

Other outcomes reported with rhBMP7 were not consistently reported and thus could not be appraised. A high risk of bias in the cohort study, due to its design and small sample size, precludes conclusions about clinical outcomes associated with rhBMP7. The overall strength of this body of evidence is low to support improved outcomes with on-label use of rhBMP7 (OP-1) for long bone non-unions (Table 10).

Key Question 3 Evidence Summary

Table 11 shows two RCTs of labeled use of rhBMP7 to treat recalcitrant long bone non-unions (see Appendixes 1 and 2 for details on study characteristics and USPSTF quality ratings). One study[78] was rated as "poor" according to the USPSTF study quality evaluation system, the other was graded as "fair."[79]

In the RCTs, patients with long bone non-unions were randomly assigned to undergo surgical fixation of the fracture site, and receive adjuvant rhBMP7, which was compared to autograft bone[79] or PRP.[78] A statistically higher prevalence of atrophic non-unions (41 percent compared with 25 percent, p=0.048) and a strong trend toward more smokers (74 percent compared with 57 percent, p=0.057) in the rhBMP7 group was reported in one RCT;[79] however, the report does not indicate whether the investigators attempted to statistically adjust for differences in study group characteristics.

Table 12 shows radiographic fusion success at 9 months' follow-up was achieved at a statistically significantly higher rate (87 percent vs. 68 percent, p=0.016) among rhBMP7 recipients than those treated with PRP and adjuvant bone graft extenders.[78] However, no significant differences were reported in the average time needed to achieve radiological (8 vs. 9 months) or clinical union (3.5 vs. 4.0 months). No adverse events related to rhBMP7 were reported.

Table 10. Overall Grade of Strength of Comparative Study Evidence for On-Label Use of rhBMP7 in Recalcitrant Long Bone Non-Unions

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What evidence of improved outcomes is associated with the on-label use of OP-1 in recalcitrant long bone non-unions? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	There are two RCTs and one retrospective cohort study. These involve different comparators, autograft bone in 2 reports, platelet-rich plasma in the third. None reported power or sample size calculations.	The risk of bias in this evidence is high. In one RCT, the intervention arm was confounded by use of a mix of bone graft extenders and it was unclear if radiographic outcomes were assessed independently. In the second RCT the BMP arm had higher risk for poor outcomes, and thus the effect of BMP could be underestimated. The third study was nonrandomized and thus had high risk of bias. Device-related harms are inconsistently reported in this literature.	Results for radiographic fusion appear consistent for rhBMP7 in that they are similar and not worse. Clinical outcomes were not completely reported in both RCTs so consistency cannot be determined.	Where outcomes were reported, the evidence is direct.	The evidence is imprecise, effects cannot be quantified.	The strength of the body of evidence on radiographic fusion, pain, and function outcomes is low. But, of note, one RCT reports similar outcomes with autografting and rhBMP7 although the BMP group is at higher risk of poor outcomes.

Table 11. On-Label Randomized Trials of rhBMP7 for Recalcitrant Long Bone Non-Unions

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Long bone non-union (78, 79)	2	rhBMP7	121	9-43	3.5-7.0	1 FAIR, 1 POOR
		AGB	61			
		PRP	60			

Abbreviations: AGB: autograft bone; mos.: months; no.: number; PRP: platelet-rich plasma; pt(s): patient(s); USPSTF: U.S. Preventive Services Task Force

Table 12. Clinical Outcomes in On-Label Randomized Trials of rhBMP7 for Recalcitrant Long Bone Non-Unions

Study (ref no.)	Group	No. Pts	BMP dose range (mg/pt)	Fusion or clinical success 9 mos. %	Time to radiologic union (md ± SD, mos.)	Time to clinical union (md ± SD, mos.)	Pain-free weight bearing 9 mos. %	USPSTF study quality
Calori et al., 2008 (78)	rhBMP7/ ACS	60	3.5-7.0 (Osigraft)	87	8±0.5	3.5±0.5	NR	POOR
	PRP	60	0	68 (p=0.016)	9±0.5	4.0±0.6	NR	
Friedlander et al., 2001 (79)	rhBMP7 /ACS	61	3.5-7.0 (OP-1 Implant)	81	NR	NR	89	FAIR
	AGB	61	0	85	NR	NR	90	

Abbreviations: ACS: absorbable collagen sponge; AGB; autograft bone; md: median; mos.: months; no.: number; PRP: platelet-rich plasma; pt(s): patient(s); SD: standard deviation; USPSTF: U.S. Preventive Services Task Force

In the other RCT,[79] there was no difference in the combined clinical success rate at 9 months (81 percent rhBMP7 vs. 85 percent AGB) which was defined as full weight-bearing with less than severe pain at the fracture site and no further intervention to enhance repair. About 90 percent of patients in both groups reached a state of pain-free weight-bearing at 9 months. Moderate-to-severe pain was reported at the autograft harvest site by 80 percent of patients in the immediate postoperative period; 13% reported mild to moderate pain at the harvest site at 12 months' follow-up. No other harvest site adverse events were reported.

Table 13 summarizes characteristics of a nonrandomized retrospective cohort study in which rhBMP7 (Osigraft [available in Europe], 3.5 mg per patient, n=15) applied via a absorbable collagen sponge was compared to ICBG (n=12) as part of surgical treatment of recalcitrant tibial fracture non-union.[83] This small, nonrandomized, poor quality study has a high risk of bias, which precludes conclusions based on its outcomes.

Table 13. On-Label Nonrandomized Comparative Study of rhBMP7 for Recalcitrant Long Bone Non-Unions

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Long bone non-union (83)	1	rhBMP7	15	29-34	3.5	POOR
		iliac crest bone graft	12	29-34	0	

Key Question 4

What is the evidence supporting improved outcomes with on-label use of rhBMP2 (InFUSE®) for the treatment of acute, open shaft tibial fractures?

As shown in Table 14, the main evidence is one RCT ("BMP2 Evaluation in Surgery for Tibial Trauma," or BESTT[74]) that compared two different doses of rhBMP2 versus standard of care. BESTT was a large (n=450) fair quality, prospective randomized clinical trial that showed a statistically significant relative advantage for adjuvant rhBMP2 at a dose of 12 mg per patient in the need for invasive second surgeries with autograft bone (18 percent versus 43 percent, p=0.0264), clinical success rate (65 percent versus 47 percent, p=0.0028), infections (24 percent versus 44 percent, p=0.047), and median healing rate (145 versus 184 days, p=0.0022). Other evidence consists of a fair quality subgroup analysis of data on Gustilo-Anderson type-III fractures (n=244) combined from BESTT[74] and an unpublished RCT (n=60) known as the "U.S. study."[81] Adjuvant rhBMP2 (12 mg per patient) was associated with a statistically significant reduction in wound infection rates (21 percent vs. 40 percent, p=0.02), and secondary autologous bone-grafting interventions (2 percent versus 20 percent, p=0.0022) for delayed union or non-union.

The strength of the body of evidence on clinical outcomes is moderate for on-label use of rhBMP2 to enhance bony fusion in acute open shaft fractures, reduce wound infections, and reduce the need for a second procedure involving autograft bone. Significant device-related adverse events were not reported.

Key Question 4 Evidence Summary

Table 15 shows two reports of rhBMP2 in acute open shaft tibial fractures. The BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) trial[74] randomized patients with open fractures of the tibial shaft according to wound severity to receive the standard of care (intramedullary [IM] nail fixation and routine soft tissue management) with rhBMP2 (InFUSE®) applied via collagen sponge at 6 mg per patient (n=151) and 12 mg per patient (n=149) or to the standard care alone without use of an autograft (n=150). The primary outcome measure was the proportion of patients that required a secondary intervention because of delayed union or non-union within 12 months after surgery. There were two significant intergroup differences in patient demographics. One was an overall difference in age (by ANOVA, otherwise not specified). The second significant intergroup difference was in the proportion of patients who underwent reamed intramedullary nailing among the treatment groups (p=0.0371). However, multiple regression analysis of potential interaction between rhBMP2 and fixation method revealed these variables independently affected the primary outcome. Recent tobacco use was noted in 45-52% of patients. This study was rated as "fair" according to the USPSTF study quality evaluation system.

A second concurrent study (unpublished) conducted in ten level-I trauma centers in the U.S. included a total of 60 patients, using design and patient selection criteria identical to BESTT. Raw patient data from this study and BESTT were combined in a subgroup analysis of clinical outcomes for patients with Gustilo-Anderson type-III open fractures (n=131, 65 controls, 66 rhBMP2 group) and those who underwent reamed IM nailing without use of autograft bone (n=113; 48 controls, 65 rhBMP2 group) type-III from that trial.[81] It presented separate results of

Table 14. Overall Grade of Strength of Comparative Study Evidence for On-Label Use of rhBMP2 for Treatment of Acute Open Shaft Fractures

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What evidence of improved outcomes is associated with the on-label use of InFUSE for the treatment of acute, open shaft fractures? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	The main evidence is in one RCT (BESTT) that compared two different doses of rhBMP2 versus standard of care. The RCT is supported by a combined subgroup analysis that pooled data from patients with Gustilo-Anderson type III fractures in BESTT with data from a second smaller unpublished RCT (n=60) with identical design.	The risk of bias is medium. The BESTT RCT had fusion outcomes independently assessed by a radiology panel. It did not specify whether the panel assessment was undertaken prospectively or retrospectively. It is not possible to assess risk of bias in the smaller RCT incorporated in the subgroup analysis because it is unpublished and unavailable to review methods. Device-related harms are inconsistently reported in this literature. Therefore there is a high risk of bias with respect to adverse events.	The evidence is consistent. The BESTT and combined subgroup analysis report statistically significant improvement in invasive secondary interventions and infection rate in Gustilo-Anderson type III fractures when rhBMP2 is used as an adjunct to standard of care. Clinical success rate was improved in the BESTT but not reported in the subgroup analysis. Median time to healing was improved in the BESTT but was not significant in the combined subgroup analysis.	Direct evidence was reported for the outcomes of interest.	The evidence is precise. The only confidence interval reported was in the BESTT for secondary invasive interventions (RR= 0.56, 95% CI=0.40-0.78).	The strength of the body of evidence on clinical outcomes is moderate for on-label use of rhBMP2 to enhance bony fusion in acute open shaft fractures. One randomized and one retrospective subgroup analysis of data from 2 RCTs consistently show that rhBMP2 enhances healing and reduces the need for invasive second procedures.

Table 15. On-Label use of rhBMP2 for Acute Open Tibial Fractures

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Open tibial fractures (74)	1 (BESTT)	rhBMP2	151	12	6	FAIR
		rhBMP2	149	12	12	
		Standard care	150	12	0	
Open tibial fractures (81)	1 (subgroup analysis)	Gustilo-Anderson III rhBMP2	66	12	12	FAIR
		Gustilo-Anderson III Standard care	65	12	0	
		Gustilo-Anderson I-III rhBMP2	65	12	12	
		Gustilo-Anderson I-III Reamed IM nailing	48	12	0	

Abbreviations: IM: intramedullary nail; mos.: months; no.: number; pt(s): patient(s); USPSTF: U.S. Preventive Services Task Force

the control treatment and the FDA-approved concentration of rhBMP2 at 12 mg per patient. The comparison group of interest was the Gustilo-Anderson type III subgroup with rhBMP2 and without.

Clinical outcomes are summarized in Table 16.

Table 16. Clinical Outcomes of On-Label use of rhBMP2 for Acute Open Tibial Fractures

Study (ref no.)	Group	Invasive secondary intervention rate (%)	Clinical success rate (%)	Median time to fracture healing (days)	Infection rate in Gustilo-Anderson type III fractures (%)
BESTT (74)	rhBMP2	18	65	145	24
	Standard care	43 (p=0.0264) (RR=0.56, 95% CI=0.40. 0.78)	47 (p=0.0028)	184 (p=0.0022)	44 (p=0.047)
Combined Data Subgroup Analysis (81)	rhBMP2	2	NR	271	21
	Standard care	20 (p=0.0065)	NR	277 (NS)	40 (p=0.02)
	rhBMP2	2	NR	234	18
	Reamed IM nailing	6	NR	251 (NS)	27 (NS)

Abbreviations: IM: intramedullary nail; mos.: months; no.: number; NR: not reported; NS: not significant;

The BESTT results[74] in patients with Gustilo-Anderson type I-III fractures suggest that rhBMP2 hastens fracture healing (defined as the presence of cortical bridging and/or disappearance of the fracture lines on at least three of four cortices on the anteroposterior and lateral radiographs), increases the proportion of patients who achieve a successful clinical outcome, and reduces the number of invasive secondary intervention with autologous bone grafting when compared to standard surgical and soft tissue management (standard of care). Among smokers, patients who received rhBMP2 had a significantly lower rate of secondary

intervention than did the standard of care patients (30 percent compared with 52 percent, p=0.0138). No significant adverse effects related to rhBMP2 were reported. The 12 mg per patient rhBMP2 group had significantly fewer (p=0.047) infections in association with Gustilo-Anderson type III fractures than the standard of care group (24 percent compared with 44 percent).

Results from the combined data subgroup analysis in Gustilo-Anderson type III fractures show a significant reduction in the rate of invasive secondary interventions among rhBMP2 recipients with minimal reduction in the median time to fracture healing. The time to achieve full weight-bearing capacity in Gustilo-Anderson type III patients in the subgroup analysis was 95 +/- 38 days in the rhBMP2 group and 126 +/- 61 days in the standard of care group (p=NR). The infection rate was significantly lower in rhBMP2 recipients than standard of care patients (p=0.02). The secondary comparison between rhBMP2 and reamed IM nailing showed no significant differences.

Key Question 5

What is the level of evidence and summary of evidence for the on-label use of rhBMP2 (InFUSE) for sinus augmentation?

As shown in Table 17, three RCTs were identified in which rhBMP2 was used according to the FDA-approved marketing label in patients undergoing staged bilateral or unilateral maxillary sinus floor augmentation[75,77] and extraction socket alveolar ridge augmentation procedures.[76] The strength of the body of evidence is moderate that rhBMP2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone. However, there is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Key Question 5 Evidence Summary

Three RCTs (Table 18) were identified in which rhBMP2 was used according to the FDA-approved marketing label in patients undergoing staged bilateral or unilateral maxillary sinus floor augmentation[75,77] or extraction socket alveolar ridge augmentation procedures.[76] Patients in those studies received rhBMP2 applied via absorbable collagen sponge in dose range of 6 to 48 mg per patient (total n=158), autograft bone (total n=93), or placebo (n=37). The mean rhBMP2 dose was reported in one study,[76] rather than total dose. AGB harvested from the iliac crest, tibia, or the oral cavity was used alone or mixed with allograft bone (ALG) in two studies.[75,77]

Clinical outcomes included new bone formation sufficient for endosseous dental implant placement, dental implant success rate following functional loading, patient success, perioperative complications, and device-related adverse events at 4–36 months' follow-up.

Two RCTs[75,77] (Table 19) were rated as "good" (75, 77) and one "fair,"[76] according to the USPSTF study quality evaluation system.

rhBMP2 does not appear to provide an advantage compared to AGB/ALG. Although statistical significance is not reported, prosthesis implantation was numerically less frequent with rhBMP2 compared to AGB/ALG. In the pivotal trial by Triplett et al.,[77] successful prosthetic functional loading occurred statistically significantly less frequently in the rhBMP2 than the

Table 17. Overall Grade of Strength of Comparative Study Evidence for On-Label Use of rhBMP2 for Sinus Augmentation

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What is the level of evidence and summary of evidence for the on-label use of InFUSE for sinus augmentation? Clinical outcomes included radiographic evidence of new bone formation sufficient to allow prosthetic implantation and functional loading, and adverse events associated with the rhBMP device and with autograft harvest.	The evidence comprises three RCTs. A pilot study which compared rhBMP2 versus autograft/allograft bone, and a larger follow-up trial that compared rhBMP2 versus autograft/allograft bone. The third trial compared four arms, two different doses of rhBMP2, placebo, and no treatment.	Risk of bias in the body of clinical evidence is low in all of the studies. All were rated as good quality with independent assessment of radiographic outcomes, intent-to-treat analysis, and reported randomization methods. Device-related harms are inconsistently reported in this literature. Therefore there is a high risk of bias with respect to adverse events.	The body of evidence is consistent showing that rhBMP2 does not provide an advantage in prosthesis implantation and functional loading compared to AGB/ALG. No statement on consistency of rhBMP2 outcomes versus placebo can be made because only one trial is available. Both trials comparing rhBMP2 to AGB/ALG reported oral sensory loss. One trial reported 8% at 1 month, the other 17% at 6 months.	Direct evidence was available for all outcomes of interest.	The evidence is imprecise. Statistical significance is not reported and it is not possible to calculate confidence intervals.	The strength of the body of evidence is moderate that rhBMP2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone. However, there is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

comparator group. Fiorellini et al.[76] reported significantly more frequent prosthesis implantation with the higher dose rhBMP2 arm than the lower dose.

Table 20 shows facial edema was reported among patients who underwent staged bilateral or unilateral maxillary sinus floor augmentation.[75,77] Transient immune sensitization to rhBMP2 was observed in recipients at 1.9 mg/pt, but this was associated with no clinical sequelae.[75,77]

Transient immune sensitization to bovine collagen also was reported in 11 to 32 percent of patients who received rhBMP2 in those studies. Adverse events associated with the autograft harvest site included edema, pain, rash, gait disturbance, and sensory loss. The larger trial[77] reported oral sensory loss in 17 percent of patients 6 months after the procedure.

Table 18. On-Label Randomized Trials of rhBMP2 for Sinus and Alveolar Ridge Augmentation

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Maxillofacial defects (75, 76, 77)	3	rhBMP2	158	4-36	6-48	3 GOOD
		AGB	93		0	
		Placebo	37		0	

Abbreviations: AGB: autograft bone; no.: number; pt(s): patient(s); ref: reference;

Table 19. Clinical Outcomes in On-Label Randomized Trials of rhBMP2 for Sinus and Alveolar Ridge Augmentation

Study (ref no.)	Group	No. pts	BMP dose range (mg/pt)	Bone height change (mn +/- SD, mm)	Prosthesis implantation into newly induced bone, %	Successful prosthetic functional loading, %	USPSTF study quality
Boyne et al., 2005 (75)	rhBMP2	18	6-24	9.47 +/- 5.72	83	100	GOOD
	rhBMP2	17	15-48	10.16 +/- 4.70	88	100	
	AGB/ALG	13	0	11.29 +/- 4.12 (4 mos.)	100	100 (36 mos.)	
Triplett et al., 2009 (77)	rhBMP2	80	12-24	7.83 +/- 3.52	82	76	GOOD
	AGB/ALG	80	0	9.46 +/- 4.11 (p=0.009)	95	91 (p=0.017)	
Fiorellini et al., 2005 (76)	rhBMP2	22	0.9	NR	55	NR	GOOD
	rhBMP2	21	1.9	NR	86	NR	
	Placebo	20	0	NR	59	NR	
	No Tx	20	0	NR	45 (p=0.009 no tx vs. 1.9 mg/pt)	NR	

Abbreviations: AGB: autograft bone; ALG: allograft bone; no.: number; pt(s): patient(s); ref: reference; Tx: treatment

Table 20. Adverse Events in On-Label Randomized Trials of rhBMP2 for Sinus and Alveolar Ridge Augmentation

Study (ref no.)	Group	Facial edema (%)	Autograft harvest-site adverse events (%)
Boyne et al., 2005 (75)	rhBMP2 (0.9 mg/pt)	39	edema (46) pain (38) rash (46) gait disturbance (16) oral sensory loss (8)
	rhBMP2 (1.9 mg/pt)	82	
	AGB/ALG	38 (p=0.0227 AGB/ALG vs. 0.9 mg gp, p=0.0152 0.9 mg gp vs. 1.9 mg gp)	
Triplett et al., 2009 (77)	rhBMP2	p=0.048 vs. AGB/ALG, numbers not reported	oral sensory loss (17) pain (NR) gait disturbance (NR)
	AGB/ALG		
Fiorellini et al., 2005 (76)	rhBMP2	NR	NA
	rhBMP2	NR	NA
	Placebo	NR	NA
	No Tx	NR	NA

Abbreviations: AGB: autograft bone; ALG: allograft bone; gp: group; NA: not applicable; no.: number; pt(s): NR: not reported; patient(s); ref: reference; Tx: treatment

Key Question 6

For which indications are there clinical studies in which BMP is used off-label? In such studies, what is the evidence of the effectiveness of BMP?

The strength of evidence for off-label uses was graded only for settings that had more than one comparative trial involving patients sufficiently similar to allow synthesis. Those comprise the lumbar-sacral spine and cervical spine, with distribution between rhBMP2 and rhBMP7 summarized in Table 21.

Lumbar-Sacral Spine

rhBMP2

Summary. There are six randomized[73, 84–88] and five nonrandomized comparative studies[99–103] of off-label use of rhBMP2 in fusion of the lumbar-sacral spine. The two largest RCTs[85, 86] were rated "fair" and are given greatest weight in this review of evidence. The strength of evidence that rhBMP2 improves radiographic fusion success is moderate. The strength of evidence that rhBMP2 improves other outcomes is low.

Off-Label Randomized Clinical Trials of rhBMP2 in Lumbar-Sacral Spine

As shown in Table 22, six reports describe the results of RCTs in which off-label use of rhBMP2 (total N=449) was compared to autograft bone (total N=383) to enhance surgical fusion of the lumbar spine.[73, 84–88]

There are several reasons to consider rhBMP2 use off-label in these studies. These include use of a nonapproved formulation, or matrix, in conjunction with the approved rhBMP2; use of a non-anterior surgical approach with InFUSE®; use of InFUSE® with a nonapproved interbody

entity; and, use in multi-level fusion. Thus, rhBMP2 (InFUSE®) was applied via an absorbable collagen sponge, alone or with an unapproved compression-resistant matrix (CRM) in two trials.[84,86] in which a 40 mg dose was used in Investigational Device Exemption (IDE) studies for the AMPLIFY device, which was under FDA review for marketing approval at the time this report was prepared. In two trials, rhBMP2 (InFUSE®) was administered in a dose range of 4.2 to 12 mg per patient, placed inside cortical threaded allograft bone dowels in one RCT[85] and for single- or multi-level, posterolateral instrumented fusion with discretionary bone graft extenders in the second.[87] Another study[73] was an FDA Investigational Device Exemption (IDE) study for InFUSE®/Mastergraft, with rhBMP2 (InFUSE®) applied at a dose of 12 mg per patient with an unapproved osteoconductive compression-resistant matrix (CRM) comprising 15 percent hydroxyapatite and 85 percent tricalcium phosphate ceramic. However, the manufacturer of this product has voluntarily withdrawn the HDE approval so this is a nonapproved formulation of an approved rhBMP2 product (InFUSE®). The last study reported on single-level posterolateral interbody fusion using InFUSE®, but it was stopped prior to full accrual.[88] In all RCTs, patients underwent primary fusion.

In all trials, autograft bone (AGB), mainly harvested from iliac crest, and additional instrumentation were used.

Four RCTs[73, 84–86] were rated as "fair" according to the USPSTF study quality evaluation system, and the other two were rated as "poor" (see Appendix 2 for details). All trials independently assessed radiographic fusion success, generally reflecting the presence of bilateral bridging bone between transverse processes at 17 to 24 months. In the InFUSE®/Mastergraft trial,[73] this outcome also reflected incorporation of the compression-resistant matrix into newly formed bone. The RCTs rated as "fair" did not report intention-to-treat (ITT) analysis or describe randomization procedures. One trial that was rated "poor"[88] did not report randomization method or ITT analysis and included a subset of data on patients from a larger, terminated trial. The second trial, rated "poor,"[87] did not report randomization procedures or ITT analysis, patient characteristics and comorbid conditions were not well described, the investigators reported use of undefined bone graft extender or filler plus local bone shavings in 100 percent of cases in both groups, and pooled outcome data from multilevel and single-level fusion patients.

Statistically significant improvement in radiographic fusion success was reported in the two largest two trials[85,86] (Table 23) . A third trial reported a statistically significant improvement in radiographic fusion success, but this result is limited by the small number of patients in the study.[84] Similarly, conclusions cannot be drawn for radiographic fusion success in the other 3 studies due to limited sample sizes. Inconsistent reporting of ODI success, ODI mean point score, leg pain mean point score, and SF-36 mean point score limits synthesis and conclusions.

Three RCTs[84,86,88] reported on autograft harvest site pain (Table 24). At discharge, scores on a 20-point numeric rating scale were 11.3, 11.6, and 16.0. By 17 to 24 months, mean pain scores had decreased to approximately 5 on a 20-point scale. In another study, pain was not reported at the graft harvest site, but an infection was reported in one patient.[73]

Table 21. Overall Grade of Strength of Comparative Study Evidence for Off-Label Use of rhBMP2 in the Lumbar-Sacral Spine

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What is the level of evidence and summary of evidence for the off-label use of rhBMP2 in fusion of the lumbar-sacral spine? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	There are six RCTs and five nonrandomized comparative studies of rhBMP2 versus autograft. Studies were deemed off-label because of a nonapproved surgical approach (84, 86-88), use of nonapproved matrix formulations of the approved rhBMP2 product (73, 84, 86), or use of the approved rhBMP2 product with nonapproved device(s) (85).	Overall there a medium risk of bias for the body of evidence. The two largest RCTs were rated "fair" and are given greatest weight in the review of evidence. The remaining evidence is four randomized and five nonrandomized comparative studies that were largely rated as poor quality or were very small in size. Risk of bias in this body of evidence for radiographic and functional outcomes is medium for the RCTs and high for the nonrandomized studies. Device-related harms are inconsistently reported in this literature. Therefore there is a high risk of bias with respect to adverse events.	Statistically significant improvement in radiographic fusion success was reported in the two largest RCTs. (86, 85) One (n = 463) involved the use of a nonapproved matrix formulation with InFUSE and a posterolateral surgical approach (86). The second RCT (n = 131) used cortical threaded allograft bone dowels rather than an approved cage device to contain the rhBMP2 product (InFUSE). (85) A third RCT (n = 27) reported a statistically significant difference in rhBMP2 recipients and controls, but this result is limited by the small number of patients (84). In the other three RCTS, no statements regarding consistency can be made due to limited sample sizes. Three RCTs that reported autograft harvest site pain showed pain at discharge, diminishing over time. (84, 87, 88) Conclusions on these observations are limited. The nonrandomized comparative studies generally reported similar results but are given low weight in this review because of poor quality.	Direct evidence was available for outcomes, but was limited for ODI success.	The evidence is imprecise.	The strength of evidence that rhBMP2 improves radiographic fusion success is moderate, based on the two largest RCTs. Among all six RCTs, interstudy variables include rhBMP2 dose, surgical approach, matrix formulation, or hardware. No conclusions can be drawn regarding the potential impact of the off-label components on radiographic fusion success. The strength of evidence that rhBMP2 improves other outcomes is low. The evidence gives moderate support to clinical benefit from the use of rhBMP2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.

Table 22. Off-Label Randomized Trials of rhBMP2 for Lumbar-Sacral Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Degenerative disc disease of the lumbar spine (73, 84-88)	6	rhBMP2	449	12-27	4.2-40	4 FAIR 2 POOR
		AGB	383		0	

Table 23. Clinical Outcomes in Off-Label Randomized Trials of rhBMP2 for Lumbar-Sacral Spinal Fusion*

Study (ref no.)	Group	No. Pts	BMP dose (mg/pt)	Off-Label Category	Radiographic fusion success %	ODI success %	ODI mean point score ↑	Leg pain mean point score ↑	SF-36 PCS mean point score ↑	USPSTF study quality
Boden et al, 2002 (84)	BMP2/BCP/TSRHSS	11	40	• unapproved formulation comprising a BCP CRM with approved rhBMP2 (InFUSE®) • posterolateral fusion • proprietary instrumentation	100	~65	~13	~3	~4	FAIR
	BMP2/BCP	11	40		100	~100	~29	~9	~16	
	ICBG/TSRHSS	5	0		40 (p=0.018, 0.028 in BMP2 grps vs. ICBG)	~80	~25	~4	~7 (p=0.070 for BMP2/BCP vs. other groups)	
Burkus et al, 2005 (85)	BMP2	79	8-12	• cortical threaded allograft bone dowels with approved rhBMP2 (InFUSE®) rather than an approved cage device	98	NR	33	6.8	16	FAIR
	ICBG	52	0		76 (p <0.001)	NR	27	4.9 (p=0.011)	12 (p=0.015)	
Dawson et al., 2009 (73)	BMP2/BCP	25	12	• unapproved formulation comprising a BCP CRM with approved rhBMP2 (InFUSE®) • HDE approval voluntarily withdrawn by Medtronic in early 2010	95	91	28	9.3	NR	FAIR
	ICBG	21	0		67	70	23	7.2	NR	

Table 23. Clinical Outcomes in Off-Label Randomized Trials of rhBMP2 for Lumbar-Sacral Spinal Fusion* (continued)

Study (ref no.)	Group	No. Pts	BMP dose (mg/pt)	Off-Label Category	Radiographic fusion success %	ODI success %	ODI mean point score ↑	Leg pain mean point score ↑	SF-36 PCS mean point score ↑	USPSTF study quality
Dimar et al., 2009 (86)	BMP2/BCP	239	40	• unapproved formulation comprising a BCP CRM with approved rhBMP2 (InFUSE®) • posterolateral surgical approach	96	NR	~26	~8	~13	FAIR
	ICBG	224	0		89 (p=0.014)	NR	~24	~9	~10	
Glassman et al., 2008 (87)	BMP2	50	8-12	• posterolateral fusion with approved rhBMP2 (InFUSE®) • multi-level fusions in some patients • additional discretionary bone graft extenders (local bone in all cases in both groups, others not described)	86	NR	15	3.6	7	POOR
	ICBG	52	0		71	NR	13	3.1	7	
Haid et al., 2004 (88)	BMP2	34	4.2-8.4	• posterolateral interbody fusion with rhBMP2 (InFUSE®)	92	69	30	7.7	~14	POOR
	ICBG	33	0		78	56	24	6.5	~11	

* Boden reported outcomes at 17 months, all others were 24 months

Abbreviations: BCP: biphasic calcium phosphate carrier; CRM: compression-resistant matrix; ICBG: iliac crest bone graft; NR: not reported; pt(s): patients(s); ODI: Oswestry Disability Index; PCS: physical component summaries; ref: reference; SF: short form; TSRHSS: Texas Scottish Rite Hospital Spinal System

Table 24. Autograft Harvest Site Pain Scores in Off-Label Randomized Studies of rhBMP2 in the Lumbar-Sacral Spine

Study (reference no.)	Pain score at discharge (20-point NRS)	Pain score at 24 months (20-point NRS)
Boden et al, 2002 (84)	11.3	5.1
Glassman et al., 2008 (87)	11.6	5.5
Haid et al., 2004 (88)	16.0	5.2 (17 months)
Burkus et al, 2005 (85)	not reported	not reported
Dawson et al., 2009 (73)	not reported	not reported
Dimar et al., 2009 (86)	not reported	not reported

Abbreviations: NRS: numeric rating scale

Off-Label Nonrandomized Comparative Studies of rhBMP2 in Lumbar-Sacral Spine

Table 25 summarizes five nonrandomized studies[99–103] (prospective and retrospective designs) of the off-label use of rhBMP2 for primary fusion in the lumbar-sacral spine. Two studies[101,103] reported on the use of rhBMP2 in anterior lumbar interbody fusion procedures. Two studies[99,102] reported results of fusion using a posterolateral approach. One study[100] reported lumbar interbody fusion using a posterolateral transforaminal route. Three studies[99,101,102] reported only fusion data; two[100,103] reported fusion results plus limited clinical outcomes.

One study[101] used stand-alone femoral ring allograft spacers packed with either ICBG or rhBMP2. The other four studies used pedicle screw instrumentation, among which one[103] used FRA interbody spacers, another[100] used polyetheretherketone (PEEK) or titanium interbody cages, and the other two[99,102] used ICBG chips wrapped in collagen sponge soaked with rhBMP2.

Table 25. Off-Label Nonrandomized Comparative Studies of rhBMP2 for Lumbar-Sacral Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Degenerative disc disease of the lumbar spine (99, 100, 101, 102, 103)	5	rhBMP2	209	3-38	3-36	1 FAIR 4 POOR
		ICBG or ALG	122		0	

Abbreviations: ALG: allograft bone; ICBG: iliac crest bone graft; mos.: months; no.: number; pt(s); patient(s)
USPSTF: U.S. Preventive Services Task Force

rhBMP2 (total N=209) was typically applied via collagen sponge in a dose range of 3 to 36 mg per patient, compared to ICBG or ALG bone, and had 3 to 38 months' follow-up. Two studies[100,102] admixed rhBMP2 and AGB, with ALGB used solely as comparator in one study.[103]

One study[101] was rated as "fair"; the other four[99,100,102,103] were rated "poor" according to the USPSTF study quality rating system.

Table 26. Clinical Outcomes in Off-Label Nonrandomized Comparative Studies of rhBMP2 for Lumbar-Sacral Spinal Fusion

Study (ref no.)	Group	No. Pts	BMP dose (mg/pt)	Radiographic fusion success 24 mos., %	USPSTF study quality
Glassman et al., 2007; USA(99)	rhBMP2	91	12	96	POOR
	ICBG	35	0	89	
Mummaneni et al., 2004; USA(100)	rhBMP2/AGB	25	8.4	96	POOR
	ICBG	19	0	95	
Pradhan et al., 2006; USA (101)	rhBMP2	9	NR	44	FAIR
	ICBG	27	0	63	
Singh et al., 2006; USA (102)	rhBMP2/ICBG	39	12-36	94	POOR
	ICBG	11	0	77 (p<0.05)	
Slosar et al., 2007; USA (103)	rhBMP2	45	3-9	99	POOR
	ALG	30	0	82 (p<0.001)	

Abbreviations: AGB: autograft bone; ALG: allograft bone; ICBG: iliac crest bone graft; mos.: months; no.: number; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

These nonrandomized studies reported radiographic fusion success at 24 months. With one exception, all reported radiographic fusion success rates with rhBMP2 that were similar or better than with ICBG. These studies were generally rated as poor quality.

Of note, in one study graft resorption and incorporation appeared to occur earlier and more aggressively with the use of rhBMP2 compared to the use of ICBG.[101] The initial osteolytic phase in particular appeared to be accelerated in the rhBMP2 group. In cases of non-union (56 percent), extensive osteolysis of and around the FRA was observed, causing fracture, fragmentation, and collapse of the graft, particularly visible on thin-slice CT with sagittal and 3-dimensional reconstructions. Bone formation eventually ensued in cases of fusion (44 percent), but not in the pseudarthrosis cases. In cases of non-union with ICBG, the structural integrity of the graft remained mostly intact, although some degree of radiolucency surrounded the graft with evidence of instability on flexion-extension.

rhBMP7

Off-Label Randomized Clinical Trials of rhBMP7 in Lumbar-Sacral Spine

Summary. The best available evidence is a single, good quality RCT[94] (Table 27). The evidence is insufficient to draw conclusions on the off-label use of rhBMP7 in fusion of the lumbar-sacral spine.

Table 27. Overall Grade of Strength of Comparative Study Evidence for Off-Label Use of rhBMP7 in the Lumbar-Sacral Spine

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What is the level of evidence and summary of evidence for the off-label use of rhBMP7 in fusion of the lumbar-sacral spine? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	The best available evidence for the efficacy of rhBMP7 used off-label for lumbar spinal fusion comes from one RCT. There are three additional small, poor quality trials.	The risk of bias for the larger Vaccaro trial was rated low with respect to fusion and functional outcomes. The three additional trials, small and of poor quality have a high risk of bias.	Consistency cannot be assessed as all but one trial were rated poor quality.	The evidence on fusion and functional outcomes is direct. However, the three poor quality trials did not fully report on functional outcomes.	The evidence is imprecise as no tests of statistical significance are reported.	The evidence is insufficient to draw conclusions on the off-label use of rhBMP7 in fusion of the lumbar-sacral spine.

Table 28 shows four RCTs[92–94] of off-label use of rhBMP7 for fusion of the lumbar-sacral spine. In all studies summarized in Table 29, radiographic fusion success reflects the presence of bilateral bridging bone or solid fusion.

Table 28. Off-Label Randomized Trials of rhBMP7 for Lumbar-Sacral Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Degenerative disc disease of the lumbar spine (92, 93, 94, 95)	4	rhBMP7	250	12-66	7	1 GOOD 3 POOR
		AGB	118		0	

Abbreviations: AGB: autograft bone; ICBG: iliac crest bone graft; mos.: months; no.: number; pt(s); patient(s) USPSTF: U.S. Preventive Services Task Force

Table 29. Clinical Outcomes in Off-Label Randomized Trials of rhBMP7 for Lumbar-Sacral Spinal Fusion

Study (ref no.)	Group	No. Pts	BMP dose (mg/pt)	Radiographic fusion success, %	ODI success 24 mos., %	ODI mean point score ↑ 24 mos.	Neurological success, %	USPSTF study quality
Johnsson et al., 2002 (92)	BMP7	10	7	60	NR	NR	NR	POOR
	ICBG	10	0	80 (12 mos.)	NR	NR	NR	
Kanayama et al., 2006 (93)	BMP7	9	7	78	NR	~17	NR	POOR
	AGB/CRM	10	0	90 (15 mos.)	NR	~24	NR	
Vaccaro et al., 2008 (94)	BMP7	207	7	75	69	25	84	GOOD
	ICBG	86	0	77 (36 mos.)	77 (36+ mos.)	27 (36+ mos.)	80 (36+ mos.)	
Vaccaro et al., 2008 (95)	BMP7	24	7	69	74	NR	NR	POOR
	ICBG	12	0	50 (48 mos.)	57 (48 mos.)	NR	NR	

Abbreviations: AGB: autograft bone; CRM: compression-resistant matrix; ICBG: iliac crest bone graft; mos.: months; no.: number; NR: not reported; ODI: Oswestry Disability Index; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

All patients underwent a single-level posterolateral fusion for symptomatic DDD. Fusions in three trials[92,94,95] were performed without instrumentation; one was performed with instrumentation and also used a HA-TCP compression-resistant matrix.[93]

All studies used rhBMP7 at a dose of 7 mg per patient (total N=250) versus AGB (total N=118), with follow-up of 12 to 66 months.

One study[94] was graded as "good", the other three[92,93,95] were rated as "poor" according to the USPSTF study quality rating criteria.

The best available evidence for the efficacy of rhBMP7 used off-label for lumbar spinal fusion comes from an open-label (with blinded radiographic assessment), randomized, prospective, multicenter (n=24) trial conducted as an Investigational Device Exemption (IDE) study.[94] This study reported similar results for rhBMP7 and autograft bone for radiographic fusion success, ODI success, ODI mean point score improvement, and neurological success, but did not report statistical significance. The three additional trials[92,93,95] are small, poor quality, and do not add to nor contradict the results of the largest RCT.[94]

In the larger Vaccaro study, autograft harvest site pain was persistent and declined slowly. At 12 months, 44% of autograft patients reported pain at the harvest site, which declined to 35% who reported mild to moderate pain at 36 month.[94]

Cervical Spine

rhBMP2

Summary. The evidence consists of one randomized trial[89] and four nonrandomized comparative studies[104–107] of off-label use of rhBMP2 for cervical spinal fusion. Two small studies, a randomized trial and a nonrandomized comparative study,[89,107] reported on fusion success and changes in mean neck disability scores. The other 3 nonrandomized studies focused mainly on complications.[104–106]

There is moderate evidence that off-label use of rhBMP2 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.

Table 31 summarizes one randomized[89] and four nonrandomized comparative studies[104–107] of off-label use of rhBMP2 for fusion of the cervical spine with follow-up of 1.5 to 36 months. Patients underwent single- or multi-level cervical spinal fusion, using an anterior approach[89,104,106,107] or posterior approach.[105] Additional instrumentation was used in all studies, including all patients in three studies,[105–107] but some underwent uninstrumented fusion in 1 study (104). In one RCT, rhBMP2 (0.6 to 1.2 mg per patient) was applied via absorbable collagen sponge (ACS) packed inside a fibular allogeneic (ALG) bone ring, with a comparator of autologous bone graft (AGB) packed inside a fibular ALG ring for DDD of the cervical spine.[89]

rhBMP2 (total N=180) was applied typically via absorbable collagen sponge in a dose range of 0.9 to 12 mg per patient, combined with a bone graft extender such as cortical ring allograft (CRA) or compression-resistant matrix (CRM) in four studies,[89,104–106] and used in PEEK cages in one study.[107] Comparators (total N=276) included ICBG alone in two studies,[104,105] CRA,[89,106] or ALG bone plus demineralized bone matrix (DBM).[107]

The RCT[89] was rated as "fair" and all four nonrandomized studies[104–106] were rated as "poor" according to criteria of the USPSTF study quality rating system.

Table 32 shows that two small studies, the RCT[89] and a nonrandomized comparative study[107] reported on radiographic fusion success and changes in mean neck disability score, that are insufficient to support conclusions. The other three nonrandomized comparative studies were largely focused on complications, which are summarized in Table 33. These nonrandomized, poor quality studies are insufficient to support conclusions on radiographic fusion success or changes in ODI scores in patients undergoing anterior cervical spinal fusion.

Table 30. Overall Grade of Strength of Comparative Study Evidence for Off-Label Use of rhBMP2 (InFUSE) in the Cervical Spine

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Overall Grade/Conclusion
What is the level of evidence and summary of evidence for the off-label use of rhBMP2 in fusion of the cervical spine? Outcomes of interest include radiographic fusion, pain, function, satisfaction measures, and adverse events.	Two small studies, an RCT and a nonrandomized comparative study reported on radiographic fusion success and changes in mean neck disability score. The other three nonrandomized comparative studies above were largely focused on complications	The risk of bias for fusion and neck disability outcomes was rated high due to the size and quality of two studies that reported those outcomes. The risk of bias for harms was rated medium. Overall, these studies were more complete than most studies in this literature in reporting harms, based on a modified McHarms scale.	There was insufficient evidence to draw conclusions about radiographic fusion success and neck disability measures. In two studies the frequency of cervical swelling and associated complications was significantly greater in the rhBMP2 arm. In the third study, these complications were similar in both arms, but the frequency was substantially higher in both arms than in the other two studies. Overall, this suggests that cervical swelling, and complications related to swelling, are more frequent with rhBMP2 and are not solely a result of the procedure.	Direct evidence was available for all outcomes reported.	The evidence on fusion and neck disability measures is imprecise. The evidence of swelling complications is precise as the two key studies report results that are highly statistically significant.	There is moderate evidence that off-label use of rhBMP2 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 measures.

Table 31. Off-Label Comparative Studies of rhBMP2 (InFUSE) for Cervical Spinal Fusion

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Randomized study: DDD of the cervical spine (89)	1	rhBMP2	18	24	0.6-1.2	FAIR
		AGB/ALG	15		0	
Nonrandomized studies: DDD of the cervical spine (104, 105, 106, 107)	4	rhBMP2/BGE	162	1.5-36	0.9-12	4 POOR
		ICBG or ALG	261		0	

Abbreviations: AGB: autograft bone; ALG: allograft bone; BGE: bone graft extender; ICBG: iliac crest bone graft; mos.: months; no.: number; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

Table 32. Clinical Outcomes in Off-Label Comparative Studies of rhBMP2 (InFUSE) for Cervical Spinal Fusion

Study (ref no.)	Group	No. Pts	BMP dose (mg/pt)	Radiographic fusion success, %	ODI mean score ↑ 24 mos.	USPSTF study quality
Baskin et al., 2003 randomized (89)	rhBMP2/ALG	18	0.6-1.2	100	53	FAIR
	ICBG/CRA	15	0	100	37 ($p<0.03$) neck disability index	
Butterman et al., 2008 nonrandomized (104)	rhBMP2/CRA	30	0.9-3.7	NR	~30	POOR
	ICBG	36	0	NR	~31	
Crawford et al., 2009 nonrandomized (105)	rhBMP2/BGE	41	4.2-12	NR	NR	POOR
	ICBG	36	0	NR	NR	
Smucker et al., 2006 nonrandomized (106)	rhBMP2/CRA	69	mn 1.32	NR	NR	POOR
	CRA	165	0	NR	NR	
Vaidya et al., 2007 nonrandomized (107)	rhBMP2	22	1-3	100	24	POOR
	ALG/DBM	24	0	96	33	

Abbreviations: AGB: autograft bone; ALG: allograft bone; BGE: bone graft extender; CRA: cortical ring allograft; DBM: demineralized bone matrix; ICBG: iliac crest bone graft; mn: mean; mos.: months; no.: number; NR: not reported; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

Table 33. Swelling and Related Complications in Off-Label Nonrandomized Comparative Studies of rhBMP2 (InFUSE) for Anterior Cervical Spinal Fusion

Study (ref no.)	Group (n)	Swelling %	Dysphagia %	Hoarseness %	Delayed Discharge %
Butterman et al., 2008 (104)	rhBMP2/CRA (30)	50	NR	NR	NR
	ICBG (36)	14 (p<0.01)	NR	NR	NR
Smucker et al., 2006 (106)	rhBMP2/CRA (69)	28	7	NR	3
	CRA (165)	4 (p<0.0001)	1	NR	0
Vaidya et al., 2007 (107)	rhBMP2 (22)	100	85	60	NR
	ALG/DBM (24)	100	56 (p=0.0092)	62	NR

Abbreviations: ALG: allograft bone; CRA: cortical ring allograft; DBM: demineralized bone matrix; ICBG: iliac crest bone graft; no.: number; NR: not reported;

Cervical neck swelling and dysphagia following anterior cervical fusion surgery were reported in three studies.[104,106,107] In two studies[104,106] the frequency of swelling was significantly greater in the rhBMP2 arm. In the third study, these complications were similar in both arms, but the frequency was substantially higher than in the other two studies. This suggests that cervical swelling, and complications related to swelling, are more frequent with rhBMP2 and are not solely a result of the procedure.

In the study by Smucker et al.,[106] five patients in the rhBMP2 group required hospital readmission for either medical or surgical management of swelling, compared to none of the control group. Results from a multivariate logistic analysis showed the use of rhBMP2 was significantly associated with cervical swelling complications ($p<0.0001$) with an odds ratio of 10.1 (95% CI: 3.8–26.6), suggesting patients who were treated with rhBMP2 were 10 times more likely to have a swelling complication versus those who did not receive this agent.

Autograft bone harvested from the iliac crest was used in two studies.[104,105] One study reported a single deep surgical site infection at the donor site that was successfully treated with irrigation and debridement surgery followed by antibiotics; no other donor site complications were reported.[105] The second study reported one patient with donor site infection that required irrigation, debridement, and antibiotics; a second patient experienced pain secondary to avulsion of the superior iliac spine that was addressed by open-reduction internal fixation.[104]

Evidence Summary for Miscellaneous Off-Label Uses of rhBMP2

Table 34 shows two small RCTs in which rhBMP2 (total N=24) was used off-label in comparison to autologous bone graft (AGB) alone or with allogeneic graft (ALG) (total N=27) to enhance bone healing at 12 to 24 months follow-up.[90,91] One was rated "fair"[90] and the other was rated "poor"[91] according to the USPSTF quality rating system.

In one RCT, rhBMP2 (12 mg per patient) was adsorbed on a collagen sponge and admixed with ALG chips to treat open tibial fractures.[90] In the second RCT, rhBMP2 (dose unclear) was applied via collagen sponge to undertake repair of unilateral cleft lip and palate defects.[91]

Table 34 also shows two small, nonrandomized comparative off-label studies of rhBMP2. The first study described treatment of treat acute tibial fractures.[108] The second described

posterior spinal fusion for ankylosing spondylitis or neuromuscular deformities.[109] Both studies were rated as "poor" according to the USPSTF study quality rating system criteria.

In one study, rhBMP2 (n=17) was applied via collagen sponge at a dose of 12 mg per patient, with various bone graft enhancers used as comparator (n=23) with follow-up of 18 months.[108] In the second study, rhBMP2 was mixed with AGB, CRM, or ALGB (n=23), in a total dose range of 64 to 320 mg per patient and compared to ICBG (n=32), with follow-up of more than 24 months.[109]

The evidence from the small, generally poor quality studies shown in Table 34 is insufficient to draw conclusions about the outcomes with rhBMP2 in these settings.

Table 34. Miscellaneous Off-Label Uses of rhBMP2

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Diaphyseal tibial fractures with cortical defect (90) randomized trial	1	rhBMP2	15	12	12	FAIR
		AGB	15	12	0	
Repair of unilateral cleft lip-palate (91) randomized trial	1	rhBMP2	9	12	4.2-12	POOR
		AGB	12	12	0	
Acute traumatic tibial plateau fractures (108) nonrandomized, comparative study	1	rhBMP2	17	18	12	POOR
		BGE	23	18	0	
Posterior spinal fusion for ankylosing spondylitis or neuromuscular deformity (109) nonrandomized, comparative study	1	rhBMP2/BGE	23	>24	64-320	POOR
		ICBG	32	>24	0	

Abbreviations: AGB: autograft bone; BGE: bone graft extender; mos.: months; no.: number; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

Evidence Summary for Miscellaneous Off-Label Uses of rhBMP7

Table 35 shows three RCTs that compared off-label use of rhBMP7 in three disparate settings; revision of scaphoid non-union,[96] high tibial osteotomy,[98] and osteotomy of the distal radius for symptomatic malunion.[97] One study[96] was rated "good," one[98] was rated "fair," and one[97] was rated "poor" according to the USPSTF study quality rating criteria.

In one RCT, rhBMP7 was applied via collagen sponge at 3.5 mg per patient with AGB or ALG (6 patients each) and compared to AGB (n=6) with 24 months' follow-up.[96] In another trial, rhBMP7 was applied via collagen sponge at 2.5 mg per patient (n=6) and compared to DBM (n=6) and type I collagen (n=6) over 12 months' follow-up.[98] The third trial compared rhBMP7 (dose not reported, n=14) to ICBG (n=16) over 12 months' follow-up.[97]

Table 35 also shows three nonrandomized comparative studies[82,110,111] of off-label rhBMP7 treatment. In one study, rhBMP7 was applied at a dose of 1 mg per patient via collagen sponge, admixed with ALG (n=21) and compared to ALG bone (n=40) in patients undergoing impaction grafting for revision of hip arthroplasty.[111] A follow-up of 60 months was prescribed, but the study was stopped early because of clinical failures. In a second, very small, pilot study, rhBMP7 was applied via collagen sponge at 2.5 mg per patient (n=3) and compared to ICBG (n=3) over 6 months' follow-up in patients undergoing maxillary sinus floor augmentation.[82] A third nonrandomized comparative study was identified in which rhBMP7 (Osigraft, dose not reported, n=20) with external fixation was compared to external fixation alone (n=20) to treat distal acute tibial fractures over follow-up of 12 to 45 months.[110]

All three nonrandomized comparative studies in Table 35[82,110,111] were rated as "poor" according to the USPSTF study quality rating criteria.

The evidence from these studies is insufficient to draw conclusions about outcomes with rhBMP7 in these settings.

Table 35. Miscellaneous Off-Label Uses of rhBMP7

Indication (ref no.)	No. of studies	Group	Total no. pts	Follow-up (mos.)	BMP dose range (mg/pt)	USPSTF study quality
Revision of scaphoid bone non-union (96) randomized trial	1	rhBMP7	12	24	3.5	GOOD
		AGB	6	24	0	
High tibial osteotomy (98) randomized trial	1	rhBMP7	6	12	2.5	FAIR
		DBM	6	12	0	
		Type I collagen	6	12	0	
Osteotomy of the distal radius for symptomatic malunion (97) randomized trial	1	rhBMP7	14	12	NR	POOR
		ICBG	16	12	0	
Distal tibial fractures (110) NRC	1	rhBMP7	20	12-45	NR	POOR
		External fixation	20	12-45	0	
Impaction grafting for revision of hip arthroplasty (111) NRC	1	rhBMP7/ALG	21	60	1	POOR
		ALG	40	60	0	
Maxillary sinus floor elevation (82) NRC	1	rhBMP7	3	6	2.5	POOR
		ICBG	3	6	0	

Abbreviations: AGB: autograft bone; ALG: allograft bone; DBM: demineralized bone matrix; ICBG: iliac crest bone graft; mos.: months; no.: number; NR: not reported; NRC: nonrandomized comparative study; pt(s); patient(s); USPSTF: U.S. Preventive Services Task Force

Key Question 7

What is the evidence of adverse events with (a) on-label use of BMP and (b) off-label use of BMP? And, at what dosage and administration do such adverse events occur?

Table 36 summarizes BMP-specific harms. Overall the evidence on BMP-specific harms summarized in Table 36 is insufficient to draw conclusions in most settings. There is moderate evidence that off-label use of rhBMP2 in cervical spinal fusion increases cervical swelling and related complications.

Table 37 summarizes autograft donor harvest site harms. The body of evidence suggests that autograft bone harvest is associated with pain at the harvest site, but it is not possible to systematically assess the frequency, duration, and clinical significance. Overall, autograft harms were inconsistently reported. It is not clear that the absence of reported harms in many studies reflects true absence, or whether the investigators did not seek such data or did not report it.

BMP-Related Harms in On-Label Comparative Studies

Six on-label comparative studies[71,72,74,75,77,79] describe specific harms attributable to the use of rhBMP2 or rhBMP7 with incidence ranging from 0.7 percent to 82 percent in a total of 630 patients who received a BMP device.

Antibody responses for bovine collagen were reported in five studies, of which four[72,72,74,75,77] employed rhBMP2, while one used rhBMP7.[79] Antibody reaction specific to rhBMP2 or rhBMP7 was observed in four studies,[72,74,77,79] ranging from 0.7 percent[72] to 2 percent.[72,74] These were all transient with no clinical sequelae.

BMP-Related Harms in Off-Label Comparative Studies

Twelve off-label comparative studies[84,85,88–90,94,97,104,106–108,110] describe specific harms attributable to the use of rhBMP2 or rhBMP7 in a total of 385 patients who received a BMP device.

Cervical neck swelling and dysphagia were reported in three anterior cervical fusion studies.[104,106,107] In two studies,[104,106] the frequency of swelling was significantly greater in the rhBMP2 arm. In the third study, these complications were similar in both arms, but the frequency was substantially higher than in the other two studies. This suggests that cervical swelling, and complications related to swelling, are more frequent with rhBMP2 and are not solely a result of the procedure.

Three studies reported extraosseous bone formation.[97,108,110] One study[108] employed rhBMP2 while two[97,110] used rhBMP7. Antibody responses for bovine collagen were reported in four studies employing rhBMP2.[85,88–90] Antibody reaction specific to rhBMP2 or rhBMP7 was observed in two studies,[84,94] ranging from 4.5 percent[84] to 94 percent.[94] These were all transient with no clinical sequelae.

Table 36. Incidence of BMP-Related Adverse Events in Comparative Studies

Study (ref no.)	Study Design	Surgical Intervention	Group	N	BMP dose (mg/pt)	Cervical Swelling %	Facial Edema %	Dysphagia or Hoarseness %	anti-BMP Immune Response %	anti-Collagen Immune Response %	Hetero-topic bone %	Extra-osseous Bone/ Calcification %
Boyne et al., 2005 USA (75) **rhBMP2 On-Label**	Multicenter randomized dose-comparison, safety and efficacy study	Maxillary sinus floor augmentation	rhBMP2	18	6-24	NR	39	NR	12	24	NR	NR
			rhBMP2	17	15-48	NR	82	NR	0	11	NR	NR
			AGB/ALG	13	0	NR	38 (p=0.0227, 0.0152, BMP high dose versus controls and lower dose, respectively)	NR	0	23	NR	NR
Triplett et al., 2009 (77) **rhBMP2 On-Label**	Multicenter, nonblinded RCT	Maxillary sinus floor augmentation	rhBMP2	80	12-24	NR	Reported in rhBMP2 group as "consistent with previous phase II study" (Boyne, above) but not quantified	NR	2	29	NR	NR
			AGB/ALG	80	0			NR	0	32	NR	NR

Table 36. Incidence of BMP-Related Adverse Events in Comparative Studies (continued)

Study (ref no.)	Study Design	Surgical Intervention	Group	N	BMP dose (mg/pt)	Cervical Swelling %	Facial Edema %	Dysphagia or Hoarseness %	anti-BMP Immune Response %	anti-Collagen Immune Response %	Hetero-topic bone %	Extra-osseous Bone/ Calcification %
Govender et al. for the BESTT study group 2002 South Africa (74) **rhBMP2 On-Label**	Multi-center, single blind, RCT	IM nail fixation and soft tissue management for open tibial fractures	rhBMP2	151	6	NR	NR	NR	2	15	Reported not to have occurred	Reported not to have occurred
			rhBMP2	149	12				6	20		
			Standard care	150	0				1	6		
Burkus et al., 2002 USA (72) **rhBMP2 On-Label**	Multicenter, nonblinded RCT	Single-level primary anterior lumbar fusion	rhBMP2	143	4.2-8.4	NR	NR	NR	0.7	NR	NR	NR
			ICBG	136	0	NR	NR	NR	0.8	NR	NR	NR
Boden et al., 2000 USA (71) **rhBMP2 On-Label**	Multicenter, nonblinded RCT	Single-level primary anterior lumbar fusion	rhBMP2	11	4.2-8.4	NR	NR	NR	0	27	NR	NR
			ICBG	3	0	NR	NR	NR	0	0	NR	NR
Haid et al., 2004 USA (88) **rhBMP2 Off-Label**	Multicenter, nonblinded RCT	Single-level primary posterior lumbar interbody fusion	rhBMP2	34	4.2-8.4	NR	NR	NR	0	9	71	NR
			ICBG	33	0	NR	NR	NR	0	15	12 (p <0.0001)	NR

Table 36. Incidence of BMP-Related Adverse Events in Comparative Studies (continued)

Study (ref no.)	Study Design	Surgical Intervention	Group	N	BMP dose (mg/pt)	Cervical Swelling %	Facial Edema %	Dysphagia or Hoarseness %	anti-BMP Immune Response %	anti-Collagen Immune Response %	Hetero-topic bone %	Extra-osseous Bone/ Calcification %
Boden et al., 2002 USA (84) **rhBMP2 Off-Label**	Multicenter nonblinded RCT	Single-level primary instrumented posterolateral lumbar fusion	rhBMP2/BCP	11	40	NR	NR	NR	4.5	NR	NR	NR
			rhBMP2/BCP	11	40	NR	NR	NR	4.5	NR	NR	NR
			ICBG	5	0	NR	NR	NR	0	NR	NR	NR
Burkus et al., 2005 USA (85) **rhBMP2 Off-Label**	Multicenter nonblinded RCT	Single-level primary anterior lumbar fusion	rhBMP2	79	8-12	NR	NR	NR	0	9	NR	NR
			ICBG	52	0	NR	NR	NR	0	8	NR	NR
Baskin et al., 2003 USA (89) **rhBMP2 Off-Label**	Multicenter, nonblinded RCT	Single- or two-level primary instrumented ACDF with rhBMP2	rhBMP2/ALG	18	0.6-1.2	NR	NR	NR	NR	6	NR	NR
			ICBG/ALG	16	0	NR	NR	NR	NR	6	NR	NR
Butterman et al., 2008 USA (104) **rhBMP2 Off-Label**	Prospective nonrandomized cohorts of consecutive patients	Single- or multi-level primary instrumented or uninstrument-ed ACDF	rhBMP2/CRA	30	0.9-3.7	50	NR	NR	NR	NR	NR	NR
			ICBG	36	0	14 ($p<0.01$)	NR	NR	NR	NR	NR	NR
Smucker et al., 2006 USA (106) **rhBMP2 Off-Label**	Retrospective case-control	Single- or multi-level instrumented ACDF	rhBMP2/CRA	69	NR	28	NR	7	NR	NR	NR	NR
			CRA	165		4 ($p<0.0001$)	NR	1	NR	NR	NR	NR

Table 36. Incidence of BMP-Related Adverse Events in Comparative Studies (continued)

Study (ref no.)	Study Design	Surgical Intervention	Group	N	BMP dose (mg/pt)	Cervical Swelling %	Facial Edema %	Dysphagia or Hoarseness %	anti-BMP Immune Response %	anti-Collagen Immune Response %	Hetero-topic bone %	Extra-osseous Bone/ Calcification %
Vaidya et al., 2007 USA (107) **rhBMP2 Off-Label**	Retrospective cohorts of consecutive patients	Single- or multi-level primary instrumented ACDF	rhBMP2	22	1-3	100	NR	85	NR	NR	NR	NR
			ALG/DBM	24	0	100	NR	39 (p=0.0092)	NR	NR	NR	NR
Friedlander et al., 2001 USA (79) **rhBMP7 On-Label**	Multicenter, partially blinded RCT	IM rod fixation	rhBMP7/BCC	61	3.5-7.0	NR	NR	NR	10	5	NR	NR
			AGB	61	0	NR	NR	NR	0	0	NR	NR
Vaccaro et al., 2008 USA (94) **rhBMP7 Off-Label**	Multicenter, nonblinded RCT	Single-level primary uninstrument-ed posterolateral lumbar fusion	rhBMP7	207	7	NR	NR	NR	26	NR	NR	NR
			ICBG	86	0	NR	NR	NR	1	NR	NR	NR
Jones et al., 2006 USA (90) **rhBMP2 Off-Label**	Multi-center prospective RCT	Reconstruction of diaphyseal tibial fractures with cortical defect	rhBMP2/ALG	15	12	NR	NR	NR	0	6.7	NR	NR
			AGB	15	0	NR	NR	NR	0	27	NR	NR

Table 36. Incidence of BMP-Related Adverse Events in Comparative Studies (continued)

Study (ref no.)	Study Design	Surgical Intervention	Group	N	BMP dose (mg/pt)	Cervical Swelling %	Facial Edema %	Dysphagia or Hoarseness %	anti-BMP Immune Response %	anti-Collagen Immune Response %	Hetero-topic bone %	Extra-osseous Bone/ Calcification %
Ekrol et al., 2008 UK (97) **rhBMP7 Off-Label**	Prospective randomized cohort	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	rhBMP7	4	NR	NR	NR	NR	NR	NR	NR	0
			AGB	6	NR	NR	NR	NR	NR	NR	NR	0
			rhBMP7 external fixation	10	NR	NR	NR	NR	NR	NR	NR	10
			AGB external fixation	10	NR	NR	NR	NR	NR	NR	NR	0
Ristiniemi et al., 2007 Finland (110) **rhBMP7 Off-Label**	Retrospective cohort of matched patients	Distal tibial fracture	rhBMP7	20	3.5-7	NR	NR	NR	NR	NR	NR	5
			External fixation	20	NR	NR	NR	NR	NR	NR	NR	0
Boraiah et al., 2009 USA (108) **rhBMP2 Off-Label**	Retrospective case series	Acute traumatic tibial plateau fractures	rhBMP2/ALG DBM/CaP	17	12	NR	NR	NR	NR	NR	59	NR
			ALG/DBM/CaP	23	0	NR	NR	NR	NR	NR	4 (p <0.001)	NR

Abbreviations: AGB: autograft bone; ALG: allograft bone; BCP: biphasic calcium phosphate; CaP: calcium phosphate; CRA: cortical ring allograft; CRM: compression-resistant matrix; DBM: demineralized bone matrix; ICBG: iliac crest bone graft; IM: intramedullary; mos.: months; no.: number; NR: not reported; pt(s); patient(s); RCT: randomized, controlled trial;

Summary of Evidence from Noncomparative On- and Off-Label Studies Reporting BMP-related Harms

Fourteen noncomparative studies describe specific harms attributable to the off-label use of rhBMP2 or rhBMP7 (total rhBMP N=463) with an incidence ranging from 2 to 100 percent. Six reports of heterotopic bone formation were found, two using rhBMP7 and four using rhBMP2 of varied doses.[114,134,138,148,150,158] Four of these were lumbar studies, the fifth[158] was a femur study and the sixth a humeral non-union study.[155]

Ectopic bone formation occurred in two studies of rhBMP2.[139,186]

Dysphagia was reported in five rhBMP2 studies[113,114,116,119,125] (N=260) with varying degrees of severity. Four were cervical spine studies[113,114,119,125] and the fifth was a lumbar spine study.[116]

A case report of a patient undergoing a TLIF with rhBMP2 and autograft had a systemic immune response after treatment.[147] Subsequent treatment of a revision surgery resulted in an increased response to the re-exposure of rhBMP2.

Because of the noncomparative design of these studies, it is not possible to strictly associate the use of a BMP device with an adverse event.

Autograft Donor Site Harms Reported in Comparative Studies

Table 37 shows a summary of harms reported at the autograft donor site in comparative BMP studies. As shown in Table 37, among 41 studies in this technology assessment, 20 (43 percent) reported the occurrence of donor site harms.

The body of evidence suggests that autograft bone harvest is associated with pain at the harvest site, but it is not possible to systematically assess the frequency, duration, and clinical significance. Overall, autograft harms were inconsistently reported. It is not clear that the absence of reported harms in many studies reflects true absence, or whether the investigators did not seek such data or did not report it.

Seven of 10 (70 percent) lumbar fusion studies[72,73,86–88,92,95,100,182] reported pain at some point following surgery, four (40 percent) reported infection at the donor site[72,73,86,182] , one reported the occurrence of hematoma.[88]

Two of three (67 percent) cervical fusion studies[89,104] reported pain at the donor site, two (67 percent) reported infection.[104,105]

Three of 3 (100 percent) maxillofacial studies[75,77,91] reported pain at autograft donor sites, one reported rash and edema.[75]

Among the other four studies, pain was reported in two[96,97] (50 percent), infection in one[83] (25 percent), with other events in three.[83,90,97]

Detailed information on these harms is reported in Appendix 4 Tables B and C.

Table 37. Autograft Donor Site Harms Reported in Comparative Studies

Study	Design	Comparison	No. Patients	Clinical Setting	Pain	Infection	Other
Dawson et al., 2009; USA (73) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP2/BCP	25	Single-level primary instrumented posterolateral lumbar fusion		x	
		ICBG	21				
Burkus et al., 2003; USA (182) **Lumbar-Sacral Fusion**	Retrospective combined comparative analysis	rhBMP2	277	Single-level primary anterior lumbar fusion with interbody fusion cages	x (32% at 2 years)	x	
		ICBG	402				
Burkus et al., 2002; USA (72) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP2	143	Single-level primary anterior lumbar fusion with interbody fusion cages	x (32% at 2 years)	x	
		ICBG	136				
Dimar et al., 2009; USA (86) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP2/BCP	239	Single-level primary instrumented posterolateral lumbar fusion	x	x	
		ICBG	224				
Glassman et al., 2008; USA (87) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP2	50	Single- or multi-level primary instrumented posterolateral lumbar fusion			
		ICBG	52				
Haid et al., 2004; USA (88) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP2	34	Single-level primary posterior lumbar interbody fusion with interbody fusion cages	x		hematoma
		ICBG	33				
Mummaneni et al., 2004; USA (100) **Lumbar-Sacral Fusion**	Retrospective single-center cohort study	rhBMP2/AGB	25	Single- or multi-level primary transforaminal lumbar interbody fusion with interbody fusion cages	x (58% at 6 mos.)		
		ICBG	19				
Vaccaro et al., 2008; USA (94) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP7	207	Single-level primary uninstrumented posterolateral lumbar fusion	x (45% at 2 years)		
		ICBG	86				
Vaccaro et al., 2008; USA (95) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP7	24	Single-level primary uninstrumented posterolateral lumbar fusion			
		ICBG	12				
Johnsson et al., 2002; Sweden (92) **Lumbar-Sacral Fusion**	Multicenter nonblinded RCT	rhBMP7	10	Single-level primary uninstrumented posterolateral lumbar fusion	x		
		ICBG	10				

Table 37. Autograft Donor Site Harms Reported in Comparative Studies (continued)

Study	Design	Comparison	No. Patients	Clinical Setting	Pain	Infection	Other
Crawford et al., 2009; USA (105) **Cervical Fusion**	Retrospective cohort of consecutive patients	rhBMP2/BGE	41	Single- or multi-level instrumented posterior cervical spinal fusion		x	
		ICBG	36				
Butterman et al., 2008; USA (104) **Cervical Fusion**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA	30	Single- or multiple-level cervical ACDF	x	x	
		ICBG	36				
Baskin et al., 2003; USA (89) **Cervical Fusion**	Multicenter nonblinded RCT	rhBMP2/ALG	18	Single- or two-level primary instrumented ACDF	x		
		ICBG/ALG	15				
Dickinson et al., 2008; USA (91) **Maxillofacial Procedures**	Single-center RCT	rhBMP2	9	Repair of unilateral cleft lip-palate with an alveolar cleft defect	x (25% at 6 mos.)		
		ICBG	12				
Boyne et al., 2005; USA (75) **Maxillofacial Procedures**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2	18	Staged bilateral or unilateral maxillary sinus floor augmentation	x		rash, edema
		rhBMP2	17				
		AGB	13				
Triplett et al., 2009; USA (77) **Maxillofacial Procedures**	Multicenter nonblinded RCT	rhBMP2/ACS	80	Staged bilateral or unilateral maxillary sinus floor augmentation	x		
		AGB	80				

Table 37. Autograft Donor Site Harms Reported in Comparative Studies (continued)

Study	Design	Comparison	No. Patients	Clinical Setting	Pain	Infection	Other
Jones et al., 2006; USA (90) **Miscellaneous Uses**	Multicenter prospective RCT	rhBMP2/ALG	15	Reconstruction of diaphyseal tibial fractures with cortical defect	x (93% at 4.5 mos.)		pustules, drainage
		AGB	15				
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Uses**	Single-center unblinded RCT	rhBMP7/AGB	6	Revision of non-union	x (100% postop)		
		rhBMP7/ALG	6				
		ICBG	6				
Ekrol et al., 2008; UK (97) **Miscellaneous Uses**	Prospective randomized cohort	rhBMP2/ext fix	4	Osteotomy of the distal radius for symptomatic malunion			hematoma
		AGB/ext fix	6				
		rhBMP2/int fix	10				
		AGB/int fix	10				
Dahabreh et al., 2008 UK, Italy (83) **Miscellaneous Uses**	Retrospective cohort study	rhBMP7/BCC	15	Open reduction internal fixation, exchange intramedullary nailing or Ilizarov		x	abscess
		ICBG	12				

The symbol "x" in the study report means the harm occurred but numerical frequency was not reported

Abbreviations: ACS: absorbable collagen sponge; AGB: autograft bone; ALG: allograft bone; CRA: cortical ring allograft; CRM: compression-resistant matrix; DBM: demineralized bone matrix; ext fix: external fixation; ICBG: iliac crest bone graft; IM: intramedullary; int fix: internal fixation; mos.: months; no.: number; NR: not reported; pt(s); patient(s); postop: postoperative; RCT: randomized, controlled trial;

Key Question 8

What is the quality of reporting of adverse events in publications? Provide summary to support conclusion.

This question was addressed specifically with respect to BMP-specific harms in comparative studies, using a modification of the McHarms survey[64] outlined in the Methods section of this technology assessment. The quality of reporting is summarized in Table 38; more specific information is compiled in Appendix 5 Tables A (on-label) and B (off-label).

The quality of reporting in the 41 comparative studies reviewed in this technology assessment 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.

Table 38. Summary of BMP-Specific Harms Reporting in Comparative Studies

A. On-Label Studies (n=13)

Study Type	Explanation of how harms identified (% studies)	Standard/valid instrument used (% studies)	Ascertainment similar in all groups (% studies)	Measure of severity reported (% studies)	Were harms attributed to intervention likely causally associated (% studies)	Were harms (# and type) reported separately for each study group (% studies)
Yes	62	16	92	15	8	77
No	38	62	8	85	69	23
Uncl/Unk	0	23	0	0	23	0

Abbreviations: Uncl/Unk: Unclear/Unknown

B. Off-Label Studies (n=28)

Study Type	Explanation of how harms identified (% studies)	Standard/valid instrument used (% studies)	Ascertainment similar in all groups (% studies)	Measure of severity reported (% studies)	Were harms attributed to intervention likely causally associated (% studies)	Were harms (# and type) reported separately for each study group (% studies)
Yes	54	7	68	4	21	64
No	46	50	4	89	58	36
Uncl/Unk	0	43	28	7	21	0

Abbreviations: Uncl/Unk: Unclear/Unknown

Overall, the quality of reporting on BMP-related harms amongst comparative studies was inconsistent. It also is 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.

Key Question 9

What is the incremental cost effectiveness of the use of BMP for spinal fusion and open tibial fracture?

Our focus was to implement Markov models in cost-effectiveness analyses of the use of BMP in open tibial fracture and spinal fusion. Markov models allow an explicit examination of the impact of changes in health state probabilities over time. We were unable to identify any prior Markov-based cost-effectiveness analyses of these topics.

Garrison et al.[26] reported two cost-effectiveness analyses for the U.K. National Health Service Health Technology Assessment Programme. The analyses, open tibial fracture and anterior lumbar interbody spinal fusion, had been performed by ABACUS International, a European consulting firm funded by a BMP manufacturer. The way in which ABACUS models calculated quality-adjusted life years (QALYs) is opaque and would be difficult to reproduce. A request to examine the MS Excel® files used by ABACUS before completion of this analysis was declined. A decision tree cost utility analysis was published by Carreon et al.,[187] focusing on single or multilevel posterolateral lumbar spinal fusion, in contrast with single-level anterior lumbar interbody fusion. These articles served as an impetus for the present analyses.

Methods

Characteristics of our cost-effectiveness analysis are summarized in Table 39. Analyses were performed from a payer perspective. The specific perspective was that of the Centers for Medicaid and Medicare Services (CMS), as all cost estimates were payments by Medicare.

For the open tibial fracture (OTF) analysis, the relevant population is represented by patients selected for the "BMP2 Evaluation in Surgery for Tibial Trauma" (BESTT) randomized trial (Govender et al., 2002[74]). Such patients had open tibial shaft fractures within Gustilo-Anderson severity types I, II, IIIA and IIIB. The BESTT trial treatment group received intramedullary nail fixation and routine soft-tissue management (standard of care) plus an implant with either 0.75 mg/mL or 1.50 mg/mL of rhBMP2. This analysis only uses outcomes reported for the group receiving the higher dose. Control group patients received standard of care alone.

The spinal fusion (SF) analysis focused on the randomized trial by Burkus et al.[72] Relevant patients are those with single-level degenerative lumbar disc disease and disabling symptoms of at least 6 months duration that had not responded to nonoperative treatments. The Burkus trial treatment group underwent open single-level anterior interbody lumbar fusion (ALIF), including an LT-Cage device filled with an absorbable collagen sponge infused with rhBMP2. Control patients had the same procedure with autogenous iliac crest bone graft instead of BMP.

Short time horizons were chosen based on limited follow-up evidence provided in the two randomized trials: 52 weeks (1 year) for open tibial fracture and 104 weeks (2 years) for spinal fusion.

Table 39. Cost-Effectiveness Analysis Characteristics

Characteristic	Description
Perspective	Payer (CMS; obtained cost estimates were payments by Medicare).
Population	OTF: The population reflects patient selection in the BMP2 Evaluation in Surgery for Tibial Trauma (BESTT) randomized trial (Govender et al., 2002). Such patients had open tibial shaft fractures within Gustilo-Anderson severity types I, II, IIIA and IIIB. SF: Based on the randomized trial by Burkus et al. [ref 72], relevant patients are those with single-level degenerative lumbar disc disease and disabling symptoms of at least 6 months duration that had not responded to nonoperative treatments.
Strategies	OTF: The BESTT trial treatment group received intramedullary nail fixation and routine soft-tissue management (standard of care) plus an implant with either 0.75 mg/mL or 1.50 mg/mL of rhBMP2. This analysis uses outcomes reported for the group receiving the higher dose. Control group patients received standard of care alone. SF: The Burkus trial treatment group underwent open single-level anterior interbody lumbar fusion (ALIF), including an LT-CAGE device filled with an absorbable collagen sponge infused with rhBMP2. Control patients had the same procedure with autogenous iliac crest bone graft instead of BMP.
Time Horizon	Short time horizons were chosen based on limited follow-up evidence provided in the two randomized trials: 52 weeks (1 year) for OTF and 104 weeks (2 years) for SF.
Type of Model	For both analyses, stationary Markov models were used (constant transition probabilities) with a cycle length of one week. OTF: There were three health states for both treatment and control groups: preunion, secondary intervention and union. SF: There were three states for the treatment group: prefusion, secondary intervention and fusion. The control group had six health states, the same three states as the treatment group, combined with bone graft donor site pain (DSP) or no DSP. Minimum time to both union and fusion was assumed to be six weeks.
Modeling Details	MS Excel was the main software program. Analyses used two approaches producing identical results: 1) area partitioned by separate exponential survival curves for health states and 2) cohort simulations (see transition probability matrices). Engauge Digitizer software was used to create area calibration sources for time to union for OTF and time to fusion and time to resolved DSP for SF. Model hazard rates were adjusted until follow-up area matched that from calibration sources. Having a secondary intervention was treated as a temporary state lasting one week; area spent in this state was calculated as the proportion of individuals having secondary interventions divided by the total number of weeks past the minimum time to union (n=46) or fusion (n=98).
Included Costs	Analyses included direct health care costs reported as Medicare payments from free publicly available sources, valued in 2007 US dollars. Cost categories included initial hospitalization (hospital and physician costs) and secondary interventions (hospital/outpatient surgical center and physician costs). In separate analyses, BMP was treated as a bundled part of DRG payments and as a separate added payment amount. Secondary intervention costs were identified for specific subcategories of procedures: for OTF, most invasive (bone graft, exchange nailing, plate fixation, fibular osteotomy or bone transport) versus less invasive (nail dynamization or exchange from internal fixation to functional brace) and for SF, removals, supplemental fixations and reoperations. A noninvasive category reported in the OTF trial was not included in this analysis because only two patients were represented. Indirect costs were excluded.
Effectiveness Metric/Analytic Output	Quality-adjusted life-year (QALY) is the effectiveness metric. The key analytic output is the incremental cost-effectiveness ratio (ICER), calculated as the difference in total costs between treatment and control divided by the between-group difference in QALYs.
Discounting	Given the short time horizons, discounting was not used for either costs or utilities.
Sensitivity Analyses	Both OTF and SF: BMP added to costs Utilities Non-BMP costs Secondary intervention costs Hazard ratio of rates of achieving union/fusion Risk ratio of having secondary interventions BMP costs SF only Probability of DSP in control patients Disutility of health states with DSP

Abbreviations: OTF: open tibial fracture; SF: spinal fusion;

For both analyses, stationary Markov models were used (constant transition probabilities) with a cycle length of one week. In the open tibial fracture analysis, there were three health states for both treatment and control groups: preunion, secondary intervention, and union (Figure 1). In the spinal fusion analysis, there were three states for the treatment group: prefusion, secondary intervention and fusion. The control group had six health states, the same three states as the treatment group, combined with bone graft donor site pain (DSP) or no donor site pain (Figure 2). For both analyses, the minimum time to both union and fusion was assumed to be six weeks.

Analyses were carried out with Microsoft Excel®. Two modeling approaches produced identical results: 1) area partitioned by separate exponential survival curves for health states and 2) cohort simulations. Engauge Digitizer software was used to create area calibration sources for time to union for open tibial fracture as well as time to fusion and time to resolved bone graft donor site pain among control group patients for spinal fusion.

Tables 40A–C provides utility and outcome parameter estimates for the open tibial fracture analysis. Open tibial fracture utility values were obtained from a study by Sprague and Bhandari[188] on treatment of closed tibial fracture and were based on expert opinion. Sensitivity analyses were performed with utilities 25 percent lower or 25 percent higher than base case values, with a limit of 0.99 for the highest valued state.

A rate of fracture healing graph reported by Govender et al.(BESTT trial[74]) was processed by Engauge Digitizer software to derive probability estimates of union at the six observed follow-up points. These probabilities allowed creation of curves by Microsoft Excel®. The Excel® curves were then digitized to give derived probability estimates at all points from 6 to 52 weeks. Derived probability estimates were used to create area calibration sources for partitioning follow-up area for preunion and union by the Markov model. Model hazard rates were adjusted until partitioned areas matched the calibration source. Transition probability matrices for open tibial fracture treatment and control are shown in Table 41.

For both open tibial fracture and spinal fusion, having a secondary intervention was treated as a temporary state lasting one week; area spent in this state was calculated as the proportion of individuals having secondary interventions divided by the total number of weeks past the minimum time to union (46 weeks) or fusion (98 weeks). These values served as area calibration sources for modeling this health state.

In the spinal fusion analysis (Table 42), utility values for the prefusion without donor site pain and fusion without donor site pain health states were based on preoperative and 6 month unpublished data collected by Burkus et al.[72,182] and described in Garrison et al.[26] SF-36 data from treatment and control patients were transformed into utilities using the Brazier et al.[189] index. Treatment and control utilities cited by the Garrison analysis[26] were similar, although this analysis assumes a 0.02 disutility among control patients for states involving donor site pain. A sensitivity analysis is performed with a larger disutility value for donor site pain (0.05). The utility for intervention without donor site pain was estimated as 0.05 lower than the prefusion without donor site pain. Sensitivity analyses were conducted with utilities that were 25 percent lower and 25 percent higher than base case values.

Figure 1.

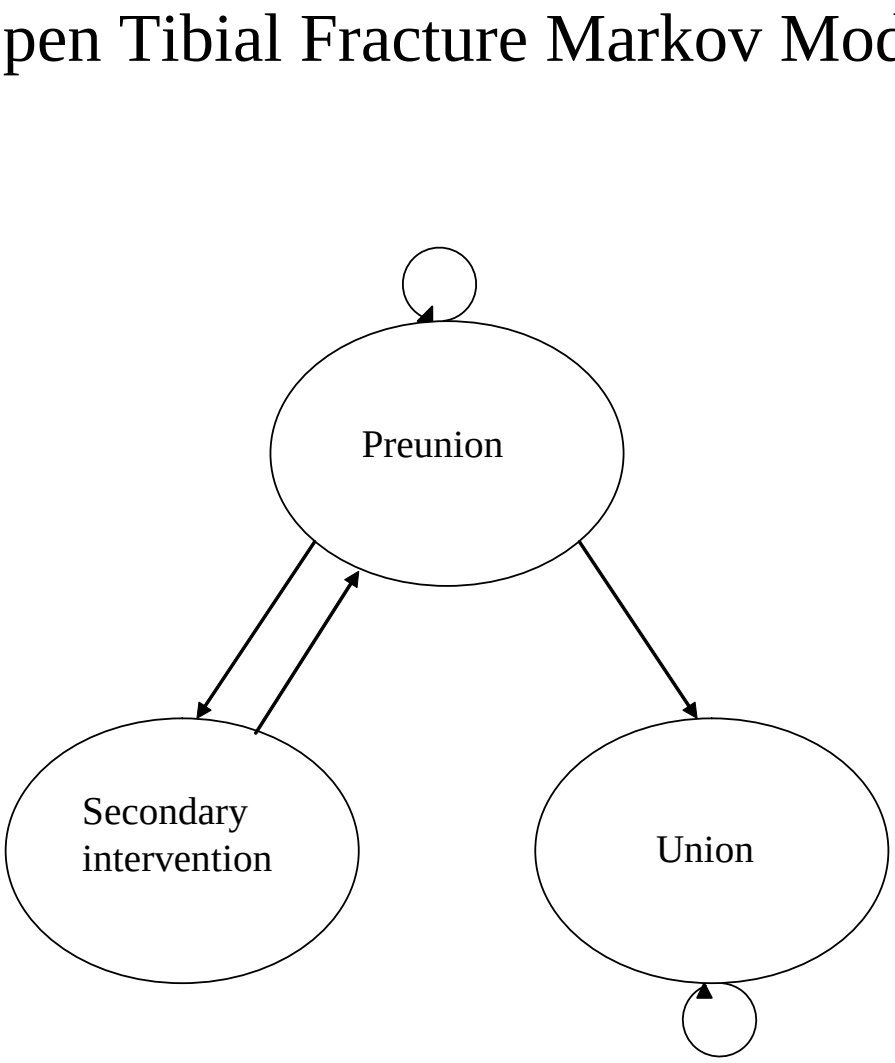
Open Tibial Fracture Markov Model
Preunion
Secondary intervention
Union

Figure 2.

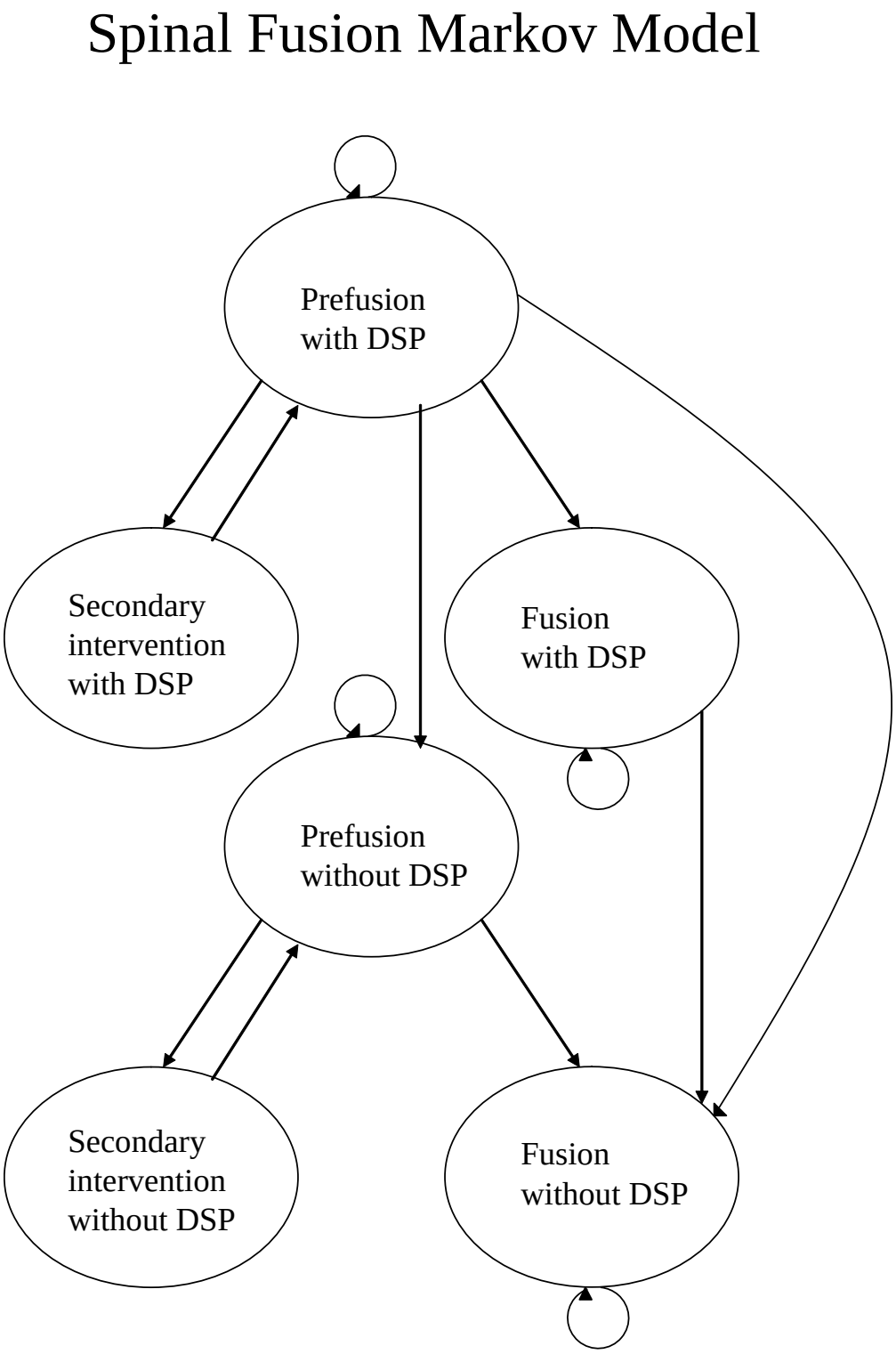
Spinal Fusion Markov Model
Prefusion with DSP
Secondary intervention with DSP
Fusion with DSP
Prefusion without DSP
Secondary intervention without DSP
Fusion without DSP

Table 40. Utility and Outcome Parameter Estimates and Sources, Open Tibial Fracture

Table 40A. Utility Estimates*

State	Utility	Source
Preunion	0.60	Sprague et al. 2002 [ref 188] (cited by Garrison et al. 2007 [ref 26]), delayed union
Secondary intervention	0.50	Sprague et al. 2002 [ref 188] (cited by Garrison et al. 2007 [ref 26]), postoperative complication
Union	0.90	Sprague et al. 2002 [ref 188] (cited by Garrison et al. 2007 [ref 26]), returning to normal activities

*Sensitivity analysis was performed for all utilities either 25% lower or 25% higher

Table 40B. Estimates of Probability of Union**

Week	Treatment %	Control %
10	14.9%	6.9%
14	35.4%	14.1%
20	51.8%	27.7%
26	58.4%	38.1%
39	66.3%	48.7%
52	71.2%	51.4%

**Source: Govender et al. 2002 (BESTT trial [ref 74]); rate of fracture healing graph was digitized to derive probability estimates at the follow-up points at left, curve created with these points by MS Excel, Excel curve digitized to give derived probability estimates at all points from 6 to 52 weeks. Derived probability estimates used to create area calibration source for partitioning follow-up area by Markov model. Derived hazard ratio (HR) for preunion state was 1.89. Arbitrary lower limit HR of 0.99 (treatment worse) was chosen, determining a comparably extreme counterpart value, in the log scale, of 3.61. Two intermediate HRs of 1.37 and 2.62 were also chosen.

Table 40C. Risk Ratio of Probability of Secondary Intervention***

Group	#	n	%	Risk Ratio	RR 95% CI Lower	RR 95% CI Upper
Treatment	30	135	22.2%	0.533	0.367	0.772
Control	58	139	41.7%			

***Govender et al. 2002 (BESTT trial [ref 74]); area spent in secondary intervention state was calculated as the proportion of individuals having secondary interventions divided by the total number of weeks past the minimum time to union (n=46).

Table 41. Transition Probability Matrices, Open Tibial Fracture

Table 41A. Transition Probability Matrices: Treatment

States	Preunion (S1)	Secondary Intervention (S2)	Union (S3)
Preunion (S1)	0.962663205	0.000012754	0.037324041
Secondary Intervention (S2)	0.0	0.962675959	0.037324041
Union (S3)	0.0	0.0	1.0

Table 41B. Transition Probability Matrices: Control

States	Preunion (S1)	Secondary Intervention (S2)	Union (S3)
Preunion (S1)	0.980082713	0.000014956	0.019902331
Secondary Intervention (S2)	0.0	0.980097669	0.019902331
Union (S3)	0.0	0.0	1.0

Table 42. Utility and Outcome Parameter Estimates and Sources, Spinal Fusion

Table 42A. Utility Estimates*

State	Utility	Source
S1 Prefusion w/o donor site pain (DSP)	0.54	Garrison et al. 2007 [ref 36], from Burkus unpublished data, SF-36 Brazier index, preoperative mean
S2 Prefusion w/ DSP	0.52	S1 reduced by 0.02
S3 Secondary Intervention w/o DSP	0.49	S1 reduced by 0.05
S4 Secondary Intervention w/ DSP	0.47	S3 reduced by 0.02
S5 Fusion w/ DSP	0.60	S6 reduced by 0.02
S6 Fusion w/o DSP	0.62	Garrison et al. 2007 [ref 26], from Burkus unpublished data, SF-36 Brazier index, 6 month mean

*Disutility associated with DSP assumed to be 0.02 for all three key health states (prefusion, secondary intervention and fusion). Sensitivity analysis also performed for larger disutility magnitude (0.05), and all utilities either 25% lower or 25% higher.

Table 42B. Estimates of Radiographic Fusion Success

Group	6-month Radiographic Fusion Success	12-month Radiographic Fusion Success	24-month Radiographic Fusion Success
Treatment	128/132 (97.0%)	127/131 (96.9%)	120/127 (94.5%)
Control	115/120 (95.8%)	112/121 (92.6%)	102/115 (88.7%)

Source: Burkus et al. 2002 randomized trial; prefusion probabilities derived from radiographic fusion success probabilities, prefusion area between 6 weeks and 6 months estimated with exponential survival curves matched on observed 6 month fusion probabilities. Exponential curves were combined with linearly interpolated areas between 6 and 24 months to produce area calibration sources for partitioning follow-up area by Markov models. Derived hazard ratio (HR) for prefusion state was 1.45. Arbitrary lower limit HR of 0.99 (treatment worse) was chosen, determining a comparably extreme counterpart value, in the log scale, of 2.13. Two intermediate HRs of 1.20 and 1.76 were also chosen.

Table 42C. Estimates of Donor-Site Pain

Week	Donor-Site Pain
0	100%
6	83%
13	56%
26	43%
52	35%
104	32%

Source: Burkus et al. 2002 [ref 72] randomized trial; probabilities of donor site pain (DSP) observed at the follow-up times at left used to create curve by MS Excel®, Excel® curve digitized to give derived probability estimates at all points from 6 to 104 weeks. Derived probability estimates used to create area calibration source for partitioning by Markov model. Area spent in DSP state in calibration source was 41.7%. This fraction was applied to pairs of health states with and without DSP (e.g., prefusion with DSP, prefusion without DSP). The exact binomial 95% confidence limits of that proportion (31.3%, 52.1%) were used in sensitivity analysis.

Table 42D. Risk Ratio of Probability of Intervention

	#	n	%	Risk Ratio	RR 95% CI Lower	RR 95% CI Upper
Treatment	18	143	12.6%	0.9510	0.5169	1.7498
Control	18	136	13.2%			

Source: Burkus et al. 2002 [ref 72] trial; area spent in secondary intervention state calculated as the proportion of individuals having secondary interventions divided by the number of weeks past the minimum time to fusion (n=98).

Prefusion probabilities were derived from clinical and radiographic fusion success probabilities reported by the Burkus et al.[72] randomized trial. The prefusion area between 6 weeks and 6 months was estimated with exponential survival curves intersecting observed 6 month fusion probabilities. Exponential curves were combined with linearly interpolated areas between 6 and 24 months to produce area calibration sources for partitioning follow-up area by Markov models. Probabilities of donor site pain observed at the six observed follow-up times were used to create a curve by Microsoft Excel®; The Excel curve was digitized to give derived probability estimates at all points from 6 to 104 weeks. Derived probability estimates were used to create area calibration sources for partitioning by the Markov model. Area spent in the donor site pain state in the calibration source was 41.7 percent. This fraction was applied to pairs of health states with and without donor site pain (e.g., prefusion with DSP, prefusion without DSP). Transition probability matrices for spinal fusion treatment and control are shown in Table 43.

Analyses included direct health care costs reported as Medicare payments from free publicly available sources, valued in 2007 U.S. dollars (Tables 44–49). Cost categories included initial hospitalization (hospital and physician costs) and secondary interventions (hospital/outpatient surgical center and physician costs). It was assumed that initial hospitalization was paid according to the diagnosis-related groups (DRG) system. Thus, base case analyses assume identical initial hospitalization costs whether BMP was used or not. In separate analyses, BMP was treated as a bundled part of DRG payments and as a separate added payment amount. Approximate cost of BMP was based on two published sources: $3,000[190] and $5,000[191], serving as the base case (mean) and upper value, respectively. A lower value of $1,000 and an extreme high value of $8,000 were also used for sensitivity analyses.

Secondary intervention costs were identified for specific subcategories of procedures: for open tibial fracture, most invasive (bone graft, exchange nailing, plate fixation, fibular osteotomy or bone transport) versus less invasive (nail dynamization or exchange from internal fixation to functional brace) and for spinal fusion, removals, supplemental fixations and reoperations. A noninvasive subcategory reported in the open tibial fracture trial was not included in this analysis because only two patients were represented. Costs for secondary interventions were calculated as weighted averages based on specific type of secondary intervention and proportions of type for both treatment and control groups. Indirect costs were excluded.

The quality-adjusted life-year (QALY) is the effectiveness metric. The key analytic output is the incremental cost-effectiveness ratio (ICER), calculated as the difference in total costs between treatment and control divided by the between-group difference in QALYs. The ICER is interpreted as the additional cost incurred to attain one additional QALY by choosing treatment over control. Given the short time horizons, discounting was not used for either costs or utilities.

Sensitivity analyses were performed for both open tibial fracture and spinal fusion for these variables: BMP added to costs, utilities, non-BMP costs, secondary intervention costs, the hazard ratio of rates of achieving union/fusion, risk ratio of having secondary interventions, and BMP costs. Additional sensitivity analyses for spinal fusion were performed on the probability of donor site pain in control patients, and the disutility of health states with donor site pain. One-way and selected two-way and three-way sensitivity analyses were performed.

Table 43. Transition Probability Matrices, Spinal Fusion

Table 43A. Transition Probability Matrices: Treatment

States	Prefusion without donor-site pain (S1)	Secondary intervention without donor-site pain (S3)	Fusion without donor site pain (S6)
Prefusion without donor-site pain (S1)	0.8901701	0.0000155	0.1098144
Secondary intervention without donor-site pain (S3)	0.0	0.8901856	0.1098144
Fusion without donor site pain (S6)	0.0	0.0	1.0

Table 43B. Transition Probability Matrices: Control

States	Prefusion without donor-site pain (S1)	Prefusion with donor-site pain (S2)	Secondary intervention without donor-site pain (S3)	Secondary intervention with donor-site pain (S4)	Fusion with donor-site pain (S5)	Fusion without donor-site pain (S6)
Prefusion without donor-site pain (S1)	0.8747582	0.0482304	0.0000047	0.0000033	0.0604576	0.0165458
Prefusion with donor-site pain (S2)	0.0	0.9229886	0.0000047	0.0000033	0.0604576	0.0165458
Secondary intervention without donor-site pain (S3)	0.0	0.0	0.9229933	0.0000033	0.0604576	0.0165458
Secondary intervention with donor-site pain (S4)	0.0	0.0	0.0	0.9229966	0.0604576	0.0165458
Fusion with donor-site pain (S5)	0.0	0.0	0.0	0.0	0.9834542	0.0165458
Fusion without donor-site pain (S6)	0.0	0.0	0.0	0.0	0.0	1.0

Table 44. Cost Parameter Estimates and Sources, Open Tibial Fracture

Procedure Type	Code Type	Code	Data Source	Cost Category	Mean	95CIL	95CIU
Internal fixation (initial)	DRG	218	HCUPnet Nationwide Inpatient Sample	Hospital	12,914	12,482	13,345
	DRG	219	HCUPnet Nationwide Inpatient Sample	Hospital	9,164	8,729	9,598
	DRG	218+219	HCUPnet Nationwide Inpatient Sample	Hospital	11,487	11,055	11,920
	CPT	27759	CMS National Payment Amount-Physician Fee Schedule	Physician	959	941	976
				Hosp+MD	12,446	11,996	12,896
BMP (initial)			Polly et al. (2003), Glassman et al. (2008)	Supplier	3,000	1,000	5,000
Bone graft (secondary)	CPT	20900	CMS Outpatient Prospective Payment System	Hospital	3,941	3,763	4,119
	CPT	20900	CMS National Payment Amount-Physician Fee Schedule	Physician	564	552	577
				Hosp+MD	4,505	4,314	4,696
Exchange nailing (secondary)	CPT	27759	CMS Outpatient Prospective Payment System	Hospital	4,690	4,366	5,014
	CPT	27759	CMS National Payment Amount-Physician Fee Schedule	Physician	959	941	976
				Hosp+MD	5,648	5,307	5,990
Plate fixation (secondary)	CPT	27758	CMS Outpatient Prospective Payment System	Hospital	3,513	3,076	3,951
	CPT	27758	CMS National Payment Amount-Physician Fee Schedule	Physician	842	826	857
				Hosp+MD	4,355	3,902	4,808
Fibular osteotomy (secondary)	CPT	27707	CMS Outpatient Prospective Payment System	Hospital	2,023	1,873	2,173
	CPT	27707	CMS National Payment Amount-Physician Fee Schedule	Physician	373	366	381
				Hosp+MD	2,396	2,238	2,554
Bone transport (secondary)	CPT	20692	CMS Outpatient Prospective Payment System	Hospital	6,869	6,408	7,330
	CPT	20692	CMS National Payment Amount-Physician Fee Schedule	Physician	398	391	405
				Hosp+MD	7,267	6,799	7,735
Nail dynamization (secondary)	CPT	27750	CMS Outpatient Prospective Payment System	Hospital	159	130	189
	CPT	27750	CMS National Payment Amount-Physician Fee Schedule	Physician	310	303	317
				Hosp+MD	470	434	506
Internal fixation to brace (secondary)	CPT	27750	CMS Outpatient Prospective Payment System	Hospital	159	130	189
	CPT	27750	CMS National Payment Amount-Physician Fee Schedule	Physician	310	303	317
				Hosp+MD	470	434	506

Table 45. Procedure Code Descriptions for Cost Parameter Estimates, Open Tibial Fracture

Procedure Type	DRG Code	Description	CPT Code	Description
Initial	218	Lower extremity & humerus procedure except hip,foot,femur with complications or comorbidities	27759	Treatment of tibial shaft fracture (with or without fibular fracture) by intramedullary implant, with or without interlocking screws and/or cerclage
	219	Lower extremity & humerus procedure except hip,foot,femur without complications or comorbidities		
Secondary: bone graft			20900	Bone graft, any donor area; minor or small (e.g., dowel or button)
Secondary: exchange nailing			27759	Treatment of tibial shaft fracture (with or without fibular fracture) by intramedullary implant, with or without interlocking screws and/or cerclage
Secondary: plate fixation			27758	Open treatment of tibial shaft fracture, (with or without fibular fracture) with plate/screws, with or without cerclage
Secondary: fibular osteotomy			27707	Osteotomy; fibula
Secondary: bone transport			20692	Application of a multiplane (pins or wires in more than 1 plane), unilateral, external fixation system (e.g., Ilizarov, Monticelli type)
Secondary: nail dynamization			27750	Closed treatment of tibial shaft fracture (with or without fibular fracture); without manipulation
Secondary: internal fixation to brace			27750	Closed treatment of tibial shaft fracture (with or without fibular fracture); without manipulation

Table 46. Calculation of Secondary Intervention Costs, Open Tibial Fracture

Table 46A. Costs of Secondary Intervention

Secondary Intervention	Mean	Lower	Upper
Mean most invasive	4,834	4,512	5,157
Mean less invasive	470	434	506

Table 46B. Secondary Intervention Rates, Treatment

Component	#	%
Treatment most invasive	12	40.0%
Treatment less invasive	18	60.0%
Total	30	

Table 46C. Weighted Average, Treatment

Weighted Average	Mean	Lower	Upper
Treatment	2,216	2,065	2,366

Table 46D. Secondary Intervention Rates, Control

Component	#	%
Control, most invasive	29	50.0%
Control, less invasive	29	50.0%
Total	58	

Table 46E. Weighted Average, Control

Weighted Average	Mean	Lower	Upper
Control weighted average	2,652	2,473	2,831

Table 47. Cost Parameter Estimates and Sources, Spinal Fusion

Procedure Type	Code Type	Code	Data Source	Cost Category	Mean	95CIL	95CIU
Spinal fusion (initial)	DRG	497	HCUPnet Nationwide Inpatient Sample	Hospital	29,104	27,823	30,385
	DRG	498	HCUPnet Nationwide Inpatient Sample	Hospital	23,997	22,993	25,000
	DRG	497+498	HCUPnet Nationwide Inpatient Sample	Hospital	27,071	25,901	28,242
	CPT	22558	CMS National Payment Amount-Physician Fee Schedule	Physician	1,410	1,386	1,433
				Hosp+MD	28,481	27,287	29,675
BMP (initial)			Polly et al. (2003 [ref 190]), Glassman et al. (2008 [ref 191])	Supplier	3,000	1,000	5,000
Reoperation (secondary)	DRG	497+498	HCUPnet Nationwide Inpatient Sample	Hospital	27,071	25,901	28,242
	CPT	22558	CMS National Payment Amount-Physician Fee Schedule	Physician	1,410	1,386	1,433
				Hosp+MD	28,481	27,287	29,675
Removal (secondary)	ICD-9-CM	78.69	HCUPnet Nationwide Inpatient Sample	Hospital	11,035	9,596	12,474
	CPT	22855	CMS National Payment Amount-Physician Fee Schedule	Physician	1,036	1,016	1,055
				Hosp+MD	12,071	10,612	13,530
Supplemental fixation (secondary)	ICD-9-CM	84.82	HCUPnet Nationwide Inpatient Sample	Hospital	24,117	18,375	29,860
	CPT	22840	CMS National Payment Amount-Physician Fee Schedule	Physician	764	750	778
				Hosp+MD	24,882	19,125	30,638
	ICD-9-CM	84.80	HCUPnet Nationwide Inpatient Sample	Hospital	11,974	10,831	13,118
	CPT	22840	CMS National Payment Amount-Physician Fee Schedule	Physician	764	750	778
				Hosp+MD	12,738	11,581	13,896

Table 48. Procedure Code Descriptions for Cost Parameter Estimates, Spinal Fusion

Procedure Type	DRG Code	Description	CPT Code	Description	ICD-9-CM Code	Description
Initial	497	Spinal fusion except cervical with complications or comorbidities	22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar		
	498	Spinal fusion except cervical without complications or comorbidities				
Secondary: reoperation	497	Spinal fusion except cervical with complications or comorbidities	22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar		
	498	Spinal fusion except cervical without complications or comorbidities				
Secondary: removal			22855	Removal of anterior instrumentation	78.69	Removal of implanted devices from bone, other (vertebrae)
Secondary: supplemental Instrumenta-tion			22840	Posterior non-segmental instrumentation (e.g., Harrington rod technique, pedicle fixation across one interspace, atlantoaxial transarticular screw fixation, sublaminar wiring at C1, facet screw fixation)	84.82	Insertion or replacement of pedicle-based dynamic stabilization device(s)

Table 49. Calculation of Secondary Intervention Costs, Spinal Fusion

Table 49A. Costs of Secondary Intervention

Secondary Intervention	Mean	Lower	Upper
Mean supplemental fixation	18,810	15,353	22,267

Table 49B. Secondary Intervention Rates, Treatment

Component	#	%
Treatment removal	2	11.1%
Treatment supplemental fixation	10	55.6%
Treatment reoperation	6	33.3%
Total	18	

Table 49C. Weighted Average, Treatment

Weighted Average	Mean	Lower	Upper
Treatment	21,285	18,804	23,765

Table 49D. Secondary Intervention Rates, Control

	#	%
Control removal	0	0.0%
Control supplemental fixation	14	77.8%
Control reoperation	4	22.2%
Total	18	

Table 49E. Weighted Average, Control

Weighted Average	Mean	Lower	Upper
Control weighted average	20,959	18,005	23,913

CEA Results

Open Tibial Fracture

The base case analysis (Table 50), with all parameters at mean or middle values, yields a cost saving for BMP over control of $612 and a gain of 0.048 QALYs, making BMP a dominant strategy. The total cost for 52 weeks is $12,938 for treatment and $13,552 for control. Total QALYs is 0.742 for the treatment group and 0.694 QALYs for the control group. Cost savings is due to the lower probability of secondary intervention in the treatment group and higher QALYs is due to the higher treatment group transition rate from preunion to union. It should be noted that the base case analysis assumes that the cost of BMP does not add to the overall DRG cost for the initial hospitalization, so initial costs for treatment and control groups are identical.

Table 50 also shows results of one-way sensitivity analyses. Adding a BMP value of $3,000 to costs results in a cost gain of $2,386 and an ICER of $49,204 per QALY gained. Lower and upper estimates of utilities produce smaller QALY differences favoring treatment, compared with the base case, but the cost savings is the same so BMP still dominates control. BMP-dominant results were also observed when analyses used lower and upper non-BMP costs and lower and upper secondary intervention costs. In both of these sets of analyses, the degree of cost savings and QALY differences were similar to the base case. When the lowest hazard ratio value for preunion is entered (0.99, favoring control), BMP is less cost-effective than control, as it less costly by $164 and results in a loss of 0.001 QALYs. If the hazard ratio for preunion is allowed to be higher than the base case, between-group differences in QALYs become greater: 0.074 when the hazard ratio is 2.62 and 0.098 when the hazard ratio is 3.61. Lower and upper values for the risk ratio of secondary intervention have a modest impact on results.

Table 51 shows the findings when BMP cost is added to two-way sensitivity analyses. For all analyses, the cost in the treatment group exceeds that for the control group. The middle BMP cost value of $3,000 is used in all but two of these analyses. Analyses on utilities, non-BMP costs, secondary intervention costs and risk ratio for secondary interventions produced ICERs in the range of $48,217 to $64,181 per QALY gained. The hazard ratio value for preunion had a strong impact on results. When the hazard ratio favors control, treatment is dominated. At an intermediate low hazard ratio, the ICER is $103,631 per QALY gained, while the highest hazard ratio yields an ICER of $24,471 per QALY gained. Cost of BMP also has a strong influence on results. When BMP is assumed to cost $1,000, the ICER is $7,960 per QALY gained, but when it takes a value of $5,000, the ICER is $90,449 per QALY gained. At an extreme high value of $8,000 for BMP, the ICER becomes $152,317 per QALY gained.

Three-way sensitivity analyses are presented in Table 52. When the cost of BMP is assumed to be $1,000, the BMP strategy is cost-effective in all cases except when the hazard ratio of preunion favors control, resulting in lower cost and lower QALYs. The ICERs for all other analyses were between $3,958 and $12,532 per QALY gained. When BMP is assumed to cost $5,000, ICERs are consistently higher. Excluding analyses on the hazard ratio for preunion, ICERs range from $89,598 to $117,979 per QALY gained. When the cost of BMP is assumed to take an extreme high value ($8,000), ICERs for analyses other than those for the hazard ratio of preunion were between $151,465 and $198,677 per QALY gained.

Table 50. Cost-Effectiveness Analysis Results, Base Case and One-Way Sensitivity Analyses, Open Tibial Fracture

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
Base case	12,938	13,552	-614	0.742	0.694	0.048	dominant
BMP added to costs	15,938	13,552	2,386	0.742	0.694	0.048	49,204
Lower utilities	12,938	13,552	-614	0.559	0.522	0.037	dominant
Upper utilities	12,938	13,552	-614	0.864	0.825	0.039	dominant
Lower non-BMP costs	12,455	13,028	-573	0.742	0.694	0.048	dominant
Upper non-BMP costs	13,422	14,077	-655	0.742	0.694	0.048	dominant
Lower secondary intervention costs	12,905	13,478	-573	0.742	0.694	0.048	dominant
Upper secondary intervention costs	12,972	13,627	-655	0.742	0.694	0.048	dominant
Lowest HR preunion	12,938	13,102	-164	0.693	0.694	-0.001	less CE
Low HR preunion	12,938	13,552	-614	0.717	0.694	0.023	dominant
High HR preunion	12,938	13,552	-614	0.768	0.694	0.074	dominant
Highest HR preunion	12,938	13,552	-614	0.791	0.694	0.098	dominant
Lower secondary intervention RR	12,785	13,552	-767	0.742	0.696	0.046	dominant
Upper secondary intervention RR	13,160	13,552	-392	0.742	0.694	0.048	dominant

Abbreviations: Ctrl: control; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

Table 51. Cost-Effectiveness Analysis Results, Two-Way Sensitivity Analysis, BMP Cost Added, Open Tibial Fracture

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
BMP added, lower utilities	15,938	13,552	2,386	0.559	0.522	0.037	64,181
BMP added, upper utilities	15,938	13,552	2,386	0.864	0.825	0.039	61,500
BMP added, lower non-BMP costs	15,455	13,028	2,427	0.742	0.694	0.048	50,056
BMP added, upper non-BMP costs	16,422	14,077	2,345	0.742	0.694	0.048	48,353
BMP added, lower secondary intervention costs	15,905	13,478	2,427	0.742	0.694	0.048	50,056
BMP added, upper secondary intervention costs	15,972	13,627	2,345	0.742	0.694	0.048	48,353
BMP added, lowest HR preunion	15,938	13,552	2,386	0.693	0.694	-0.001	dominated
BMP added, low HR preunion	15,938	13,552	2,386	0.717	0.694	0.023	103,631
BMP added, high HR preunion	15,938	13,552	2,386	0.768	0.694	0.074	32,151
BMP added, highest HR preunion	15,938	13,552	2,386	0.791	0.694	0.098	24,471
BMP added, lower secondary intervention RR	15,785	13,552	2,233	0.742	0.696	0.046	48,217
BMP added, upper secondary intervention RR	16,160	13,552	2,608	0.742	0.694	0.048	53,780
BMP added, lower BMP costs	13,938	13,552	386	0.742	0.694	0.048	7,960
BMP added, upper BMP costs	17,938	13,552	4,386	0.742	0.694	0.048	90,449
BMP added, extreme high BMP costs	20,938	13,552	7,386	0.742	0.694	0.048	152,317

Abbreviations: Ctrl: control; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

Table 52. Cost-Effectiveness Analysis Results, Three-Way Sensitivity Analysis, BMP Cost Added, BMP Cost Levels, Open Tibial Fracture

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	TxQALY	CtrlQALY	Tx-Ctrl QALY	ICER
BMP added, lower BMP costs, lower utilities	13,938	13,552	386	0.559	0.522	0.037	10,382
BMP added, lower BMP costs, upper utilities	13,938	13,552	386	0.864	0.825	0.039	9,949
BMP added, lower BMP costs, lower non-BMP costs	13,455	13,028	427	0.742	0.694	0.048	8,811
BMP added, lower BMP costs, upper non-BMP costs	14,422	14,077	345	0.742	0.694	0.048	7,108
BMP added, lower BMP costs, lower secondary intervention costs	13,905	13,478	427	0.742	0.694	0.048	8,811
BMP added, lower BMP costs, upper secondary intervention costs	13,972	13,627	345	0.742	0.694	0.048	7,108
BMP added, lower BMP costs, lowest HR preunion	13,938	13,552	386	0.693	0.694	-0.001	dominated
BMP added, lower BMP costs, lowest HR preunion	12,938	13,552	-614	0.693	0.694	-0.001	less CE
BMP added, lower BMP costs, low HR preunion	13,938	13,552	386	0.717	0.694	0.023	16,771
BMP added, lower BMP costs, high HR preunion	13,938	13,552	386	0.768	0.694	0.074	5,201
BMP added, lower BMP costs, highest HR preunion	13,938	13,552	386	0.791	0.694	0.098	3,958
BMP added, lower BMP costs, lower secondary intervention RR	13,785	13,552	233	0.742	0.696	0.046	5,033
BMP added, lower BMP costs, upper secondary intervention RR	14,160	13,552	608	0.742	0.694	0.048	12,532
BMP added, upper BMP costs, lower utilities	17,938	13,552	4,386	0.559	0.522	0.037	117,979
BMP added, upper BMP costs, upper utilities	17,938	13,552	4,386	0.864	0.825	0.039	113,052
BMP added, upper BMP costs, lower non-BMP costs	17,455	13,028	4,427	0.742	0.694	0.048	91,301
BMP added, upper BMP costs, upper non-BMP costs	18,422	14,077	4,345	0.742	0.694	0.048	89,598
BMP added, upper BMP costs, lower secondary intervention costs	17,905	13,478	4,427	0.742	0.694	0.048	91,301
BMP added, upper BMP costs, upper secondary intervention costs	17,972	13,627	4,345	0.742	0.694	0.048	89,598
BMP added, upper BMP costs, lowest HR preunion	17,938	13,552	4,386	0.693	0.694	-0.001	dominated
BMP added, upper BMP costs, low HR preunion	17,938	13,552	4,386	0.717	0.694	0.023	190,491
BMP added, upper BMP costs, high HR preunion	17,938	13,552	4,386	0.768	0.694	0.074	59,101
BMP added, upper BMP costs, highest HR preunion	17,938	13,552	4,386	0.791	0.694	0.098	44,983
BMP added, upper BMP costs, lower secondary intervention RR	17,785	13,552	4,233	0.742	0.696	0.046	91,401
BMP added, upper BMP costs, upper secondary intervention RR	18,160	13,552	4,608	0.742	0.694	0.048	95,029

Table 52. Cost-Effectiveness Analysis Results, Three-Way Sensitivity Analysis, BMP Cost Added, BMP Cost Levels, Open Tibial Fracture (continued)

	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	TxQALY	CtrlQALY	Tx-Ctrl QALY	ICER
BMP added, extreme high BMP costs, lower utilities	20,938	13,552	7,386	0.559	0.522	0.037	198,677
BMP added, extreme high BMP costs, upper utilities	20,938	13,552	7,386	0.864	0.825	0.039	190,380
BMP added, extreme high BMP costs, lower non-BMP costs	20,455	13,028	7,427	0.742	0.694	0.048	153,168
BMP added, extreme high BMP costs, upper non-BMP costs	21,422	14,077	7,345	0.742	0.694	0.048	151,465
BMP added, extreme high BMP costs, lower 2^{o} interv costs	20,905	13,478	7,427	0.742	0.694	0.048	153,168
BMP added, extreme high BMP costs, upper 2^{o} interv costs	20,972	13,627	7,345	0.742	0.694	0.048	151,465
BMP added, extreme high BMP costs, lowest HR preunion	20,938	13,552	7,386	0.693	0.694	-0.001	dominated
BMP added, extreme high BMP costs, low HR preunion	20,938	13,552	7,386	0.717	0.694	0.023	320,780
BMP added, extreme high BMP costs, high HR preunion	20,938	13,552	7,386	0.768	0.694	0.074	99,525
BMP added, extreme high BMP costs, highest HR preunion	20,938	13,552	7,386	0.791	0.694	0.098	75,751
BMP added, extreme high BMP costs, lower 2^{o} interv RR	20,785	13,552	7,233	0.742	0.696	0.046	156,176
BMP added, extreme high BMP costs, upper 2^{o} interv RR	21,160	13,552	7,608	0.742	0.694	0.048	156,902

Abbreviations: Ctrl: control; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

Spinal Fusion

Table 53 shows base case and one-way sensitivity analysis results. For the base, case, all parameters were set at mean or middle values, yielding a cost saving for BMP over control of $94 and an increase in QALYs of 0.024, making BMP the dominant strategy over control. Over 104 weeks, the total cost for the treatment group was $31,159, compared with $31,253 for control. Total QALYs was 1.218 in the treatment group and 1.194 in the control group. Lower cost in the treatment group was due to the slightly lower probability of secondary intervention in the treatment group. Higher QALYs are attributable primarily to the disutility of DSP in the control group. Base case analysis assumes that BMP costs are bundled into DRG payments, so initial hospitalization costs are the same in treatment and control groups.

One-way sensitivity analyses are also shown in Table 53. Again, BMP cost is excluded from treatment group costs except in one of these analyses. When BMP is assumed to be an added cost of $3,000, the total cost in the treatment group rises to $34,159, resulting in a cost excess for the treatment group of $2,906 and an ICER or $121,160 per QALY gained. BMP is the dominant strategy in all other one-way sensitivity analyses except one. When the upper value of the risk ratio for secondary intervention is entered, the cost difference between strategies is $2,153 and the ICER is $89,765 per QALY gained.

Table 54 shows two-way sensitivity analyses defined by adding BMP to treatment group costs. In all but two instances, the middle value for BMP cost of $3,000 is used. Among analyses using the $3,000 amount, when the disutility of donor-site pain is assumed to be larger (a decrement of 0.05) than the base case value (0.02), the lowest ICER is observed: $56,959 per QALY gained. Other analyses using the $3,000 value produce results for the ICER between $70,467 and $214,834 per QALY gained. If BMP cost is assumed to be $1,000, the ICER is $37,785 per QALY gained, in contrast to a result of $204,536 per QALY gained when the cost is $5,000 and $329,599 per QALY gained when the cost is $8,000.

Three-way sensitivity analyses on the level of BMP cost are presented in Table 55. Among analyses assuming a BMP cost of $1,000, the most influential variable was the risk ratio of secondary intervention. At the low risk ratio value of 0.52 (favoring the treatment group), the treatment group strategy is dominant, but at the high value of 1.75 (favoring the control group), the ICER is $131,455 per QALY gained. All other sensitivity analyses with the $1,000 BMP amount produce ICERs between $17,763 and $50,557 per QALY gained. When BMP is assumed to cost $5,000, the BMP strategy becomes much less cost-effective. ICERs are between $96,155 (larger DSP disutility) and $298,213 per QALY gained (upper risk ratio for secondary intervention). At an extreme high value of $8,000 for the cost of BMP, ICERs range between $154,948 and $443,385 per QALY gained.

Key Question 9, Discussion and Conclusion

The use of the Medicare DRG payment system in the initial hospitalization of open tibial fracture and spinal fusion patients presents a challenge for interpreting the cost-effectiveness analyses presented here. Base case and one-way sensitivity analyses largely assume that BMP cost is bundled into the DRG payment. Based on this assumption, initial costs were identical for treatment and control groups, forcing results that use of BMP is a dominant strategy. A more plausible assumption may be that DRG payments for patients receiving BMP will be higher than

Table 53. Cost-Effectiveness Analysis Results, Base Case and One-Way Sensitivity Analyses, Spinal Fusion

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
Base case	31,159	31,253	-94	1.218	1.194	0.024	dominant
BMP added to costs	34,159	31,253	2,906	1.218	1.194	0.024	121,160
Lower utilities	31,159	31,253	-94	0.924	0.901	0.022	dominant
Upper utilities	31,159	31,253	-94	1.533	1.498	0.034	dominant
Large DSP disutility	31,159	31,253	-94	1.218	1.167	0.051	dominant
Lower non-BMP costs	29,653	29,668	-15	1.218	1.194	0.024	dominant
Upper non-BMP costs	32,665	32,837	-172	1.218	1.194	0.024	dominant
Lower secondary intervention costs	30,847	30,862	-15	1.218	1.194	0.024	dominant
Upper secondary intervention costs	31,471	31,644	-172	1.218	1.194	0.024	dominant
Lowest prefusion HR	31,159	31,253	-94	1.212	1.194	0.018	dominant
Low prefusion HR	31,159	31,253	-94	1.216	1.194	0.021	dominant
High prefusion HR	31,159	31,253	-94	1.221	1.194	0.026	dominant
Highest prefusion HR	31,159	31,253	-94	1.223	1.194	0.028	dominant
Lower secondary intervention RR	29,943	31,253	-1,310	1.218	1.194	0.024	dominant
Upper secondary intervention RR	33,406	31,253	2,153	1.218	1.194	0.024	89,765
Lower DSP risk	31,159	31,253	-94	1.218	1.198	0.020	dominant
Upper DSP risk	31,159	31,253	-94	1.218	1.190	0.028	dominant

Abbreviations: Ctrl: control; DSP: donor-site pain; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

Table 54. Cost-Effectiveness Analysis Results, Two-Way Sensitivity Analysis, BMP Cost Added, Spinal Fusion

	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
BMP added, lower utilities	34,159	31,253	2,906	0.924	0.901	0.022	129,188
BMP added, upper utilities	34,159	31,253	2,906	1.533	1.498	0.034	84,264
BMP added, larger DSP disutility	34,159	31,253	2,906	1.218	1.167	0.051	56,959
BMP added, lower non-BMP costs	32,653	29,668	2,985	1.218	1.194	0.024	124,435
BMP added, upper non-BMP costs	35,665	32,837	2,828	1.218	1.194	0.024	117,885
BMP added, lower secondary intervention costs	33,847	30,862	2,985	1.218	1.194	0.024	124,435
BMP added, upper secondary intervention costs	34,471	31,644	2,828	1.218	1.194	0.024	117,885
BMP added, lowest prefusion HR	34,159	31,253	2,906	1.212	1.194	0.018	162,994
BMP added, low prefusion HR	34,159	31,253	2,906	1.216	1.194	0.021	136,953
BMP added, high prefusion HR	34,159	31,253	2,906	1.221	1.194	0.026	110,479
BMP added, highest prefusion HR	34,159	31,253	2,906	1.223	1.194	0.028	103,079
BMP added, lower secondary intervention RR	32,943	31,253	1,690	1.218	1.194	0.024	70,467
BMP added, upper secondary intervention costs RR	36,406	31,253	5,153	1.218	1.194	0.024	214,834
BMP added, lower DSP risk	34,159	31,253	2,906	1.218	1.198	0.020	144,827
BMP added, upper DSP risk	34,159	31,253	2,906	1.218	1.190	0.028	104,142
BMP added, lower BMP	32,159	31,253	906	1.218	1.194	0.024	37,785
BMP added, upper BMP	36,159	31,253	4,906	1.218	1.194	0.024	204,536
BMP added, extreme high BMP	39,159	31,253	7,906	1.218	1.194	0.024	329,599

Abbreviations: Ctrl: control; DSP: donor-site pain; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

Table 55. Cost-Effectiveness Analysis Results, Three-Way Sensitivity Analysis, BMP Cost Added, BMP Cost Levels, Spinal Fusion

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
BMP added, lower BMP costs, lower utilities	32,159	31,253	906	0.924	0.901	0.022	40,288
BMP added, lower BMP costs, upper utilities	32,159	31,253	906	1.533	1.498	0.034	26,279
BMP added, lower BMP costs, larger DSP disutility	32,159	31,253	906	1.218	1.167	0.051	17,763
BMP added, lower BMP costs, lower non-BMP costs	30,653	29,668	985	1.218	1.194	0.024	41,060
BMP added, lower BMP costs, upper non-BMP costs	33,665	32,837	828	1.218	1.194	0.024	34,510
BMP added, lower BMP costs, lower secondary intervention costs	31,847	30,862	985	1.218	1.194	0.024	41,060
BMP added, lower BMP costs, upper secondary intervention costs	32,471	31,644	828	1.218	1.194	0.024	34,510
BMP added, lower BMP costs, lowest HR prefusion	32,159	31,253	906	1.212	1.194	0.018	50,838
BMP added, lower BMP costs, low HR prefusion	32,159	31,253	906	1.216	1.194	0.021	42,691
BMP added, lower BMP costs, high HR prefusion	32,159	31,253	906	1.221	1.194	0.026	34,437
BMP added, lower BMP costs, highest HR prefusion	32,159	31,253	906	1.223	1.194	0.028	32,138
BMP added, lower BMP costs, lower secondary intervention RR	30,943	31,253	-310	1.218	1.194	0.024	dominant
BMP added, lower BMP costs, upper secondary intervention RR	34,406	31,253	3,153	1.218	1.194	0.024	131,455
BMP added, lower BMP costs, lower DSP risk	32,159	31,253	906	1.218	1.198	0.020	45,165
BMP added, lower BMP costs, upper DSP risk	32,159	31,253	906	1.218	1.190	0.028	32,477

Table 55. Cost-Effectiveness Analysis Results, Three-Way Sensitivity Analysis, BMP Cost Added, BMP Cost Levels, Spinal Fusion (continued)

Analyses	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
BMP added, upper BMP costs, lower utilities	36,159	31,253	4,906	0.924	0.901	0.022	218,088
BMP added, upper BMP costs, upper utilities	36,159	31,253	4,906	1.533	1.498	0.034	142,250
BMP added, upper BMP costs, larger DSP disutility	36,159	31,253	4,906	1.218	1.167	0.051	96,155
BMP added, upper BMP costs, lower non-BMP costs	34,653	29,668	4,985	1.218	1.194	0.024	207,810
BMP added, upper BMP costs, upper non-BMP costs	37,665	32,837	4,828	1.218	1.194	0.024	201,261
BMP added, upper BMP costs, lower secondary intervention costs	35,847	30,862	4,985	1.218	1.194	0.024	207,810
BMP added, upper BMP costs, upper secondary intervention costs	36,471	31,644	4,828	1.218	1.194	0.024	201,261
BMP added, upper BMP costs, lowest HR prefusion	36,159	31,253	4,906	1.212	1.194	0.018	275,150
BMP added, upper BMP costs, low HR prefusion	36,159	31,253	4,906	1.216	1.194	0.021	231,215
BMP added, upper BMP costs, high HR prefusion	36,159	31,253	4,906	1.221	1.194	0.026	186,521
BMP added, upper BMP costs, highest HR prefusion	36,159	31,253	4,906	1.223	1.194	0.028	174,020
BMP added, upper BMP costs, lower secondary intervention RR	34,943	31,253	3,690	1.218	1.194	0.024	153,841
BMP added, upper BMP costs, upper secondary intervention RR	38,406	31,253	7,153	1.218	1.194	0.024	298,213
BMP added, upper BMP costs, lower DSP risk	36,159	31,253	4,906	1.218	1.198	0.020	244,489
BMP added, upper BMP costs, upper DSP risk	36,159	31,253	4,906	1.218	1.190	0.028	175,806

Table 55. Cost-Effectiveness Analysis Results, Three-Way Sensitivity Analysis, BMP Cost Added, BMP Cost Levels, Spinal Fusion (continued)

	Tx Cost	Ctrl Cost	Tx-Ctrl Cost	Tx QALY	Ctrl QALY	Tx-Ctrl QALY	ICER
BMP added, extreme high BMP costs, lower utilities	39,159	31,253	7,906	0.924	0.901	0.022	351,437
BMP added, extreme high BMP costs, upper utilities	39,159	31,253	7,906	1.533	1.498	0.034	229,229
BMP added, extreme high BMP costs, larger DSP disutility	39,159	31,253	7,906	1.218	1.167	0.051	154,948
BMP added, extreme high BMP costs, lower non-BMP costs	37,653	29,668	7,985	1.218	1.194	0.024	332,874
BMP added, extreme high BMP costs, upper non-BMP costs	40,665	32,837	7,828	1.218	1.194	0.024	326,324
BMP added, extreme high BMP costs, lower 2^{o} interv costs	38,847	30,862	7,985	1.218	1.194	0.024	332,874
BMP added, extreme high BMP costs, upper 2^{o} interv costs	39,471	31,644	7,828	1.218	1.194	0.024	326,324
BMP added, extreme high BMP costs, lowest HR prefusion	39,159	31,253	7,906	1.212	1.194	0.018	443,385
BMP added, extreme high BMP costs, low HR prefusion	39,159	31,253	7,906	1.216	1.194	0.021	372,609
BMP added, extreme high BMP costs, high HR prefusion	39,159	31,253	7,906	1.221	1.194	0.026	300,584
BMP added, extreme high BMP costs, highest HR prefusion	39,159	31,253	7,906	1.223	1.194	0.028	280,432
BMP added, extreme high BMP costs, lower 2^{o} interv RR	37,943	31,253	6,690	1.218	1.194	0.024	278,901
BMP added, extreme high BMP costs, upper 2^{o} interv RR	41,406	31,253	10,153	1.218	1.194	0.024	423,281
BMP added, extreme high BMP costs, lower DSP risk	39,159	31,253	7,906	1.218	1.198	0.020	393,981
BMP added, extreme high BMP costs, upper DSP risk	39,159	31,253	7,906	1.218	1.190	0.028	283,302

Abbreviations: Ctrl: control; DSP: donor-site pain; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; Tx: treatment;

DRGs for patients treated without it, for example, using additional outlier payments. Thus, emphasis should be placed on this report's analyses that assume added BMP costs (at amounts of $1,000, $3,000, $5,000 and $8,000).

Table 56. Summary Table of Open Tibial Fracture Cost-Effectiveness Analysis Results

BMP Cost	Mean ICER*	Restricted Range of ICERs**
$1,000	7,960	5,201–16,771
$3,000	49,204	24,471–64,181
$5,000	90,449	59,101–190,491
$8,000	152,317	99,525–198,677

*ICER values are treatment minus control difference in cost in US$ divided by difference in QALYs (dollar amount needed to gain one extra QALY by choosing treatment over control).
**The range of ICERs across sensitivity analyses excluded the lowest and highest hazard ratios for preunion.

Analyses of open tibial fracture consistently found higher quantities of QALYs and higher costs for the group receiving BMP. Differences in QALYs between treatment and control are largely attributable to the faster rate of achieving union in the treatment group. The summary table above shows that the ICER for choosing treatment over control is very sensitive to the added cost of BMP. These data exclude the lowest and highest values of the hazard ratio for preunion, which also had a strong influence on results.

Table 57. Summary Table of Spinal Fusion Cost-Effectiveness Analysis Results

BMP Cost	Mean ICER	Restricted Range of ICERs***
$1,000	37,785	17,763–50,557
$3,000	121,160	56,959–162,714
$5,000	204,536	96,155–274,870
$8,000	329,599	154,948–443,385

***The range of ICERs across sensitivity analyses excluding the lower and upper risk ratios for secondary intervention.

Spinal fusion analyses also found that the group treated with BMP had higher QALYs and higher costs. However, compared with open tibial fracture, the QALY difference was generally smaller and the cost difference greater, accounting for less favorable ICERs. Differences in QALYs were largely attributable to the disutility of DSP in the control group. Results in the summary table above show that ICERs were very sensitive to the assumed added cost of BMP. The results exclude the lower and upper values of this risk ratio for secondary intervention, a variable that was very influential on results.

A key strength of these cost-effectiveness analyses is the use of Markov models, explicitly taking into account changes in health states over time, in contrast with than simpler modeling techniques. Another strength is the use of area calibration sources, facilitated by short time horizons, which allowed modeled time in health states to precisely match estimates of observed time. In the spinal fusion analyses, one strength was inclusion of states in which patients experienced donor site pain.

One limitation of these analyses is the use of free publicly available cost estimates. While more limited access cost sources may provide more accurate cost estimates, it is unlikely that they would have a substantial impact on the results of these analyses. Another limitation is the exclusion of health state and cost estimates for infection in the open tibial fracture analyses. While the BESTT trial reported significantly lower infection rates for BMP patients, no data were given about the distribution of durations of infection, so the Markov model used here did

not include it. There was a limited evidence base for both open tibial fracture and spinal fusion, each consisting of a single randomized controlled trial. Biases may have existed in the source studies, for example possibly biased assessment of outcomes would result in inaccurate transition probabilities. Probabilistic sensitivity analyses were not performed, but would be unlikely to affect the interpretation of these analyses' findings.

The results of these cost-effectiveness analyses are consistent with finding of this technology assessment's systematic review. Preceding discussion of the effects of rhBMP2 in on-label treatment of acute open tibial shaft fracture concludes evidence is moderate that healing is enhanced and need for secondary intervention is reduced, and these outcomes are reflected in QALY differences captured in the Markov model. Evidence is also moderate for on-label lumbar spinal fusion consistently showing similar and possibly better frequency of fusion and avoidance of bone graft harvest adverse events. The spinal fusion cost-effectiveness analysis relies primarily in the effectiveness component results on the avoidance of bone graft donor site pain.

Key Question 10

What is the age distribution of study patients compared to the Medicare population (age 65 and older)?

The age range of study populations in the comparative studies compiled in this assessment is abstracted in detail in Appendix 1 Table C (on-label studies) and Appendix 1 Table D (off-label studies).

Among all studies the mean reported age was typically in the mid- to upper-50 years range. The lowest mean age for a group of patients in any study arm was 16 years for patients who underwent surgery to repair unilateral cleft lip with an alveolar cleft defect.[91] The highest mean age reported for any group was 70 years for patients who underwent posterolateral lumbar spinal fusion.[87] Considering all patients in comparative studies, individual ages ranged from a minimum 16 years to a maximum 87 years.[74] Among 28 comparative studies compiled in this assessment, 9 reported the proportion of patients who were at least 65 years old, which ranged from 0 percent[82,91,92,96] to 50 percent.[94]

What are the considerations in generalizing evidence from trials to the age 65 and older Medicare populations (such as comorbid conditions in the Medicare population and this population's susceptibility to adverse events).

A randomized trial performed by Glassman and colleagues[87] is the study identified as most relevant to the age 65 years and older Medicare population. All patients in the trial underwent a lumbar spinal fusion, were older than 60 years, with mean age 69 +/- 6 years in rhBMP2 recipients and 70 +/- 6 years in ICBG recipients.

The radiographic fusion success rate at 24 months (Table 58) was numerically larger with rhBMP2 than autograft bone, but statistical significance was not reported. All other outcomes with autograft bone reported in the Glassman study[87] are similar to those achieved with rhBMP2. The patient characteristics in the Glassman study were not well described, nor were any comorbid conditions that could affect fusion outcomes in this age group. The investigators reported use of undefined bone graft extender or filler in 100 percent of BMP cases and 67

percent of ICBG cases, plus local bone shavings in 100% of cases in both groups. They also presented pooled outcome data from multilevel and single-level fusion patients.

Table 58. Clinical Outcomes in Off-Label Randomized Trial of rhBMP2 for Lumbar-Sacral Spinal Fusion in Medicare Age Patients

Study (ref no.)	Grp	No. Pts	BMP dose (mg/pt)	Radio-graphic fusion suc-cess 24 mos., %	ODI success 24 mos. %	ODI mean point score ↑ 24 mos.	Leg pain mean point score ↑ 24 mos.	SF-36 PCS mean point score ↑ 24 mos.	USPSTF study quality
Glassman et al., 2008 (87)	BMP2	50	8-12 (InFUSE)	86	NR	15	3.6	7	POOR
	ICBG	52	0	71	NR	13	3.1	7	

Abbreviations: ICBG: iliac crest bone graft; mos.: months; NR: not reported; ODI: Oswestry Disability Index; SF: short form;

The study by Glassman[87] illustrates the considerations relevant to generalizing from studies in the non-Medicare population. These include patient age and presence of comorbidities such as osteoporosis or diabetes. However in generalizing from available studies to the Medicare population, BMP dose and surgical methods should also be considered.

Summary and Conclusions

The electronic literature search for this assessment yielded 1,992 records, of which 1,738 were excluded at initial title and abstract review and 254 were retrieved for full text examination. Forty-one articles describing results of comparative studies were abstracted.

Overall, the frequency of reporting of power calculations and/or the adequacy of sample size in this literature is low. Among on-label studies, 4 of 13 (31%) had some level of reporting of power and/or sample size, while 2 of 28 (7%) off-label studies had some level of reporting of power and/or sample size. This finding is consistent with the generally fair to poor quality of comparative studies that comprise the evidence base for BMP efficacy and safety.

Table 59 summarizes the conclusions for each Key Question.

Key Questions	Conclusion
1. What is the evidence supporting improved outcomes with on-label* use of rhBMP2 (InFUSE®) for fusion of the lumbar-sacral spine? * Spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at 1 level from L2-S1	The strength of the body of evidence for improved outcomes with on-label use of rhBMP2 (InFUSE®) was graded as moderate. Two RCTs reported radiographic fusion outcomes to be similar to that of autograft bone. No significant adverse events were attributed to rhBMP2 in any study. However, the size and duration of the RCTs are not sufficient to precisely determine the frequency and severity of adverse events. Thus, the evidence gives moderate support to clinical benefit from the use of rhBMP2 as patients can avoid the additional procedure of autograft bone harvest and its associated adverse events.
2. What is the evidence supporting improved outcomes with on-label* use of rhBMP7 (OP-1®) for fusion in the lumbar spine? * Revision posterolateral lumbar spinal fusion	No comparative studies were identified for this Key Question. The strength of evidence is insufficient, thus no conclusions can be reached.
3. What is the evidence supporting improved outcomes with on-label* use of rhBMP7 (OP-1®) in recalcitrant long bone non-unions? ***** Alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed	There are two RCTs and one retrospective cohort study. The risk of bias in this evidence is high. In one RCT, the intervention arm was confounded by use of a mix of bone graft extenders, and it was unclear if radiographic outcomes were assessed independently. In the second RCT the BMP arm had higher risk for poor outcomes, and thus the effect of BMP could be underestimated. The third study was nonrandomized and thus had high risk of bias. Device-related harms are inconsistently reported in this literature. The strength of the body of evidence on radiographic fusion, pain, and function outcomes is low.
4. What is the evidence supporting improved outcomes with on-label* use of rhBMP2 (InFUSE®) for the treatment of acute, open shaft tibial fractures? ***** Acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. The device must be applied within 14 days after the initial fracture.	The main evidence is in one RCT (n=450) (BESTT) that compared two different doses of rhBMP2 versus standard of care. The RCT is supported by a combined subgroup analysis that pooled data from patients with Gustilo-Anderson type III fractures in BESTT with data from a second smaller unpublished RCT (n=60) with identical design. The strength of the body of evidence on clinical outcomes is moderate for on-label use of rhBMP2 to enhance bony fusion in acute open shaft fractures.

Key Questions	Conclusion
5. What is the level of evidence and summary of evidence for the on-label* use of rhBMP2 (InFUSE) for sinus augmentation? ***** Sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets	Three RCTs were identified in which rhBMP2 was used according to the FDA-approved marketing label in patients undergoing staged bilateral or unilateral maxillary sinus floor augmentation and extraction socket alveolar ridge augmentation procedures. The strength of the body of evidence is moderate that rhBMP2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone. However, there is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Key Questions	Conclusion
6. For which indications are there clinical studies in which BMP is used off-label? In such studies, what is the evidence of the effectiveness of BMP?	The strength of evidence for off-label uses was graded only for settings that had more than one comparative trial involving patients with bony defects sufficiently similar to allow synthesis. **Lumbar-Sacral Spine** **rhBMP2** There are six randomized and five nonrandomized comparative studies of off-label use of rhBMP2 in fusion of the lumbar-sacral spine. The two largest RCTs were rated "fair" and are given greatest weight in this review of evidence. Among all six RCTs, interstudy variables included rhBMP2 dose, surgical approach, carrier matrix formulation, and interbody devices. Despite the use of different surgical approaches and unapproved formulations and instrumentation, the strength of evidence that rhBMP2 improves radiographic fusion success is moderate. No conclusions can be drawn regarding the potential impact of the off-label components on radiographic fusion success. The strength of evidence that rhBMP2 improves other outcomes is low. **rhBMP7** The best available evidence for the efficacy of rhBMP7 used off-label for lumbar spinal fusion comes from one randomized trial. There are three additional small, poor quality trials. The evidence is insufficient to draw conclusions on the off-label use of rhBMP7 in fusion of the lumbar-sacral spine. **Cervical Spine** **rhBMP2** The evidence consists of one randomized trial and four nonrandomized comparative studies of off-label use of rhBMP2 for cervical spinal fusion. Two small studies, a randomized trial and a nonrandomized comparative study, reported on radiographic fusion success and changes in mean neck disability scores. The other 3 nonrandomized studies focused mainly on complications. There is moderate evidence that off-label use of rhBMP2 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. There are 10 additional off-label uses, each with a single small study, most rated as poor quality. There is insufficient evidence to draw conclusions about any of these off-label uses.

Key Questions	Conclusion
7. What is the evidence of adverse events with (a) on-label use of BMP and (b) off-label use of BMP? And, at what dosage and administration do such adverse events occur?	Overall the evidence on BMP-specific harms is insufficient to draw conclusions in most settings. There is moderate evidence that off-label use of rhBMP2 in anterior cervical spinal fusion increases cervical swelling and related complications. The body of evidence suggests that autograft bone harvest is associated with pain at the harvest site, but it is not possible to systematically assess the frequency, duration, and clinical significance. Overall, autograft harms were inconsistently reported. It is not clear that the absence of reported harms in many studies reflects true absence, or whether the investigators did not seek such data or did not report it.
8. What is the quality of reporting of adverse events in publications? Provide summary to support conclusion.	BMP-specific harms in comparative studies were assessed using a modification of the McHarms survey. The quality of reporting in the 41 comparative studies reviewed in this assessment 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 also is 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.

Key Questions	Conclusion
9. What is the incremental cost effectiveness of the use of BMP for spinal fusion and tibial fracture?	The incremental cost-effectiveness ratios (ICERs) for both open tibial fracture and spinal fusion are highly influenced by the assumed added cost of rhBMP2. **Open Tibial Fracture** Assuming rhBMP-2 to be an added cost of $3,000, the ICER when all other variables were at mean or middle values was $49,204 per quality-adjusted life year (QALY) gained. Excluding the lowest and highest values for one influential variable, ICERs ranged between $24,471 and $64,181 per QALY gained. Assuming the cost of rhBMP2 to be $1,000 yields a mean ICER of $7,960 per QALY gained and a restricted range between $5,201 and $16,771 per QALY gained. When rhBMP2 is assumed to cost $5,000, rhBMP2 becomes much less cost-effective, with a mean ICER of $90,449 per QALY gained and a range of $59,101 to $190,491 per QALY gained. At a cost for rhBMP2 of $8,000, the mean ICER is $152,317 per QALY gained, with a range of $99,525 to $198,677 per QALY gained. As concluded in Key Question 4, of the effects of rhBMP2 in on-label treatment of acute open tibial shaft fracture, evidence is moderate that healing is enhanced and need for secondary intervention is reduced. These outcomes are reflected in QALY differences captured in the Markov model. **Spinal Fusion** Assuming that rhBMP2 was an added cost of $3,000, the ICER for all other variables at mean or middle value was $121,160 per QALY gained. Excluding the lower and upper values of one influential variable, the restricted range of ICERs was between $56,959 and $162,714 per QALY gained. At a cost of $1,000, the mean ICER is $37,785 per QALY gained and the range is between $17,763 and $50,557. If rhBMP2 is assumed to cost $5,000, the mean ICER is $204,536, and range is from $96,155 to $274,870 per QALY gained. When the cost of rhBMP2 is assumed to be $8,000, the mean ICER is $329,599 per QALY gained and the range is from $154,948 to $443,385 per QALY gained. As concluded in Key Question 1, of the effects of on-label lumbar spinal fusion, evidence is moderate, consistently showing similar and possibly better frequency of fusion and avoidance of bone graft harvest adverse events. The spinal fusion cost-effectiveness analysis relies primarily in the effectiveness component results on the avoidance of bone graft donor site pain.

Key Questions	Conclusion
10. What is the age distribution of study patients compared to the Medicare population (age 65 and older)? What are the considerations in generalizing evidence from trials to the age 65 and older Medicare populations (such as comorbid conditions in the Medicare population and this population's susceptibility to adverse events).	Among all studies the mean reported age was typically in the mid- to upper-50-years range. A randomized trial performed by Glassman and colleagues is the study identified as most relevant to the age 65 years and older Medicare population. The Glassman study does not specifically relate outcomes to age or comorbidities. The considerations relevant to generalizing from studies in the non-Medicare population include patient age, presence of comorbidities such as osteoporosis or diabetes. However, in generalizing from available studies to the Medicare population, BMP dose and surgical methods should also be considered.

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Appendix 1

Comparative Study Evidence Abstraction Tables

Appendix 1 Table A. On-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Surgical intervention	Inclusion/exclusion criteria	Outcomes measured	Duration of F/U (rng)	Withdrawal or loss to F/U (%)	USPSTF quality rating	Comment
Boden et al., 2000 USA (71) **Lumbar spine**	Multicenter, nonblinded RCT	rhBMP2 n=11 (4.2-8.4 mg/pt) ICBG n=3	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level anterior lumbar fusion, DDD, age 18-65 yrs, grade I spondylolisthesis, symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: spinal condition other than DDD, use of drugs that inhibit bone healing, osteopenia, BMI > 40%, tobacco use, endocrine bone disorder	Radiographic fusion using plain film radiographs and CT analysis, SF-36, Oswestry Low Back Pain Disability Index, neurological functional status, pain medication use, perioperative data, second surgeries, work status, complications and adverse events	24 mos.	0	FAIR	Pilot study using rhBMP2 soaked absorbable collagen sponges (ACS) as carrier inside tapered lumbar interbody fusion cages
Burkus et al., 2002 USA (72) **Lumbar spine**	Multicenter, nonblinded RCT	rhBMP2 n=143 (4.2-8.4 mg/pt) ICBG n=136	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level anterior lumbar fusion, DDD, symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: NR	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, neurologic functional status, back, leg and graft site pain numerical rating scales, perioperative	24 mos.	rhBMP2 20 (14%) ICBG 27 (20%)	FAIR	Pivotal trial using rhBMP2 soaked absorbable collagen sponges (ACS) as carrier inside tapered lumbar interbody fusion cages

					data, second surgeries, return to work, complications and adverse events				
Burkus et al., 2003 USA (182) **Lumbar spine** Note: may include pts in Burkus et al., 2003 (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR) ICBG n=402	single-level primary anterior lumbar fusion with interbody fusion cages	Same as Burkus et al., 2002 (72)	Radiographic fusion using plain film radiographs and CT analysis, SF-36, Oswestry Low Back Pain Disability Index, perioperative data, second surgeries, work status, complications and adverse events	24 mos.	rhBMP2 30 (11%) ICBG 75 (19%)	POOR	Analysis of combined data from 2 published studies (Burkus et al., 2002, [72], and Kleeman et al., 2001, [183]) plus unpublished data from a third study. rhBMP2 soaked absorbable collagen sponges (ACS)
Dawson et al., 2009 USA (73) **Lumbar spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level lumbar DDD, low back pain or radicular leg pain unresponsive to minimum 6 mos. nonoperative therapies, grade I or less spondylolisthesis Exclusion: NR	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, SF-36 physical component and physical function subscales, neurological functional status, back, leg and graft site pain numerical rating scales, perioperative data, second	24 mos.	rhBMP2/CRM 3 (12%) 1 death, 2 second-surgery failures ICBG 3 (14%) 1 pt without 24 mos. visit, 2 second-surgery failures	GOOD	Pilot study for Infuse/Mastergraft device,which has received FDA marketing approval Infuse/Mastergraft comprises rhBMP2, an osteoconductive, compression-resistant matrix (CRM) composed of 15% hydroxyapatite and 85% tricalcium phosphate ceramic bulking agent, plus

					surgeries, work status, complications and adverse events Overall success defined as combination of successful fusion, improvement in ODI score > 15%, absence of severe device-related adverse events, no second surgical procedure involving the index level, maintenance or improvement of neurological status				absorbable collagen sponge (ACS)
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multicenter, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	IM nail fixation and soft tissue management	Inclusion: Open tibial fracture of which the major component was diaphyseal.	Radiographic evidence of fracture fusion and full weight bearing and lack of tenderness at the fracture site on palpation. Failure was determined by a recommendation of secondary intervention by the investigators.	12 mos. (0-73 weeks)	(1) 9 (6%) (2) 8 (5%) (3) 12 (8%)	FAIR	rhBMP2 soaked absorbable collagen sponges (ACS)

Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	IM nail fixation and soft tissue management	Type III open tibial fractures and reamed IM nailing groups Had to complete full 12 months of follow-up in parent study.	Radiographic evidence of fracture fusion and full weight bearing and lack of tenderness at the fracture site on palpation.	12 mos.	0	FAIR	rhBMP2 soaked absorbable collagen sponges (ACS)
Boyne et al., 2005 USA (75) **Maxillofacial Defects**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18 rhBMP2/ACS (15-48 mg/pt) n=17 AGB n=13	staged bilateral or unilateral maxillary sinus floor augmentation	Inclusion: age 18 and older, inadequate alveolar bone height (< 6 mm confirmed on CT scan) in th epostedrior maxilla Exclusion: acute or chronic sinus disease or pathology, untreated periodontal disease, caries, or oral infection, onlay ridge augmentation to achieve adequate bone for endosseous dental implant placement, use of nicotine-containing product within 2 wks of surgery, pregnancy, insulin-dependent diabetes mellitus, medications or treatments	New bone formation sufficient for endosseous dental implant placement, dental implant success rate following functional loading, perioperative and device-related complications and adverse events	36 mos.	0	GOOD	Randomized dose-comparison and efficacy study of rhBMP2/ACS versus AGB with or without ALG

				known to affect bone turnover, disease affecting bone metabolism					
Fiorellini et al., 2005 USA (76) **Maxillofacial Defects**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22 rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	extraction socket augmentation	Inclusion: necessity for local alveolar ridge preservation or augmentation of buccal wall defects (≥ 50% buccal bone loss of the extraction socket) followng extraction of maxillary teeth (bicuspids forward) Exclusion: NR	Bone induction, bone volume for dental implant placement, bone density, adverse events and complications	4 mos.	0	FAIR	Randomized dose-comparison and efficacy study of rhBMP2/ACS versus placebo or no treatment
Triplett et al., 2009 USA (77) **Maxillofacial Defects**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	staged bilateral or unilateral maxillary sinus floor augmentation	Inclusion: age 18 and older, inadequate alveolar bone height (< 6 mm confirmed on CT scan) in the posterior maxilla Exclusion: acute or chronic sinus disease or pathology, untreated periodontal disease, caries, or oral infection, onlay ridge augmentation to achieve adequate bone for endosseous dental implant placement, history of cancer within 5 years (except basal cell	New bone formation sufficient for endosseous dental implant placement, dental implant success rate following functional loading, patient success, perioperative complications and device-related adverse events	24 mos.	9 (6)	GOOD	Randomized comparison of rhBMP2/ACS versus AGB with or without ALG

				or squamous cell carcinoma or in situ cervical cancer), use of nicotine-containing product within 3 wks of surgery, lactation, insulin-dependent diabetes mellitus, medications or treatments known to affect bone turnover (except estrogen/progesterone), disease affecting bone metabolism (excluding idiopathic osteoporosis), autoimmune disease, allergies to components of the device, prior exposure to components of the device, tetracycline allergy, plans to be treated with an investigational drug					
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial Defects**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	maxillary sinus floor augmentation	Inclusion: general good condition (excluding ASA class III and IV), age 18-60 years, inadequate native alveolar process and bone Exclusion: mental retardation, smoking, pregnancy, collagen allergy, diabetes mellitus, metabolic bone disease, cancer, rheumatoid arthritis or	New bone formation	6 mos.	0	POOR	Open label pilot study of rhBMP7/ACS

				other autoimmune disease, prior radiotherapy or immunosuppression, history of chronic paranasal sinus inflammation or Caldwell-Luc operations					
Calori et al., 2008 Italy (78) **Long Bone Nonunions**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	Inclusion: post-traumatic atrophic nonunion for ≥ 9 mos., with no signs of healing over the last 3 mos., considered as non-treatable only by means of fixation revision Exclusion: skeletal immaturity, insufficient skin to cover fracture site, systemic infection or infected nonunion, pathological fracture, autoimmune or active neoplastic disease, previous treatment with any growth factor, need for autologous bone graft	Radiographic fusion, pain-free weight-bearing or movement, perioperative complications	minimum 9 mos. mn 12 (9-43)	0	POOR	rhBMP7 (Osigraft, EU) was compared to platelet rich plasma (PRP), both interventions applied with or without adjuvant bone graft extender(s) such as homologous bone, xenograft, or composites such as hydroxyapatite
Dahabreh et al., 2008 UK, Italy (83) **Long Bone Nonunions**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7/ACS	Inclusion: patients who received ICBG or rhBMP7/ACS treatment to enhance healing following declaration of tibial fracture nonunion Exclusion: infected nonunion,	Radiographic fusion, painless full-weight bearing, perioperative complications, second surgeries	29-34 mos.	NR	POOR	rhBMP7 (Osigraft, EU) compared to ICBG in a retrospective cohort of patients selected for the cost study on the basis of successful treatment

			or ICBG	skeletal immaturity, presence of tumor, chronic debilitation, previous treatment of nonunion					
Friedlaender et al., 2001 USA (79) **Long Bone Nonunions**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	IM rod fixation with rhBMP7/ACS or AGB	Inclusion: tibial nonunion for ≥ 9 mos. with no signs of healing over previous 3 mos Exclusion: skeletal immaturity, unable to complete F/U, severely compromised soft-tissue coverage at nonunion site, pathological nonunions, radiation, chemotherapy, immunosuppressant or chronic steroid therapy, pregnancy or lactation, systemic or local infection at nonunion site, other investigational therapy, congenital or synovial tibial pseudarthrosis, neuropathy that interferes with walking or pain sensation, multiple nonunions other than tibia, autoimmune disease, immune sensitivity to collagen	Radiographic fusion, pain (none, mild, moderate, severe) at fracture site and ability to bear weight (none, partial or full), surgeon's satisfaction with healing, perioperative outcomes, adverse events	minimum 9 mos., up to 24 mos.	0	FAIR	IDE study for rhBMP7/ACS (OP-1) versus autograft bone (AGB) in treatment of tibial nonunions

Appendix 1 Table B. Off-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Surgical intervention	Inclusion/exclusion criteria	Outcomes measured	Duration of F/U (rng)	Withdrawal or loss to F/U (%)	USPSTF quality rating	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11 (40 mg/pt) rhBMP2/CRM alone n=11 (40 mg/pt) ICBG plus TSRHSS n=5	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	Inclusion: primary symptomatic single-level lumbar DDD, low back or leg pain unresponsive to minimum 6 mos. nonoperative therapies, grade I or less spondylolisthesis, 18 years or older, Oswestry DI score at least 30 Exclusion: prior fusion at index level, medications that interfere with fusion, scan-confirmed osteoporosis, autoimmune disease, prior exposure to BMP, endocrine disorders that affect osteogenesis,	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, SF-36 physical component subscale, neurological functional status, back, leg and graft site pain numerical rating scales, perioperative data, second surgeries, complications and adverse events	mean 17 mos (12-27 mos.)	rhBMP2/CRM alone 2 (18%) were found to have > grade I spondylolisthesis and were excluded from analysis	FAIR	IDE pilot study for device which has not received FDA marketing approval Pilot study of rhBMP2 plus an osteoconductive compression-resistant matrix (CRM) composed of 60% hydroxyapatite and 40% tricalcium phosphate bulking agent, plus absorbable collagen sponge (ACS)

				tumor, infection					
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt) ICBG N=52	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	Inclusion: radiographic documentation of primary symptomatic single-level lumbar DDD, age ≥ 18 years, spondylolisthesis grade ≤ 1, symptoms related to neuroradiographic findings unresponsive to minimum 6 mos. nonoperative therapies Exclusion: spinal conditions other than DDD, DDD at disc space levels other than L4-L5 or L5-S-1, previous anterior fusion at index level, obesity (> 40% above ideal wt), active bacterial infection, medication(s) that could interfere with fusion (e.g., steroids, NSAIDs)	Radiographic fusion based on plain film radiographs with use of anteroposterior, lateral, and flexion-extension views, 1-mm slice CT scans with coronal and sagittal reconstructions, Oswestry Low Back Pain Disability Index, SF-36 physical component subscale, back, leg and graft site pain numerical rating scales, work status perioperative data, second surgeries, complications and adverse events	24 mos	rhBMP2 3 (3.8%) ICBG 2 (3.8%)	FAIR	rhBMP2 soaked absorbable collagen sponges (ACS)

Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG n=224	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Inclusion: primary symptomatic single-level lumbar DDD, low back pain or radicular leg pain unresponsive to minimum 6 mos. nonoperative therapies, grade I or less spondylolisthesis, 18 years or older, Oswestry DI score at least 30 Exclusion: prior fusion at index level, medications that interfere with fusion, scan-confirmed osteoporosis, autoimmune disease, prior exposure to BMP or collagen, endocrine disorders that affect osteogenesis, tumor, infection, pregnancy, or inability to harvest bone graft	Radiographic fusion using plain film radiographs and CT analysis, Oswestry Low Back Pain Disability Index, SF-36 physical component subscale, neurological functional status, back, leg and graft site pain numerical rating scales, perioperative data, second surgeries, complications and adverse events	24 mos	rhBMP2/CRM 23 (9.6%) ICBG 30 (13%)	FAIR	IDE trial for AMPLIFY device, which has not received FDA marketing approval AMPLIFY comprises rhBMP2, an osteoconductive, compression-resistant matrix (CRM) composed of 15% hydroxyapatite and 85% tricalcium phosphate ceramic bulking agent plus absorbable collagen sponge (ACS)

Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	Inclusion: not explicitly delineated Exclusion: not explicitly delineated	Radiographic fusion based on plain film radiographs and 1-mm slice CT scans with coronal and sagittal reconstructions	mn 27 mos (24-38)	91 patients received rhBMP2, only 48 (53%) comparable to ICBG historical controls	POOR	ICBG historical control group taken from Glassman et al., 2005 (rec# 8040) rhBMP2 soaked absorbable collagen sponges (ACS)
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	single- or multi-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Inclusion: patients > 60 years, primary symptomatic lumbar DDD with spinal stenosis, spondylolisthesis, instability, adjacent level degeneration Exclusion: Not reported	Radiographic fusion based on 1-mm slice CT scans with coronal and sagittal reconstructions, Oswestry Low Back Pain DI, SF-36 physical component subscale, back and leg pain numerical rating scales	24 mos	106 enrolled, 100 (94%) available for 24 mos. F/U 4 excluded (2 from each arm) in perioperative period due to improper fusion level (1), fusion not performed (1), refusal to follow-up (1), cross-over (1), 2 died	POOR	All patients > 60 years old, but includes those with single- and multi-level DDD, with fusion performed according to each surgeon's preferences using the same instrumentation rhBMP2 soaked absorbable collagen sponges (ACS) Enrollment not strictly limited to Medicare population
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4) ICBG N=33	single-level primary posterior lumbar interbody fusion (PLIF) with interbody fusion cages plus rhBMP2 or ICBG	Inclusion: symptomatic, single-level lumbar DDD, grade I spondylolisthesis, with disabling low back or leg pain, unresponsive to minimum 6 mos.	Radiographic fusion based on plain film radiographs with lateral and flexion-extension views, and 1-mm slice CT scans, Oswestry Low Back Pain Disability Index,	24 mos	rhBMP2 4 (12%) ICBG 0	POOR	Trial was halted after preliminary CT scans showed bone growth posterior to the PLIF cages, and was not restarted

				nonoperative therapies Exclusion: NR	back, leg and graft site pain numerical rating scales, SF-36 physical component subscale, neurological status, work status perioperative data, second surgeries, complications and adverse events				
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Inclusion: radiographic evidence of lumbar DDD, L5 spondylolisthesis, maximal vertebral slip of 50%, intractable lumbosacral pain unresponsive to 6 mos. nonoperative therapies, no radiating leg pain, age > 20 years Exclusion: NR	Radiographic fusion with plain film radiographs, radiostereometric analysis (RSA), patient's subjective evaluation of back pain	12 mos	1 (declined)	POOR	Efficacy study compared rhBMP7 (OP-1 Putty) and ICBG, based on RSA results
Kanayama et al., 2006 Japan, USA (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	Inclusion: radiographic evidence of lumbar DDD, grade I spondylolisthesis with stenosis, neurogenic	Radiographic fusion with plain film radiographs and CT scan, surgical exploration of fusion mass, Oswestry Low Back Pain DI	rhBMP7 mn 16 mos AGB mn 13 mos	rhBMP7 1 (declined to complete study)	POOR	rhBMP7 Putty (OP-1 Putty) compared to local autograft bone admixed with hydroxyapatite plus tricalcium phosphate biphasic cerami cgranules

				claudication, unresponsive to minimum 3 mos. nonoperative therapies, age < 85 years Exclusion: > 5 degrees kyphosis in flexion, history of fusion at index level, active spinal or systemic infection, known sensitivity to any component of the BMP device, pregnancy or lactation, possible need for additional lumbar surgery within 6 mos					
Mummanen i et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level primary transforamin al lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	Inclusion: symptomatic, single-level lumbar DDD, grade I spondylolisthesis, with disabling low back or leg pain, unresponsive to minimum 6 mos. nonoperative therapies Exclusion:	Radiographic fusion based on static and dynamic plain film radiographs, modified Prolo Scale that evaluates pain, functional status, economic status, and medication use (Salehi et al., 2004)	mn 9 mos (3-18 mos)	4 of 44 (9)	POOR	Study compared rhBMP2 in conjunction with ICBG or local autograft bone and ICBG alone

				NR					
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	Inclusion: primary single-level ALIF, low back pain with or without referred leg pain and sciatica, symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: any prior anterior lumbar spine surgery or posterior destabilizing surgery, osteopenia, osteoporosis, osteomalacia, bone growth stimulation	Radiographic fusion based on plain film radiographs and 1-mm slice CT scans	rhBMP2 mn 26 (rng 23-29) ICBG mn 36 (rng 29-55)	0	FAIR	Reported radiographic and adverse outcomes rhBMP2 soaked absorbable collagen sponges (ACS)
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	Inclusion: radiographic evidence of DDD, grade I-II spondylolisthesis, lower extremity radiculopathy in a defined dermatomal distribution, unresponsive to	Radiographic fusion based on 2-mm slice CT scans with sagittal and coronal reconstructions	24 mos	2 (4.9) from rhBMP2/ICBG group	POOR	Study compared rhBMP2 in conjunction with ICBG or local autograft bone and ICBG alone Provided radiographic outcomes only

				minimum 6 mos. nonoperative therapies Exclusion: active smokers, prior fusion at the index level(s) malignancy, metabolic bone disease that would preclude instrumentation or inhibit osteogenesis (i.e., Paget disease, osteomalacia, osteogenesis imperfecta), local or systemic bacterial infection, temperature > 38 degrees at surgery, alcohol or drug abuse in treatment, historyof titanium alloy allergy					
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft	Inclusion: primary single- or multi-level symptomatic DDD, grade I-II spondylolisthesis, unresponsive to minimum 6 mos. nonoperative therapies	Radiographic fusion based on plain film radiographs and CT scans, Oswestry Low Back Pain Disability Index, Numerical Rating Scale (NRS) for	24 mos	rhBMP2 2 (4) ALG 1 (3)	POOR	FRA inserts used instead of interbody fusion cages to contain rhBMP2 on ACS or ALG

			(FRA) plus rhBMP2 or allograft bone chips (ALG)	Exclusion: DDD at > 3 levels, grade > 2 spondylolisthesis, tumor, infection, psychological contraindications	pain (location not specified)				
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Inclusion: radiographic evidence of lumbar DDD grade I or II lumbar spondylolisthesis, neurogenic claudication, unresponsive to minimum 6 mos. nonoperative therapies, skeletally mature Exclusion:	Primary Overall Success at 24 mos, a composite measure that required success in all of the following: a 20% improvement in Oswestry Low Back Pain DI, absence of treatment-emergent serious adverse events related to the device, absence of	rhBMP7 mn 53 mos (44-65)	335 enrolled and randomized, 295 (88%) were treated rhBMP7 20 voluntarily withdrew or were disqualified based on the inclusion and exclusion criteria	GOOD	IDE study for rhBMP7 device (OP-1 Putty) that did not receive FDA marketing approval Summarize data from 36+ mos. F/U
		ICBG n=86		> Grade II spondylolisthesis, nondegenerative spondylolisthesis of any grade, spinal instability on flexion-extension radiographs with > 50% translation of vertebral body or > 20 degrees of angular motion,	a decrease in neurologic status (assessing muscle strength, reflexes, sensation, and straight leg raise), and radiographic fusion success Modified Overall Success at 36 + mos, a composite measure that required success in	ICBG 54 (45-66)	ICBG 20 refused autograft or did not qualify after randomization based on the inclusion and exclusion criteria		

				active spinal or systemic infection, systemic disease precluding participation (eg, neuropathy), current nicotine use, history of smoking, morbid obesity, known sensitivity to collagen	all of the following: a 20% improvement in Oswestry Low Back Pain DI, absence of treatment-emergent serious adverse events related to the device, absence of a decrease in neurologic status (assessing muscle strength, reflexes, sensation, and straight leg raise) at 24 mos, and radiographic fusion success indicated by CT evidence for the presence of new bone, angulation ≤ 5 degrees, translation movement ≤ 3 mm on flexion/extension radiographs, and absence of retreatment to promote fusion at 36+ mos				
Vaccaro et al., 2008 USA (95)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt)	single-level primary uninstrumented	Inclusion: radiographic evidence of lumbar DDD	Radiographic fusion based on anteroposterior, lateral, and	48 mos	Radiographic results rhBMP7 9 (38%)	POOR	IDE study for rhBMP7 device (OP-1 Putty) that did not receive FDA

Lumbar Spine Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185) **Lumbar Spine**			posterolateral lumbar fusion with rhBMP7 or ICBG	grade I or II lumbar spondylolisthesis, neurogenic claudication, unresponsive to minimum 6 mos. nonoperative therapies, minimum Oswestry Low Back Pain Disability Index score 30 Exclusion: prior lumbar fusion or ICBG harvesting, active infection, history of tobacco use, morbid obesity, known sensitivity to collagen, grade III or IV spondylolisthesis, > 20% angular motion of the listhetic segment	dynamic flexion-extension lateral plain film radiographs Oswestry Low Back Pain DI, SF-36 physical and mental componemt subscales, adverse events and complications		Clinical results rhBMP7 5 (21%) Radiographic results ICBG 6 (50%) Clinical results ICBG 5 (42%)		marketing approval
		ICBG n=12							
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	Inclusion: primary symptomatic single- or two-level cervical DDD with radiculopathy, myelopathy, or both, herniated	Radiographic fusion using plain film radiographs and CT analysis, Neck Disability Index, neck and arm pain, SF-36 physical and mental component	24 mos	rhBMP2/ALG 3 (17%) ICBG/ALG 1 (7%)	FAIR	Pilot study using rhBMP2 soaked ACS packed inside fibular allograft (ALG) bone
		ICBG/ALG n=15							

				disc, posterior osteophytes or both at index level(s), symptoms unresponsive to minimum 6 mos. nonoperative therapies Exclusion: NR	subscales, neurologic status (motor and sensory function), patient satisfaction, complications and adverse events				
Butterman et al., 2008 USA (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	Inclusion: primary symptomatic single- or multi-level cervical DDD Exclusion: Prior ACDF at any level, corpectomy, deformity, presence of tumor, inflammatory joint disease, or cervical spine discitis	Radiographic fusion using plain film radiographs and high-resolution CT, Oswestry Neck Disability Index, neck and arm pain, pain medication use, patients' overall opinion of treatment success	24-36 mos	0	POOR	rhBMP2/ACS was placed inside the CRA, with resected osteophytes and local bone shavings, compared to ICBG alone
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	Inclusion: single- or multi-level symptomatic posterior cervical stenosis, ACDF non-union, or segmentally unstable spondylosis	Perioperative complications, surgical data	≤ 3 mos	0	POOR	rhBMP2/ACS was combined with bone graft extenders (BGE) including local autograft bone, allograft, or ceramics

				Exclusion: acute trauma, infection, presence of tumor, concomitant anterior fusion					
Smucker et al., 2006 USA (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	Inclusion: NR Exclusion: NR	Cervical swelling complications	≤ 6 wks	NR	POOR	Most patients received cortical ring allograft (CRA) (88% with rhBMP, 81% of controls)
Vaidya et al., 2007 USA (107) **Cervical Spine**	Retrospective cohorts of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	Inclusion: primary symptomatic single- or multi-level cervical DDD amenable to ACDF Exclusion: Prior ACDF at index level(s), trauma, presence of tumor, those more amenable to posterior surgery or combined surgery	Radiographic fusion using plain film radiographs and CT, Oswestry Neck Disability Index, arm and neck pain, perioperative outcomes and complications including swelling, hoarseness, and dysphagia	24 mos	NR	POOR	rhBMP2/ACS was placed in polyetheretherketone (PEEK) interbody fusion cages, compared to use of allograft (ALG) spacers with demineralized bone matrix (DBM)
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Acute traumatic tibial plateau fractures	Not stated	Radiographic fusion Additional surgeries complications	18 mos. (12-26)	0	POOR	Type I collagen sponge as carrier Various other void fillers were used making assessment of BMP difficult

									They were unclear about the dose so does is estimated from the label.
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips (2) n=15 autogenous bone graft	Reconstruction of diaphyseal tibial fractures with cortical defect	Inclusion: Skeletally mature male or non-pregnant or lactating female age 16 or greater, dyaphyseal tibial fracture with a residual fracture defect consistent with cortical defect, had primary treatment with IM nail or external skeletal fixation.	Surgical morbidity Radiographic evidence of fracture healing Impact on health related quality of life (SMFA)	12 mos	6 patients (20%)	FAIR	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone 43 fracture (OREF) N=20	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Inclusion: Zone 43 tibial fracture, fixation with two-ring hybrid external fixation, treatment with rhBMP7 (controls matched from other patients undergoing Zone 43 external fixation)	AP and lateral radiographs Radiographic evidence of fracture fusion and full weight bearing Range of motion of ankle joint IOWA ankle score RAND	BMP 12 months (11-13) Matched 28 months (12 to 45)	1 BMP death due to unrelated causes – union had healed at time of patient's death (2.5%) Matched 2 pts unavailable for long term followup (5%)	POOR	
Bilic et al., 2006 Croatia,	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt)	revision of nonunion	Inclusion: symptomatic proximal pole	Radiographic union, pain, movement, grip	24 mos	1	GOOD	Mixed rhBMP7/ACS with either ALG or AGB

Netherlands (96) **Miscella-neous Uses**		rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6		scaphoid nonunion of ≥ 9 mos. duration with no evidence of progressive healing over previous 3 mos, presence of ≥ 100 sq mm pre-existing sclerotic bone in the proximal scaphoid pole Exclusion: prior surgical treatment, carpal collapse, skeletal immaturity, inability or unwillingness to fulfill F/U requirements	strength				
Dickinson et al., 2008 USA (91) **Miscella-neous Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	repair of unilateral cleft lip-palate with an alveolar cleft defect	Inclusion: skeletally mature Exclusion: previous alveolar surgery, contraindication to rhBMP2 treatment, incomplete records	Bone healing of alveolar ridge and augmentation of the nasal alar base, using NewTom maxillofacial CT scans, periapical radiographs to grade alveolar ridge bone healing	12 mos	0	POOR	rhBMP2/ACS
Ekrol et al., 2008 UK (97) **Miscella-**	Prospective randomized cohort	RhBMP2 Non bridging external fixation	Osteotomy of the distal radius for symptomatic	Inclusion: malunion of distal radius (more than 10 degrees of	Clinical/radiographic functioning and complications at 2, 6, 12, 26, 52 wks	52 wks	0%	POOR	RhBMP-7 dose not given

neous Uses		N=4 Bone graft Non bridging external fixation N=6 RhBMP-7 internal fixation w/ pi-plate N=10 Bone graft internal fixation w/ pi-plate N=10	malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	dorsal angulation, more than 2 mm of radial shortening, carpal malalighnment or a combination of these)	Pain (VAS) Range of motion Hand grip strength				
Geesink et al., 1999 Netherlands (98) **Miscella-neous Uses**	Prospective double-blind randomized study	Untreated N=6 DMB N=6 Collagen type I N=6 OP-1 (2.5mg) with Collagen type I N=6	High tibial osteotomy with three osteoinductive materials	Pts with high tibial osteotomy who complied with study criteria	Clinical evaluation: HHS score, pain at site of osteotomy, patient satisfaction Radiological evaluation: AP and lateral radiographs taken to determine briding and bone formation. Dexa BMD measurements Immunologic testing	12 months	0% (three patients missed 1 of the six follow up appointments, none were lost to FU)	FAIR	
Karrholm et al., 2006 UK (111) **Miscella-**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10 n=11	impaction grafting for revision of hip arthroplasty	NR	Radiostereometric analysis of implant position, Harris hip score, pain	60 mos	Cups rhBMP7/ALG 18	POOR	Mixed rhBMP7/ACS with ALG Study stopped early because of clinical failures

neous Uses		Cups ALG n=10 Stems rhBMP7/ALG (1 g/pt) Stems ALG n=30					Cups ALG 10 Stems rhBMP&/ALG 0 Stems ALG 10		
Maeda et al., 2009 USA, Japan (109 **Miscella-neous Uses**)	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	Inclusion: ambulatory patients without other musculoskeletal diagnoses (eg, ankylosing spondylitis or neuromuscular deformity)	Radiographic union, loss of fixation, as shown by progression of deformity with or without pain, disc space collapse, motion across suspected pseudarthrosis	> 24 mos rhBMP2/BGE 2.7± 0.9 yrs ICBG 4.9±1.9 yrs (p < 0.01)	0	POOR	Mixed rhBMP2 with AGB, CRM, or ALG, but compiled data

Appendix 1 Table C. On-Label Comparative Studies Patient Characteristics

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Defect severity and characteristics (%)	Age mean ± SD yrs (rng)	≥ 65 yrs (%)	Males (%)	Weight mean ± SD lbs (rng)	Comorbidities (%)	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	grade I spondylolisthesis	rhBMP2 42±3 (30-62)	NR	rhBMP2 46	rhBMP2 166±11 (125-228)	Tobacco use rhBMP2 0 Frequent alcohol use rhBMP2 36.4	No significant differences between groups
		ICBG n=3				ICBG 40±0.6 (38-42)		ICBG 67	ICBG 211±11 (190-249)	Tobacco use ICBG 33.3 Frequent alcohol use ICBG 33.3	
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	NR	rhBMP2 43	NR	rhBMP2 54	rhBMP2 179	Tobacco use rhBMP2 33	No significant differences between groups
		ICBG n=136				ICBG 42		ICBG 50	ICBG 181	ICBG 36	
Burkus et al., 2003 USA (182) **Lumbar Spine**	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody	NR	rhBMP2 42±10	NR	rhBMP2 48.7	rhBMP2 175±36	Tobacco use rhBMP2 31.4 Alcohol use rhBMP2	Other significant differences include previous back

Note: may include pts in Burkus et al., 2003 (80)				fusion cages						37.9	surgeries (lower in ICBG group), use of non-narcotic, weak narcotic, and muscle relaxant medications (all higher in rhBMP2 group)
		ICBG n=402				ICBG 41±10		ICBG 52.2	ICBG 179±38	Tobacco use ICBG 32.8	
						p=0.007				Alcohol use ICBG 34.1	
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	grade I spondylolisthesis	rhBMP2/CRM 56	NR	rhBMP2/CRM 40	rhBMP2/CRM 176	Tobacco use rhBMP2/CRM 24 ICBG 24 Previous back surgery rhBMP2/CRM 24 ICBG 29	Previous back surgery not at index level
		ICBG n=21				ICBG 57		ICBG 43	ICBG 185		
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 n=151 (6 mg/patient)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	Gustilo-Anderson Types I (29), II (51), IIIA (43), IIIB (22)	37 (17-78)	NR	364 (81%)	NR	Tobacco Use 73 (50%)	
		rhBMP2 n=149 (12 mg/patient)			I(32), II(50), IIIA (38), IIIB (25)	33 (18-77)				75 (52%)	
		n=150			I (34), II (54)	37 (17-87)				66 (45%)	

		Standard care (IM nail fixation and soft tissue management)			IIIA (42), IIIB (17)						
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient)	Acute open tibial fracture	IM nail fixation and soft tissue management	Gustilo-Anderson Types (1) BESTT, I (21.1%) II, (33.6 %), IIIA and IIIB (44%) USS, I(15%), II(45%), IIIA and IIIB (40%)	(1) BESTT, 33.4 years USS, 35.2 years	NR	(1) BESTT, 84.6% USS, 85%	(1) BESTT, 166 USS,193	Smokers (1) BESTT, 51.7% USS,40%	
		(2) n=169 Standard care (IM nail fixation and soft tissue management)			(2) BESTT, I (23.3%), II (36.7%), IIIA and IIIB, 40.6%) USS, I (15.8%), II(31.6%), IIIA and IIIB, (52.6%)	(2) BESTT, 36.8 years USS, 33.6 years		(2) BESTT, 78.7% USS, 89.5%	(2) BESTT, 166 USS, 176	(2) BESTT, 44.9% USS, 52.6%	
Boyne et al., 2005 USA (75) **Maxillofac-ial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Partially/totally edentulous rhBMP2/ACS 0.75 mg/mL 72/28	rhBMP2/ACS 0.75 mg/mL 57±12	NR	rhBMP2/ACS 0.75 mg/mL 44	rhBMP2/ACS 0.75 mg/mL 151±32	Alcohol use rhBMP2/ACS 0.75 mg/mL 44	No significant differences between groups
		rhBMP2/ACS (15-48 mg/pt) n=17			rhBMP2/ACS 1.50 mg/mL 59/41	rhBMP2/ACS 1.50 mg/mL		rhBMP2/ACS 1.50 mg/mL	rhBMP2/ACS 1.50 mg/mL	rhBMP2/ACS 1.50 mg/mL	

						52±9		35	157±32	53	
		AGB n=13			AGB 69/31	AGB 57±11		AGB 38	AGB 164±52	AGB 46	
Fiorellini et al., 2005 USA (76) **Maxillofa-cial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	NR	47 (all pts)	NR	54 (all pts)	NR	NR	Poorly described demographics
		(mn dose 1.9 mg/pt) n=21									
		Placebo n=17									
		No Tx n=20									
Triplett et al., 2009 USA (77) **Maxillofa-cial and Dental**	Multicenter nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt)	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Partially or totally edentulous, not reported	rhBMP2/ACS 54 (23-76)	rhBMP2/ACS 21	rhBMP2/ACS 56	NR	NR	
		AGB n=80				AGB 51 (24-75)	AGB 8	AGB 32			
							(p=0.024)	(p=0.003)			
van den Bergh et al., 2000 Netherlands (82) **Maxillofa-cial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt)	partly edentulous	maxillary sinus floor augmentation	NR	rhBMP7/ACS 54±5	0	rhBMP7/ACS 33	NR	NR	
		ICBG n=3				ICBG 53±5		ICBG 33			
Calori et al., 2008 Italy (78)	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt)	post-traumatic atrophic nonunion	open reduction internal fixation	rhBMP7 15 tibial, 10 femoral, 15 humeral, 12	rhBMP7 md 44 (19-65))	NR	rhBMP7 53	NR	Tobacco use rhBMP7 33	No significant differences between

Long Bone Nonunion			for ≥ 9 mos, with no signs of healing over the last 3 mos	(ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	ulnar, 8 radial						groups
					4 open at injury, (1 Gustilo grade II, 2 grade IIIa, 1 grade IIIb)						
					md duration 20±2 mos					Previous surgery rhBMP7 md 2 (1-5)	
					prior autograft 38%						
		PRP n=60			PRP 19 tibial, 8 femoral, 16 humeral, 8 ulnar, 9 radial	PRP md 41 (21-62		PRP 58		Tobacco use PRP 28	
					5 open at injury (1 Gustilo grade I, 1 grade II, 2 grade IIIa, 1 grade IIIb)						
					md duration 19±3 mos					Previous surgery PRP md 2 (1-5)	
					prior autograft 35%						
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or	rhBMP7/ACS Gustilo II, IIIa, IIIb 4 (27)	rhBMP7/ACS 41 (16-64)	NR	rhBMP7/ACS 67	NR	NR	No significant differences between groups
		ICBG n=12			ICBG Gustilo II, IIIb 4 (33)	ICBG 38 (20-79)		ICBG 75			

			mos. following initial fracture stabilization	ICBG							
Friedlaender et al., 2001 (79) **Long Bone Nonunion**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt)	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	rhBMP7/ACS atrophic nonunion 25 (41%)	rhBMP7/ACS 38±16	NR	rhBMP7/ACS 67	rhBMP7/ACS 171±47	Tobacco use rhBMP7/ACS 74	No significant differences between groups except proportion of atrophic nonunions
					comminuted fracture at injury 41 (67%)						
					open fracture at injury 35 (58%)						
					Gustilo grade III, IIIa, IIIb, or IIIc at injury 18 (30%)						
					md duration 27±26 mos						
					prior autograft 26 (43%)						
					prior IM rod 33 (54%)						
		AGB n=61			AGB atrophic nonunion 15 (25%) (p=0.048)	AGB 34±11		AGB 77	AGB 187±40	AGB 57	
					comminuted fracture at						

					injury 34 (56%)						
					open fracture at injury 35 (57%)						
					Gustilo grade III, IIIa, IIIb, or IIIc at injury 22 (36%)						
					md duration 33±46 mos						
					prior autograft 19 (31%)						
					prior IM rod 27 (44%)						

Appendix 1 Table D. Off-Label Comparative Studies Patient Characteristics

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Defect severity and characteristics (%)	Age mean ± SD yrs (rng)	≥ 65 yrs (%)	Males (%)	Weight mean ± SD lbs (rng)	Comorbidities (%)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	grade I spondylo-listhesis	rhBMP2/CRM /TSRHSS 58±4	NR	rhBMP2/CRM /TSRHSS 27	NR	Tobacco use rhBMP2/CRM /TSRHSS 0 Alcohol use rhBMP2/CRM /TSRHSS 54 Diabetes rhBMP2/CRM /TSRHSS 0 Previous back surgery rhBMP2/TSRHSS 27%	Other than diabetes, no significant differences between groups
		(40 mg/pt) rhBMP2/CRM alone n=11				rhBMP2/CRM alone 52±6		rhBMP2/CRM alone 56		Tobacco use rhBMP2/CRM alone 12 Alcohol use rhBMP2/CRM alone 25 Diabetes rhBMP2/CRM alone 0 Previous back surgery rhBMP2 alone 12%	

		(40 mg/pt) ICBG plus TSRHSS n=5				ICBG/TSRHSS 53±10		ICBG/TSRHSS 40		Tobacco use ICBG/TSRHSS 20 Alcohol use ICBG/TSRHSS 40 Diabetes ICBG/TSRHSS 40 (p=0.036 for diabetes) Previous Surgery?	
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt) ICBG N=52	single-level lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2 40 ICBG 44	NR	rhBMP2 40 ICBG 36	rhBMP2 172 ICBG 173	Tobacco use rhBMP2 33 Previous back surgery rhBMP2 37 Tobacco use ICBG 33 Previous back surgery ICBG 33	No significant differences between groups
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec#	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2/CRM 53 (20-82) ICBG	NR	rhBMP2/CRM 45 ICBG	rhBMP2/CRM 187 (103-361) ICBG	Tobacco use rhBMP2/CRM 26 Alcohol use rhBMP2/CRM 38 Previous back surgery rhBMP2 30 Tobacco use	No significant differences between groups

5480; Glassman et al., 2005, rec# 8040		n=224				52 (18-86)		42	189 (99-312)	ICBG 26 Alcohol use ICBG 35 Previous back surgery ICBG 28	
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	Not reported	rhBMP2 60 (27-84) ICBG 53 (33-80)	NR	rhBMP2 40 ICBG 43	NR	Tobacco use rhBMP2 15 ICBG 23	No statistically significant differences between primary single-level pts in rhbMP2 or ICBG group
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Not reported	rhBMP2 69±6 ICBG 70±6	NR all > 60	rhBMP2 30 ICBG 33	NR BMI rhBMP2 29±6 ICBG 28±6	Tobacco use rhBMP2 22 ICBG 17	No significant differences between groups, including mean number of surgical levels (rhBMP2=1.96, ICBG=1.98)
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4 mg/pt)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) with interbody fusion cages plus rhBMP2 or ICBG	grade I spondylo-listhesis	rhBMP2 46 (26-66)	NR	rhBMP2 50	rhBMP2 180±38	Tobacco use rhBMP2 53 Alcohol use rhBMP2 44 Previous back surgery rhBMP2 35	No significant differences between groups

		ICBG N=33				ICBG 46 (28-71)		ICBG 46	ICBG 173±36	Tobacco use ICBG 46 Alcohol use ICBG 27 Previous back surgery ICBG 39	
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	rhBMP7 43±11	0	rhBMP7 30	NR	rhBMP7 40	Poorly described patients samples
		ICBG n=10				ICBG 40±10		ICBG 70		ICBG 30	
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	grade I spondylo-listhesis	rhBMP7 70±8	NR	rhBMP7 56	NR	NR	Poorly described patient samples, significantly older pts in rhBMP7 group
		AGB/CRM n=10				AGB/CRM 59±9 ($p < 0.05$)		AGB/CRM 60			
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	grade I spondylo-listhesis	rhBMP2/AGB 56±12 (33-76)	rhBMP2/AGB 24	rhBMP2/AGB 68	NR	Tobacco use rhBMP2/AGB 12 Prior surgery rhBMP/AGB 40 Tobacco use ICBG 5 Prior surgery ICBG 67	More older pts and males in the rhBMP2/AGB group than ICBG group, but small numbers limit comparison
		ICBG N=19				ICBG 49±10 (33-64)	ICBG 0 ($p < 0.01$)	ICBG 47			
Pradhan et al., 2006	Prospective consecutive	rhBMP2 n=9	single-level lumbar DDD	single-level primary	grade I spondylo-	rhBMP2 51	3 (1 of 36)	rhBMP2 33	NR	NR	Patient sample demographics

USA (101) **Lumbar Spine**	patient single-center cohort study	(dose NR) ICBG n=27		aAAnterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	listhesis	 ICBG 53		 ICBG 18			not well described
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	grade I-II spondylo-listhesis	rhBMP2/ICBG 65 ICBG 54	NR	rhBMP2/ICBG 44 ICBG 46	NR	NR	Patients in rhBMP2/ICBG group appear to be older, but no statistical analysis was done to confirm
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	grade I-II spondylo-listhesis	rhBMP2 45 ALG 44	NR	rhBMP2 60 ALG 51	NR	Tobacco use rhBMP2 18 Previous back surgery rhBMP2 46 Tobacco use ALG 8 Previous back surgery ALG 37	Both groups were similar in demographics and number of levels fused
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	grade I-II spondylo-listhesis	rhBMP7 68±10 ICBG	at least 50% in both groups rhBMP7 med=68 ICBG	rhBMP7 34 ICBG	NR NSD reported	NR	No significant differences between groups

		n=86				69±8	med=71	30			
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	grade I-II spondylo-listhesis	rhBMP7 63 (43-80) ICBG 67 (51-79)	NR	rhBMP7 46 ICBG 42	rhBMP7 198 (125-299) ICBG 176 (130-220)	NR	Patients in rhBMP7 group appear to be younger and heavier than in ICBG group, but no statistical analysis was done
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt) ICBG/ALG n=15	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	NR	rhBMP2/ALG 51 ICBG/ALG 47	NR	rhBMP2/ALG 44 ICBG/ALG 47	rhBMP2/ALG 170 ICBG/ALG 174	Tobacco use rhBMP2/ALG 28 ICBG/ALG 47	No significant differences between groups
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	NR	rhBMP2/CRA 49±10 ICBG 48±9	NR	rhBMP2/CRA 50 ICBG 33	NR	Tobacco use rhBMP2/CRA 37 Adjacent level DDD rhBMP2 63 Tobacco use rhBMP2/CRA ICBG 53 Adjacent level DDD ICBG 64	No significant differences between pt groups except a greater number of levels were treated in the rhBMP2/CRA group compared to the ICBG group (mn 1.6 vs. 2.2, p=0.003)
Crawford et al.,	Retrospective	rhBMP2/BGE	single- or multi-	single- or multi-	NR	rhBMP2/BGE	NR	rhBMP2/BGE	NR	Tobacco use	No significant

2009 USA (105) **Cervical Spine**	cohort of consecutive patients	n=41 (4.2-12 mg/pt) ICBG n=36	level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG		56±11 ICBG 54±12		32 ICBG 42		rhBMP2/BGE 24 ICBG 36	differences between groups
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	rhBMP2/CRA 52 CRA 50	NR	rhBMP2/CRA 49 CRA 49	NR	Tobacco use rhBMP2/CRA 29 Prior ACDF rhBMP2/CRA 28 ≥ 3 levels fused rhBMP2/CRA 13 Tobacco use CRA 14 (p=0.02) Prior ACDF CRA 10 (p=0.001) ≥ 3 levels fused CRA 2 (p=0.003)	Patients in rhBMP2/CRA (cortical ring allograft) group had significantly higher rates of comorbidities that can adversely affect fusion
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	rhBMP2 50 (29-70) ALG/DBM 48 (30-69)	NR	rhBMP2 32 ALG/DBM 45	NR	NR	No significant differences between groups
Boraiah et al.,	Retrospective	rhBMP2	Complex tibial	Surgery for	NR	53 years	NR	22 (55%)	NR	NR	

2009 USA (108) **Acute Tibial Fractures**	case series	(1) n=17 (12 mg/pt) (2) n=23 no BMP	plateau fractures	Acute traumatic tibial plateau fractures		(17-83)					
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	Open BMP 14 (93%) Closed BMP 1 (7%) Defect location Proximal third BMP 3 (20%) Middle third BMP 8 (53%) Distal third BMP 4 (27%) Gustilo-Anderson I or II BMP 1 (7%) IIIA BMP 9 (64%) IIIB BMP 4(29%) OTA classification Simple fracture BMP 1(7%)	BMP 36 (18-51)	NR	BMP 14 (93%)	NR	Tobacco use BMP 6(40%)	

					Wedge Fracture BMP 5(33%)					Diabetes BMP 3(30%)	
					Complex Fract BMP 9(60%)					Cardiovascular disease BMP 1 (7%)	
		(2) n=15 autogenous bone graft			No BMP 13(87%)	Non BMP 38 (18-71)		No BMP 13 (87%)		Tobacco use No BMP 4 (27%)	
					No BMP 2(13%)						
					No BMP 5(33%)						
					No BMP 7(47%)						
					No BMP 3(23%)						
					No BMP 2(15%)						
					No BMP 8(62%)						
					No BMP 3(23%)						
					No BMP 0						
					No BMP 8(53%)					Diabetes No BMP 1 (7%)	
					No BMP					Cardiovascular	

					7(47%)					disease No BMP 3 (20%)	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Inclusion: Zone 43 tibial fracture, fixation with two-ring hybrid external fixation, treatment with rhBMP7 (controls matched from other patients undergoing Zone 43 external fixation)	BMP: High energy injury 10(50%) Bone defects: BMP: 6(30%)	BMP: 41.3 (23 to 79)	NR	BMP: 11 (55%)	nr	Smokers (1) 10 (50%)	
		Matched Zone 43 fracture (OREF) N=20			Matched: high energy injury 11 (55%) Boney defects: Matched: 2(10%)	Matched: 47.2 (28 to 78)		Matched: 10 (50%)		(2) 8 (40%)	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt)	symptomatic proximal pole scaphoid nonunion	revision of nonunion	≥ 9 mos. duration, no evidence of healing over past 3 mos	rhBMP7/AGB 23±5	0	100	BMI (kg/m2) rhBMP7/AGB 20.1±1.5	Tobacco use rhBMP7/AGB 50 Nonunion duration (mos) rhBMP7/AGB 15±5	No significant differences between groups
		rhBMP7/ALG n=6 (3.5 mg/pt)				rhBMP7/ALG 19±4			rhBMP7/ALG 21.3±2.1	Tobacco use rhBMP7/ALG 50 Nonunion duration (mos) rhBMP7/ALG 14±5	
		ICBG n=6				ICBG 22±5			ICBG 19.8±1.3	Tobacco use ICBG 33 Nonunion	

										duration (mos) ICBG 13±4	
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	rhBMP2/ACS 16±1 ICBG 16±2	0	43	NR	NR	
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	RhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation N=6 RhBMP-7 internal fixation w/ pi-plate N=10 Bone graft internal fixation w/ pi-plate N=10	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	Inclusion: malunion of distal radius (more than 10 degrees of dorsal angulation, more than 2 mm of radial shortening, carpal malalighnment or a combination of these)		Internal fixation w/ pi plate bone graft: 57(49-68) Internal fixation w/ pi plate rhBMP-7: 62(35-78) External fixation rhBMP7: 58(41-81) External fixation bone graft: 61(25-79)	NR	Internal fixation w/ pi plate bone graft: 3(30%) Internal fixation w/ pi plate rhBMP-7: 0(0%) External fixation rhBMP7: 1(25%) External fixation bone graft: 1(16.6%)	NR	NR	
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6 DMB N=6 Collagen type I N=6 OP-1 (2.5mg)	High tibial osteotomy with three osteoinductive materials	Pts with high tibial osteotomy who complied with study criteria	15.6mm in untreated, 13.4 mm in DMB 14.2 mm in collagen only 16.4mm in	50 years (25 to 73)	NR	11 (45%)	NR	NR	

		with Collagen type I N=6			OP-1						
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	NR	Cups rhBMP7/ALG 68 (51-78)	NR	Cups rhBMP7/ALG 50	Cups rhBMP7/AKG 152 (128-187)	Osteoarthritis 100% both groups	No significant differences between groups
		Cupss ALG n=10				Cups ALG 65 (48-75)		Cups ALG 50	Cups ALG 158 (106-216)		
		Stems rhBMP7/ALG (1 g/pt) n=11				Stems rhBMP7/ALG 68 (51-77)		Stems rhBMP7/ALG 54	Stems rhBMP7/ALG 154 (119-187)		
		Stems ALG n=30				Stems ALG 67 (37-79)		Stems ALG 60	Stems ALG 165 (128-220)		
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt)	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	preoperative major curve Cobb angle (mn ± SD degrees) rhBMP2/BGE 54±20	rhBMP2/BGE 56±10	NR	NR	BMI rhBMP2/BGE 26±10	Tobacco use rhBMP2/BGE 13	No significant differences between groups
		ICBG n=32			ICBG 58±13	ICBG 53±10			ICBG 25±4	ICBG 12	

Appendix 1 Table E. On-Label Comparative Study Surgery and Perioperative Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Mean OR time (hr)	Mean estimated blood loss (mL)	Mean hospital LOS (days)	Perioperative complications (n)	Second surgeries (n)	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	rhBMP2 1.9±0.2 (2.3-4.2)	rhBMP2 95±31 (25-400)	rhBMP2 2.0±0.6 (0-6)	rhBMP2 wound dehiscence (1) low back pain prior to 6 mos. F/U (1)	ICBG 1 (supplemental instrumentation on fusion at 18 mos)	Besides OR time, no other significant differences reported
		ICBG n=3			ICBG 3.3±0.6 (1.0-3.2) p=0.006	ICBG 167±117 (50-400)	ICBG 3.3±1.4 (1-6)	ICBG urinary retention (1)		
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	rhBMP2 1.6	rhBMP2 110	rhBMP2 3.1	rhBMP2 vascular (6)	rhBMP2 11 (2 implant removals, 7 supplemental posterior fixations for pseudarthrosis, 2 others for pain)	No significant differences reported
		ICBG n=136			ICBG 2.0	ICBG 153	ICBG 3.3	ICBG vascular (5) iliac crest pain (8)	ICBG 14 (supplemental posterior fixation)	
Burkus et al., 2003 USA	Retrospective combined comparative	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior	rhBMP2 1.8±0.8	rhBMP2 127±295	rhBMP2 2.2±1.7	NR	rhBMP2 75 (8 revisions, 7	Significantly more reoperations

(182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	analysis			lumbar fusion with interbody fusion cages					removals, 28 supplemental fixations, 32 reoperations)	were reported in ICBG group than rhBMP2 group (p=0.0036)
		ICBG n=402			ICBG 2.7±1.3 p< 0.001	ICBG 193±414 p=0.024	ICBG 3.1±3.2 p < 0.001		ICBG 30 (1 revision, 2 removals, 7 supplemental fixations, 2 reoperations)	
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	rhBMP2/CRM 2.4±0.7 (95% CI, 2.1, 2.7)	rhBMP2/CRM 329±212 (95% CI, 241, 417)	rhBMP2/CRM 4.0±1.4 (95% CI, 3.4, 4.6)	rhBMP2/CRM incidental durotomy (1)	rhBMP2/CRM 2 (failures at index site)	No significant differences reported between groups
								wound infection (1)		
		ICBG n=21			ICBG 2.8±0.8 (95% CI, 2.2, 3.0)	ICBG 452±210 (95% CI, 357, 548)	ICBG 4.1±1.1 (95% CI, 3.6, 4.6)	ICBG incidental durotomy (1)	ICBG 2 (revisions for pseudarthrosis)	
								wound infection (1)		
								infection at graft donor site (1)		
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multicenter, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	NR	NR	NR	Infection (1) Types I and II 12 (15%) Types IIIA and IIIB 19 (29%)	(1) 47	
								Hardware Failure (1) 25 (17%)		
								Pain all body (1) 97 (67%)		

								Death One per group		
								Antibodies to BMP-2 (1) 3, 2%		
								Antibodies to Type I collagen (1) 22, 15%		
		rhBMP2 (2) n=149 (12 mg/patient)						Infection (2) Types I and II 15 (21%) Types IIIA and IIIB 15 (24%)	(2) 30	
								Hardware Failure (2) 16 (11%)		
								Pain all body (2) 98 (68%)		
								Antibodies to BMP-2 (2) 9, 6%		
								Antibodies to Type I collagen (2) 29, 20%		
		(3) n=150 Standard care (IM nail fixation and soft tissue management						Infection (3) Types I and II 13 (15%) Types IIIA and IIIB 26 (44%)	(3) 58	
								Hardware Failure		

								(3) 90 (65%) Pain all body (3) 116 (79%) Antibodies to BMP-2 (3) 1, 1% Antibodies to Type I collagen (3) 9, 6%		
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	NR	NR	Type III subgroup Infection (1) 13 (21%) Reamed nailing subgroup (1) 12(18%) Type III subgroup Infection (2) 26 (40%) Reamed nailing subgroup (2) 13(27%)	Type III subgroup (1) 6 (9%) Reamed nailing subgroup (1) 5 (8%) Type III subgroup Infection (2) 18 (28%) Reamed nailing subgroup (2) 7 (15)	Data was analyzed only for two subgroups Type III and reamed nailing
Boyne et al., 2005 USA (75) **Maxillofac-ial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18 rhBMP2/ACS (15-48 mg/pt)	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR	NR	NR	Total 546, of which 261 occurred durnig first 4 mos, 56% were mild, 38% moderate,	rhBMP2/ACS 0.75 mg/mL 3 (11%) (additional augmentation) rhBMP2/ACS 1.50 mg/mL	Perioperative complications were generally consistent with the surgical procedures,

		n=17 AGB n=13						transient	2 (12%) (additional augmentation) AGB 0	distributed equally between groups except for edema (AGB> rhBMP2/ACS), face edema (rhBMP2 > AGB), and skin rash (AGB > rhBMP2/ACS)
Fiorellini et al., 2005 USA (76) **Maxillofac-ial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22 rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	NR	NR	NR	Total 250 for 78 of 80 pts but not specified except for facial edema in pts who received rhBMP2/ACS	Secondary sugmentation for dental implant rhBMP2/ACS 0.75 mg/mL 10 (45%) rhBMP2/ACS 1.50 mg/mL 3 (14%) Placebo 7 (41%) No Tx 11 (55%) ($p < 0.01$ vs no tx)	
Triplett et al., 2009 USA	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB	< 6 mm alveolar bone height in the posterior	staged bilateral or unilateral maxillary	NR	NR	NR	NR	NR	Perioperative complications were generally

(77) **Maxillofac-ial and Dental**		n=80	maxilla	sinus floor augmentation						consistent woth the surgical procedures
van den Bergh et al., 2000 Netherlands (82) **Maxillofac-ial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	NR	NR	NR	NR	NR	
Calori et al., 2008 Italy (78) **Long Bone Nonunion**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt)	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	NR	NR	NR	NR	rhBMP7 3 (2 had no radiologically visible callus formation)	None of the patients who did not form callus reached a state of union
		PRP n=60							PRP 13 (9 had no callus formation)	
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	NR	NR	rhBMP7/ACS 8.7 (7-11)	rhBMP7/ACS wound infection 1	rhBMP7/ACS 1 (nail dynamization)	
		ICBG n=12					ICBG 10.7 (9-13)	ICBG wound infection 1	ICBG 3 (2 exchange IM nailing, 1 nail dynamization)	
Friedlaender et al.,	Multicenter, partially	rhBMP7/ACS n=61	tibial nonunion for	IM rod fixation with	rhBMP7/ACS 2.8	rhBMP7/ACS 254	rhBMP7/ACS 3.7	rhBMP7/ACS arthralgia,	rhBMP7/ACS 1 (1.6%)	Second surgeries not

2001 (79) **Long Bone Nonunion**	blinded RCT		≥ 9 mos, with no signs of healing over the last 3 mos	rhBMP7/ACS or AGB	(0.97-7)	(10-1150)	(0-18)	lower leg 8 (13%)		described
								pain, multiple sites 8 (13%)		
								osteomyelitis lower leg 2 (3%)		
								pyrexia 31 (51%)		
								vomiting 18 (30%)		
								leg edema 5 (8%)		
								hardware complication 25 (41%)		
								hematoma 5 (8%)		
								infection 14 (23%)		
		AGB (3.5-7.0 mg/pt) n=61			AGB 2.97 (0.97-7)	AGB 345 (35-1200)	AGB 4.1 (1-24)	AGB arthralgia, lower leg 5 (%)	AGB 6 (9.8%)	
								pain, multiple sites 9 (15%)		
								osteomyelitis lower leg 13 (21%) (p=0.002)		
								pyrexia 28 (46%)		
								vomiting 19 (31%)		
								leg edema 7 (11%)		

								hardware complication 34 (56%) hematoma 8 (13%) infection 12 (20%)		

Appendix 1 Table F. Off-Label Comparative Study Surgery and Perioperative Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Mean OR time (hr)	Mean estimated blood loss (mL)	Mean hospital LOS (days)	Perioperative complications (n)	Second surgeries (n)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	rhBMP2/CRM /TSRHSS 3.7±0.3	rhBMP2/CRM /TSRHSS 577±113	rhBMP2/CRM /TSRHSS 3.3±0.1	rhBMP2/CRM /TSRHSS 2 (1 transient leg pain, 1 epidural hematoma)	rhBMP2/CRM /TSRHSS 2 (1 decompression 1 level above index to relieve leg pain, 1 decompression 3 levels above index to relieve stenosis)	No significant intergroup differences other than mean OR time
		(40 mg/pt) rhBMP2/CRM alone n=11			rhBMP2/CRM alone 2.0±0.2	rhBMP2/CRM alone 333±121	rhBMP2/CRM alone 4.0±0.9	rhBMP2/CRM alone 2 (1 persistent leg pain, 1 superficial hematoma)	rhBMP2/CRM alone 1 (anterior lumbar interbody fusion to relieve low back and leg pain)	
		(40 mg/pt) ICBG plus TSRHSS n=5			ICBG/TSRHSS 3.1±0.4 (p=0.002 rhBMP2/CRM	ICBG/TSRHSS 430±82	ICBG/TSRHSS 4.4±0.5	ICBG/TSRHSS 0	ICBG/TSRHSS 0	

					alone vs other 2 groups)					
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	rhBMP2 1.4	rhBMP2 87	rhBMP2 2.9	NR	rhBMP2 2 (2 supplemental fixations)	Perioperative outcomes were significantly better in the rhBMP2 group than the ICBG group
		ICBG N=52			ICBG 1.9 (p < 0.001)	ICBG 185 (p < 0.001)	ICBG 3.3 (p=0.20)		ICBG 8 (8 supplemental fixations)	
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	rhBMP2/CRM 2.5±0.09	rhBMP2/CRM 343±265	rhBMP2/CRM 4.1±2.3	rhBMP2/CRM technical difficulty (1)	rhBMP2/CRM 20 (4 revisions, 10 nonelective removal of graft, 6 supplemental fixation)	No surgical reintervention was related to recurrent stenosis or inadequate decompression
								(2) dural injury		
								cardiovascular (13)		
								malpositioned implant (1)		
								other (1)		

								vertebral fracture (3)		
		ICBG n=224			ICBG 2.9±1.0 (p < 0.001)	ICBG 449±302 (p < 0.001)	ICBG 4.0±1.9	ICBG technical difficulty (0)	ICBG 36 (4 revisions, 23 nonelective removals, 9 supplemental fixations) (p=0.015 for total number of surgeries)	
								cardiovascular (0)		
								dural injury (18)		
								malpositioned implant (0)		
								other (0)		
								vertebral fracture (3)		
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt)	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	rhBMP2 3.2 (1.5-6)	rhBMP2 542 (100-3,600)	NR	NR	rhBMP2 5 of 48 (10) 1-level primary fusions	No significant differences noted
		ICBG n=35			ICBG NR	ICBG NR			ICBG NR	
Glassman et al., 2008 USA	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not	single- or multi-level lumbar DDD	single- or multi-level primary	rhBMP2 4.1±0.6	rhBMP2 670±487	NR	rhBMP2 8 (16) (1 cardiac, 1	rhBMP2 4 (8) (1 wound	Bone graft filler/extender used in 100%

(87) **Lumbar Spine**		reported)		instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG				wound infection, 1 line-related sepsis, 2 GI, 1 UTI, 1 shingles, 1 broken toe))	infection, 1 adjacent level fracture, 1 nonunion, 1 adjacent level degeneration)	rhBMP2 and 67% ICBG cases, available local bone used in all cases
								Overall complications rhBMP2 8		
		ICBG n=52			ICBG 4.5±1.0 (p=0.024)	ICBG 675±456		ICBG 12 (23) (7 cardiac, 4 wound infection, 3 back or leg pain requiring readmission or epidural steroids, 3 GI, 1 UTI, 1 neurologic deficit)	ICBG 11 (2 wound infection, 1 pedicle screw reposition, 5 nonunions, 1 late screw removal, 1 pain pump insertion, 1 adjacent level degeneration)	
								Overall complications ICBG 20 (p=0.014)		
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF)	rhBMP2 2.6	rhBMP2 323	rhBMP2 3.4	rhBMP2 3 (3 dural tears)	rhBMP2 6 (3 failures, 3 fusion at different level)	No significant differences between pt groups

		ICBG N=33		interbody fusion cages plus rhBMP2 or ICBG	ICBG 3.0	ICBG 373	ICBG 5.2 (p=0.065)	ICBG 3 (1 DVT, 2 dural tears)	ICBG 6 (3 failures, 3 fusions at different level)	
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	NR	NR	None reported	rhBMP7 2 ICBG 1	No perioperative results reported
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	NR	NR	NR	NR	NR	No perioperative results reported
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	NR	NR	NR	NR	NR	
Pradhan et al., 2006 USA (101)	Prospective consecutive patient single-center	rhBMP2 n=9 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar	NR	NR	NR	NR	rhBMP2 3 (3 instrumented	Salvage posterior fusions performed

Lumbar Spine	cohort study			interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG					posterior salvage fusions)	secondary to subsequent pseudarthrosis and intractable symptoms
		ICBG n=27							ICBG 7 (7 instrumented posterior salvage fusions)	
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	NR	NR	NR	rhBMP2/ICBG 2 (dural tear)	rhBMP7 1 (lumbar decompression above index level)	
		ICBG N=11						ICBG None reported	ICBG None	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	NR	NR	NR	rhBMP2 2 (1 wound infection, 1 dural tear))	rhBMP2 0	Salvage posterior fusions performed secondary to subsequent pseudarthrosis
		ALG N=30						ALG 1 (wound dehiscence	ALG 4 (salvage posterolateral fusion)	
Vaccaro et al., 2008 USA (94)	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented	rhBMP7 2.4	rhBMP7 309	NSD but data not provided (p=0.529)	Proportion with treatment-related SAE	rhBMP7 21	Significantly shorter OR time and less blood loss on

Lumbar Spine				posterolateral lumbar fusion with rhBMP7 or ICBG				rhBMP7 20%		average in rhBMP7 pts compared to ICBG
		ICBG n=86			ICBG 2.7 (p=0.006)	ICBG 471 (p=0.00004)		ICBG 26%	ICBG 11 (p=0.242)	
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	rhBMP7 2.3±0.7 (0.8-3.7) ICBG 2.6±0.5) (1.9-3.6) (Data from Vaccaro et al., 2005, rec# 7310)	NR	rhBMP7 3.9±1.7 (2-10) ICBG 4.3±2.0 (3-9) (Data from Vaccaro et al., 2005, rec# 7310)	rhBMP7 89 total (includes 16 procedural, 40 referable to musculoskeletal and connective tissue, 6 infections) ICBG 51 total (includes 14 procedural, 21 referable to musculoskeletal and connective tissue, 1 infection)	rhBMP7 2 (2 revision decompression)	No significant differences between pt groups
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	rhBMP2/ALG 1.8	rhBMP2/ALG 91	rhBMP2/ALG 1.4	None reported	rhBMP2/ALG 1 (unrelated to index procedure, but required removal of anterior cervical plate)	No significant intergroup differences reported
		ICBG/ALG n=15			ICBG/ALG 1.8	ICBG/ALG 123	ICBG/ALG 1.1			

Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	rhBMP2/CRA 1.9±0.4	rhBMP2/CRA 65±51	rhBMP2/CRA 1.3±0.5	Cervical swelling rhBMP2/CRA 15 (50%) Re-admit rhBMP2/CRA 3 (10%) MD evaluation rhBMP2/CRA 7 (23%) Phone call (RN) rhBMP2/CRA 10 (33%)	rhBMP2/CRA 1 (adjacent level ACDF with decompression due to disc herniation)	Cervical swelling caused dysphagia that was more severe in rhBMP2/CRA group than ICBG group, at 4 days after surgery and persisting for 21 days
		ICBG n=36			ICBG 1.9±0.4	ICBG 65±84	ICBG 1.2±0.4	Cervical swelling ICBG 5 (14%) ($p < 0.01$) Re-admit ICBG 0 MD evaluation ICBG 3 (8%) Phone call (RN) ICBG 4 (11%)	ICBG 1 (pseudarthrosis repair)	
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt)	single- or multi-level posterior cervical stenosis, ACDF	single- or multi-level instrumented posterior cervical spinal fusion	rhBMP2/BGE 2.8±1.0	rhBMP2/BGE 275±224	rhBMP2/BGE 4.2±2.6	Wound complications rhBMP2/BGE 6 (15%) Prolonged drainage	NR	No significant differences reported between groups

			nonunion, or unstable spondylosis	with rhBMP2/BGE or ICBG				rhBMP2 2 (5%)		
								Presumed deep infection rhBMP2/BGE 4 (10%)		
								Medical rhBMP2/BGE 0		
		ICBG n=36			ICBG 2.7±0.9	ICBG 337±317	ICBG 3.5±1.2	Wound complications ICBG 1 (3%)		
								Prolonged drainage ICBG 1 (3%)		
								Presumed deep infection ICBG 0		
								Medical ICBG 3 (8%)		
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR)	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	NR	Cervical swelling (total) rhBMP2/CRA 19 (28%)	NR	Bivariate unadjusted logistic regression model showed significant association between cervical swelling and rhBMP2 ($p < 0.0001$), C4-C5 level

										surgery (p=0.003), age ≥ 50 years (p=0.003), surgery at ≥ 3 levels (p=0.007), combined sugery (p=0.04)
								Swelling Complications :Discharge delay rhBMP2/CRA 9 (13%)		Adjustment for demographic differences showed only rhBMP2 use was significantly associated with cervical swelling (OR 10.1, 95% CI 3.4, 29.7, p < 0.0001)
								Readmission for medical management rhBMP2/CRA 2 (3%)		Timing and presentation of cervical swelling in rhBMP2 recipients was reported distinct from that typically seen after ACDF, usually about 4 days after
								ER or ENT consult rhBMP2/CRA 5 (7%)		
								Incision and drainage of site rhBMP2/CRA		

								3 (4%)		surgery and qualitatively different
								Reintubation, PEG, Tracheostomy, delayed extubation rhBMP2/CRA 4 (6%)		
								Severe dysphagia rhBMP2/CRA 5 (7%)		
		CRA n=165						Cervical swelling (total) CRA 6 (4%) ($p < 0.0001$)		
								Swelling Complications :Discharge delay CRA 5 (3%)		
								Readmission for medical management CRA 0		
								ER or ENT consult CRA		

								1 (1%) Incision and drainage of site CRA 0 Reintubation, PEG, Tracheostomy, delayed extubation CRA 4 (2%) Severe dysphagia CRA 2 (1%)		
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	NR	rhBMP2 2.9 (1-9) ALG/DBM 2.3 (1-6)	Dysphagia IPO, 0.5, 1.5, 24 mos rhBMP2 17, 17, 13, 4 Hoarseness rhBMP2 20 (60%) Cervical swelling ALG/DBM 24 (100%) Dysphagia IPO, 0.5, 1.5, 24 mos ALG/DBM 10, 7, 4, 4 Hoarseness	rhBMP2 2 (1 for swelling, 1 below index level)) ALG/DBM 1 (non-union)	Cervical swelling was significantly greater in the rhBMP2 group compared to the ALG/DBM group for 6 weeks postsurgery

								ALG/DBM 11 (62%)		
Boraiah et al., 2009 USA (108) **Open Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt)	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	NR	Development of HO BMP group 10 (59%)	4 patients in BMP group had ectopic bone removed. No other surgeries reported	
		(2) n=23 no BMP						No BMP 1 (4%)		
Jones et al., 2006 USA (90) **Open Tibial Fractures**	Multicenter prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	BMP 150min ± 82.7	BMP 117 ±100.3	NR	Soft tissue swelling BMP 12 (80%)	2 per group	
								Epidermal erythema BMP 5(33%)		
								Infection BMP 3(20%)		
								Screw breakage BMP 0		
								Hererotopic ossification BMP 1(7%)		
								Anti-bodies to BMP-2 BMP 0		
								Antibodies to type I bovine collagen BMP 0		
		(2) n=15 autogenous bone graft			No BMP 169min ±49.3 Note: This is duration of anesthesia	No BMP 353 ± 284.4		Soft tissue swelling No BMP 9(60%)		
								Epidermal erythema		

								No BMP 0 Infection No BMP 1(7%) Screw breakage No BMP 2(13%) Hererotopic ossification No BMP 0 Acute pain at iliac crest donor site No BMP 14(93%) Pustules or drainage at donor site No BMP 3(20%) Antibodies to type I bovine collagen Non BMP 1(7%)		
Ristiniemi et al., 2007 Finland (110) **Open Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone 43 fracture	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	NR	NR	NR	Infection One pin track 6 Three pin track 1 Calcification in the wound 1 Infection One pin track 4	rhBMP7 n=2 Matched n=7	

		(OREF) N=20						Three pin track 0 Calcification in the wound 0		
Bilic et al., 2006 Croatia, Netherlands (96) **Miscella-neous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	symptomatic proximal pole scaphoid nonunion	revision of nonunion	rhBMP7/AGB 2.3 rhBMP7/ALG 1.6 ICBG 2.3	NR	NR	NR	NR	Patients who were treated with rhBMP7/ALG lost estimated 50 mL less blood than those in the other two groups
Dickinson et al., 2008 USA (91) **Miscella-neous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	NR	rhBMP2/ACS 0.4±0.4 ICBG 1.8±0.8	NR	NR	
Ekrol et al., 2008 UK (97) **Miscella-neous Off-Label Uses**	Prospective randomized cohort	RhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	NR	NR	NR	RhBMP2 Non bridging external fixation: N=2 pts. Developed extensive osteolysis, 1 pt dorsal defect Bone graft Non bridging external fixation: n= 1	RhBMP2 Non bridging external fixation: n=1 Bone graft internal fixation w/ pi-plate	

		N=6						pt had recurrence of deformity	N=7 for plate removal	
		RhBMP-7 internal fixation w/ pi-plate N=10						RhBMP-7 internal fixation w/ pi-plate N=5 pts had dorsal defect, 2 pts had non-union, 1 rupture of extensor pollicis longus	RhBMP-7 internal fixation w/ pi-plate N=3 for plate removal	
		Bone graft internal fixation w/ pi-plate N=10						Bone graft internal fixation w/ pi-plate N=5 donor site hematoma, 1 pt rupture all extensor tendons on the dorsum of wrist	Bone graft internal fixation w/ pi-plate N = 0	
Geesink et al., 1999 Netherlands (98) **Miscella-neous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductiv e materials	NR	NR	NR	Wound Complications :	NR	
		DMB N=6						OP-1 n=1 (16.6%) hematoma on lateral side of leg, spontaneousl y resolved		
		Collagen						Collagen n=1		

		type I N=6 OP-1 (2.5mg) with Collagen type I N=6						(16.6%) oozing fibular wound (no intervention)		
Karrholm et al., 2006 UK (111) **Miscella-neous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10 Cups: ALG n=10 Stems rhBMP7/ALG (1 g/pt) n=11 Stems: ALG n=30	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	NR	NR	NR	NR	Cups rhBMP7/ALG 2 Cups ALG 0 Stems rhBMP7/ALG 2 Stems ALG 1	
Maeda et al., 2009 USA, Japan (109) **Miscella-neous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	NR	NR	NR	rhBMP2/BGE 1 (acute tubular necrosis)	rhBMP2/BGE 1 (4) ICBG 6 (19)	All patients who underwent second surgeries had a fusion site pseudarthrosis

Appendix 1 Table G. On-Label Comparative Study BMP-Related Adverse Events

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	No. adverse events (%) p-value	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11 ICBG n=3	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	rhBMP2 3 of 11 (27) had increased antibovine collagen Type I titers	No adverse sequelae reported
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143 ICBG n=136	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	0.7% and 0.8% of each group had anti-rhBMP2 titers 3mos. postsurgery	No adverse sequelae reported
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR) ICBG n=402	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	None reported	
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	None reported	
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) (2)rhBMP2/CRM n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	None reported except for BMP-2 antibodies (1) 2% (2) 6% (3) 1%	

		management)				
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	
Boyne et al., 2005 USA (75) **Maxillofacial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Facial edema rhBMP2/ACS 0.75 mg/mL 7 (39%)	Most (67%) immune responses were transient No clinical manifestations of an immune response or neutralizing effect toward rhBMP2 were identified
					Immune sensitization to rhBMP2 0.75 mg/mL 0	
					Immune sensitization to collagen rhBMP2/ACS 0.75 mg/mL 2 (11%)	
		rhBMP2/ACS (15-48 mg/pt) n=17			Facial edema 1.50 mg/mL 14 (82%)	
					Immune sensitization to rhBMP2 1.50 mg/mL 2 (12%)	
					Immune sensitization to collagen 1.50 mg/mL 4 (24%)	
		AGB n=13			Facial edema AGB 5 (38%)	

					(p=0.0227, 0.0152, 1.50 mg/mL vs AGB and 0.75 mg/mL groups) Immune sensitization to rhBMP2 AGB 0 Immune sensitization to collagen AGB 3 (23%)	
Fiorellini et al., 2005 USA (76) **Maxillofacial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22 rhBMP2/ACS(mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	None reported	
Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Facial edema occurred at a significantly higher rate (p=0.048) in rhBMP2/ACS recipients than in AGB recipients (data not reported in paper) Immune sensitization to rhBMP7 2 (2%) Immune sensitization to collagen rhBMP7/ACS 24 (29%) Immune sensitization to rhBMP7 AGB 0 Immune sensitization to collagen	No clinical manifestations of an immune response or neutralizing effect toward rhBMP2 were identified

					AGB 25 (32%)	
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	None reported	
Calori et al., 2008 Italy (78) **Long Bone Nonunion**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	None reported	Did not perform immunological analysis for antibodies to rhBMP7
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	None reported	
Friedlaender et al., 2001 (79) **Long Bone Nonunion**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	Transient, low titers of anti-rhBMP7 antibodies reported in 6 patients (10%) Anticollagen antibodies reported in 3 patients treated with rhBMP7/ACS	No adverse events were related to sensitization

Appendix 1 Table H. Off-Label Comparative Study BMP-Related Adverse Events

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	No. adverse events (%) p-value	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	1 of 22 (4.5) rhBMP2/CRM recipients had transient anti-rhBMP2 titer postsurgery	No adverse sequelae reported, nor complications attributable to rhBMP2/CRM
		rhBMP2/CRM alone n=11 (40 mg/pt)				
		ICBG plus TSRHSS n=5				
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	Among 78 patients tested in the rhBMP2 group, none had elevated antibody response to the protein	Origin of antibody responsiveness to bovine collagen unclear
		ICBG N=52			7 (9) in the rhBMP2 group, and 4 (8) in ICBG group had uneventful elevated antibody reponse to bovine collagen	
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	None reported	
		ICBG n=224				

rec# 5480; Glassman et al., 2005, rec# 8040						
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	None reported	
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported) ICBG n=52	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	None reported	
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4) ICBG N=33	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG	None reported 3 (9%) in the rhBMP2 group, and 5 (15%) in ICBG group had uneventful elevated antibody reponse to bovine collagen	No adverse sequelae reported
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	None reported	No adverse events of any type were reported
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	None reported	
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2	None reported	

				plus AGB or ICBG alone		
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	None reported	
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	None reported	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	None reported	
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Among pts tested for rhBMP7 antibody titers, 26% were positive for anti-rhBMP7 neutralizing antibodies versus 1.2% of ICBG recipients	No significant associations were observed between neutralizing antibody activity, clinical success, and safety parameters No other adverse events related to rhBMP7 were reported
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184),	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	None reported	

and Vaccaro et al., 2005, (185)						
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt) ICBG/ALG n=15	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	None reported	
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	None reported except cervical swelling	See table on perioperative complications for data on cervical swelling
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	single- or multi-level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	NR	
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	Adjustment for demographic differences showed only rhBMP2 use was significantly associated with cervical swelling (OR 10.1, 95% CI 3.4, 29.7, p < 0.0001)	See table on perioperative complications for data on cervical swelling
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	None reported except cervical swelling	See table on perioperative complications for data on cervical swelling
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	Development of HO BMP 10(59%) No BMP 1(4%)	
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	Soft tissue swelling BMP 12 (80%) Epidermal erythema BMP 5(33%) Infection	

					BMP 3(20%) Heterotopic ossification BMP 1(7%) Soft tissue swelling No BMP 9(60%) Epidermal erythema No BMP 0 Infection No BMP 1(7%)	
		(2) n=15 autogenous bone graft				
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Pin track infection (discharge, redness, swelling pain, and positive bacterial culture) were found in 6 BMP patients (30%) and four in matched patients (20%)	
		Matched Zone 43 fracture (OREF) N=20			In BMP group 1 pt developed symptomless calcification of soft tissue	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt)	symptomatic proximal pole scaphoid nonunion	revision of nonunion	None reported	
		rhBMP7/ALG n=6 (3.5 mg/pt)				
		ICBG n=6				
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given)	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	None reported	
		ICBG n=12				
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	RhBMP2 Non bridging external fixation N=4	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	rhBMP2 Non bridging external fixation: 2 pts. developed extensive osteolysis, 1 pt dorsal defect	
		Bone graft Non			Bone graft	

		bridging external fixation N=6			Non bridging external fixation: 1 pt had recurrence of deformity	
		RhBMP-7 internal fixation w/ pi-plate N=10			RhBMP-7 internal fixation w/ pi-plate 5 pts had dorsal defect, 2 pts had non-union, 1 rupture of extensor pollicis longus	
		Bone graft internal fixation w/ pi-plate N=10			Bone graft internal fixation w/ pi-plate: 5 donor site hematoma, 1 pt rupture all extensor tendons on the dorsum of wrist	
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	Positive antibody reaction in two pts for anti-collagen at 10 weeks in collagen type I group (33.3%)	
		DMB N=6				
		Collagen type I N=6			1 pt in OP-1 group had pseudo arthrosis requiring resection 1.5 yrs post-op (16.6%)	
		OP-1 (2.5mg) with Collagen type I N=6				
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	None reported	
		Cups ALG n=10				
		Stems rhBMP7/ALG (1 g/pt) n=11				

		Stems ALG n=30				
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	None reported	

Appendix 1 Table I. On-Label Comparative Study Radiographic Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Successful outcome (%) (p-value)	Time to successful outcome mn ± SD (rng) (p-value)	Definition of successful outcome	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11 ICBG n=3	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	3, 6, 12, 24 mos. rhBMP2 91, 100, 100, 100 ICBG 67 at all times	NR	Plain radiograph: < 5 degrees of angular motion on flexion-extension film, and absence of radiolucent lines covering 50% or more of implant surfaces CT: presence of continuous trabecular bone growing through both cages Fusion success required agreement among all 5 independent readers unaware of treatment	No evidence of clinically significant (1 mm) graft subsidence in either group, no anteroposterior migration or rotation
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143 ICBG n=136	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2 97, 97, 94 ICBG 96, 93, 89	NR	Plain radiograph: < 3mm translation, < 5 degrees angular motion on flexion-extension film, and absence of radiolucent lines covering 50% or more of implant surfaces CT: presence of	Secondary surgeries were classified as fusion failures regardless of independent radiologic assessment

							continuous trabecular bone growing through both cages Fusion evaluated by two independent radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR) ICBG n=402	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	6, 12, 24 mos rhBMP2 95, 96, 94 ICBG 96, 93, 89 (p=0.022 at 24 mos)	NR	Same as Burkus et al., 2002 (rec#11620)	Fusion success difference at 24 mos. statistically significant by ANCOVA
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2/CRM 91, 89, 95 ICBG 58, 65, 67 (p=0.032 at 6 mos)	NR	Presence of bridging trabecular bone between the transverse processes, absence of motion, defined as 3 mm or less of translation and < 5 degrees of angular motion on flexion-extension views, and absence of radiolucent lines through the fusion mass Fusion evaluated by two independent	Thin-cut CT showed progressive formation of bridging bone across the transverse processes and incorporation of the ceramic component

							radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) rhBMP2 (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	(1) 54% (2) 65% P-value 0.0028 in comparison to (3) control group (3) 47%	50% union by (1) 187 days (2) 145 days (3) 184 days	Radiographic evidence of union and fulfillment of clinical criteria including full weight bearing and lack of tenderness at the fracture site.	
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	Type III subgroup (1) 271 days Reamed nailing subgroup (1) 234 Type III subgroup (2) 277 days Reamed nailing subgroup (2) 251	Radiographic evidence of union	Data was analyzed only for two subgroups those with type III open tibial fractures and those who received IM reamed nailing
Boyne et al., 2005 USA (75)	Multicenter randomized dose-comparison,	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the	staged bilateral or unilateral maxillary sinus floor	Mean bone height change from baseline at 4 mos. (mm) rhBMP2/ACS	NR	NR	

Maxillofacial and Dental	safety and efficacy study		posterior maxilla	augmentation	0.75 mg/mL 9.47±5.72			
		rhBMP2/ACS (15-48 mg/pt) n=17			1.50 mg/mL 10.16±4.7			
		AGB n=13			AGB 11.29±4.12			
Fiorellini et al., 2005 USA (76) **Maxillofacial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	Implant positions with adequate bone formation 25, 50, 75% ESL rhBMP2/ACS 0.75 mg/mL 25, 30, 30	NR	Adequate alveolar bone defined as > 6mm in width at narrowest point (buccal to palatal) based on CT scans Three independent masked CT scan reviewers	
		rhBMP2/ACS (mn dose 1.9 mg/pt) n=21			1.50 mg/mL 56, 41, 32			
		Placebo n=17			Placebo 6, 20, 21			
		No Tx n=20			No tx 12, 9, 14			
Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt)	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Mean bone height change from baseline at 6 mos. (mm) rhBMP2/ACS 7.83±3.52	NR	NR	Significant overall bone height gain occurred in both groups
		AGB n=80			AGB 9.46±4.11 (p=0.009)			
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt)	partly edentulous	maxillary sinus floor augmentation	Good quality bone formation at 6 mos rhBMP7/ACS 33	NR	Based on histological analysis, visual bone appearance	
					Mean vertical alveolar process height increase (mm) at 6 mos rhBMP7/ACS			

					5.8±1.6			
		ICBG n=3			Good quality bone formation at 6 mos ICBG 100			
					Mean vertical alveolar process height increase (mm) at 6 mos rhBMP7/ACS ICBG 9.8±2.3			
Calori et al., 2008 Italy (78) **Long Bone Nonunio**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt)	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	9 mos rhBMP7 87	rhBMP7 md 8±0.5 mos	Radiological union: presence and staging of callus at 3 of 4 cortices on both anteroposterior and lateral plain film views, as well as the type of osseointegration (undefined)	Successful completion of treatment was defined as the accomplishment of both radiological and clinical union 4 (7%) in rhBMP7 group and 5 (8%) in PRP group were complicated by infection and failed to progress to union
		PRP n=60			PRP 68 (p=0.016)	PRP md 9±0.5 mos		
Dahabreh et al., 2008 (83) **Long Bone Nonunio**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	Radiological union rhBMP7ACS 100	rhBMP7/ACS 5.5 (4.7-6.2)	Radiological evidence of bridging callus of all cortices in the two standard planes of plian film radiographs (radiological union)	
		ICBG n=12			ICBG 100	ICBG 6.9 (6.1-7.6) (p < 0.001)		
Friedlaender et al.,	Multicenter, partially	rhBMP7/ACS n=61	tibial nonunion for	IM rod fixation with	9, 24 mos rhBMP7/ACS	NR	Combination of the presence of bridging	Prior autograft procedure had no

2001 (79) **Long Bone Nonunio**	blinded RCT	(3.5-7.0 mg/pt)	≥ 9 mos, with no signs of healing over the last 3 mos	rhBMP7/ACS or AGB	81, 82 Radiographic bridging in at least 1 view rhBMP7/ACS 75		by new bone across the fracture site and on how many of the 4 views this bridging was apparent Consensus of at least 2 of 3 musculoskeletal radiologists unaware of treatment and time following surgery independently assessed anteroposterior, lateral and 2 oblique projection radiographs	influence on clinical and radiographic success rates
					Radiographic bridging in at least 3 views rhBMP7/ACS 62			
		AGB n=61			9, 24 mos AGB 85, 82			
					Radiographic bridging in at least 1 view AGB 84			
					Radiographic bridging in at least 3 views AGB 74			

Appendix 1 Table J. Off-Label Comparative Study Radiographic Outcomes

	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Successful outcome (%) (p-value)	Time to successful outcome mn ± SD (rng) (p-value)	Definition of successful outcome	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	24 mos. (22/27 pts) rhBMP2/CRM/TSRHSS 100	NR	Presence of bridging trabecular bone between the transverse processes, absence of motion, defined as 3 mm or less of translation and < 5 degrees of angular motion on flexion-extension views, and absence of radiolucent lines through the fusion mass Fusion evaluated by two independent radiologists who were unaware of treatment	By 12 mos. and continuing at 24 mos, the opacity of the ceramic CRM changed from a pale gray speckled pattern to a more uniform, well-marginated whiter mass
		(40 mg/pt) rhBMP2/CRM alone n=11			rhBMP2/CRM alone 100			
		(40 mg/pt) ICBG plus TSRHSS n=5			ICBG/TSRHSS 40 (p=0.018, 0.028 in BMP2 groups vs ICBG)			
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002,	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2 96, 99, 98	NR	Presence of bridging bone connecting adjacent vertebral bodies, either through the FRA or around the FRA, < 5 degrees of angular motion, ≤ 3 mm translation, and absence of radiolucent lines around > 50% of the	Fusion was deemed successful only if all criteria were met In the ICBG group, no patient had a fracture, migration, or extrusion of the FRA 14 (18%) of 79 patients in the rhBMP2 group
		ICBG N=52			ICBG 85, 89, 76 (p=0.047, 0.035, < 0.001)			

rec# 11510; same pts as Burkus et al., 2006, rec# 6640							graft Fusion evaluated by two independent radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	had transient localized areas of bone remodeling in the vertebral body adjacent to a FRA, visible between 3 and 12 mos. postsurgery, but resolved by 24 mos
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al, 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG n=224	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	6, 12, 24 mos rhBMP2/CRM 79, 88, 96 ICBG 65, 83, 89 (p=0.002, 0.107, 0.014)	NR	Presence of bridging trabecular bone between the transverse processes, absence of motion, defined as 3 mm or less of translation and < 5 degrees of angular motion on flexion-extension views, and absence of radiolucent lines through the fusion mass Fusion evaluated by two independent radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	Thin-cut CT showed progressive formation of bridging bone across the transverse processes
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability,	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	rhBMP2 24 mos 46 of 48 (96)	NR	Plain radiographs: fusion mass graded as solid fusion, probabale fusion, or nonunion CT fusion rating	Fusion grade a composite score from 2 reviewers of CT scans

			spinal stenosis, adjacent level degeneration				scale: Grade 1=no fusion Grade 2=partial or limited unilateral fusion Grade 3=partial or limited bilateral fusion Grade 4=solid unilateral fusion Grade 5=solid bilateral fusion Fusion evaluated by two independent radiologists who were unaware of treatment	
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported) ICBG n=52	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	rhBMP2 86 Average CT fusion grade at 24 mos rhBMP2 4.3±1.3 ICBG 71 Average CT fusion grade at 24 mos ICBG 3.8±0.9 (p=0.030)	NR	CT fusion rating scale: Grade 1=no fusion Grade 2=partial or limited unilateral fusion Grade 3=partial or limited bilateral fusion Grade 4=solid unilateral fusion Grade 5=solid bilateral fusion Fusion evaluated independently by 3 orthopedic spine surgeons unaware of treatment	Fusion grade a composite score from 3 reviewers of CT scans
Haid et al., 2004 USA (88)	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single-level lumbar DDD	single-level primary posterior lumbar	6, 12, 24 mos rhBMP2 93, 85, 92	NR	Presence of bridging bone connecting adjacent vertebral bodies, < 5 degrees	Secondary surgeries were classified as fusion failures regardless of

Lumbar Spine		ICBG N=33		interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG	ICBG 93, 92, 78		of angular motion, ≤ 3 mm translation, and absence of radiolucent lines around > 50% of the graft Fusion evaluated by two independent radiologists who were unaware of treatment, a third was consulted for adjudication of disagreement	independent radiologic assessment New bone formation extending outside the disc space and into the spinal canal or neuroforamina was observed in 24 rhBMP2 (71) and 4 (12) ICBG recipients ($p < 0.0001$) but was not correlated with recurrence or increase in leg pain from the preoperative status
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Radiographic fusion 12 mos rhBMP7 60 bilateral bridging bone 30 partial bone formation 10 no bone formation	NR	Bone formation classified as radiographic evidence of bilaterally bridging bone, partial bone formation, or no bone formation	RSA analysis showed no significant differences in L5 stabilization or movement
		ICBG n=10			ICBG 80 bilateral bridging bone 20 partial bone formation			
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	Radiographic fusion criteria at 15.3 mos rhBMP7 78 Surgical evidence of solid fusion rhBMP7 57 (4 of 7)	NR	Presence of bridging bone on CT scan in posterolateral lumbar area, ≤ 5 degrees of angulation and ≤ 2 mm of translation at the index level	No significant differences in fusion,but small pt numbers limit ersults
		AGB/CRM			Radiographic fusion			

		n=10			criteria at 15.3 mos AGB/CRM 90 Surgical evidence of solid fusion AGB/CRM 78 (7 of 9)			
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	rhBMP2/AGB 96 at average 8 mos. F/U ICBG 95 at average 11 mos. F/U	rhBMP2/AGB 3.6±2.0 (1-9) ICBG 6.4±2.4 (3-12)	Presence of bridging bone connecting adjacent vertebral bodies, lack of motion on dynamic flexion-extension radiographs, absence of halo around screws Fusion analysis method not mentioned	Only used plain radiographs for fusion studies
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	24 mos rhBMP2 4 of 9 (44) Non-unions rhBMP 5 (56) 24 mos ICBG 17 of 27 (63) Non-unions ICBG 10 (37)	NR	Presence of bridging bone connecting adjacent vertebral bodies, either through the FRA or around the FRA, < 5 degrees of angular motion, ≤ 3 mm translation, and absence of radiolucent lines around > 50% of the graft Fusion evaluated by a radiologist who was unaware of treatment	Fusion was deemed successful only if all criteria were met Graft and endplate resorption reported to occur earlier and more aggressively in pts treated with rhBMP2 compared with ICBG, which may be related to number of non-unions and delayed unions
Singh et al., 2006 USA	Prospective single-center case-matched	rhBMP2/ICBG n=39 (12-36 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented	24 mos rhBMP2/ICBG 94 (68 of 70 levels)	NR	Presence of continuous trabecular bone between	Fusion quality was subjectively assessed as excellent in 92% of

(102) **Lumbar Spine**	cohort study	 ICBG N=11		posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	 ICBG 77 (17 of 22 levels) ($p < 0.05$)		intertransverse processes, cortication at the peripheral edge of the fusion mass, and absence of identifiable radiographic cleft on CT assessment Fusion evaluated by two orthopedic surgeons and a radiologist, all unaware of treatment	rhBMP2/ICBG recipients and 27% of ICBG recipients ($p < 0.05$)
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	6, 12, 24 mos rhBMP2 79, 96, 99 ALG 23, 73, 82 ($p < 0.001$ at all times)	NR	Molinari-Bridwell grading (Molinari et al., 1999) scale used: Grade 1: fused with remodeling and trabeculae present Grade 2: Graft intact, not fully remodeled and incorporated, no lucency Grade 3: Graft intact, potential lucency present at top or bottom of graft Grade 4: Fusion absent with collapse/resorption of graft Grades 1-2 were considered fused, Grades 3-4	No osteolysis or fragmentations of FRA were observed

							considered not fused All studies were reviewed by independent reviewers uaware of treatment	
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Bridging bone (CT) 36+ mos rhBMP2 75	NR	Presence of new bone formation bridging across the transverse processes, angulation ≤ 5 degrees, and ≤ 3 mm of translation were required Fusion evaluated independently by 2 primary spine surgeons unaware of treatment, a third was consulted for adjudication of disagreement	Overall radiographic comprised 3 components necessary to define fusion No significant differences seen in fusion parameters at 36+ mos. F/U
					≤ 5 degrees angulation (plain film) rhBMP7 69			
					≤ 3 mm translation (plain film) rhBMP7 76			
		ICBG n=86			Bridging bone (CT) 36+ mos ICBG 77			
					≤ 5 degrees angulation (plain film) ICBG 68			
					≤ 3 mm translation (plain film) ICBG 75			
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note:	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Solid fusion 48 mos rhBMP7 69 (11 of 16 with data)	NR	Complete bridging bone between transverse processes, ≤ 5 degrees of angulation and ≤ 2 mm of translation	Both groups showed equivalent reductions in disc height as well as angular and translational motion at the treated level
					Bridging bone 48 mos rhBMP7			

Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)		ICBG n=12			81 (13 of 16 with data) Solid fusion ICBG 50 (3 of 6 with data) Bridging bone 48 mos ICBG 50 (3 of 6 with data)		Fusion evaluated independently by 2 neuroradiologists unaware of treatment, a third was consulted for adjudication of disagreement	
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt) ICBG/ALG n=15	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	6, 12, 24 mos rhBMP2/ALG 100 at all times ICBG/ALG 100 at all times	NR	Plain radiograph: < 4 degrees difference in angular motion between flexion and extension, no radiolucency > 2 mm thick covering > 50% of the inferior or superior graft surface, presence of bridging trabecular bone CT: presence of bridging trabecular bone	Two pts in rhBMP2/ALG and one in the ICBG/ALG group demonstrated bone formation immediately anterior to segments adjacent to the index level
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	NR	NR	Plain films: Presence of bridging trabecular bone across disc space, < 1 mm gapping of spinous processes on flexion-extension films and selected high-resolution CT scans	2 pseudarthroses in ICBG group, 1 in the rhBMP2/CRA group
Crawford et al., 2009 USA	Retrospective cohort of consecutive	rhBMP2/BGE n=41 (4.2-12 mg/pt)	single- or multi-level posterior cervical	single- or multi-level instrumented	NR	NR	NR	

(105) **Cervical Spine**	patients	ICBG n=36	stenosis, ACDF nonunion, or unstable spondylosis	posterior cervical spinal fusion with rhBMP2/BGE or ICBG				
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	NR	
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	rhBMP2 100 ALG/DBM 96	NR	For the rhBMP2 group, bone formation was assessed as no new bone, visible new bone, possible fusion, and probable fusion For the ALG/DBM group fusion was assessed at the graft endplate junction, classified as not united, possibly united, and probably united	End plate resorption was noted in 100% of the levels where rhBMP2 was used, starting at 1.5 mos. and lasting until 6 mos
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	NR	Data was collected an analyzed to look at prediction of HO
Jones et al., 2006 USA (90) **Acute**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	BMP 13(87%)	Median time to healing BMP 184 days	Radiographic evidence of extracortical bridging callus on three of the four cortices as	

Tibial Fractures		(2) n=15 autogenous bone graft			No BMP 10(67%)	No BMP 176 days	viewed on anteroposterior and lateral radiographs	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone 43 fracture (OREF) N=20	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	All fractures in both groups united	BMP: 15.7 weeks (7 to 43) Matched: 23.5 weeks (11 to 63) P=.002	Fractures classified as united based on presence of briding callus at 3 of 4 corticies and appearance of trabecular bridging and healing	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscella-neous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	symptomatic proximal pole scaphoid nonunion	revision of nonunion	Radiographic bridging 1, 2, 24 mos rhBMP7/AGB 70-95, 90-100, 100 Mean sclerotic bone area (mm2) 3, 9, 24 mos rhBMP7/AGB 74±14, 45±11, 32±7 Radiographic bridging 1, 2, 24 mos rhBMP7/ALG 60-80, 75-90, 100 Mean sclerotic bone area (mm2) 3, 9, 24 mos rhBMP7/ALG 104±13, 77±8, 56±12 Radiographic bridging 1, 2, 24 mos ICBG 60-80, 75-90, 100 Mean sclerotic bone area (mm2) 3, 9, 24 mos	NR	Radiographic determination of graft replacement by newly formed, well-incorporated bone, with full mineralization at end of F/U	All three groups showed significant ($p < 0.05$) reduction of sclerotic bone area at 3 mos, but only the two rhBMP7-treated groups had significant reductions at 9 and 24 mos.

					ICBG 138±15, 119±19, 112±9 (p < 0.05 rhBMP7/AGB, rhBMP7/ALG vs ICBG at 24 mos)			
Dickinson et al., 2008 USA (91) **Miscella-neous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given)	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	Percent alveolar defect filled 12 mos rhBMP2/ACS 95	NR	Panorex and 3-D CT scores ranged from 0-3, with 0 representing minimum or no bone defect mineralization, 3 representing 75-100% mineralization Periapical film radiographic outcome scored using 4-point grading system, with 0 being no healing, 4 being total healing on periapical film Defect filling was evaluated by three blinded reviewers	
					Mean Panorex score 12 mos rhBMP2/ACS 2.9±0.3			
					Mean 3-D CT scan score 12 mos rhBMP2/ACS 2.9±0.3			
					Mean periapical film score 12 mos rhBMP2/ACS 3.4±0.3			
		ICBG n=12			Percent alveolar defect filled 12 mos ICBG 63 (p < 0.01)			
					Mean Panorex score 12 mos ICBG 2.0±0.8 (p < 0.05)			
					Mean 3-D CT scan score 12 mos			

					ICBG 2.0±0.8 (p < 0.05) Mean periapical film score 12 mos ICBG 2.8±0.4 (p < 0.05)			
Ekrol et al., 2008 UK (97) **Miscella-neous Off-Label Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation N=4	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	RhBMP2 Non bridging external fixation: Partial union 3, nonunion 1 (0%)	rhBMP2 Non bridging external fixation: 13 weeks (8-18)	Defect considered healed when at least 75% of the defect had been filled with trabecular bone on both radiological views	
		Bone graft Non bridging external fixation N=6			Bone graft Non bridging external fixation: 6 pts successful union (100%)	Bone graft Non bridging external fixation: 7 weeks (4-12) P=.05 (external fixation bmp vs graft)		
		RhBMP-7 internal fixation w/ pi-plate N=10			RhBMP-7 internal fixation w/ pi-plate: 6 partial union (dorsal defects), 2 non-union (20%)	RhBMP-7 internal fixation w/ pi-plate: 18 weeks (4-46)		
		Bone graft internal fixation w/ pi-plate N=10			Bone graft internal fixation w/ pi-plate: 10 successful union (100%) p value comparing bone graft and RhBMP-7 internal fixation w/ pi-	Bone graft internal fixation w/ pi-plate: 7 weeks (4-13) P=.019 (pi-		

					plate partial union=.015	plate fixation bmp vs graft)		
Geesink et al., 1999 Netherlands (98) **Miscella-neous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	New bone formation at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,0,1,1,2,3	NR	Response was classified as demonstrating bone formation that bridged the distal and proximal parts of fibular defect, bone formation that doesn't bridge defect, and no bone formation	
					New bone formation and bridging at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,0,0,0,0,0			
		DMB N=6			New bone formation at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,6,6,6,6,6			
					New bone formation and bridging at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,1,4,4,4,4			
		Collagen type I N=6			New bone formation at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,2,3,3,2,2			
					New bone formation and bridging at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,0,0,0,0,0			
		OP-1 (2.5mg) with Collagen type I N=6			New bone formation at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,5,5,5,5,5			

					New bone formation and bridging at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, and 12 mths: 0,4,5,4,4,5			
Karrholm et al., 2006 UK (111) **Miscella-neous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	Cups No. hips with radiolucent lines at 5 yrs No. hips with graft remodeling (total) at 5 yrs	NR	Graft remodeling classified according to most common appearance (pattern found in at least 2-3 of 3 modified Charnley-DeLee regions with equal size.	
					AP view (% total interface) 0, < 50, 51-99, 100 rhBMP7/ALG 2, 5, 2, 1			
					Lateral view (% interface) 0, < 50, 51-99, 100 rhBMP7/ALG 3, 2, 2, 1			
					AP view rhBMP7/ALG 10			
					Lateral view rhBMP7/ALG 6			
		Cups ALG n=10			AP view (% total interface) 0, < 50, 51-99, 100 ALG 2, 6, 2, 0			
					Lateral view (% interface) 0, < 50, 51-99, 100 ALG 5, 2, 3, 0			
					AP view			

					ALG 9			
					Lateral view ALG 8			
		Stems rhBMP7/ALG (1 g/pt) n=11			Stems No. hips with radiolucent lines at 5 yrs			
					AP view (% total interface) 0, < 50, 51-99, 100 rhBMP7/ALG 2, 7, 0, 0			
					Lateral view (% interface) 0, < 50, 51-99, 100 rhBMP7/ALG 5, 4, 0, 0			
					No. hips with graft remodeling (total) at 5 yrs			
					AP view rhBMP7/ALG 9			
					Lateral view rhBMP7/ALG 6			
		Stems ALG n=30			Stems AP view (% total interface) 0, < 50, 51-99, 100 ALG 9, 18, 12, 12			
					Lateral view (% interface) 0, < 50, 51-99, 100 ALG			

					11, 11, 2, 1 AP view ALG 29 Lateral view ALG 27			
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	Solid fusion rhBMP2/BGE 96 Cobb angle correction rhBMP2/BGE 51 Solid fusion ICBG 72 (p=0.057) Cobb angle correction ICBG 42	NR	Plain anteroposterior and lateral standing radiographs used to assess fusion, based on absence of pseudarthrosis as defined by: loss of fixation, progression of deformity, disc space collapse within fused portion, motion across the suspected pseudarthrosis; suspicion of nonunion was confirmed by CT scan	

Appendix 1 Table K. On-Label Comparative Study Pain Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Percent improved or success (p-value)	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 9, 12, 22, 25	Oswestry DI ≥ 15% improvement 3, 6, 12, 24 mos rhBMP2 55, 64, 91, 91	Success for ODI defined as ≥ 15% improvement over baseline score
		ICBG n=3			Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos ICBG 35, -18, 7, 8, 15	ICBG 0, 67, 67, 67	
					Iliac crest pain postharvest NR		
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Oswestry DI Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 12, 20, 25, 28, 30	Oswestry DI 12, 24 mos rhBMP2 85, 84	Success for ODI defined as ≥ 15% improvement over baseline score Both groups showed significant improvements from baseline, but there were no significant differences between groups in mean score or rates
					Back pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 6.5, 7.1, 7.2, 7.8, 8.5	Back pain (> 3 point improvement) 1.5, 3, 6, 12, 24 mos rhBMP 77, 74, 78, 79, 75	
					Leg pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 5.0, 5.7, 6.2, 6.2, 6.2	Leg pain (> 3 point improvement if baseline score > 10 points, or maintenance of score if < 10) 12, 24 mos rhBMP2 72, 80	
		ICBG n=136			Oswestry DI Mean score improvement (points)	Oswestry DI 12, 24 mos	

					1.5, 3, 6, 12, 24 mos ICBG 55, 14, 21, 26, 29, 31	ICBG 86, 82	
					Back pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG 7.3, 7.1, 7.2, 7.7, 8.2	Back pain (> 3 point improvement) 1.5, 3, 6, 12, 24 mos ICBG 76, 78, 72, 73, 79	
					Leg pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG 4.1, 5.7, 6.2, 5.9, 6.2	Leg pain (> 3 point improvement if baseline score > 10 points, or maintenance of score if < 10) 12, 24 mos ICBG 73, 74	
					Iliac crest pain postharvest Mean score (20 point VAS) 0, 24 mos 12.7, 1.8	Iliac crest pain postharvest % at 24 mos 32	
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 31, 26, 30, 31	NR	Both groups improved over time
					SF-36 pain index subscale Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 27, 32, 36, 39		
		ICBG n=402			Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos ICBG 5, 20, 23, 26 (p=0.0041, 0.0053, 0.0013, 0.0023 rhBMP2 vs ICBG)		

					SF-36 pain index subscale Mean score improvement (points) 3, 6, 12, 24 mos ICBG 20, 24, 29, 33 (p=0.0002 at 3, 6, 12 mos. and 0.0008 at 24 mos, rhBMP2 vs ICBG)		
					Iliac crest pain postharvest NR		
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	Oswestry DI Mean score improvement (points) 24 mos rhBMP2/CRM 28	Oswestry DI > 20% improvement 24 mos rhBMP2/CRM 91	Overall success rate was 81% in rhBMP2/CRM group and 55% in the ICBG group (p NSD)
					Back pain Mean score improvement (points) 24 mos rhBMP2/CRM 9.6		
					Leg pain Mean score improvement (points) 24 mos rhBMP2/CRM 9.3		
		ICBG n=21			Oswestry DI Mean score improvement (points) 24 mos ICBG 23	ICBG 70	
					Back pain Mean score improvement (points) 24 mos ICBG 7.2		
					Leg pain Mean score improvement (points) 24 mos		

					ICBG 7.2 Iliac crest pain postharvest NR		
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) rhBMP2 (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	Overall pain (1) 67% (2) 68% (3) 79% (0.0389 for comparison with 1, and 2) Iliac crest pain postharvest NR	NR	
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR Iliac crest pain postharvest NR	NR	
Boyne et al., 2005 USA (75) **Maxillofacial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18 rhBMP2/ACS (15-48 mg/pt) n=17 AGB n=13	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR Iliac crest pain postharvest 4 mos 38	NR	
Fiorellini et al.,	Double-blind,	rhBMP2/ACS	≥ 50% buccal	extraction	NR	NR	

2005 USA (76) **Maxillofacial and Dental**	multicenter randomized, placebo-control dose-comparison, safety and efficacy study	(mn dose 0.9 mg/pt) n=22 rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	bone loss of the extraction socket(s)	socket augmentation			
Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	Iliac crest pain postharvest Reported to have occurred in "many" patients Intraoral harvest site pain % at 6 mos 17	NR	
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	Iliac crest pain postharvest NR	NR	
Calori et al., 2008 Italy (78) **Long Bone Nonunion**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	Time to reach clinical union rhBMP7 md 3.5±0.5 mos PRP md 4±0.6 mos	Clinical union rhBMP7 87 Proportion pain-free 9 mos rhBMP7 upper extremity 97 lower extremity 80 Clinical union PRP 68 (p=0.016) Proportion pain-free	Clinical union: pain-free full-weight bearing for lower extremity fractures, pain-free movement for upper extremity fractures

						9 mos PRP upper extremity 91	
						lower extremity 81	
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	Patient-controlled analgesia for iliac crest pain postharvest % postoperative 33	Clinical union rhBMP7/ACS 100	Clinical union defined as painless full-weight bearing
		ICBG n=12				ICBG 100	
Friedlaender et al., 2001 (79) **Long Bone Nonunion**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt)	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	Autograft harvest site pain 0, 6, 12 mos 100 (80% moderate or severe), 20, 13	Pain on weight-bearing 9 mos rhBMP7/ACS 89	Clinical success defined as full-weight bearing with les than severe pain at the fracture site, and no further surgical intervention fo rth epurpose of enhancing repair
						Combined clinical success 9 mos rhBMP7/ACS 81	
		AGB n=61				Pain on weight-bearing 9 mos AGB 90	
						Combined clinical success 9 mos AGB 85	

Appendix 1 Table L. Off-Label Comparative Study Pain Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Percent improved or success (p-value)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	Oswestry DI Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~3, ~18, ~20, ~13	Oswestry DI ≥ 15% improvement 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~38, ~80, ~80, ~65	All pain outcomes showed significant improvement in both groups at 17-24 mos. but no significant intergroup differences except for SF-36 score at 17 mos
					Back pain Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~6, ~8, ~7, ~5		
					Leg pain Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~3, ~4, ~1, ~3		
					SF-36 bodily pain subscale Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~3, ~10, ~23, ~15		
		(40 mg/pt) rhBMP2/CRM alone n=11			Oswestry DI Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM alone ~19, ~22, ~25, ~29	rhBMP2 alone ~88, ~88, ~88, ~100	
					Back pain Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM alone ~8, ~9, ~9, ~10		

					Leg pain Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM ~8, ~9, ~7, ~9		
					SF-36 bodily pain subscale Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM alone ~22, ~32, ~35, ~35		
		(40 mg/pt) ICBG plus TSRHSS n=5			Oswestry DI Mean score improvement (points) 1.5, 3, 6, 17 mos ICBG/TSRHSS ~10, ~15, ~17, ~25	ICBG/TSRHSS ~80, ~60, ~80, ~80	
					Back pain Mean score improvement (points) 1.5, 3, 6, 17 mos ICBG/TSRHSS ~7, ~5, ~4, ~5		
					Leg pain Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ICBG/TSRHSS ~7, ~3, ~3, ~4		
					SF-36 bodily pain subscale Mean score improvement (points) 1.5, 3, 6, 17 mos ICBG/TSRHSS ~3, ~10, ~23, ~15 (rhBMP2/CRM alone, p=0.049 vs the other 2 groups)		
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded			Both groups had statistically significant improvement in the mean ODI,
		ICBG					

pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640		N=52		allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG			back, and leg pain scores compared to preoperative values Statistically signficant intergroup differences favoring rhBMP2 seen in all three indexes at specific times
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG n=224	single- or multi-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG		NR	All pain outcomes showed significant improvement in both groups at 24 mos. but no significant intergroup differences
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single-level lumbar DDD	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	NR	NR	Study only reported fusion data
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported)	single-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion	Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 14, 18, 19, 15	NR	Mean pain scores were similar in both groups at all time intervals,

				plus rhBMP2 or ICBG	Back pain Mean score improvement (points) 1.5, 6, 12, 24 rhBMP2 4.3, 4.1, 4.1, 3.1		with statistically significant improvement compared to preoperative mean scores but no significant intergroup differences
					Leg pain Mean score improvement (points) 1.5, 6, 12, 24 mos rhBMP2 4.6, 4.4, 3.8, 3.6		
		ICBG n=52			Oswestry DI Mean score improvement (points) 3, 6, 12, 24 mos ICBG 13, 17, 18, 13		
					Back pain Mean score improvement (points) 1.5, 6, 12, 24 ICBG 4.0, 4.0. 3.9, 3.0		
					Leg pain Mean score improvement (points) 1.5, 6, 12, 24 mos ICBG 4.1, 4.2, 3.9, 3.1		
					Iliac crest pain postharvest NR		
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single- or multi-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or	Oswestry DI Mean score improvement (points) 24 mos rhBMP2 30	Oswestry DI ≥ 15% improvement 24 mos rhBMP2 69	Both groups had statistically significant improvements in mean ODI, back, and leg pain at all times compared to preoperative
					Back pain Mean score improvement (points) 24 mos rhBMP2		

				ICBG	9 Leg pain Mean score improvement (points) 24 mos rhBMP2 7.7		values
		ICBG N=33			Oswestry DI Mean score improvement (points) 24 mos ICBG 25	ICBG 56	
					Back pain Mean score improvement (points) 24 mos ICBG 4.5 (p=0.009)		
					Leg pain Mean score improvement (points) 24 mos ICBG 6.5		
					Iliac crest pain postharvest Mean score (points) 24 mos 5.5		
					% with pain at 24 mos 60		
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR Iliac crest pain	Subjective evaluation of back pain 12 mos rhBMP7 None (4 pts)	Patients had similar pain outcomes, but no statistical analysis was done
						Minor w/out medication (4 pts)	
						Major with medication (2)	
		ICBG n=10				Subjective evaluation of back pain	

						12 mos ICBG None (5 pts)	
						Minor w/out medication (2 pts)	
						Major with medication (3 pts)	
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	Oswestry DI Mean score improvement (points) 3, 6, 9, 12 mos rhBMP7 ~15, ~23, ~16, ~17	NR	Both groups had signficant decreases in pain from baseline ($p < 0.05$, ANOVA), but NSD between groups
		AGB/CRM n=10			AGB/CRM ~17, ~31, ~24, ~24		
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	single-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	Prolo Scale Pain subscale Mean score at F/U (points) rhBMP2/AGB 3.8±0.9	NR	Statistical analysis not done
		ICBG N=19			Prolo Scale Pain subscale Mean score at F/U (points) ICBG 4.0±0.7		
					% with pain 6 mos 58		
					Mean pain score (points) 6 mos 5		
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR)	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy	single-level primary anterior lumbar interbody fusion (ALIF) with femoral	NR	NR	Study only reported fusion data
		ICBG n=27			Iliac crest pain NR		

			instability, spinal stenosis, adjacent level degeneration	ring allograft (FRA) plus rhBMP2 or ICBG			
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	NR Iliac crest pain NR	NR	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single-level lumbar lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	Oswestry DI Mean score improvement (points) 6, 12, 24 mos rhBMP2 27, 30, 33 NRS (undefined) Mean score improvement (points) 6, 12, 24 mos rhBMP2 4.2, 4.7, 4.8 Oswestry DI Mean score improvement (points) 6, 12, 24 mos ALG 17, 26, 30 ($p < 0.001$ at 6 mos) NRS (undefined) Mean score improvement (points) 6, 12, 24 mos ALG 2.8, 4.4, 4.3 ($p < 0.001$ at 6 mos)	NR	Both groups had statistically significant improvements in mean ODI and NRS at all times compared to preoperative values
Vaccaro et al., 2008 USA (94)	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented posterolateral	Oswestry DI mean percent improvement from baseline 36+ mos rhBMP7	Modified Overall Success 36+ mos rhBMP7 47	Both groups had significant decreases in pain from

Lumbar Spine				lumbar fusion with rhBMP7 or ICBG	52		baseline levels
					VAS scores 36+ mos NSD	Oswestry DI ≥ 20% improvement 36+ mos rhBMP7 69	
					SF-36 scores NSD		
		ICBG n=86			Oswestry DI mean percent improvement from baseline 36+ mos ICBG 54	Modified Overall Success 36+ mos ICBG 47 (p for noninferiority=0.025)	
					Iliac crest pain postharvest % with pain 12, 24, 36+ mos 44, 45, 35	Oswestry DI ≥ 20% improvement 36+ mos ICBG 77	
					Mean pain score (points) 1.5, 12, 24, 36+ mos 2.1, 1.6, 1.2, 1.1		
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt)	single- or multi-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	Oswestry DI mean score NR	Oswestry DI ≥ 20% improvement 48 mos rhBMP7 74 (14 of 19 with data) (95% CI, 49, 91)	Overall success is a composite measure comprising definitive spinal fusion, minimum 20% improvement in Oswestry DI, and absence of surgical retreatment
						Overall success 48 mos rhBMP7 62 (10 of 16 with data)	
						Overall success 48 mos, LOCF analysis rhBMP7 46 (95% CI, 26, 67)	
		ICBG n=12			Iliac crest pain NR	Oswestry DI ≥ 20% improvement 48 mos ICBG	

						57 (4 of 7 with data) (95% CI, 18, 90)	
						Overall success 48 mos ICBG 33 (2 of 6 with data)	
						Overall success 48 mos, LOCF analysis ICBG 25 (95% CI, 6-57)	
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	Neck Disability Index Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 37, 39, 48, 46, 53	Neck pain 24 mos rhBMP2/ALG 100	Both groups showed significant improvements from baseline, but there were no significant differences between groups in mean score or rates
					Neck pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 11, 11, 11, 12, 13		
					Arm pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 14, 14, 15, 14, 14		
		ICBG/ALG n=15			Neck Disability Index Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 33, 34, 39, 41, 37 ($p < 0.03$ at 24 mos)	ICBG/ALG 100	
					Neck pain Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 7, 8, 10, 9, 9		
					Arm pain		

					Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 9, 8, 10, 10, 8 ($p < 0.03$ at 24 mos) Iliac crest pain postharvest 1.5, 6, 24mos Pain reported at each time, but not quantified		
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	Oswestry Disability Index Mean score improvement (points) 7-12, 13-24, 25-36 mos rhBMP2/CRA ~14, ~25, ~30 Neck pain Mean score improvement (points) 7-12, 13-24, 25-36 mos rhBMP2/CRA ~4, ~4.5, ~5 Arm pain Mean score improvement (points) 7-12, 13-24, 25-36 mos rhBMP2/CRA ~3.3, ~4.2, ~5.5 Narcotic pain medication use (%) preop, 7-12, 13-24, 25-36 mos rhBMP2/CRA 53, 30, 23, 10 Oswestry Disability Index Mean score improvement (points) 7-12, 13-24, 25-36 mos ICBG ~11, ~17, ~31 Neck pain Mean score improvement (points) 7-12, 13-24, 25-36 mos ICBG ~4, ~4, ~5 Arm pain Mean score improvement (points) 7-12, 13-24, 25-36 mos ICBG ~3.9, ~3.8, ~4.8	NR	Both groups showed significant improvements from baseline, but there were no significant differences between groups in mean score or rates

					Narcotic pain medication use (%) preop, 7-12, 13-24, 25-36 mos ICBG 61, 39, 19, 6 Iliac crest pain postharvest		
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	single- or multi-level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	NR Iliac crest pain postharvest	NR	
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	Oswestry Disability Index Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos rhBMP2 -3.6, 6, 8, 8, 14, 24 Neck pain Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos rhBMP2 2, 2, 2, 2, 3, 4 Arm pain Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos rhBMP2 1, 1, 2, 2, 3, 4 Oswestry Disability Index Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos ALG/DBM	NR	Both groups showed significant improvements from baseline, but there were no significant differences between groups in mean score or rates

					2, 6, 10, 21, 28, 33 Neck pain Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos ALG/DBM 4, 4, 4, 4, 5, 6 Arm pain Mean score improvement (points) 0.5, 1.5, 3, 6, 12, 24 mos ALG/DBM 3, 4, 3, 5, 5, 5		
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR Iliac crest pain postharvest NR	NR	
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips (2) n=15 autogenous bone graft	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	NR Iliac crest pain postharvest % with pain at 5 days-4.5 mos 100, 1 had residual pain at 12 mos	NR	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Iowa Ankle Score: BMP: 84(70 to 100) Restriction in Range of motion Dorsiflection (1) -12 (-42-5) Plantar flexion (1) -10 (-50-5) Iowa Ankle Score:	NR	

		43 fracture (OREF) N=20			Matched: 81.6 (46 to 98) P=.6		
					Restriction in Range of motion Dorsiflection (2) -8 (-33-6) P-value 0.7		
					Plantar flexion (2) -6 (-20-8) P-value 0.3		
					Iliac crest pain postharvest NR		
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt)	symptomatic proximal pole scaphoid nonunion	revision of nonunion	Pain at rest 4, 12 mos 0 in all three groups	NR	Pain score range 0-100 points
					Pain during maximal grip 4, 12 mos rhBMP7/AGB 0, 3±1		
					Pain in maximal dorsiflexion 4, 12 mos rhBMP7/AGB 0, 6±1		
		rhBMP7/ALG n=6 (3.5 mg/pt)			Pain during maximal grip 4, 12 mos rhBMP7/ALG 3±1, 0		
					Pain in maximal dorsiflexion 4, 12 mos rhBMP7/ALG 3±1, 0		
		ICBG n=6			Pain during maximal grip 4, 12 mos ICBG 5±1, 6±1		
					Pain in maximal dorsiflexion 4, 12 mos ICBG		

					15±2,11±2 Iliac crest pain postharvest Patients in both autograft groups reported pain, but not quantified		
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR Iliac crest pain postharvest % with pain 0, 6 mos 100, 25	NR	
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation N=6 RhBMP-7 internal fixation w/ pi-plate N=10 Bone graft internal fixation w/ pi-plate N=10	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	Pain (10 cm VAS mean) at pre-op, 52 wks, and % change: rhBMP2 Non bridging external fixation: 4,3,25% Bone graft Non bridging external fixation: 5,3,30% NS p value RhBMP-7 internal fixation w/ pi-plate: 5,2,60% Bone graft internal fixation w/ pi-plate 5,4,20% NS p value Iliac crest pain postharvest	rhBMP2 Non bridging external fixation: 25% improvement Bone graft Non bridging external fixation: 30% improvement RhBMP-7 internal fixation w/ pi-plate: 60% improvement Bone graft internal fixation w/ pi-plate 20% improvement No significant P values	
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	Severity of pain on fibular osteotomy 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, 12 mths: (none, mild, moderate, severe) Untreated: (0,2,3,1), (4,2,0,0), (5,1,0,0),		

					(5,1,0,0),(5,1,0,0), (6,0,0,0)		
		DMB N=6			DMB: (0,4,2,0), (4,2,0,0), (6,0,0,0), (5,1,0,0),(4,2,0,0) , (6,0,0,0)		
		Collagen type I N=6			Collagen type 1: (6,0,0,0), (4,2,0,0), (2,4,0,0), (5,1,0,0), (5,1,0,0) , (6,0,0,0)		
		OP-1 (2.5mg) with Collagen type I N=6			OP-1 on collagen type 1: (2,4,0,0), (2,4,0,0), (1,4,1,0), (3,2,1,0), (1,2,3,0), (3,2,1,0)		
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	Cups Median pain score (rng) 0, 2, 5 yrs rhBMP7/ALG 20 (0-44), 44 (30-44), 44 (40-44)	NR	
					Median Harris hip score (rng) 0, 2, 5 yrs rhBMP7/ALG 52 (18-83), 98 (72-100), 94 (68-99)		
		Cups ALG n=10			Cups Median pain score (rng) 0, 2, 5 yrs ALG 20 (10-44), 44 (30-44), 44 (40-44)		
					Median Harris hip score (rng) 0, 2, 5 yrs ALG 49 (11-93), 84 (72-98), 83 (76-100) (p=0.02 at 2 yrs)		
		Stems rhBMP7/ALG (1 g/pt) n=11			Stems Median pain score (rng) 0, 2, 5 yrs rhBMP7/ALG		

					20 (0-44), 44 (30-44), 44 (40-44) Median Harris hip score (rng) 0, 2, 5 yrs rhBMP7/ALG 49 (18-82), 93 (68-100), 89 (75-99)		
		Stems ALG n=30			Stems Cups Median pain score (rng) 0, 2, 5 yrs ALG 20 (0-44), 44 (20-44), 44 (20-44) Median Harris hip score (rng) 0, 2, 5 yrs ALG 49 (11-95), 85 (46-100), 85 (55-100)		
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt)	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	NR	NR	Study reported only radiographic fusion results
		ICBG n=32			Iliac crest pain postharvest NR		

Appendix 1 Table M. On-Label Comparative Study Functional Outcomes

Investigator (yr, country, ref #)	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Outcome measure % improved or success (p-value)	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	SF-36 physical function subscale Mean score improvement (points) 3, 6, 12. 24 mos rhBMP2 10, 18, 27, 38	Work status at 24 mos rhBMP2 10 of 11 (91%) pts working	No significant differences between groups
		ICBG n=3			ICBG 13, 27, 37, 37	ICBG 2 of 3 (67%)	
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	Median days return to work rhBMP2 64	Neurological status 1.5, 3, 6, 12, 24 mos rhBMP2 80, 84, 78, 82, 83	No significant differences between groups
						Work status 3, 6, 12, 24 mos rhBMP2 38, 51, 55, 66 working	
		ICBG n=136			ICBG 65	Neurological status 1.5, 3, 6, 12, 24 mos ICBG 84, 77, 81, 85, 84	
						Work status 3, 6, 12, 24 mos ICBG 28, 46, 50, 56 working	

Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	SF-36 physical component subscale Mean score improvement (points) pre, 3, 6, 12, 24 mos rhBMP2 9, 12, 14, 16	Work status at 24 mos rhBMP2 103 (75%) who were working presurgery returned to work	rhBMP recipients returned to work a median 55 days sooner than ICBG graft recipients (adjusted p=0.0156)
		ICBG n=402			ICBG 5, 8, 10, 12 (p=0.0015, 0.0004, 0.0003, 0.0007)	ICBG 109 (65%) who were working presurgery returned to work (p NSD)	
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	SF-36 physical component subscale Mean score improvement (points) 24 mos rhBMP2/CRM 13	Work status at 24 mos rhBMP2/CRM 8 of 23 (3%5) working	The rhBMP2/CRM group appeared to improve faster than the ICBG group, but this impression was not statistically supported
					SF-36 physical function subscale Mean score improvement (points) 24 mos rhBMP2/CRM 36		
		ICBG n=21			SF-36 physical component subscale Mean score improvement (points) 24 mos ICBG 10	ICBG 6 of 20 (30%) working	

					SF-36 physical function subscale Mean score improvement (points) 24 mos ICBG 18		
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) rhBMP2 (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	NR	NR	
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	NR	

on 131 of the same patients included in Govender et al., 2002 (74)		(2) n=169 Standard care (IM nail fixation and soft tissue management)					
Boyne et al., 2005 USA (75) **Maxillofacial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR	Prosthesis implantation into newly induced bone rhBMP2/ACS 0.75 mg/mL 83 Successful prosthetic functional loading at 36 mos. (% patients) rhBMP2/ACS 0.75 mg/mL 100/67 (12 of 12 observed/12 of 18 enrolled) Bone quality at dental implant placement (Branemark criteria) I, >I-II, >II-III, >III-IV (%) rhBMP7/ACS 0.75 mg/mL (n=15) 0, 7, 53, 40	Patient success was defined as having an augmentation procedure with at least one implant placed into newly formed bone without additional augmentation, achieved osseointegration of sufficient number of implants to allow prosthetic device implant, and maintained prosthetic use for 36 mos. following functional loading

		rhBMP2/ACS (15-48 mg/pt) n=17				Prosthesis implantation into newly induced bone rhBMP2/ACS 1.50 mg/mL 88	
						Successful prosthetic functional loading at 36 mos. (% patients) rhBMP2/ACS 1.50 mg/mL 100/76 (13 of 13 observed/13 of 17 enrolled)	
						Bone quality at dental implant placement (Branemark criteria) I, >I-II, >II-III, >III-IV (%) rhBMP7/ACS 1.50 mg/mL (n=15) 0, 20, 60, 20	
		AGB n=13				Prosthesis implantation into newly induced bone rhBMP2/ACS AGB 100	

						Successful prosthetic functional loading at 36 mos. (% patients) AGB 100/62 (8 of 8 observed/8 of 13 enrolled)	
						Bone quality at dental implant placement (Branemark criteria) I, >I-II, >II-III, >III-IV (%) rhBMP7/ACS AGB (n=12) 0, 8, 58, 33	
Fiorellini et al., 2005 USA (76) **Maxillofacial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	NR	Dental implant placement without secondary augmentation rhBMP2/ACS 0.75 mg/mL 55	
		rhBMP2/ACS (mn dose 1.9 mg/pt) n=21				1.50 mg/mL 86	
		Placebo n=17				Placebo 59	
		No Tx n=20				No tx 45 (p=0.009 vs no tx)	

Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt)	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR	Prosthesis implantation into newly induced bone rhBMP2/ACS 82	Patient success was defined as having an augmentation procedure with at least one implant placed into newly formed bone without additional augmentation, achieved osseointegration of sufficient number of implants to allow prosthetic device implant, and maintained prosthetic use for 24 mos. following functional loading
						Successful prosthetic functional loading at 24 mos. (% patients) rhBMP2/ACS 76	
		AGB n=80				Prosthesis implantation into newly induced bone AGB 95	
						Successful prosthetic functional loading at 24 mos. (% patients) AGB 91 (p=0.0166)	
van den Bergh et al., 2000 Netherlands (82)	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt)	partly edentulous	maxillary sinus floor augmentation	NR	Implant placement at 6 mos rhBMP7/ACS 33	Statistical analysis not done, too few observations

Maxillofacial and Dental		ICBG n=3				ICBG 100	
Calori et al., 2008 Italy (78) **Long Bone Nonunion**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	NR	NR	
Dahabreh et al., 2008 (83) **Long Bone Nonunion**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	NR	NR	

Friedlaender et al., 2001 (79) **Long Bone Nonunion**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt)	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	NR	Weight-bearing 9 mos rhBMP7/ACS 86	
		AGB n=61				AGB 85	

Appendix 1 Table N. Off-Label Comparative Study Functional Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score (p-value)	Outcome measure % improved or success (p-value)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS ~1, ~0, ~5, ~4	NR	Both rhBMP2/CRM groups showed statistically significant improvements over baseline, the ICBG group did not
		(40 mg/pt) rhBMP2/CRM alone n=11			rhBMP2/CRM alone ~1, ~9, ~11, ~16		
		(40 mg/pt) ICBG plus TSRHSS n=5			ICBG/TSRHSS ~1, ~3, ~2, ~17		
Burkus et al., 2005 USA (85) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft	SF-36 physical component subscale Mean score improvement (points) 6, 12, 24 mos rhBMP2 43, 45, 45	NR	SF-36 scores in both groups showed steady improvement from 6 to 24 mos. postsurgery

Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640				cortical bone dowels (CBD) plus rhBMP2 or ICBG	Average days to return to work rhBMP2 89		
		ICBG N=52			SF-36 physical component subscale Mean score improvement (points) 6, 12, 24 mos ICBG 37, 39, 39 (p=0.001, 0.003, 0.015)		
					Average days to return to work ICBG 96 (p=not significant)		
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007,	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/CRM ~4, ~9, ~13, ~13, ~13	Work status at 24 mos rhBMP2/CRM 87 of 207 (42) working	SF-36 physical component scale mean score improvements at 24 mos. exceeded a 5.41 point threshold proposed to be clinically significant (Ware

rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040		ICBG n=224			ICBG ~4, ~8, ~9, ~10, ~10	ICBG 89 of 184 (48) working	et al., 1994)
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	NR	NR	Study only reported fusion data
Glassman et al., 2008 USA (87) **Lumbar**	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral	SF-36 physical component subscale Mean score improvement (points) 3, 6, 12, 24 mos rhBMP2 7, 8, 10, 7	NR	Both groups showed substantial improvements over baseline, with

Spine		ICBG n=52		lumbar fusion plus rhBMP2 or ICBG	ICBG 7, 9, 10, 7		no significant intergroup differences
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2 ~5, ~10, ~12, ~14, ~14	Overall neurological success 24 mos rhBMP2 100	Overall neurological success rate represents a combination of the four neurological measurements
					Motor function Mean score improvement (points) 24 mos rhBMP2 4.5		
					Sensory function Mean score improvement (points) 24 mos rhBMP2 8.0		
					Reflex function Mean score improvement (points) 24 mos rhBMP2 7.0		

					Straight leg raise Mean score improvement (points) 24 mos rhBMP2 48		
					Median days to return to work rhBMP2 43		
		ICBG N=33			SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG ~2, ~6, ~6, ~6, ~11	ICBG 100	
					Motor function Mean score improvement (points) 24 mos ICBG 2.8		
					Sensory function Mean score improvement (points) 24 mos ICBG 2.8		

					Reflex function Mean score improvement (points) 24 mos ICBG 5.4		
					Straight leg raise Mean score improvement (points) 24 mos ICBG 39		
					Median days to return to work ICBG 137 (p=NSD)		
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	NR	
Kanayama et al., 2006 Japan, Cleveland	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral	NR	NR	

(93) **Lumbar Spine**		AGB/CRM n=10		lumbar fusion with rhBMP7 or AGB/CRM			
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	Prolo Scale Functional status subscale Mean score at F/U rhBMP2/AGB 3.8±0.9	NR	No statistical analysis
		ICBG N=19			ICBG 4.0±0.7		
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	NR	NR	Study only reported fusion data
		ICBG n=27					
Singh et al., 2006 USA (102) **Lumbar**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral	NR	NR	

Spine		ICBG N=11		lumbar fusion with rhBMP2 plus ICBG or ICBG alone			
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	NR	NR	
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	Neurological success 36+ mos rhBMP7 84 ICBG 80	Neurological success is a composite outcome comprising muscle strength, reflexes, sensation, and straight leg raise

Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	Patients in both groups displayed increases in the SF-36 physical component subscale, increasing from the 25th percentile, reaching age-matched normative values at 48 mos. (data not shown)	
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 9, 13, 14, 14, 17 SF-36 mental component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 19, 16, 22, 22, 22	SF-36 physical component subscale 24 mos rhBMP2/ALG 92 SF-36 mental component subscale 24 mos rhBMP2/ALG 92	No significant differences between group

						Neurological status 1.5, 3, 6, 12, 24 mos rhBMP2/ALG 94, 100, 88, 100, 100	
		ICBG/ALG n=15			SF-36 physical component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 7, 12, 14, 16, 16	SF-36 physical component subscale 24 mos ICBG/ALG 100	
					SF-36 mental component subscale Mean score improvement (points) 1.5, 3, 6, 12, 24 mos ICBG/ALG 10, 5, 12, 8, 7	SF-36 mental component subscale 24 mos ICBG/ALG 75	
						Neurological status 1.5, 3, 6, 12, 24 mos ICBG/ALG 100, 100, 100, 93, 100	
Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumente	NR	Neurological deficits manifested as weakness and altered sensation rhBMP2/CRA 100	

		ICBG n=36		d ACDF with rhBMP2/CRA or ICBG		ICBG 100	
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	single- or multi-level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	NR	NR	
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	NR	

Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips (2) n=15 autogenous bone graft	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	NR only in a graph	SMFA performance index Mean change from baseline to 12 months BMP -23.9 SMFA bother indec BMP -24.6 SMFA performance index Mean change from baseline to 12 months No BMP -22.2 SMFA bother indec No BMP -20.3	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Mean duration of external fixation in weeks: BMP: 15(9 to 37) Mean length of sick leave in months: BMP: 6.3 (3 to 13)	NR	

					Restriction in range of movement dorsiflexion: BMP: 12 (-42 to 5)		
					Restriction in range of movement plantar flexion: BMP: 13 (50 to 5)		
					Secondary intervention due to delayed healing: BMP: 2		
		Matched Zone 43 fracture (OREF) N=20			Mean duration of external fixation in weeks: Matched 21.4 (10 to 40) P=.037		
					Mean length of sick leave in months: Matched 9 (4 to 15) P= .018		
					Restriction in range of movement dorsiflexion: Matched 10 (-33 to 6) P=.71		
					Restriction in range of movement plantar flexion: Matched: 7 (20 to 8) P=.3		

					Secondary intervention due to delayed healing: Matched 7 P=.13		
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG	symptomatic proximal pole scaphoid nonunion	revision of nonunion	Mean grip strength (kg) 4, 12 mos rhBMP7/AGB 36±4, 41±5	NR	Patients in all 3 groups showed improvement of all functional measures and clinical outcomes throughout the 24 mos. F/U
					Mean pinch strength (kg) 4, 12 mos rhBMP7/AGB 8±2, 10±2		
		n=6 (3.5 mg/pt)			Mean grip strength (kg) 4, 12 mos rhBMP7/ALG 31±3, 37±3		
					Mean pinch strength (kg) 4, 12 mos rhBMP7/ALG 6±1, 9±2		
		ICBG n=6			Mean grip strength (kg) 4, 12 mos ICBG 28±4, 35±4		

					Mean pinch strength (kg) 4, 12 mos ICBG 6±1, 9±2		
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	NR	
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation N=4	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	Pre-op, 52-wks, % change Ability to undertake daily living activities: rhBMP2 Non bridging external fixation 77,85,10%	P values all non significant for outcome measures.	
					Grip strength: rhBMP2 Non bridging external fixation 69,78,13%	Ability to undertake daily living activities: rhBMP2 Non bridging external fixation 10%	
					Pronation: rhBMP2 Non bridging external fixation 81,85,5%	Grip strength: rhBMP2 Non bridging external fixation 13%	

					Supination rhBMP2 Non bridging external fixation 74,58,-22%	Pronation: rhBMP2 Non bridging external fixation 5%	
					Flexion rhBMP2 Non bridging external fixation 40,48,20%	Supination rhBMP2 Non bridging external fixation -22%	
					Extension rhBMP2 Non bridging external fixation 57,53,-7%	Flexion rhBMP2 Non bridging external fixation 20%	
					Ulnar deviation rhBMP2 Non bridging external fixation 24,23,-4%	Extension rhBMP2 Non bridging external fixation -7%	
					Radial deviation rhBMP2 Non bridging external fixation 20,28,40%	Ulnar deviation rhBMP2 Non bridging external fixation -4%	
					No significant P values	Radial deviation rhBMP2 Non bridging external fixation 40%	

		Bone graft Non bridging external fixation N=6			Pre-op, 52-wks, % change Ability to undertake daily living activities: Bone graft Non bridging external fixation 65,100,54%	Ability to undertake daily living activities: Bone graft Non bridging external fixation 54%	
					Grip strength: Bone graft Non bridging external fixation 38,69,82%	Grip strength: Bone graft Non bridging external fixation 82%	
					Pronation: Bone graft Non bridging external fixation 86,82,-5%	Pronation: Bone graft Non bridging external fixation -5%	
					Supination Bone graft Non bridging external fixation 68,82,21%	Supination Bone graft Non bridging external fixation 21%	
					Flexion Bone graft Non bridging external fixation 42,60,43%	Flexion Bone graft Non bridging external fixation 43%	
					Extension Bone graft Non bridging external fixation 46,49,7%	Extension Bone graft Non bridging external fixation	

					Ulnar deviation Bone graft Non bridging external fixation 22,30,36%	Ulnar deviation Bone graft Non bridging external fixation 36%	
					Radial deviation Bone graft Non bridging external fixation 22,25,14%	Radial deviation Bone graft Non bridging external fixation 14%	
		RhBMP-7 internal fixation w/ pi-plate N=10			Pre-op, 52-wks, % change Ability to undertake daily living activities: RhBMP-7 internal fixation w/ pi-plate 49, 91, 86%	Ability to undertake daily living activities: RhBMP-7 internal fixation w/ pi-plate 86%	
					Grip strength: RhBMP-7 internal fixation w/ pi-plate 37, 81,119%	Grip strength: RhBMP-7 internal fixation w/ pi-plate 119%	
					Pronation: RhBMP-7 internal fixation w/ pi-plate 66,81, 23%	Pronation: RhBMP-7 internal fixation w/ pi-plate 23%	
					Supination RhBMP-7 internal fixation w/ pi-plate 60,79,32%	Supination RhBMP-7 internal fixation w/ pi-plate 32%	

					Flexion RhBMP-7 internal fixation w/ pi-plate 35,38,9%	Flexion RhBMP-7 internal fixation w/ pi-plate 9%	
					Extension RhBMP-7 internal fixation w/ pi-plate 50,43,-14%	Extension RhBMP-7 internal fixation w/ pi-plate -14%	
					Ulnar deviation RhBMP-7 internal fixation w/ pi-plate 18,25,39%	Ulnar deviation RhBMP-7 internal fixation w/ pi-plate 39%	
					Radial deviation RhBMP-7 internal fixation w/ pi-plate 16,23,44%	Radial deviation RhBMP-7 internal fixation w/ pi-plate 44%	
		Bone graft internal fixation w/ pi-plate N=10			Pre-op, 52-wks, % change Ability to undertake daily living activities: Bone graft internal fixation w/ pi-plate 61,84, 38%	Ability to undertake daily living activities: Bone graft internal fixation w/ pi-plate 38%	
					Grip strength: Bone graft internal fixation w/ pi-plate 48,73,52%	Grip strength: Bone graft internal fixation w/ pi-plate 52%	

					Pronation: Bone graft internal fixation w/ pi-plate 67,82,22%	Pronation: Bone graft internal fixation w/ pi-plate 22%	
					Supination Bone graft internal fixation w/ pi-plate 63,78,24%	Supination Bone graft internal fixation w/ pi-plate 24%	
					Flexion Bone graft internal fixation w/ pi-plate 24,31,29%	Flexion Bone graft internal fixation w/ pi-plate 29%	
					Extension Bone graft internal fixation w/ pi-plate 43,37,-14%	Extension Bone graft internal fixation w/ pi-plate -14%	
					Ulnar deviation Bone graft internal fixation w/ pi-plate 17,28,65%	Ulnar deviation Bone graft internal fixation w/ pi-plate 65%	

					Radial deviation Bone graft internal fixation w/ pi-plate 19,25,32%	Radial deviation Bone graft internal fixation w/ pi-plate 32%	
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	Mean BMD (g/cm^2) of the fibular defect at 1 wk, 6 wks, 10 wks, 4 mths, 6 mths, 12 mths: (untreated, dmb, collagen type I, OP-1 on collagen type I): .44, .48, .47, .46, .43, .44	Untreated and collagen groups BMD stayed approximately the same while OP-1 and DMB group increased by about 80%. Untreated + collagen vs. DMB p=.001, Untreated + collagen vs OP-1 p=.0038	
		DMB N=6			.51, .51, .57, .70, .80, 1.01		
		Collagen type I N=6			.38, .43, .42, .43, .43, .44		
		OP-1 (2.5mg) with Collagen type I N=6			.45, .47, .53, .64, .69, .82		
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	Harris hip score is a composite that measures pain and activities of daily living, including walking, sitting, ability to dress oneself, presence of a limp (see table on pain outcomes for HHS results)	NR	
		Cups ALG n=10					
		Stems rhBMP7/ALG (1 g/pt) n=11					
		Stems ALG n=30					

Maeda et al., 2009 USA, Japan (109) **Miscellaneous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	NR	NR	

Appendix 1 Table O. On-Label Comparative Study Quality of Life and Satisfaction Outcomes

Investigator (yr, country, ref #)	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score	Outcome measure % improved or success (p-value)	Comment
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=11	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	SF-36 general health perception subscale Mean score improvement 0, 3, 6, 12, 24 mos rhBMP2 68, 74, 68, 70, 73	All improved over 24 mos. (p not reported)	At 24 mos. 11 of 11 pts in rhBMP2 group rated outcome as excellent; 1 of controls rated outcome as excellent, 1 each good and fair. Mean neurologic scores were increased over baseline at all time points in both groups.
		ICBG n=3			ICBG 59, 57, 75, 64, 67		
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 (4.2-8.4 mg/pt) n=143	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages plus rhBMP2 or ICBG	NR	Patient satisfaction 24 mos rhBMP2 81% satisfied	82% of rhBMP group indicated they would undergo same procedure, compared with 77% of ICBG group
		ICBG n=136				ICBG 80% satisfied	
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar fusion with interbody fusion cages	NR	NR	
		ICBG n=402					
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral	NR	NR	

		ICBG n=21		lumbar fusion plus rhBMP2 or ICBG			
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient) rhBMP2 (2) n=149 (12 mg/patient) (3) n=150 Standard care (IM nail fixation and soft tissue management)	Open tibial fracture where the major component was diaphyseal	IM nail fixation and soft tissue management	NR	NR	
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient) (2) n=169 Standard care (IM nail fixation and soft tissue management)	Acute open tibial fracture	IM nail fixation and soft tissue management	NR	NR	
Boyne et al., 2005 USA (75) **Maxillofacial and Dental**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18 rhBMP2/ACS (15-48 mg/pt) n=17 AGB n=13	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR	NR	

Fiorellini et al., 2005 USA (76) **Maxillofacial and Dental**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22 rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20	≥ 50% buccal bone loss of the extraction socket(s)	extraction socket augmentation	NR	NR	
Triplett et al., 2009 USA (77) **Maxillofacial and Dental**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	< 6 mm alveolar bone height in the posterior maxilla	staged bilateral or unilateral maxillary sinus floor augmentation	NR	NR	
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial and Dental**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	partly edentulous	maxillary sinus floor augmentation	NR	NR	
Calori et al., 2008 Italy (78) **Long Bone Nonunio**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	post-traumatic atrophic nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	open reduction internal fixation (ORIF), external fixation (EF), or reamed intramedullary nailing (IM) with rhBMP7 or PRP	NR	NR	

Dahabreh et al., 2008 (83) **Long Bone Nonunio**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt)	tibial fracture nonunion with clinical and radiographic failure to progress to union for ≥ 9 mos. following initial fracture stabilization	open reduction internal fixation (ORIF), exchange intramedullary nailing (IM), or Ilizarov, with rhBMP7 or ICBG	NR	NR	
		ICBG n=12					
Friedlaender et al., 2001 (79) **Long Bone Nonunio**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt)	tibial nonunion for ≥ 9 mos, with no signs of healing over the last 3 mos	IM rod fixation with rhBMP7/ACS or AGB	NR	Physician satisfaction 9 mos rhBMP7 86	
		AGB n=61				AGB 90	

Appendix 1 Table P. Off-Label Comparative Study Quality of Life and Satisfaction Outcomes

Investigator (yr, country, ref #)	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Outcome measure mean score	Outcome measure % improved or success (p-value)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	NR	Patient satisfaction (% good/excellent) pre, 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS 0, ~75, ~58, ~60, ~60	Patient satisfaction measurements generally paralleled results of SF-36 pain survey and Oswestry DI
						Physician impression (% good/excellent) pre, 1.5, 3, 6, 17 mos rhBMP2/CRM/TSRHSS 0, ~90, ~80, ~80, ~80	
		(40 mg/pt) rhBMP2/CRM alone n=11				Patient satisfaction (% good/excellent) pre, 1.5, 3, 6, 17 mos rhBMP2/CRM alone 0, ~100, ~88, ~88, ~100	
						Physician impression (% good/excellent) pre, 1.5, 3, 6, 17 mos rhBMP2/CRMalone 0, ~100, ~85, ~80, ~85	
		(40 mg/pt) ICBG plus TSRHSS n=5				Patient satisfaction (% good/excellent) pre, 1.5, 3, 6, 17 mos ICBG/TSRHSS 0, ~80, ~60, ~80, ~60	
						Physician impression (% good/excellent) pre, 1.5, 3, 6, 17 mos ICBG/TSRHSS 0, ~60, ~80, ~60, ~60	

Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt) ICBG N=52	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	NR	NR	
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG n=224	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	NR	NR	
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	NR	NR	Study only reported fusion data
Glassman et al., 2008 USA (87)	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not reported)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral	NR	NR	

Lumbar Spine		ICBG n=52		lumbar fusion plus rhBMP2 or ICBG			
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4) ICBG N=33	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF) interbody fusion cages plus rhBMP2 or ICBG		Patient satisfaction at 24 mos rhBMP2 72 ICBG 80	Patient satisfaction rates comprise results for pts who report definitely and mostly true that they were satisfied with their surgical outcomes
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	NR	
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	NR	NR	
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	Prolo Scale Economic status subscale Mean score at F/U rhBMP2/AGB 3.8±0.8 Medication use subscale Mean score at F/U rhBMP2/AGB 3.8±0.9	NR	Statistical analysis not done

		ICBG N=19			Prolo Scale Economic status subscale Mean score at F/U ICBG 4.1±0.7 Medication use subscale Mean score at F/U ICBG 4.2±0.8		
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	single-level lumbar DDD	single-level primary anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG	NR	NR	Study only reported fusion data
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	NR	NR	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion	NR	Patient satisfaction at 24 mos rhBMP2 86	None of the pts who underwent revision fusions in ALG group expressed satisfaction with their outcomes

		ALG N=30		(ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)		ALG 79	
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	NR	
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004 (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	Patients in both groups displayed increases in the SF-36 mental health component subscale, increasing from the 25th percentile, reaching age-matched normative values at 48 mos. (data not shown)	
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt) ICBG/ALG n=15	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	NR	Patient satisfaction 24 mos > 90% in both groups	Patient satisfaction related to whether they were satisfied with their results, whether they were helped as much as anticipated, and whether they would have the surgery again
Butterman et al., 2008 USA (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with	NR	Patient-reported success 13-24, 25-36 mos rhBMP2/CRA 90, 89	Patient satisfaction related to whether they were satisfied with their results, whether they would have the surgery

		ICBG n=36		rhBMP2/CRA or ICBG		ICBG 94, 97	again, and whether they would recommmend ot to others (97% in both groups)
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	single- or multi-level posterior cervical stenosis, ACDF nonunion, or unstable spondylosis	single- or multi-level instrumented posterior cervical spinal fusion with rhBMP2/BGE or ICBG	NR	NR	
Smucker et al., 2006 USA (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	
Vaidya et al., 2007 USA (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	NR	
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt) (2) n=23 no BMP	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multicenter prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	NR	NR	

		(2) n=15 autogenous bone graft					
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone 43 fracture (OREF) N=20	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	Iowa Ankle Score: BMP: 84(70 to 100) Matched: 81.6 (46 to 98) P=.6	NR	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	symptomatic proximal pole scaphoid nonunion	revision of nonunion	NR	NR	
Dickinson et al., 2008 USA (91) **Miscellaneous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	NR	
Ekrol et al., 2008 UK (97) **Miscellaneous Off-Label Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation N=6 RhBMP-7 internal fixation w/ pi-plate N=10	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	NR	NR	

		Bone graft internal fixation w/ pi-plate N=10					
Geesink et al., 1999 Netherlands (98) **Miscellaneous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6 DMB N=6 Collagen type I N=6 OP-1 (2.5mg) with Collagen type I N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductive materials	HSS mean score increased in all groups over time and was comparable at every followup. 68 before operation and 90 post-op	21 overall satisfied, 3 not satisfied. 1 unsatisfied in untreated, 1 op-1, 1 DMB	
Karrholm et al., 2006 UK (111) **Miscellaneous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10 Cups ALG n=10 Stems rhBMP7/ALG (1 g/pt) n=11 Stems ALG n=30	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	NR	NR	
Maeda et al., 2009 USA, Japan (109)	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	NR	NR	

Appendix 2

USPSTF Comparative Study Quality Rating

Appendix 2 Table A. USPSTF Comparative Study Quality

Study (ref #)	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable, Clearly Defined	Appropriate Analysis of Results	Funding or Sponsorship Source Acknowledged	Overall Rating
Baskin et al., 2003 (89)	U Randomization method not described Combined patients with one- and two-level DDD	U Low loss to F/U but unclear if groups were comparable at inception	Y	Y	U Cannot blind patients or surgeons to treatment, but used independent analyses of fusion Did not describe statistical analyses used	Y Medtronic Sofamor Danek	FAIR
Bilic et al., 2006 (96)	Y	Y	Y	Y	Y Surgeons were unaware of treatment group each patient was assigned after randomization Used independent analyses of fusion	N	GOOD
Boden et al., 2000 (71)	U Randomization method not described	Y	Y	Y	U No explicit ITT analysis Cannot blind patients or surgeons to	Y Medtronic Sofamor Danek	FAIR

					treatment, but used independent analyses of fusion		
Boden et al., 2002 (84)	U Randomization method not described	Y	Y	Y	U No explicit ITT analysis Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Sponsor not specified	FAIR
Boraiah et al., 2009 (108)	U Retrospective study of consecutive patients	U	N There was no blinding of outcome assessment	U Does not provide the BMP-2 dose used	Y	N	POOR
Boyne et al., 2005 (75)	Y Multicenter randomized, dose-comparison, safety and efficacy study	Y	Y	U Mixed autograft and allograft bone in some patients, did not define numbers	Y Used ITT analysis and three independent masked CT scan reviewers	Y Wyeth/Genetics Institute	GOOD
Burkus et al., 2005 (85) Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Y	Y	Y	Y	U No explicit ITT analysis Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Medtronic Sofamor Danek	FAIR
Burkus et al., 2003 (182)	N Retrospective combined analysis of data from 3 studies showing	N Patients not accounted for amount to 16%-	Y	Y	Y Used analysis of covariance to adjust for influence of prognostic	Y Medtronic Sofamor Danek	POOR

	significant between group differences in 6 prognostic factors	30% at end of 24 mos F/U			factors Cannot blind patients or surgeons to treatment, but used independent analyses of fusion		
Burkus et al., 2003 (80) Note: may be subset of Burkus et al., 2002, (72)	U Patient demographic data very limited (only mean age, gender, tobacco use provided, no statistical comparisons)	Y	Y	Y	U ITT analysis not explicit Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Not specified	FAIR
Burkus et al., 2002 (72) Note: may include pts in Burkus et al., 2003, (80)	U Randomization method not described	U Asserts > 90% F/U but based on ”expected” calculation	Y	Y	U ITT analysis not explicit Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	N	FAIR
Butterman et al., 2008 (104)	U Prospective non-randomized study of patients encountered in author’s clinical practice	U Patients made treatment decisions	Y	N Treatment differed based on patient’s decision Mixed local bone with BMP but did not discriminate	N Reported compiled results for groups with more than one level DDD Cannot blind patients or surgeons to treatment, did not report independent analyses of fusion	Y None	POOR
Calori et al.,	Y	Y	Y	N	U	Y	POOR

2008 (78)				Adjuvant bone grafts used according to surgeon's choice Revision of fixation according to surgeon's choice	Unclear if analysis of fusion was independent and blinded	None	
Crawford et al., 2009 (105)	U Not a randomized study Consecutive patients	U	U Only reported complications	N Bone graft extenders used at surgeon's discretion but not reported	Y Analysis of complications based on independent chart review by individual uninvolved with patient treatment	Y None	POOR
Dahabreh et al., 2008 (83)	U Retrospective study of consecutive patients Primarily a cost study	U	U No clinical health outcomes reported	U Do not report dose of rhBMP7 that was used per pt	U No clinical health outcomes reported	N	POOR
Dawson et al., 2009 (90)	Y Randomization stratified by site with fixed block size of 4	Y	Y	Y	Y Used modified ITT analysis that accounted for second surgery failures Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Medtronic Sofamor Danek	GOOD
Dickinson et al., 2008 (91)	U Randomization method not described	U	U Validity of outcome scoring systems is	U Did not provide dose information for	Y Cannot blind patients of surgeons, but used	Y Academic award	POOR

			unclear	rhBMP2	independent analyses of CT scans		
Dimar et al., 2009 (86) Note: contains all pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Y	Y	Y	Y	N Primary analysis predefined to be as-treated for assessing a noninferiority hypothesis Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Medtronic Sofamor Danek	FAIR
Ekrol et al., 2008 (97)	N Randomization not specified After 10 of 30 pts, treatment changed from external fixation to ORIF w/ pi-plate	Y 0 pts. lost to FU	Y	Y	U No explicit ITT analysis, authors Independent radiographic analysis blinded to treatment	Y Authors state no conflict of interest	POOR
Fiorellini et al., 2005 (76)	U Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study Scant demographic data	U Cannot ascertain comparability of patient groups because data not provided	Y	Y	Y Used ITT analysis and three independent masked CT scan reviewers	Y Wyeth/Genetics Institute	FAIR
Friedlaender et al., 2001 (79)	N Statistically higher number of atrophic nonunions and trend to	Y	Y	Y	Y Surgeons not blinded to treatment, but used independent analyses	Y Stryker Biotech	FAIR

	more smokers in rhBMP7 group Surgeons were aware of assigned treatment group after randomization				of fusion		
Geesnik et al., 1999 (98)	Patient randomization method not mentioned. Comparison of OP-1 on type I collagen sponge vs. collagen sponge alone was randomized, double-blinded	Y No pts. lost to FU 2 pts missed 1 FU appointment	Y	Y	N Missing values for 2 missed FU appointments not imputed Radiographic analysis conducted by 2 surgeons blinded to treatment	Y Stryker Biotech	FAIR
Glassman et al., 2008 (87)	U Randomization method not described	Y	Y	N Reported preparation of BMP according to label, but do not provide dose Reported use of bone graft extender in 100% of BMP cases and 67% of ICBG cases, plus local bone in 100% cases in both groups,	N No explicit ITT analysis Reported compiled data for multilevel fusions	Y Norton Healthcare	POOR
Glassman et al., 2007 (99)	N Retrospective study using historical controls	Y	N Did not report clinical health outcomes	N Reported use of bone graft extender in 100% of BMP cases,	Y Reported fusion data from disparate groups separately	Y Norton Healthcare	POOR

				compared to ICBG controls	Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Medtronic Sofamor Danek	
Govender et al, 2002 (74)	N Statistically significant difference in age rhBMP2 (12mg group) was younger 37 (for standard of care and the other treatment group) vs. 33 years Few demographics provided, and significance testing is not shown. Surgeons were not blinded to treatment assignment after randomization	Y	Y	Y	Y Surgeons not blinded but they used their conclusions in conjunction with an independent board who analyzed fusion	Y Wyeth/Genetics Institute	FAIR
Haid et al., 2004 (88)	U Randomization method not described Reports subset of pts from a larger terminated trial	U Do not know how reported patients compare to larger sample that would have been enrolled	Y	Y	U No explicit ITT analysis Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Medtronic Sofamor Danek	POOR
Johnsson et al., 2002 (92)	U Minimal demographic data	Y	U Short F/U	Y	N Cannot blind patients or surgeons to	Y Stryker Biotech provided rhBMP7	POOR

			Did not use CT analysis to supplement plain radiographs		treatment, but used independent analyses of fusion Used patient subjective evaluation of back pain as only health outcome measure		
Jones et al., 2006 (90)	U Randomization method not described	Y On the border with 20% loss to follow-up	N There was no blinding of outcome assessment however an independent review by a blinded assessor agreed with the clinical assessment	Y	Y There was no blinding of outcome assessment however an independent review by a blinded assessor agreed with the clinical assessment	Y Wyeth/Genetics Institute	FAIR
Kanayama et al., 2006 (93)	N Randomization method not described Minimal demographic data Significantly older pts in rhBMP7 group than ICBG group ($p < 0.05$)	N Groups different from beginning of study	Y	Y	N Cannot blind patients or surgeons to treatment, did not report independent analysis of fusion	Y None	POOR
Karrholm et al., 2006 (111)	Y Case-control study	Y	Y	U Reported use of one OP-1 kit per patient according to manufacturer instructions	N Did not report statistical analyses Study stopped early	Y Smith&Nephew Stryker Biotech	POOR
Maeda et al.,	N	U	Y	Y	N	Y	POOR

2009 (109)	Demographics appear similar, but used a nonconcurrent control group				Reported compiled fusion data for rhBMP2 group but interventions differed	None	
Mummameni et al., 2004 (100)	U Not a randomized study Unknown if consecutive pts	U	N	N Used rhBMP2 plus local autograft bone or iliac crest bone Do not describe how pts were allocated to interventions	N No statistical analysis done Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	N	POOR
Pradhan et al., 2006 (101)	U Non-randomized prospective cohort study	Y	Y	Y	Y Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y None	FAIR
Ristiniemi et al., 2007 (110) (same as Ristiniemi et al., 2007, rec# 4560)	U Prospective study of consecutive patients who were matched to a control	U	Y	U Does not provide the BMP-7 dose used	Y	N	POOR
Singh et al., 2006 (102)	N Not a randomized study Consecutive sex-matched patients	Y	Y	U	N Did not seem to account for apparent large age differential Cannot blind patients or surgeons to treatment, but used	N	POOR

					independent analyses of fusion		
Slosar et al., 2007 (103)	U Prospective, sequential enrollment, not randomized Patients with multilevel fusion mixed with single-level fusion, scoliosis	U	Y	Y	U Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Medtronic Sofamor Danek	POOR
Smucker et al., 2006 (106)	N Retrospective case-control study with consecutive patients	U Low loss to F/U but groups were clearly not comparable at inception	U Only reported complications	N Aspects of treatment with BMP varied according to surgeon's discretion	Y Used multiple logistic regression to assess association between BMP use, complications and other variables	Y None	POOR
Swiontkowski et al., 2006 (81) Note: This paper reports on 131 of the same patients included in Govender (74)	N Few demographics provided, and significance testing is not shown. Surgeon's were not blinded to treatment assignment after randomization Better description of the parent study randomization was needed	Y	Y	Y	Y	Y Wyeth/Genetics Institute Medtronic Sofamor Danek	FAIR
Triplett et al., 2009 (77)	Y Multicenter RCT	Y	Y	U Mixed autograft and	Y Used ITT analysis and	N	GOOD

				allograft bone in some patients, did not define numbers	three independent masked CT scan reviewers		
Vaccaro et al., 2008 (94)	Y	Y	Y	Y	Y Used modified ITT analysis Noninferiority design Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y None	GOOD
Vaccaro et al., 2008 (95) Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Y	N Only had full radiographic data for 61% of pts, and full clinical data for 72% of pts	Y	Y	U Analyzed and presented data as-treated and also with last-observation-carried forward method from 24 mos F/U Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	Y Stryker Biotech	POOR
Vaidya et al., 2007 (107)	U Retrospective study with consecutive patients	U Low loss to F/U but unclear if groups were comparable	Y	Y	Y Cannot blind patients or surgeons to treatment, but used independent analyses of fusion	N	POOR
van den Bergh et al., 2000	N	U	Y	Y	U	N	POOR

(82)	Retrospective consecutive cohort	All patients accounted for, but comparability is unclear			Open label pilot study, not clear if radiographic results were indepdently assessed		

Appendix 3

Reporting of Power and Sample Size Calculations in BMP Comparative Studies

Appendix 3 Table A. Assessment of Power and Sample Size in On-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical site	Study design	Comparison(s) No. pts (BMP dose)	Were power and sample size calculated by the authors	Did the study enroll sufficient sample size to meet the sample size requirements	Comments
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=11 (4.2-8.4 mg/pt) ICBG n=3	N	NA	
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=143 (4.2-8.4 mg/pt) ICBG n=136	N	NA	
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003 (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR) ICBG n=402	N	NA	
Dawson et al., 2009 USA (73) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt) ICBG n=21	N	NA	
Govender et al. for the BESTT study group 2002 South Africa (74)	Multi-center, single blind, RCT	rhBMP2 n=151 (6 mg/patient management)	Y	Needed 150 per group. Enrolled 150, 151, 149 Numbers completing the final study visit 138, 142, 141	

Open Tibial Fracture		rhBMP2 n=149 (12 mg/patient)			
		n=150 Standard care (IM nail fixation and soft tissue			
Swiontkowski et al., 2006 USA (81) **Open Tibial Fracture** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 n=169 (12 mg/patient)	N	NA	
		n=169 Standard care (IM nail fixation and soft tissue management)			
Boyne et al., 2005 USA (75) **Maxillofacial Defects**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	N	NA	
		rhBMP2/ACS (15-48 mg/pt) n=17			
		AGB n=13			
Fiorellini et al., 2005 USA (76) **Maxillofacial Defects**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	Y	Y	Looks like this was retrospectively determined.
		rhBMP2/ACS (mn dose 1.9 mg/pt) n=21			
		Placebo n=17			
		No Tx n=20			
Triplett et al., 2009 USA	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt)	Y	Y	

(77) **Maxillofacial Defects**		AGB n=80			
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial Defects**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	N	NA	
Calori et al., 2008 Italy (78) **Long Bone Nonunions**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	No	Power analysis showed that they had 78.5% power with the number of participants they enrolled. This was in the results section as a one liner. No methods included.	
Dahabreh et al., 2008 UK, Italy (83) **Long Bone Nonunions**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	N	NA	
Friedlaender et al., 2001 USA (79) **Long Bone Nonunions**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	N	NA	

Appendix 3 Table B. Assessment of Power and Sample Size in Off-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Were power and sample size calculated by the authors	Did the study enroll sufficient sample size to meet the sample size requirements	Comments
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11 (40 mg/pt)	N	NA	
		rhBMP2/CRM alone n=11 (40 mg/pt)			
		ICBG plus TSRHSS n=5			
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	N	NA	
		ICBG N=52			
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al.,2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	N	NA	
		ICBG n=224			
Glassman et al., 2007 USA	Retrospective with historical control group	rhBMP2 n=91	N	NA	

(99) **Lumbar Spine**		(12 mg/pt) ICBG n=35			
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	N	NA	
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 34 (4.2-8.4) ICBG N=33	N	NA	
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	N	NA	
Kanayama et al., 2006 Japan, USA (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	N	NA	
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	N	NA	
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	N	NA	
Singh et al., 2006 USA (102)	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt)	N	NA	

Lumbar Spine		ICBG N=11			
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt)	N	NA	
		ALG N=30			
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	Y	No they needed 180 in op-1 groups and 90 in the autograft group but only recruited 87 autograft. At 24 months they had 183 op-1 and 74 autograft at 36 months they had 144 OP-1 and 58 autograft.	
		ICBG n=86			
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt)	N	NA	Pilot study
		ICBG n=12			
Baskin et al., 2003 USA (89) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	N	NA	
		ICBG/ALG n=15			
Butterman et al., 2008 USA (104) **Lumbar Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	N	NA	
		ICBG n=36			
Crawford et al., 2009 USA (105) **Lumbar Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt)	N	NA	
		ICBG n=36			

Smucker et al., 2006 USA (106) **Lumbar Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	N	NA	
Vaidya et al., 2007 USA (107) **Lumbar Spine**	Retrospective cohorts of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	N	NA	
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 n=17 (12 mg/pt) n=23 no BMP	N	NA	
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 n=15 (12 mg/pt with allograft bone chips n=15 autogenous bone graft	Y	Y	Retrospectively established
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same as rec# 4560)	Retrospective cohort of matched patients	rhBMP7 n=20 Matched Zone 43 fracture (OREF) n=20	N	NA	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	N	NA	
Dickinson et al., 2008 USA	Single-center RCT	rhBMP2/ACS n=9 (dose not given)	N	NA	

(91) **Miscellaneous Uses**		ICBG n=12			
Ekrol et al., 2008 UK (97) **Miscellaneous Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation n=4	N	NA	
		Bone graft non bridging external fixation n=6			
		rhBMP7 internal fixation w/ pi-plate n=10			
		Bone graft internal fixation w/ pi-plate n=10			
Geesink et al., 1999 Netherlands (98) **Miscellaneous Uses**	Prospective double-blind randomized study	Untreated n=6	N	NA	
		DMB n=6			
		Collagen type I n=6			
		rhBMP7 (2.5mg) with collagen type I n=6			
Karrholm et al., 2006 UK (111) **Miscellaneous Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10	N	NA	
		Cups ALG n=10			
		Stems rhBMP7/ALG (1 g/pt) n=11			
		Stems ALG n=30			

Maeda et al., 2009 USA, Japan (109) **Miscellaneous Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	N	NA	

Appendix 4

Appendix 4 Table A. Specific Harms Associated with BMP in Noncomparative Studies

Investigators (ref #)	Surgical Intervention	No. pts	BMP Type	Dose (mg/pt)	FDA Status	Specific Harms	Incidence (%)
Dickerman et al., 2009 (150)	Posterolateral lumbar fusion	1	rhBMP2	NA	Off	Heterotopic bone formation in the psoas and iliacus	100
Brower et al., 2008 (148)	Posterior lumbar interbody fusion	1	rhBMP2	NA	Off	Psoas ossification	100
Moshel et al., 2008 (147)	L5-S1 TLIF (3 operations)	1	rhBMP2	NA	Off	Serum BMP2 antibodies detected	100
Shah et al., 2008 (181)	Cranial reconstruction for craniosynotosis	1	rhBMP2	NA	Off	Unusual swelling and edema that resolved after the removal of the rhBMP2 strips	100
D'Agostino et al., 2007 (158)	Allograft w/ rhBMP7 femoral fusion	1	rhBMP7	NA	Off	Heterotopic ossification	100
Wysocki et al., 2007 (155)	Revision of distal humeral non-union	1	rhBMP7	3.5	Off	Profound heterotopic ossification	100
Perri et al., 2007 (125)	Anterior cervical disectomy and fusion	1	rhBMP2	NA	Off	Soft tissue swelling in neck and dysphagia	100
Aryan et al., 2007 (116)	Corpectomy of osteomylitic patients in 1-3 levels	15	rhBMP2	4.2	Off	Dysphonia or dysphagia	66
Meisel et al, 2008 (138)	Posterior lumbar interbody fusion	17	rhBMP2	12	Off	Hererotopic ossification of humeral shaft	50
Meisel et al, 2008 (138)	Posterior lumbar interbody fusion	17	rhBMP2	12	Off	Hererotopic ossification of distal humerus	25
Joseph et al., 2007 (134)	Instrumented lumbar interbody PLIF and TLIF fusions	23	rhBMP2	4.2 per lever	Off	Heterotopic epidural bone formation in 5 levels	21
Boakye et al., 2005 (114)	Anterior cervical discectomy and fusion	24	rhBMP2	4.2 per level	Off	Heterotopic bone formation	13
Boakye et al., 2005 (114)	Anterior cervical discectomy 1-3 levels	24	rhBMP2	4.2 per level	Off	Transient dysphagia	9
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	Significant dysphagia	7
Aryan et al., 2007 (116)	Corpectomy of osteomylitic	15	rhBMP2	4.2	Off	Persistent dysphagia	7

	patients in 1-3 levels						
Lanman et al. 2004 (113)	Anterior cervical interbody fusion 1-3 levels	20	rhBMP2	NA	Off	Dysphagia	5
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	Mild dysphagia	3
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	Severe dysphagia	3
Rihn et al., 2009 (139)	Single level TLIF	86	rhBMP2	8.4	Off	Ectopic bone formation	2
Rihn et al. 2009 (186)	Single level TLIF	48	rhBMP2	NA	Off	Ectopic bone formation	2
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	Readmission for difficulty breathing or swallowing in 1 week post-op	2
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	Moderate dysphagia	2
Tumialan et al. 2008 (119)	ACDF 1-4 levels	200	rhBMP2	2.1-0.7 per level	Off	PEG tube	2

Appendix 4 Table B. Graft Donor Site Harms in On-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical site	Study design	Comparison(s) No. pts (BMP dose)	Did the study assess harms at the graft donor site?	Were there any infections at the graft donor site (#)	What harms were reported at the graft donor site?	Comments
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=11 (4.2-8.4 mg/pt)	N	NA	NA	
		ICBG n=3				
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=143 (4.2-8.4 mg/pt)	Y	Y(1)	8 adverse events related to harvesting were identified. Injury to lateral femoral nerve (3)	
					Avulsion fractures (2)	
					Infection (1)	
		ICBG n=136			Hematoma (1)	
					Pain at harvest site 12.7 on 20 point scale immediately after surgery. At 24 months 32% still experienced pain of 1.8 on 20 point scale and 16% were bothered by graft site appearance.	
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR)	Y	Y (5)	32% reported pain at harvest site 2 years post surgery.	
		ICBG n=402			5 other adverse events at harvest site.	
Dawson et al., 2009 USA (73)	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	Y	Y (1)	Infection	

Lumbar Spine						
		ICBG n=21				
Govender et al. for the BESTT study group 2002 South Africa (74) **Lumbar Spine**	Multi-center, single blind, RCT	rhBMP2 (1) n=151 (6 mg/patient)	N	NA	NA	
		(2) n=149 (12 mg/patient)				
		(3) n=150 Standard care (IM nail fixation and soft tissue management)				
Swiontkowski et al., 2006 USA (81) **Lumbar Spine** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 (1) n=169 (12 mg/patient)	N	NA	NA	No reporting
		(2) n=169 Standard care (IM nail fixation and soft tissue management)				
Boyne et al., 2005 USA (75) **Maxillofacial Defects**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS (6-24 mg/pt) n=18	Y	N	Edema, rash and pain at the harvest site.	
		rhBMPS2/ACS (15-48 mg/pt) n=17				
		AGB n=13				
Fiorellini et al., 2005 USA	Double-blind, multicenter randomized, placebo-control dose-comparison,	rhBMP2/ACS (mn dose 0.9 mg/pt) n=22	N	NA	NA	No reporting

(76) **Maxillofacial Defects**	safety and efficacy study	rhBMP2/ACS (mn dose 1.9 mg/pt) n=21 Placebo n=17 No Tx n=20				
Triplett et al., 2009 USA (77) **Maxillofacial Defects**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	Y	N	Pain at harvest site	
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial Defects**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	N	NA	NA	
Calori et al., 2008 Italy (78) **Long Bone Nonunions**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	N	NA	NA	
Dahabreh et al., 2008 UK, Italy (83) **Long Bone Nonunions**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	Y	Y (1)	Wound infection and abscess at the donor site in one patient.	
Friedlaender et al., 2001 USA (79) **Long Bone Nonunions**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	N	NA	NA	

Appendix 4 Table C. Graft Donor Site Harms in Off-Label BMP Comparative Studies

Investigator (yr, country, ref #) Surgical site	Study design	Comparison(s) No. pts (BMP dose)	Did the study assess harms at the graft donor site?	Were there any infections at the graft donor site (#)	What harms were reported at the graft donor site?	Comments
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11 (40 mg/pt) rhBMP2/CRM alone n=11 (40 mg/pt) ICBG plus TSRHSS n=5	N	NA	NA	No harms reporting
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt) ICBG N=52	N	N	N	
Dimar et al., 2009 USA (86) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	Y	45 infections in the bone-graft group. Unclear how many of those were at infection site.	Pain at graft site mean pain score at discharge (11.3), 7.9 at 6 weeks, 6.3 at three months with minimal improvement after that.	

Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al.,2006 rec# 5480; Glassman et al., 2005, rec# 8040		ICBG n=224			60% of patients had persistent donor-site pain, with a mean score of 5.1 at 24 months. Total of 17 graft site related events.	
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	N	NA	No harms reporting	
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	N	Unclear 4 wound infections reported as perioperative complications. Unclear if this is at the donor site or not.		
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4) ICBG N=33	Y	N	Pain (1) Hematoma (1)	At 24 months 60% of patients still were experiencing pain. Pain scores at 2 years were 5.5 on 20 point scale and 13.3% still felt the appearance of the graft site was bothersome.
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	Y	N	Persistent minor pain at harvest site (1)	
Kanayama et al., 2006 Japan, USA (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	N	NA	NA	No reporting
Mummaneni et al., 2004 USA (100)	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt)	Y	N	58% of patients at 6 months reported donor site pain with a mean score of 5 on 10 point	

Lumbar Spine		ICBG N=19			VAS.	
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	N	NA	NA	
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	N	NA	NA	No reporting
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	N	NA	NA	
Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	Y	N	VAS assessment of donor site pain at 12, 24 and 36 months showed 44% , 45%, and 35% of participants reporting pain at donor site. VAS rating was 2.1 at 12 months, 1.2 at 24 and 1.1 at 36 months.	
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004 (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	Y	N	None	
Baskin et al., 2003 USA (89)	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	Y	N	Pain at the graft site Appearance of the graft site.	No differences between groups at 6 months. At 12 months some patients still

Cervical Spine		ICBG/ALG n=15				had pain and only rated the appearance of the graft site as fair.
Butterman et al., 2008 USA (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	Y	Y (1)	Infection (1)	
		ICBG n=36			ASIS fracture (1)	
					At 1 year follow-up those in the IBG group graft site, the VAS pain at donor site was only 0.2	
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt)	Y	Y (1)	Iliac site deep infection (1)	
		ICBG n=36				
Smucker et al., 2006 USA (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR)	N	NA	NA	No reporting
		CRA n=165				
Vaidya et al., 2007 USA (107) **Cervical Spine**	Retrospective cohorts of consecutive patients	rhBMP2 n=22 (1-3 mg/pt)	N	NA	None reported	
		ALG/DBM n=24				
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 n=17 (12 mg/pt)	N	NA	NA	No harms reporting
		n=23 no BMP				
Jones et al., 2006 USA (90) **Acute Tibial Fractures**	Multi-center prospective RCT	rhBMP2 n=15 (12 mg/pt with allograft bone chips	Y	N	14/15 in autograft group reported acute onset of pain at the donor site, lasted about 5 days to 4.5 months. Residual tenderness present in one patient through 12 months.	

		n=15 autogenous bone graft			3 patients reported pustules or drainage at the donor site that lasted as long as 2 weeks	
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures**	Retrospective cohort of matched patients	rhBMP7 n =20 Matched Zone 43 fracture (OREF) n=20	N	NA	NA	
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	Y	N	Pain at the donor site	
Dickinson et al., 2008 USA (91) **Miscellaneous Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	Y	N	Pain at the harvest site 100% reported pain post op 3/12 reported pain 6 months after surgery	
Ekrol et al., 2008 UK (97) **Miscellaneous Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation n=4 Bone graft Non bridging external fixation n=6 rhBMP7 internal fixation w/ pi-plate n=10 Bone graft internal fixation w/ pi-plate n=10	Y	N	Minor hematomas at the donor site (8)	

Geesink et al., 1999 Netherlands (98) **Miscellaneous Uses**	Prospective double-blind randomized study	Untreated n=6 DMB n=6 Collagen type I n=6 OP-1 (2.5mg) with Collagen type I n=6	N	NA	NA	
Karrholm et al., 2006 UK (111) **Miscellaneous Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10 Cups ALG n=10 Stems rhBMP7/ALG (1 g/pt) n=11 Stems ALG n=30	N	NA	NA	No harms reporting
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	N	NA	NA	

Appendix 5

Quality of Reporting of BMP-Related Adverse Events in BMP Comparative Studies

Appendix 5 Table A. Reporting of BMP-Specific Harms in On-Label Comparative Studies

Investigator (yr, country, ref #) Surgical Site	Study design	Comparison(s) No. pts (BMP dose)	Explanation of how harms identified	Standard/valid instrument used	Ascertainment similar in all groups	Measure of severity reported	Were harms attributed to intervention likely causally associated	Were harms (# and type) reported separately for each study group	Comments
Boden et al., 2000 USA (71) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=11 (4.2-8.4 mg/pt) ICBG n=3	Y	N	Y	N	N	Y	No patients had increased BMP-2 anti-bodies after treatment
Burkus et al., 2002 USA (72) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=143 (4.2-8.4 mg/pt) ICBG n=136	N	N	Y	N	N	Y	Antibody testing results similar between groups
Burkus et al., 2003 USA (182) **Lumbar Spine** Note: may include pts in Burkus et al., 2003, (80)	Retrospective combined comparative analysis	rhBMP2 n=277 (dose NR) ICBG n=402	N	Unclear	Y	N	Unclear	N	No harms reporting
Dawson et al., 2009 USA (73)	Multicenter nonblinded RCT	rhBMP2/CRM n=25 (12 mg/pt)	N	N	Y	N	N	Y	Text reporting

Lumbar Spine		ICBG n=21							
Govender et al. for the BESTT study group 2002 South Africa (74) **Open Tibial Fractures**	Multi-center, single blind, RCT	rhBMP2 n=151 (6 mg/patient) rhBMP2 n=149 (12 mg/patient) n=150 Standard care (IM nail fixation and soft tissue management)	Y	N	Y	N	N	Y	Mostly text reporting Antibodies present in 1, 3, 9 patients in each group.
Swiontkowski et al., 2006 USA (81) **Open Tibial Fractures** Note: This paper reports on 131 of the same patients included in Govender et al., 2002 (74)	Subgroup analysis of combined data from two prospective randomized trials with identical designs	rhBMP2 n=169 (12 mg/patient) n=169 Standard care (IM nail fixation and soft tissue management)	N	Unknown	Unknown	N	Unknown	N	No harms reporting
Boyne et al., 2005 USA (75) **Maxillofacial**	Multicenter randomized dose-comparison, safety and efficacy study	rhBMP2/ACS n=18 (6-24 mg/pt)	Y	N	Y	N	N	Y	Facial edema related to BMP groups 4% (2 patients)

Defects		rhBMP2/ACS n=17 (15-48 mg/pt) AGB n=13							had immune response to BMP-2 after treatment. Both were transient.
Fiorellini et al., 2005 USA (76) **Maxillofacial Defects**	Double-blind, multicenter randomized, placebo-control dose-comparison, safety and efficacy study	rhBMP2/ACS n=22 (mn dose 0.9 mg/pt) rhBMP2/ACS n=21 (mn dose 1.9 mg/pt) Placebo n=17 No Tx n=20	Y	N	Y	N	N	N	No antibodies detected.
Triplett et al., 2009 USA (77) **Maxillofacial Defects**	Multicenter, nonblinded RCT	rhBMP2/ACS n=80 (12-24 mg/pt) AGB n=80	Y	N	Y	N	Y	Y	Facial edema 2 patients developed anti-bodies after treatment
van den Bergh et al., 2000 Netherlands (82) **Maxillofacial Defects**	Retrospective cohort study	rhBMP7/ACS n=3 (2.5 mg/pt) ICBG n=3	N	Unclear	Y	N	Unclear	Y	
Calori et al., 2008 Italy (78) **Long Bone Nonunions**	Single-center, nonblinded RCT	rhBMP7/ACS n=60 (3.5-7.0 mg/pt) PRP n=60	Y	Y	Y	Y	N	Y	Infections were the only harm reported

Dahabreh et al., 2008 UK, Italy (83) **Long Bone Nonunions**	Retrospective cohort study	rhBMP7/ACS n=15 (3.5 mg/pt) ICBG n=12	Y	N	Y	N	N	Y	Very brief in text
Friedlaender et al., 2001 USA (79) **Long Bone Nonunions**	Multicenter, partially blinded RCT	rhBMP7/ACS n=61 (3.5-7.0 mg/pt) AGB n=61	Y	Y	Y	Y	N	Y	10% developed anti-bodies to OP-1 all were transient.

Appendix 5 Table B. Reporting of BMP-Specific Harms in Off-Label Comparative Studies

Investigator (yr, country, ref #)	Study design	Comparison(s) No. pts (BMP dose)	Explanation of how harms identified	Standard/valid instrument used	Ascertainment similar in all groups	Measure of severity reported	Were harms attributed to intervention likely causally associated	Were harms (# and type) reported separately for each study group	Comments
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11 (40 mg/pt)	Y	N	Y	N	N	Y	Text reporting Incidence of anti-BMP-2 antibodies 4.5% in BMP-2 groups vs. 0 in auto-graft group. These were transient.
		rhBMP2/CRM alone n=11 (40 mg/pt)							
		ICBG plus TSRHSS n=5							
Burkus et al., 2005 USA (85) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	N	Unknown	Y	N	N	Y	No patient had antibodies to BMP-2

Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640		ICBG N=52							
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al.,2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt) ICBG n=224	N	N	Y	N	N	Y	
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt) ICBG n=35	N	Unclear	Unclear	N	Unclear	N	No harms reporting
Glassman et al., 2008 USA (87) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2 n=50 (dose not reported) ICBG n=52	Y	N	Unclear	N	N	Y	
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4 mg/pt) ICBG N=33	N	Unclear	Y	N	Y	Y	No antibodies to BMP-2 Extra bone formation outside disk space

Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	N	Unclear	Y	N	N	Y	In text
Kanayama et al., 2006 Japan, USA (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	N	Unknown	Unknown	NA	Unknown	N	No harms reporting
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	N	Unclear	Unclear	NA	Unclear	N	No harms reporting
Pradhan et al., 2006 USA (101) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=9 (dose NR) ICBG n=27	N	Unknown	Unknown	N	Unknown	N	No harms reporting
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt) ICBG N=11	N	Unknown	Y	N	N	N	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt) ALG N=30	N	Unknown	Unknown	N	N	N	In the text it states " no complications attributable to the use of BMP-2"

Vaccaro et al., 2008 USA (94) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP7 n=207 (7 mg/pt) ICBG n=86	Y	N	N	N	N	N	There were no harms reported. The success rate defined as absence of SAE was provided for each group. Immunologic analysis was completed. 93.7% of those receiving op-1 putty were antibody positive at any time point versus 20.9% of auto-graft group. In the OP-1 group, 25.6% of participants became positive for anti-OP-1 neutralizing antibodies versus 1.2% of auto-graft patients.
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, rec# 9100, and Vaccaro et al., 2005, rec# 7310	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	Y	N	Y	N	N	Y	
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	Y	N	Y	N	N	N	No patient had antibodies to BMP-2

		ICBG/ALG n=15							
Butterman et al., 2008 USA (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt) ICBG n=36	Y	N	Y	N	N	Y	Neck swelling
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt) ICBG n=36	Y	N	Unclear	N	N	Y	
Smucker et al., 2006 USA (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR) CRA n=165	Y	Y	Y	Y	Y	Y	Cervical swelling 10.1 fold increase in risk of cervical swelling for those in BMP-2 group vs. controls.
Vaidya et al., 2007 USA (107) **Cervical Spine**	Retrospective cohorts of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	Y	Y	Y	N	Y	Y	Dysphagia 85% in BMP group and 56% in allograft group reported difficulty swallowing in the post-op period. Number of levels affected the incidence of dysphagia.
Boraiah et al., 2009 USA (108) **Acute Tibial Fractures**	Retrospective case series	rhBMP2 n=17 (12 mg/pt) n=23 no BMP	Y	N	Y	N	Y	Y	HO around the knee
Jones et al., 2006 USA (90) **Acute Tibial**	Multi-center prospective RCT	rhBMP2 n=15 (12 mg/pt with allograft bone	Y	N	Y	N	N	Y	In text reporting No patient developed anti-bodies to BMP-2

Fractures		chips) n=15 autogenous bone graft							
Ristiniemi et al., 2007 Finland (110) **Acute Tibial Fractures** (same as rec# 4560)	Retrospective cohort of matched patients	rhBMP7 n=20 Matched Zone 43 fracture (OREF) n=20	Y	N	Y	N	Y	Y	Harms reported in text Patient developed soft tissue calcification but without symptoms
Bilic et al., 2006 Croatia, Netherlands (96) **Miscellaneous Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	N	Unknown	Y	N	N	Y	In text " No reported adverse events"
Dickinson et al., 2008 USA (91) **Miscellaneous Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	Y	N	Y	N	N	Y	
Ekrol et al., 2008 UK (97) **Miscellaneous Uses**	Prospective randomized cohort	rhBMP2 Non bridging external fixation n=4	Y	N	Y	N	Y	Y	This is all text reporting that is very difficult to follow. One patient developed

		Bone graft Non bridging external fixation n=6							extra-osseous bone formation
		rhBMP-7 internal fixation w/ pi-plate n=10							
		Bone graft internal fixation w/ pi-plate n=10							
Geesink et al., 1999 Netherlands (98) **Miscellaneous Uses**	Prospective double-blind randomized study	Untreated n=6	Y	N	Y	N	N	Y	No anti-body increase after treatment
		DMB n=6							
		Collagen type I n=6							
		OP-1 (2.5mg) with Collagen type I n=6							
Karrholm et al., 2006 UK (111) **Miscellaneous Uses**	Single-center case-control	Cups: rhBMP7/ALG (1 g/pt) n=10	N	Unknown	Unknown	N	Unknown	N	No harms reporting
		Cups: ALG n=10							
		Stems: rhBMP7/ALG (1 g/pt) n=11							

		Stems: ALG n=30							
Maeda et al., 2009 USA, Japan (109) **Miscellaneous Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt)	N	Unknown	Y	N	Unknown	N	No harms reporting
		ICBG n=32							

Appendix 6

Electronic Database Search Strategies

Overall

#	Search	No. Articles
#61	Search #56 OR #60	1608
#60	Search (#55 NOT #56) NOT (animal OR dog OR dogs OR mice OR mouse OR canine OR bovine OR ovine OR rabbit* OR equine OR rat OR rats OR plant OR plants)	79
#58	Search #55 NOT #56	1280
#56	Search #52 AND #53 Limits: Entrez Date from 1998 to 2009, Humans, English	1529
#55	Search #52 AND #53 Limits: Entrez Date from 1998 to 2009, English	2809
#54	Search #52 AND #53	3525
#53	Search #50 OR #51	11610
#52	Search #43 OR #47 OR #48	4477848
#51	Search "bone morphogen*" OR BMP OR BMP-2 OR BMP2 OR BMP-7 OR BMP7 OR rBMP OR rBMP-2 OR rBMP2 OR rBMP-7 OR rBMP7 OR r-BMP OR r-BMP-2 OR r-BMP2 OR r-BMP-7 OR r-BMP7 OR rhBMP OR rhBMP-2 OR rhBMP2 OR rhBMP-7 OR rhBMP7 OR rh-BMP OR rh-BMP-2 OR rh-BMP2 OR rh-BMP-7 OR rh-BMP7 OR RHOP OR RHOP-1 OR op-1 OR op1	9501
#50	Search "Bone Morphogenetic Proteins"[Mesh]	8665
#48	Search fracture* OR non-union* OR nonunion* OR fusion* OR allograft* OR autograft* OR arthrodes* OR malunion* OR dental OR alveolar	796705
#47	Search ("therapeutic use "[Subheading] OR "surgery "[Subheading]) OR "injuries "[Subheading]	3916363
#43	Search ((((("Fractures, Bone"[Mesh] OR "Spinal Fusion"[Mesh]) OR "Fusion"[Mesh]) OR "Alveolar Bone Loss"[Mesh]) OR "Alveolar Ridge Augmentation"[Mesh]) OR "Dental Implants"[Mesh]	142836

Search Strategy for Cochrane Database of Randomized Trials

"Random Allocation"[MeSH] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH] OR "Double-Blind Method"[MeSH] OR "Single-Blind Method"[MeSH] OR ("Clinical Trial"[Publication Type] OR "Clinical Trials"[MeSH]) OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR "Placebos"[MeSH] OR "Research Design"[MeSH] OR "Comparative Study"[MeSH] OR "Evaluation Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Prospective Studies"[MeSH] OR placebo* OR random* OR control* OR prospectiv* OR volunteer*

Appendix 7
Excluded Article List

BMP General ProCite Review Guide

Instructions: In field 12, enter Retrieval code after initial screen, and Selection Decision code after full article review. For those coded DNG in first review, or EXC in second review, enter 1-2 Full Review codes as initial entries in field 42, to explain basis of decision. Next, enter at least 1 Full Review code of each other type (as many as apply). Additional codes not needed for ANM, LTR. For COM, EDT, GUI, NRA add code for general content, from IV, V, VI, and VII as appropriate.

Retrieval Code (field 12)

DNG	do not retrieve full copy
GET	retrieve full copy
UNC	uncertain; needs check by second reviewer

Selection Decision Code
(after reviewing retrieved article, enter into field 12)

INC	include
EXC	exclude (with codes for exclusion reasons)

Full Review Codes (field 42)

I. Key Question (KQ) Codes

NRQ	not relevant question (note if ANM, NDE, NRD, NRO, NRT)
Q1-5	on-label efficacy
Q6	off-label efficacy
Q7	adverse effects
Q8	Quality of adverse effects reporting
Q9	Cost effectiveness
Q10	Age distribution
Q#?	unclear KQ relevance

II. Study Design Codes

ADB	administrative database
ANM	animal study
CEA	cost/cost-effectiveness analysis
CCS	case-control study
COH	cohort study
COM	commentary
CR	case report (n≤5)
CS	case series
D?	design unclear/possibly relevant
EDT	editorial
FLA	Foreign language article
GUI	guideline
INV	in vitro
LTR	letter
MA	meta-analysis
NAB	no abstract
NDE	not relevant design
NPD	no primary data
NRA	narrative review article
NRD	not relevant disease
PI	phase I trial
PII	phase II trial
PRO	prospective single-arm
QEX	quasi-experimental study
RCT	randomized controlled trial
REG	registry
RET	retrospective study
SR	systematic review

III. Sample Size Code (single-arm only)

FEW	n < 10
N10	10 ≤ n < 25
N25	25 ≤ n < 50
N50	50 ≤ n < 100
N100	n ≥ 100
N?	n unclear

IV. Intervention Codes

BMP2	Infuse
BMP7	OP-1
BMP?	Not specified in abstract
OTH	Other

V. Comparator Codes

ABG	Autologous bone graft
ALG	Allogeneic bone graft
BGU	Bone graft, unspecified
BMA	Bone marrow aspirate
COL	Collagen
COM?	Comparator unclear
COR	Coralline
CPH	Calcium phosphate
CSF	Calcium sulfate
DBM	Demineralized bone matrix
ESW	Extracorporeal shock wave
FIX	Fixation alone
GTX	Gene therapy
LPU	Low-intensity pulsed ultrasound
NBS	Nonbiological substance
PEF	Pulsed electric field
PRP	Platelet-rich plasma
PTH	Parathyroid hormone
SUR	Surgery alone
TCP	Tricalcium phosphate
TEN	Tissue engineering

VI. Basic Disease Codes

ALV	Alveolar ridge
BDS	Bone density study
CRN	Craniofacial
CSP	Cervical spine
DEL	Delayed union
FRC	Fracture
GEX	Gene expression study
HST	Bone healing study
LSP	Lumbar spine
MAX	Maxillofacial
NON	Non-union
OTH	Other site
PSD	Pseudarthrosis
SIN	Sinus augmentation
SPN	Spine (not specified)

VII. Disease Code Modifiers

ANK	Ankle
ANT	Anterior spinal approach
DDD	Degenerative disc disease
FEM	Femur
FIB	Fibula
FIN	Finger
FOT	Foot
HIP	Hip
HND	Hand
HUM	Humerus
MAN	Mandible
MLC	Multi-level cervical spine
MLL	Multi-level lumbar spine
PAL	Palate
PEL	Pelvis
POS	Posterior spinal approach
RAD	Radial
SCH	Scaphoid
SLC	Single-level cervical spine
SLL	Single-level lumbar spine
SPN1	Spondolysthesis grade 1
SPN2	Spondolysthesis > grade 1
STN	Sternum
TIB	Tibia
TLIF	Transforaminal LIF
TRM	Traumatic
ULN	Ulna

VIII. Label Status

LBL?	Unclear if on- or off-label
OFL	Clearly off-label use
ONL	Clearly on-label use

IX. Outcome Codes

ADL	Activity of daily living
AEF	Adverse effect
ECT	Ectopic bone
FCN	Functional
MOB	Mobility
OST	Osteolysis
PER	Perioperative outcomes
PN	Pain
QOL	Quality of life
RAD	Radiographic healing
SIV	Secondary interventions
WTB	Weight bearing

Ackerman SJ , Mafilios MS, Polly DW Jr. Economic evaluation of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion: an evidence-based modeling approach. Spine (Phila Pa 1976) 2002; 27(16 Suppl 1):S94-9.
Rec #: 11840
Notes: CEA

Alt V, Chhabra A, Franke J, Cuche M, Schnettler R, Le Huec JC. An economic analysis of using rhBMP-2 for lumbar fusion in Germany, France and UK from a societal perspective. Eur Spine J 2009; 18(6):800-6.
Rec #: 550
Notes: CEA

Alt V, Donell ST, Chhabra A, Bentley A, Eicher A, Schnettler R. A health economic analysis of the use of rhBMP-2 in Gustilo-Anderson grade III open tibial fractures for the UK, Germany, and France. Injury 2009.
Rec #: 140
Notes: CEA

Alt V, Eicher A, Bitschnau A, Schnettler R. Cost-benefit analysis of the use of rhBMP-2in open tibial fractures. Savings from a health insurer's perspective: Kosten-nutzen-betrachtung des einsatzes vonrhBMP-2bei offenen tibiafrakturen. Nettoeinsparungen aus krankenkassensicht erzielbar. Unfallchirurg 2006; 109(6):463-70.
Rec #: 18930
Notes: CEA FLA

Alt V, Haas H, Rauschmann MA *et al*. Health-economic considerations for the use ofBMP-2 for spinal surgery in Germany: Gesundheitsokonomische uberlegungen fur den einsatz des knochenwachstumsfaktorsBMP-2 in der wirbelsaulenchirurgie fur das Deutsche gesundheitssystem. Z. Orthop. Ihre Grenzgeb. 2006; 144(6):577-82.
Rec #: 18580
Notes: CEA FLA

Alt V, Heissel A. Economic considerations for the use of recombinant human bone morphogenetic protein-2 in open tibial fractures in Europe: the German model. Curr Med Res Opin 2006; 22 Suppl 1:S19-22.
Rec #: 5920
Notes: CEA

Axelsson P, Johnsson R, Stromqvist B. Radiostereometry in lumbar spine research. Acta Orthop Suppl 2006; 77(323):1-42.
Rec #: 4980
Notes: NRQ

Barrios JMR , Collado FA, Contreras DS, Tudela LL. Economic evaluation of the rhBMP-2(Inductos) in the treatment of vertebral fusion for chronic low back pain in Spain: Evaluacion economica de larhBMP-2(Inductos(registered trademark)) en el tratamiento de lafusionvertebral para la lumbalgia cronica en Espana. Pharmacoecon. Span. Res. Artic. 2008; 5(4):109-18.
Rec #: 16930
Notes: CEA

Bauer TW. An overview of the histology of skeletal substitute materials. Arch Pathol Lab Med 2007; 131(2):217-24.
Rec #: 5000
Notes: NRA

Benglis D, Wang MY, Levi AD. A comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. Neurosurgery 2008; 62(5 Suppl 2):ONS423-31; discussion ONS431.
Rec #: 2060
Notes: SR

Bianchi J, Fiorellini JP, Howell TH *et al*. Measuring the efficacy of rhBMP-2 to regenerate bone: a radiographic study using a commercially available software program. Int J Periodontics Restorative Dent 2004; 24(6):579-87.
Rec #: 8960
Notes: NDE

Biasibetti A., Salomone C., Di Gregorio A., Navas M.M. , Gallinaro P. Clinical treatment with bone morphogenetic proteins (BMP-7 ; OP-1). The Journal of Bone and Joint Surgery (Proceedings) 2006; 88-B(Suppl I):130-d.
Rec #: 16240
Notes: Abstract

Bibbo C. Talar fractures. Curr. Orthop. Pract. 2008; 19(3):234-41.
Rec #: 17570
Notes: NRA

Bishop GB, Einhorn TA. Current and future clinical applications of bone morphogenetic proteins in orthopaedic trauma surgery. Int Orthop 2007; 31(6):721-7.
Rec #: 3950
Notes: NRA

Block MS, Achong R. Bone morphogenetic protein for sinus augmentation. Atlas Oral Maxillofac Surg Clin North Am 2006; 14(1):99-105.
Rec #: 6850
Notes: NRA

Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. Spine (Phila Pa 1976) 2003; 28(4):372-7.
Rec #: 11280
Notes: Subset of REC# 11160

Burkus JK, Gornet MF, Schuler TC, Kleeman TJ, Zdeblick TA. Six-year outcomes of anterior lumbar interbody arthrodesis with use of interbody fusion cages and recombinant human bone morphogenetic protein-2. J Bone Joint Surg Am 2009; 91(5):1181-9.
Rec #: 330
Notes: Postmarketing follow-up, large dropout

Burkus JK, Heim SE, Gornet MF, Zdeblick TA. The effectiveness of rhBMP-2 in replacing autograft: an integrated analysis of three human spine studies. Orthopedics 2004; 27(7):723-8.
Rec #: 9380
Notes: NRA

Burkus JK, Sandhu HS, Gornet MF. Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft. Spine (Phila Pa 1976) 2006; 31(7):775-81.
Rec #: 6640
Notes: Different analysis of same patients as REC# 8320

Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine (Phila Pa 1976) 2002; 27(21):2396-408.
Rec #: 11510
Notes: Subset of REC# 8320

Burkus JK. Bone morphogenetic proteins in anterior lumbar interbody fusion: old techniques and new technologies. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine 2004; 1(3):254-60.
Rec #: 9160
Notes: NRA

Cahill KS, Chi JH, Day A, Claus EB. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. JAMA 2009; 302(1):58-66.
Rec #: 110
Notes: CEA

Calori GM, D'Avino M, Tagliabue L, Albisetti W, d'Imporzano M, Peretti G. An ongoing research for evaluation of treatment with BMPs or AGFs in long bone non-union: protocol description and preliminary results. Injury 2006; 37 Suppl 3:S43-50.
Rec #: 5720
Notes: Preliminary study

Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. Spine J 2005; 5(6 Suppl):240S-9S.
Rec #: 7580
Notes: NRA

Carreon LY, Glassman SD, Djurasovic M *et al*. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion in patients over 60 years of age: a cost-utility study. Spine (Phila Pa 1976) 2009; 34(3):238-43.
Rec #: 830
Notes: CEA

Cochran DL, Jones AA, Lilly LC, Fiorellini JP, Howell H. Evaluation of recombinant human bone morphogenetic protein-2 in oral applications including the use of endosseous implants: 3-year results of a pilot study in humans. J Periodontol 2000; 71(8):1241-57.
Rec #: 14030
Notes: CS

Cook SD, Barrack RL, Shimmin A, Morgan D, Carvajal JP. The use of osteogenic protein-1 in reconstructive surgery of the hip. J Arthroplasty 2001; 16(8 Suppl 1):88-94.
Rec #: 12700
Notes: NRA

Csimma C, Swiontkowski MF. Large clinical trials in musculoskeletal trauma: are they possible? Lessons learned from the international study of the use of rhBMP-2 in open tibial fractures. J Bone Joint Surg Am 2005; 87(1):218-22.
Rec #: 8950
Notes: NRA

Daentzer D. The efficacy ofrhBMP-2for posterolateral lumbarfusionin smokers: Comment: Die wirksamkeit vonrhBMP-2auf die posterolumbalefusionbei rauchern. Z. Orthop. Unfallchir. 2007; 145(5):552.
Rec #: 18010
Notes: FLA

Dahabreh Z, Calori GM, Kanakaris NK, Nikolaou VS, Giannoudis PV. A cost analysis of treatment of tibial fracture nonunion by bone grafting or bone morphogenetic protein-7. Int Orthop 2008.
Rec #: 1090
Notes: CEA

Dahabreh Z, Dimitriou R, Giannoudis PV. Health economics: a cost analysis of treatment of persistent fracture non-unions using bone morphogenetic protein-7. Injury 2007; 38(3):371-7.
Rec #: 5370
Notes: CEA

De Long WG Jr, Einhorn TA, Koval K *et al*. Bone grafts and bone graft substitutes in orthopaedic trauma surgery. A critical analysis. J Bone Joint Surg Am 2007; 89(3):649-58.
Rec #: 4900
Notes: NRA

Desmyter S, Goubau Y, Benahmed N, de Wever A, Verdonk R. The role of bone morphogenetic protein-7 (Osteogenic Protein-1) in the treatment of tibial fracture non-unions. An overview of the use in Belgium. Acta Orthop Belg 2008; 74(4):534-7.
Rec #: 1560
Notes: Survey, CS

Dickerman RD , Reynolds AS, Morgan BC, Tompkins J, Cattorini J, Bennett M. rh-BMP-2 can be used safely in the cervical spine: dose and containment are the keys! Spine J 2007; 7(4):508-9.
Rec #: 4310
Notes: COM

Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. Spine (Phila Pa 1976) 2006; 31(22):2534-9; discussion 2540.
Rec #: 5480
Notes: Subset of REC# 250

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Notes: CEA

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