

**Washington State Health Care Authority, HTA Program
Final Key Questions****Bone Morphogenic Proteins for use in Spinal Fusion****Introduction**

HTA has selected Bone Morphogenic Proteins (BMP) for use as adjuncts in spinal fusion surgery to undergo a health technology assessment where an independent vendor will systematically review the evidence available on its safety, efficacy, and cost-effectiveness. HTA originally posted the topic as Bone Graft Products (autograft, allograft, and synthetic), now modified, and gathered public input on all available evidence. Recombinant bone morphogenetic proteins (rhBMPs) are currently used in place of or in addition to autograft (e.g., iliac crest bone graft or ICBG) or allograft bone (e.g., cadaver bone) as an adjunct to spinal fusion and other bone fusion procedures. To date, two rhBMPs (rhBMP-2 and rhBMP-7) and associated delivery vehicles have received approval from the Food and Drug Administration (FDA).

Key questions guide the development of the evidence report. HTA seeks to identify the appropriate clinical topics (e.g., population, indications, comparators, outcomes, policy considerations) to address the statutory elements of evidence on safety, efficacy, and cost effectiveness relevant to coverage determinations.

This topic was originally more broadly defined as 'bone graft products' to include BMP and other autograft, allograft or synthetic materials used to aid in bone healing or fusion surgery. The topic was focused on BMP based on: 1) the availability of a comprehensive systematic review from the AHRQ published in December 2010 and, 2) subsequent new published information related to safety concerns focused on BMP.

Key Questions

When used in patients undergoing spinal fusion:

- (1). What are the expected treatment outcomes of primary single or multilevel lumbar or cervical spinal fusion for degenerative disc disease (DDD), and of revision posterolateral lumbar spinal fusion in compromised patients (i.e., osteoporosis, smoking, diabetes)? Are there validated instruments related to outcomes in patients undergoing these procedures? Has clinically meaningful improvement in outcomes been defined in these patient populations?
- (2). Compared with spinal fusion using ICBG or alternative bone graft substitutes, what is the evidence of efficacy and effectiveness of:
 - a) rhBMP-2 (InFUSE) for on-label lumbosacral spine fusion in patients with DDD?
 - b) rhBMP-7 (OP-1) for on-label revision posterolateral lumbar spine fusion in compromised (e.g., osteoporosis, smoking, diabetes) patients?

- c) rhBMP-2 (InFUSE) for off-label lumbosacral spine fusion?
- d) rhBMP-7 (OP-1) for off-label lumbosacral spine fusion?
- e) rhBMP-2 (InFUSE) for off-label cervical spine fusion?
- f) rhBMP-7 (OP-1) for off-label cervical spine fusion?

Including consideration of perioperative outcomes (including length of surgery) as well as short term and long term:

- o Impact on function, pain, radiographic fusion, patient satisfaction, quality of life, activities of daily living and return to work
 - o Other reported measures
- (3). What is the evidence of the safety of on- or off-label use of rhBMP-2 or rhBMP-7 for spinal fusion compared with spinal fusion using ICBG or alternative bone graft substitutes? Including consideration of:
- o Short- and long term adverse events and complications type and frequency (pain, donor site morbidity, resorption/osteolysis, heterotopic bone formation, graft subsidence, graft migration, dysphagia or respiratory difficulties, elevated antibody responses to BMPs or collagen, wound complications (infection, hematoma, seroma, or dehiscence), local or systemic toxicity, mispositioned graft, neurological complications, retrograde ejaculation, urogenital complications, allergic reactions, mortality, other major morbidity).
 - o Revision/re-operation rates
- (4). What is the evidence that on- or off-label use of rhBMP-2 or rhBMP-7 for spinal fusion compared with spinal fusion using ICBG or alternative bone graft substitutes has differential efficacy or safety issues in sub-populations? Including consideration of:
- o Gender
 - o Age
 - o Baseline functional or pain status
 - o Comorbidities (including but not limited to tobacco use, alcohol use, psychological or psychological)
 - o Other patient characteristics or evidence-based patient selection criteria
 - o Provider type, setting or other provider characteristics
 - o Payor/ beneficiary type: including worker's compensation, Medicaid, state employees
- (5). What evidence of cost implications and cost-effectiveness of on- or off-label use of use of rhBMP-2 or rhBMP-7 exists? Including consideration of:
- o Costs (direct and indirect) and cost effectiveness
 - o Short term and long term

Policy Context:

In addition to other applications, BMPs are applied as adjuncts during spinal fusion surgeries.

Technology Description:

Bone morphogenic proteins are naturally produced cell regulating proteins (TGF-B family) necessary for bone healing and regeneration, but also involved in other tissue configuration processes. Recombinant DNA methods have been used to produce higher quantities of bone morphogenic proteins than could be harvested from cadaver sources (due to minute naturally available amounts) for commercial application. Recombinant BMP products have been used since 2001 in procedures where bone healing or fusion is required; they are used in conjunction with collagen scaffolding materials and/or metallic cages.

BMP products provide the potential to avoid bone harvesting procedures necessary for use of autograft (self donated bone material), or to avoid allograft (use of bone from cadavers). Autograft requires bone harvesting, a separate surgical procedure that itself may result in pain and carries some risk related to the procedure and removal of bone, frequently from the iliac crest (hip). If BMP is a safe and effective alternative to autograft, patients may avoid a procedure and associated risk.

Issues:

There have been recent concerns about safety due to adverse event reports and questions about clinical trial methodology and reporting of potential adverse events. Questions were raised about the safety of BMP based on observed effects including excess bone growth (heterotopic bone formation), and other adverse events including possible increased rates of retrograde ejaculation (RE) in men. Publication in June 2011 of a series of papers addressed these concerns as well as concerns about the methods used to determine rates of adverse effects in the original trials designed to test the safety of the then new products. Therefore, significant questions remain about the safety, efficacy and effectiveness, and cost effectiveness of recombinant bone morphogenic proteins when used in spinal surgery.