



**Kaiser Foundation Health Plan
of Washington**

Clinical Review Criteria

InFUSE™ Bone Graft

- [InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device \(Bone Morphogenetic Protein-2\)](#)

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc., provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in their benefits. Always consult the patient's Medical Coverage Agreement or call Kaiser Permanente Customer Service to determine coverage for a specific medical service.**

Criteria

For Medicare Members

Medical necessity review is no longer required for Medicare members.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies (and/or) provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Degenerative disc disease (DDD) resulting from wear and tear of the discs between vertebrae can lead to a painful condition that may require spinal fusion (arthrodesis) of the vertebrae on both sides of the degenerative disc. Spinal arthrodesis was introduced over a century ago for treating vertebral fractures, spinal tuberculosis, tumors and severe scoliosis. These indications were later expanded to include spondylolisthesis, spondylosis, intervertebral disc disorders, and discogenic low back pain. Spinal interbody fusion restricts the unstable spinal motion segment and may provide relief from the pain associated with DDD, when all other methods have failed. It involves the removal of the degenerated intervertebral disc and fusion of the adjacent vertebral bodies. This can be achieved through an anterior approach (anterior lumbar interbody fusion or ALIF), posterior fusion (PLIF), or transforaminal approach (TLIF)(Blumenthal 1988, Baskin 2003, Glassman 2005,papakostidis 2008, Fu 2013, Skovrlj 2014, Noshchenko 2014, Bodalia 2016, Hofstetter 2016).

Vertebral fusions usually use graft material to stimulate the fusion. For decades autogenous iliac crest bone (ICB) has been, and is still considered, the gold standard bone grafting material for its superior osteoinductive and osteogenic properties. However, its harvest may be associated with postoperative complications including persistent pain from the donor site, deep infection, scarring, and other donor site morbidity. Another limitation of using iliac crest bone graft (ICBG) is the relative inadequate supply of graft tissue for multilevel fusions. Spine surgeons have thus been looking for alternative methods to promote spinal fusion. A variety of bone graft materials and substitutes such as local bone, bones from bone banks, demineralized bone matrix, synthetic grafts, platelet gels, and other materials have been introduced into clinical practice, but did not prove to be as effective as ICBG (Blumenthal 1988, Baskin 2003, Glassman 2005,papakostidis 2008, Fu 2013, Skovrlj 2014, Noshchenko 2014, Bodalia 2016, Hofstetter 2016).

Bone morphogenetic protein (BMP), a prototypical osteoinductive protein, was first described by Marshall Urist in 1965. BMPs are members of the superfamily of transforming growth factor-beta and play an important role in embryonic development including bone formation. In the late 1990s recombinant human bone morphogenetic protein type 2, a genetically engineered osteoinductive protein, was tested for use in lumbar fusion among humans in preclinical and clinical studies (Zhang 2014, Hofstetter 2016).

InFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is a recombinant human bone morphogenetic protein type-2 (rhBMP-2) applied to an absorbable collagen sponge (ACS) carrier that localizes the protein at the site of implantation and provides a scaffold for the formation of the new bone. The sponge is manufactured from bovine Type I collagen and is designed to resorb over time. InFUSE® Bone Graft is used in conjunction with a proprietary small thimble like titanium lordotic tapered cage (LT-Cage) implant, which is intended to restore the degenerated disc space to its original height. The LT-Cage Devices come in multiple sizes (from XX Small to Large II) to match various patient anatomies. The InFUSE® Bone Graft/LT-Cage® Lumbar Tapered Fusion Device is implanted through an open or laparoscopic anterior surgical approach. The bone graft is prepared immediately prior to its use during surgery*; the protein solution is soaked into the sponge, which is then inserted into the LT-Cage. After removing the contents of the disc space, two devices are implanted side by side in the prepared intervertebral disc space. The fusion cage maintains the spacing and temporarily stabilizes the diseased region of the spine while the InFUSE® Bone Graft induces new bone tissue at the site of implantation to fuse this portion of the spine. The fusion process requires several months to complete (Baskin 2003, Glassman 2005, Medtronic website accessed 2017)

*Once prepared, the InFUSE® Bone Graft contains rhBMP-2 at a concentration of 1.5 mg/mL

In 2002, the US Food and Drug Administration (FDA) approved the use of InFUSE® Bone Graft for anterior interbody fusion as an alternative to the iliac crest bone graft for use in conjunction with lordotic tapered cages (LT-CAGE) lumbar fusion device. According to the FDA, the device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at a single level from L4-S1. Patients should have had at least six months of nonoperative treatment prior to treatment with the InFuse Bone Graft. Later the FDA approved rhBMP-2 with other interbody fusion devices (INTER FIX™ Threaded Spinal Fusion Device and INTER FIX™ RP Threaded Fusion Device) also manufactured by Medtronic.

InFUSE® Bone Graft is contraindicated in patients who are pregnant, who may be allergic to any of the materials contained in the device, have an infection in the area of the incision, are skeletally immature, or with an existing or removed tumor in the area.

Medical Technology Assessment Committee (MTAC)

InFuse Bone Graft

10/08/2003: MTAC REVIEW

Evidence Conclusion: The trial reviewed does not provide sufficient evidence to conclude that InFUSE Bone Graft is equivalent or superior to the standard treatment. It was randomized and controlled; yet the authors compared improvements associated with the InFUSE Bone Graft with the preoperative condition, and not with the standard treatment. The trial shows that both treatments led to significant improvement in the back pain, leg pain, as well as pain associated with activity when compared to the preoperative scores. The two procedures were also associated with post-operative vs. baseline, high neurological success, patient satisfaction and bone fusion. The authors noted that the success rates and pain scores were similar between the two groups, based on the values observed and not on statistical tests of significance. It seems unlikely that there are any significant differences between the two groups, as the numbers, and scores are close. This may suggest that the effect of the two treatments may be similar, but the study isn't conclusive as it may have been underpowered to detect a difference, and was not designed as an equivalence trial that requires a larger sample size, and a different method of analysis than superiority trials.

Articles: The search revealed 4 randomized controlled studies and one case series. Three of the RCTs were conducted by the same principle investigator, and included patients from the same center: one large trial with 279 patients, and two smaller RCTs with 46, and 42 patients. The other trial revealed included only 14 patients. The search also revealed an article where the same principle investigator of the three RCTs pooled data from his trial as well as other 3 unpublished studies, two of which were non-randomized. It had a poor methodology, and cannot be categorized as a meta-analysis. The largest of the three RCTs conducted by the same investigator group was selected for critical appraisal. *The following study was critically appraised:* Burkus JK,

Gornet MF, Dickman CA, et al. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech.* 2002;15:337-49. See [Evidence Table](#).

The use of recombinant human bone morphogenetic protein (rhBMP-2) placed on an absorbable collagen sponge (ACS) in the treatment of degenerative disc disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

12/07/2009: MTAC REVIEW

InFuse Bone Graft

Evidence Conclusion: There is a lack published material on the use of InFUSE Bone Graft for anterior lumbar interbody fusion, the indication for which the technology received the FDA approval. Glassman and colleagues' trial (2008) had the advantage of comparing rhBMP-2 to iliac crest bone graft in a randomized controlled trial with 2-year follow-up duration. However, the technology was used off-label for a posterolateral lumbar fusion among patients older than 60 years of age. Moreover, the trial was not blinded, and the authors did not discuss the method of randomization, or clearly describe the inclusion/ exclusion criteria. Non-blinding may be a source of observation bias, especially with the subjective primary outcomes of the trial. The investigators tried to partially overcome this limitation by blinding the orthopedic surgeons who evaluated the radiological outcomes. The authors also did not discuss any power analysis for determining the sample size, and analysis was not based on intention to treat. Overall, the results of the trial show significant improvements in health related quality of life, as well as the leg, and back pains at one and two years of follow-up among the patients in the two treatment groups, when compared to the preoperative status. There were no significant differences in the primary outcomes between the two interventions. The outcomes may appear similar, but the lack of significant statistical significance does not necessarily imply equivalence. The study was relatively small and might have been underpowered to detect significant differences between the study groups. It was not designed as an equivalence trial that requires a larger sample size and different method of analysis than a superiority trial. Radiographic evaluations at two years showed higher fusion rate with rhBMP-2 vs. ICBG (86.3% and 70.8%, respectively). In conclusion there is insufficient published evidence to conclude that InFUSE Bone Graft is equivalent, noninferior, or superior to the standard iliac crest bone graft in improving functional ability and quality of life of patients with symptomatic degenerative disc disease.

Articles: The search revealed over 30 articles on rhBMP-2 /InFUSE Bone Graft. Many were unrelated to the current reviews; others used rhBMP-2 in different formulations or in combination with other elements e.g. ceramic granules. Two articles (Glassman, et al 2005 and 2008) reporting on one and two years results of a randomized controlled study comparing the use of rhBMP-2 versus iliac crest bone graft (ICBG) for lumbar spine fusion, were identified as well as a small nonrandomized trial and two case series studies on the use of InFUSE Bone Graft. The RCT with the 2-year follow-up was selected for critical appraisal. Glassman SD, Carreon LY, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: A randomized, controlled trial in patients over sixty years of age. *Spine.* 2008;33:2843-9. See [Evidence Table](#).

The use of recombinant human bone morphogenetic protein (rhBMP-2) placed on an absorbable collagen sponge (ACS) in the treatment of degenerative disc disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/21/2017: MTAC REVIEW

InFuse Bone Graft

Evidence Conclusion: As indicated in the previous section, the literature search did not identify any more recent RCTs evaluating InFUSE® Bone Graft for ALIF, but a number of qualitative reviews and quantitative meta-analyses of the published trials. All trials were open-label, the great majority was industry sponsored, and the principal authors had financial ties with the industry.

Efficacy and safety of InFUSE® Bone Graft compared to the gold standard autogenous iliac crest bone graft (ICBG) Carragee and colleagues (2011) conducted a systematic review and critical analysis of the original peer reviewed industry-sponsored publications and compared their results and conclusions versus the available FDA summaries, follow-up publications, and administrative and organizational database analyses. According to the authors, the systematic review was prompted by complaints to the editorial board of the *Spine Journal* including allegations of research bias, failure to report adverse event recorded by the study surgeons, and discrepancies between FDA summaries and published data. The authors reviewed the results of 13 original industry-sponsored rhBMP-2 publications regarding safety and efficacy, including reports and analyses of 780

patients receiving rhBMP-2 within prospective controlled study protocols. These included studies using anterior, posterior and posterolateral interbody fusion. The estimated rate of adverse events associated with rhBMP-2 use in spinal interbody fusion ranged from 10% to 50% depending on the approach and spinal level of fusion.

- Anterior interbody lumbar with rhBMP-2 was associated with higher rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation versus the controls.
- Posterior lumbar interbody fusion was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes.
- In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early back pain and leg pain adverse events. Higher doses of rhBMP-2 were associated with a greater apparent risk of new malignancy.
- Anterior cervical fusion with rhBMP-2 had an estimated 40% greater risk of adverse events in the early postoperative period including life-threatening events.

The authors provided evidence showing discrepancy between the FDA documents and the published results of industry-sponsored trials on rhBMP-2. He noted that while the authors of the industry sponsored trials on ALIF, reported no adverse events, the FDA concluded that the original data from the trials indicate that “The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational [rhBMP-2] groups compared to the control group” (Carragee 2011). Carragee and colleagues summarized the areas of concern regarding the safety and efficacy reported by the industry sponsored trials as follows:

1. Underestimation of adverse events and serious harms associated with rhBMP-2.
2. Presence and magnitude of conflict of interest and potential for reporting bias.
3. Invalid assumption and methodology used for estimating adverse events associated with iliac crest bone grafts, which led to exaggeration of the benefits underestimating the morbidity of rhBMP-2.
4. Significant bias against the selection of the control and techniques used in the PLIF and PLF.

The reviewers concluded that Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications. [Fu and colleagues, 2013 \(Evidence Table 1\)](#) performed a meta-analysis to evaluate the effectiveness and harms of rhBMP-2 in spinal fusion and to assess the reporting bias in industry sponsored journal publications. The authors used data from the literature and individual patient level data of the rhBMP-2 trials (including unpublished data from the trials) provided by the manufacturer through the Yale Open Data Aces (YODA) Project. The latter project was sponsored by the manufacturer for an independent review of all published and unpublished data. The analysis included 13 RCTs (12 sponsored by Medtronic) and 31 cohort studies, 47 intervention series, and 35 case series or reports. The primary outcome was the overall success and fusion. The meta-analysis had generally valid methodology, and the studies included were rated by the authors to be of moderate quality. However, all were unblinded; industry sponsored, and according to the authors, had poor ascertainment of harm. The authors analyzed anterior and posterior fusion separately as well as cervical and lumbar fusion. The pooled results of studies comparing rhBMP-2 versus ICBG for ALIF, showed no significant differences in overall success except for very slight improvement in leg pain at 6 weeks with rhBMP-2. There were higher rates to urogenital complications and retrograde ejaculation with rhBMP-2, the difference was not significant but could be due to insufficient power. The cancer risk was significantly higher with rh-BMP-2. The authors of the meta-analysis noted that early journal publications misrepresented the effectiveness and harms through selective reporting, under-reporting, and duplicate publications. They concluded that there technology had no proven advantage over bone graft and may be associated with important harms. [Simmonds et al, 2013 meta-analysis \(Evidence Table 2\)](#) also used data from the YODA project to evaluate the safety and effectiveness of rhBMP-2 compared to ICBG. The analysis included 12 RCTs (11 Medtronic sponsored) for effectiveness plus 35 additional controlled adverse events studies for safety analysis. The primary outcomes were patient centered pain and function, fusion and adverse events. The results of the analysis showed that from 6 months after surgery up to 2-years, rhBMP-2 led to greater pain reduction compared to ICBG. The authors noted however, the difference may not be clinically significant as patients in both treatment groups experienced considerable reduction in pain. Successful fusion rates were found to be higher with rhBMP-2 but there was significant heterogeneity between studies in the relative risk of fusion, and the authors noted that Medtronic definitions of fusion may have been stringent as only 69% of ICBG recipients achieved fusion in 24

months. The authors found no correlation between successful fusion with rhBMP-2 and pain reduction. As regards safety, the analysis showed that pain (which was reported as an outcome and as an adverse effect) was significantly higher with rhBMP-2 shortly after surgery and lower at 24 months, compared to ICBG. Other adverse events including Implant-related events, neurologic events, retrograde ejaculation, vascular events, wound complications, and cancer, all occurred at a higher rate with rh-BMP-2, but the difference did not reach a significant level, which could be attributed to the small number of events. [Zhang and colleagues, 2014 \(Evidence table 3\)](#) conducted a meta-analysis of randomized controlled trials to compare the effectiveness and safety of fusion with BMPs (-2 or -7) versus ICBG for the treatment of degenerative lumbar conditions. The analysis included 19 RCTs involving 1,852 patients. The studies recruited patients with a variety of spinal disorders and different approaches were used for the fusion. In 14 of the 19 trials rhBMP was used off-label. The co-primary outcomes of the analysis were solid fusion rate, clinical outcomes, complications, and reoperation rate. The pooled results showed that the rate of fusion was significantly higher among patients in BMPs group; however this difference was no longer significant with the sensitivity analysis that excluded 7 studies with high risk of bias. There were statistically significant differences in the overall success of clinical outcomes, complication rate, blood loss, hospital stay, patient satisfaction, or work status. Significant reductions in the operating time and reoperation rate were found in BMPs. This was a high quality meta-analysis as regards its methodology, analysis and grading the evidence for each outcome. However, the quality of the results of a meta-analysis relies heavily on the quality of the studies it includes. Due to the nature of the intervention, all published trials evaluating rh-BMP-2 were unblinded, which is a source of bias, especially with subjective outcomes. In addition, there were other limitations to the published studies regarding methods of randomization and allocation procedures. There were variations between the trials in BMP used and the approach for fusion as well the methods and standards used for assessing the bone fusion which. The studies included in the meta-analysis used plain radiography, CT scan, or surgical exploration for evaluating the fusion rate. The authors explained that imaging was used to assess the status of spinal fusion, and that it provides less accurate data compared to direct operative exploration. In addition, the majority of the studies were industry sponsored and some of the authors reported conflict of interest. Overall, the authors concluded that the limited evidence does not show that BMP is superior to ICBG for the treatment of lumbar DDD and that more high-quality trials with long-term outcomes are needed. Other published meta-analyses (Chen, 2012 and Noshchenko, 2014) included the same industry sponsored RCTs, and had similar results showing that rhBMP-2 may lead to slightly higher fusion rates compared to ICBG, but with possible harm and no significant clinical improvement. **Impact of patient characteristics on the effectiveness and harms of rhBMP-2 compared with ICBG.** [Laurie and colleagues' \(2016\) meta-analysis](#) used the data from the YODA project to examine the impact of patient characteristics on the effectiveness and harms of rhBMP-2 as compared with ICBG. The analysis included 10 industry sponsored RCTs involving 1,255 participants. 5 trials used the anterior lumbar approach, 4 used the posterior lumbar, and one used the posterolateral lumbar approach for the interbody fusion with rhBMP-2. The population sizes of the individual trials varied from 10 to 463 participants. The results of the analysis suggest that there may be a differential treatment effect between rhBMP-2 and ICBG according to some patient characteristics. Fusion success was found to be higher with rhBMP-2 vs. ICBG in patients under the age of 60 at 6 months after the surgery and among smokers and normal weight individuals at 24 months postoperatively. No significant differences were observed between the two procedures for overweight or obese patients. The analysis also showed that the rate of device-related adverse events with rhBMP-2 was lower in individuals with no previous back surgery. **Impact of rh-BMP-2 dosing on outcomes** The BMP dose varied widely among the published studies which may indicate that is uncertainty regarding the optimal dose for the spinal fusion procedures. Hofstetter and colleagues' meta-analysis (2016) examined the effect of BMP dosing on successful fusion and morbidity with the common fusion procedures. The analysis included 48 articles involving 5,890 patients. 9 trials were on ALIF, 17 on transforaminal or posterior lumbar interbody fusion (TLIF/PLIF), 7 on anterior cervical discectomy and fusion (ACDF), and 9 trials on posterior lumbar fusion (PLF) supplemented with BMP. The authors performed separate meta-analyses for each procedure. The results of the analyses suggest that there is a wide range in the BMP dosing used for specific spinal fusion procedures (from 2.5mg/level for posterior cervical fusion [PCF] to 10.5mg/level in ACDF). The meta-analysis of studies on ALIF showed a trend toward an association between the likelihood of complications and the dose of BMP. In reports of ALIF supplemented with high doses of BMP (4.3-12.0 mg/level) the rates of endplate resorption and graft subsidence were high. More studies are needed to determine the safe and effective BMP dosing for the different applications.

Conclusion:

- The published literature does not provide sufficient evidence to determine that rh-BMP-2 has superior or equivalent effectiveness and safety compared standard iliac crest bone graft for adult

patients with symptomatic lumbar degenerative disc disease referred to anterior interbody lumbar fusion.

- A number of meta-analyses and systematic reviews, including those using data from the Yale University Open Database Project, suggest that spinal interbody fusion using InFUSE® Bone Graft had a small or no advantage when compared to the standard use of iliac crest bone graft (ICBG), and may be associated with more serious adverse events.

Articles: The updated literature search did not reveal any recent trials that examined the efficacy and safety of using InFUSE® Bone Graft for anterior lumbar interbody fusion (ALIF) in patients with symptomatic single level degenerative disc disease from L1-L4. There was a number of systematic reviews with or without meta-analyses as well as several retrospective analyses on the effectiveness and safety of rhBMP-2 for spinal fusion. There were more publications and studies on the use of InFUSE® Bone Graft for cervical interbody fusion, or using the posterior, lateral, or posterolateral approaches for lumbar interbody fusion, all of which are off-label use of InFUSE® and out of scope for the current review. Two meta-analyses that included individual patient data of the rhBMP-2 trials provided by the manufacturer through the Yale Open Data Access (YODA) project, as well as another meta-analysis of published trials were selected for critical appraisal. Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med.* 2013 Jun 18; 158(12):890-902. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. *Ann Intern Med.* 2013 Jun 18; 158(12):877-889. Zhang H, Wang F, Ding L, Zhang Z, et al. A meta-analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous iliac crest bone graft. *PLoS One.* 2014 Jun 2; 9(6):e97049.

The use of the InFUSE® Bone Graft/LT-Cage® Lumbar Tapered Fusion Device for Anterior Lumbar Interbody Fusion (Recombinant Bone Morphogenetic Protein Type 2 [rhBMP-2]) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Date Reviewed	Date Last Revised
10/08/2003	10/08/2003 ^{MPC} , 12/07/2009 ^{MPC} , 07/07/2015 ^{MPC} , 05/03/2016 ^{MPC} , 06/07/2016 ^{MPC} , 02/07/2017 ^{MPC} , 12/05/2017 ^{MPC} , 10/02/2018 ^{MPC}	08/01/2017

^{MPC} Medical Policy Committee

Revision History	Description
08/01/2017	Added MTAC second review

Codes

There is no specific code for InFUSE™ Bone Graft