



**SANDHILLS
CENTER**



Bone graft substitutes

Clinical Policy ID: CCP.1232

Recent review date: 5/2021

Next review date: 9/2022

Policy contains: Bone graft substitutes; recombinant human bone morphogenetic protein-2.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

The following bone graft substitutes are clinically proven and, therefore, medically necessary for enhancement of bone healing (Fischer, 2013; Laurencin, 2006; McNamara, 2015; Papageorgiou, 2016):

- Autograft based, used alone.
- Allograft-based, allograft bone used alone or in combination with other materials, including demineralized bone matrix.
- Ceramic or polymer-based synthetic bone graft substitutes, used alone or in combination with other materials.
- Bone graft substitutes containing an organic bone material (e.g., bovine or coral) when used alone or combined with another medically necessary bone graft substitute.

Recombinant human bone morphogenetic protein-2 is clinically proven and, therefore, medically necessary when used in accordance with U.S. Food and Drug Administration approved indications and labelling instructions:

- INFUSE® Bone Graft (Medtronic Inc., Minneapolis, Minnesota) for:
 - Primary treatment for skeletally mature members with acute, open tibial shaft fractures stabilized with intramedullary nail fixation after appropriate wound management, if applied within 14 days after the initial fracture (U.S. Food and Drug Administration, 2004).
 - Dental localized alveolar ridge augmentation for defects associated with extraction sockets and sinus augmentation (U.S. Food and Drug Administration, 2007).

- INFUSE® Bone Graft LT-CAGE (Medtronic, Inc., Minneapolis, Minnesota) when used only with the INFUSE Bone Graft for single-level lumbar spinal fusion and all of the following criteria (U.S. Food and Drug Administration, 2002):
 - When autologous iliac crest bone graft is not feasible.
 - Skeletally mature patients (older than 18 years of age or no radiographic evidence of epiphyseal closure) with degenerative disc disease from L4 to S1; grade I spondylolisthesis at the involved level may be present.
 - At least six months of non-operative treatment.
 - Using an anterior open or laparoscopic approach.

Limitations

All other uses of bone graft substitutes are not medically necessary.

Mesenchymal stem cell therapy is not medically necessary for all orthopedic applications, including, but not limited to, use in repair or regeneration of musculoskeletal tissue (Killington, 2018).

Allograft bone products containing viable stem cells are not medically necessary for all orthopedic applications, including, but not limited to, demineralized bone matrix with stem cells.

All other uses of recombinant human bone morphogenetic protein-2 are not medically necessary.

Contraindications to the INFUSE Bone Graft include, but are not limited to:

- Known hypersensitivity to the components of the formulation or the titanium cage.
- Near the vicinity of a resected or extant tumor, any active malignancy, or a malignancy undergoing treatment.
- Active infection at the operative site.
- Inadequate neurovascular status.
- Compartment syndrome of the affected limb.
- Pregnancy.

For Medicare members only

The Medicare Local Coverage Determination L33382 Lumbar Spinal Fusion for Instability and Degenerative Disc Conditions does not address lumbar spinal fusion techniques, devices, and instrumentation or bone graft substitutes. Some of the emerging techniques and associated tools (e.g., devices, spinal instrumentation, and bone graft substitutes) are investigational, and this Local Coverage Determination does not endorse such procedures. The scope of this Local Coverage Determination is the indications and medical need of lumbar spinal fusion for instability and degenerative disc conditions.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Bone grafting is a surgical procedure that replaces missing bone with material from patient's own body, or an artificial, synthetic, or natural substitute. Bone grafting exploits the bone tissue's ability to regenerate completely if provided the space into which to grow. As natural bone grows, it generally replaces the graft material completely, resulting in a fully integrated region of new bone.

Autologous cancellous bone graft remains the gold standard, because it provides the three elements required for bone regeneration: osteoconduction, osteoinduction, and osteogenic cells (Grabowski, 2013). The

complications and morbidity from harvesting autologous bone have driven the search for reliable and safe bone graft substitutes (Giannoudis, 2005).

Bone graft substitutes include cancellous and cortical allograft bone, ceramics, demineralized bone matrix, bone marrow, and composite grafts. Currently, no single alternative graft material provides all three elements for bone regeneration. Synthetic bone substitutes or xenografts can be used as an alternative to autologous graft to overcome problems of additional surgeries or limited graft availability, but synthetic grafts, often made of hydroxyapatite or other naturally occurring and biocompatible substances, lack osteoinductive or osteogenic properties. Composite grafts combine scaffolding properties with biological elements, such as demineralized bone matrix or bone derivatives, to stimulate cell proliferation and differentiation and, eventually, osteogenesis. Xenografts, such as a bovine species, are used as a calcified matrix (Grabowski, 2013).

Classification of bone grafts is based on material, grouped as follows (Laurencin, 2006):

- Autograft-based — used alone. Properties of action are osteoconductive, osteoinductive, and osteogenic.
- Allograft-based — allograft bone used alone or in combination with other materials. Properties of action are osteoconductive and osteoinductive.
- Natural and recombinant growth factor-based — used alone or in combination with other materials. Properties of action are osteoinductive and both osteoconductive and osteoinductive with carrier materials.
- Cell-based — used to generate new tissue alone or seeded onto a support matrix. Properties of action are osteogenic and both osteogenic and osteoconductive with carrier materials.
- Ceramic-based — calcium phosphate, calcium sulfate, and bioactive glass used alone or in combination. Properties of action are osteoconductive and limited osteoinductive when mixed with bone marrow.
- Polymer-based — degradable and nondegradable polymers used alone and in combination with other materials. Properties of action are osteoconductive and bioresorbable in degradable polymer.
- Miscellaneous — uses coral hydrogel-hydroxyapatite granules, blocks, and composite. Properties of action are osteoconductive and bioresorbable.

Findings

The clinical applications for each type of material are dictated by its particular structural and biochemical properties (Laurencin, 2006). The most common use of bone grafting is restoring the edentulous area of a missing tooth in application of dental implants. In general, bone grafts are either used in block (such as from chin or ascending ramus area of lower jaw) or are particulated to adapt better to a defect. The grafted, vascularized fibulas have been used to restore skeletal integrity to long bones of limbs in which congenital bone defects exist and to replace segments of bone after trauma or malignant tumor invasion. Other uses include fusing joints to prevent movement, repairing broken bones that have bone loss, and repairing broken bones that have not yet healed.

The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use, and cost-effective. Currently marketed products are variable in their composition and claimed mechanisms of action. It is reasonable that not all bone graft substitute products will perform the same.

Future biosynthetic bone implants may obviate the need for autologous bone grafts. There is increasing interest in combining an osteoconductive protein in an osteoconductive carrier medium to facilitate timed-release delivery and/or to provide a material scaffold for bone formation (Laurencin, 2006). Further, advances in tissue engineering, with “the integration of the biological, physical, and engineering sciences,” will generate new carrier constructs that repair, regenerate, and restore tissue to its functional state. These constructs are likely to

encompass additional families of growth factors, evolving biological scaffolds, and incorporation of mesenchymal stem cells. Ultimately, the development of ex vivo bioreactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue-engineered constructs for direct use in the skeletal system. Finally, as researchers continue to find new materials and biologic approaches to bone repair, the future of bone graft substitutes continues to be an expanding topic of interest.

The major concerns associated with allografts are antigenicity and risk of disease transmission from donor to recipient (Centers for Disease Control and Prevention, 2002). To minimize this risk, the production of an allograft worthy of distribution and implantation requires strict attention to detail through a comprehensive process. With an increasing clinical requirement for bone grafting procedures, there is a commensurate increase in patients' demands for assurance that bank bone will not be infected with pathogens. The U.S. Food and Drug Administration (2018) requires that manufacturers of human allograft products, including bone, be registered.

A narrative review (Zhang, 2017) assessed the need for natural bone substitutes with specific mention of nacre, or mother-of-pearl, as an organic matrix-calcium carbonate coupled shell structure. Nacre is produced by mollusks. In vivo and in vitro studies have revealed that nacre is osteoinductive, osteoconductive, biocompatible, and biodegradable. The authors concluded that there is great potential clinically for nacre as a bone graft substitute.

In 2018, we added three systematic reviews (Fischer, 2013; McNamara, 2015; Papageorgiou; 2016) to this policy, and we received a specific request to evaluate the medical necessity of recombinant human bone morphogenetic protein as an alternative or adjunct to autologous bone grafts for osteoinduction and bone healing. Two products have been approved that use recombinant human bone morphogenetic protein -2 (also known as dibotermis alfa) as the main ingredient (U.S. Food and Drug Administration, 2002, 2004, 2007):

- INFUSE bone graft for tibial shaft fractures, dental sinus augmentation, and alveolar ridge augmentation.
- INFUSE titanium LT-CAGE when used with the INFUSE bone graft for single level spinal fusion procedures from L4 to S1.

INFUSE offers at least comparable osteoinductive advantages to those of autologous grafts, particularly when autologous grafts are not feasible, but a range of adverse events and several off-label uses have been reported (Krishnakumar, 2017; Poorman, 2017; Zadegan, 2017). Inconsistent and often inadequate reporting of adverse events makes assessment of the relative benefits and harms associated with recombinant human bone morphogenetic protein -2 and other surgical alternatives difficult to determine. The evidence is sufficient to support INFUSE for the approved indications that have a more predictable safety profile when used in accordance with labelling requirements, and, particularly, when autologous bone grafting alone is not feasible (Fu, 2013; Kelly, 2016; Lin, 2016; Simmonds, 2013).

In 2019, we added two systematic reviews (Cicciu, 2018; Killington, 2018) with no changes to the policy coverage.

In 2020, we added eight systematic reviews and meta-analyses to the policy: five addressed bone augmentation in oral surgery (Al-Moraissi, 2020; Avila-Ortiz, 2019; Dragonas, 2019; Liu, 2019; Stumbras, 2019); one addressed bony defects caused by giant cell tumor (Vaishya, 2019); and two addressed application of bone morphogenetic protein-2 to the spine (Mariscal, 2020; Stark, 2019). The new information is consistent with the current policy, and no policy changes are warranted.

In 2021, we added three systematic reviews and meta-analyses to the policy. Cottrill (2020) analyzed three randomized controlled trials and seven case series of the radiographic and clinical outcomes of a newer-generation synthetic ceramic called silicate-substituted calcium phosphate bone grafts, which is designed to maximize osteoinduction and osteoconduction in spinal fusion (Cottrill, 2020). From the case series (n = 694 patients treated with the intervention), 93% of patients successfully achieved arthrodesis, along with significant

improvements in back pain (visual analog score -3.3 points), leg pain (visual analog score -4.8 points), and Oswestry Disability Index (-31.6 points) by last follow-up that ranged from six months to 36 months ($P < .001$ for each). Fusion rates were similar regardless of surgical approach, spine levels involved, or other procedures used. In the randomized controlled trials, fusion rates were similar between patients treated with silicate-substituted calcium phosphate bone grafts and those treated with recombinant human bone morphogenetic protein-2 supplemented grafts (odds ratio 1.11, $P = .83$). However, the heterogeneity of the data and lack of comparative data to other graft materials limits the generalizability of these results.

Two systematic reviews and meta-analyses confirm the relative safety and effectiveness of recombinant human bone morphogenetic protein and autologous bone graft in lumbar fusion (Liu, 2020) and in cleft lip and palate augmentation (Xiao, 2020). The new information requires no policy changes.

References

On February 11, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “Bone Transplantation” (MeSH), “Bone Substitutes,” (MeSH), “allograft,” “autograft,” “bone reconstruction,” “bone repair,” “calcium sulphate,” “ceramic,” “hydroxyapatite,” “implant,” and “polymer.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Al-Moraissi EA, Oginni FO, Mahyoub Holkom MA, Mohamed AAS, Al-Sharani HM. Tissue-engineered bone using mesenchymal stem cells versus conventional bone grafts in the regeneration of maxillary alveolar bone: A systematic review and meta-analysis. *J Oral Maxillofac Surg.* 2020;35(1):79–90. Doi: 10.11607/jomi.7682.

Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: A systematic review and meta-analysis. *J Clin Periodontol.* 2019;46 Suppl 21:195-223. Doi: 10.1111/jcpe.13057.

Centers for Disease Control and Prevention. Update: Allograft-associated bacterial infections: United States, 2002. *MMWR Morb Mortal Wkly Rep.* 2002;51:207-210.
<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5110a2.htm>.

Centers for Medicare & Medicaid Services. Local Coverage Determination L33382 Lumbar spinal fusion for instability and degenerative disc conditions. <https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>.

Cicciu M, Cervino G, Herford AS, et al. Facial bone reconstruction using both marine or non-marine bone substitutes: Evaluation of current outcomes in a systematic literature review. *Mar Drugs.* 2018;16(1);27. Published 2018 Jan 13. Doi: 10.3390/md16010027.

Cottrill E, Premananthan C, Pennington Z, et al. Radiographic and clinical outcomes of silicate-substituted calcium phosphate (SiCAP) bone grafts in spinal fusion: Systematic review and meta-analysis. *J Clin Neurosci.* 2020;81:353-366. Doi: 10.1016/j.jocn.2020.09.073.

Dragonas P, Schiavo JH, Avila-Ortiz G, Palaiologou A, Katsaros T. Plasma rich in growth factors (PRGF) in intraoral bone grafting procedures: A systematic review. *J Craniomaxillofac Surg.* 2019;47(3):443-453. Doi: 10.1016/j.jcms.2019.01.012.

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;158(12):890-902. Doi: 10.7326/0003-4819-158-12-201306180-00006.

Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: An update. *Injury.* 2005;36(Suppl 3):S20-S27. Doi: 10.1016/j.injury.2005.07.029.

Grabowski M, Gregory D; Cornett A. Bone graft and bone graft substitutes in spine surgery: Current concepts and controversies. *J Am Acad Orthop Surg.* 2013;21(1):51-60. Doi: 10.5435/jaaos-21-01-51.

Kelly MP, Vaughn OL, Anderson PA. Systematic review and meta-analysis of recombinant human bone morphogenetic protein-2 in localized alveolar ridge and maxillary sinus augmentation. *J Oral Maxillofac Surg.* 2016;74(5):928-939. Doi: 10.1016/j.joms.2015.11.027.

Killington K, Mafi R, Mafi P, Khan WS. A systematic review of clinical studies investigating mesenchymal stem cells for fracture non-union and bone defects. *Curr Stem Cell Res Ther.* 2018;13(4):284-291. Doi: 10.2174/1574888x12666170915121137.

Krishnakumar GS, Roffi A, Reale D, Kon E, Filardo G. Clinical application of bone morphogenetic proteins for bone healing: A systematic review. *Int Orthop.* 2017;41(6):1073-1083. Doi: 10.1007/s00264-017-3471-9.

Laurencin C, Khan Y, El-Amin SF. Bone graft substitutes. *Expert Rev Med Devices.* *Indian J Med Res.* 2006;3:49-57. Doi: 10.1586/17434440.3.1.49.

Lin GH, Lim G, Chan HL, Giannobile WV, Wang HL. Recombinant human bone morphogenetic protein 2 outcomes for maxillary sinus floor augmentation: A systematic review and meta-analysis. *Clin Oral Implants Res.* 2016;27(11):1349-1359. Doi: 10.1111/clr.12737.

Liu S, Wang Y, Liang Z, Zhou M, Chen C. Comparative clinical effectiveness and safety of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion: A meta-analysis and systematic review. *Spine.* 2020;45(12):E729-e741. Doi: 10.1097/brs.0000000000003372.

Liu R, Yan M, Chen S, et al. Effectiveness of platelet-rich fibrin as an adjunctive material to bone graft in maxillary sinus augmentation: A meta-analysis of randomized controlled trials. *BioMed Res Int.* 2019;2019:7267062-7267062. Doi: 10.1155/2019/7267062.

Mariscal G, Nuñez JH, Barrios C, Domenech-Fernández P. A meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for the posterolateral fusion of the lumbar spine. *J Bone Miner Metab.* 2020;38(1):54-62. Doi: 10.1007/s00774-019-01025-9.

Poorman GW, Jalai CM, Boniello A, et al. Bone morphogenetic protein in adult spinal deformity surgery: A meta-analysis. *Eur Spine J.* 2017;26(8):2094-2102. Doi: 10.1007/s00586-016-4841-5.

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;158(12):877-889. Doi: 10.7326/0003-4819-158-12-201306180-00005.

Stark JR, Hsieh J, Waller D. Bone graft substitutes in single- or double-level anterior cervical discectomy and fusion: A systematic review. *Spine.* 2019;44(10):E618-E628. Doi: 10.1097/BRS.0000000000002925.

Stumbras A, Krukis MM, Januzis G, Juodzbaly G. Regenerative bone potential after sinus floor elevation using various bone graft materials: A systematic review. *Quintessence Int.* 2019;50(7):548-558. Doi: 10.3290/j.qi.a42482.

U.S. Food and Drug Administration. FDA human cell and tissue establishment registration — public query database.

https://www.accessdata.fda.gov/scripts/cber/CFAppsPub/tiss/Index.cfm?fuseaction=fuse_DisplaySearch&CFID=23091837&CFTOKEN=985566c088c8989f-1F22E2A5-CD46-2D0D-FE6C7A28B417F791. Updated November 20, 2020.

U.S. Food and Drug Administration. INFUSE® Bone Graft. Pre-market approval letter P050053. https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050053A.pdf. Published March 9, 2007.

U.S. Food and Drug Administration. INFUSE® Bone Graft. Pre-market approval letter P000054. https://www.accessdata.fda.gov/cdrh_docs/pdf/p000054c.pdf. Published April 30, 2004.

U.S. Food and Drug Administration. INFUSE™ Bone Graft/LT-CAGET™ Lumbar Tapered Fusion Device. Pre-market approval letter P000058. https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058A.pdf. Published July 2, 2002.

Vaishya R, Pokhrel A, Agarwal AK, Vijay V. Current status of bone cementing and bone grafting for giant cell tumour of bone: A systemic review. *Ann R Coll Surg Engl*. 2019;101(2):79-85. Doi: 10.1308/rcsann.2019.0004.

Xiao WL, Jia KN, Yu G, Zhao N. Outcomes of bone morphogenetic protein-2 and iliac cancellous bone transplantation on alveolar cleft bone grafting: A meta-analysis. *J Plast Reconstr Aesthet Surg*. 2020;73(6):1135-1142. Doi: 10.1016/j.bjps.2020.01.011.

Zadegan SA, Abedi A, Jazayeri SB, et al. Bone morphogenetic proteins in anterior cervical fusion: A systematic review and meta-analysis. *World Neurosurg*. 2017;104:752-787. Doi: 10.1016/j.wneu.2017.02.098.

Zhang G, Brion A, Willemin AS, et al. Nacre, a natural, multi-use, and timely biomaterial for bone graft substitution. *J Biomed Mater Res A*. 2017;105(2):662-671. Doi: 10.1002/jbm.a.35939.

Policy updates

5/2016: initial review date and clinical policy effective date: 7/2016

7/2017: Policy references updated.

7/2018: Policy references updated. Coverage expanded to include recombinant human bone morphogenetic protein -2 (INFUSE) products.

5/2019: Policy references updated.

5/2020: Policy references updated.

5/2021: Policy references updated.