INFUSE Bone Graft

August 2024

Device Overview

INFUSE Bone Graft is comprised of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), which is delivered on a sterile absorbable collagen sponge and applied to the implant to assist in bone formation. With the use of INFUSE, the patient's body is not used for bone harvesting, since the graft stimulates new bone formation. Low back pain or degenerative disc disease afflicts a large number of the population and is associated with billions of dollars of healthcare expenditures. INFUSE provides a treatment alternative to iliac crest bone graft (ICBG) for eligible, skeletally mature patients and has been also used for lumbar spinal fusion, open tibial shaft fractures, and in oral surgical procedures. [1,2]

FDA Approval

The INFUSE Bone Graft was initially approved by the FDA in 2002 for treating **lumbar degenerative disc disease**, in 2004 for **open tibial shaft fractures**, and in 2007 for **sinus and alveolar ridge augmentations**. This does not include all the FDA approvals for other expanded indications. [3,4] In May 2004, Medtronic was awarded an FDA breakthrough designation for use in transforaminal lumbar interbody fusion. [5]

Actions for Consideration

PARTNER

ENGAGE SUBJECT MATTER EXPERTS
Assess current utilization of INFUSE and engage key physician specialties including surgeons (Spine, Orthopedics, Oral Surgery), nurses, and value analysis leaders.

CONSIDER GUIDELINES FOR USE
Develop 'criteria for use' guidelines, sharing pricing & size (volume) utilization information. Consider criteria for use by patient and specialty.

UNDERSTAND CONCERNS
Continue conversations with key specialties and leverage physician input. Connect with other health systems.

CONNECT

SEEK CLINICAL IMPACT
Review data & physician utilization by procedure to support improved quality of care and patient outcomes.

CONDUCT ANALYSIS
Compare cost of surgeries with or without INFUSE Bone Graft, include pricing, reimbursement, and outcomes information to inform decision making.

DETERMINE POPULATION
Work with key stakeholders to determine appropriate patients, procedures, and sizes for utilization. Consider FDA-approved indications, contraindications, and adverse events.

COMMUNICATE

EDUCATE AND TRAIN
Provide information on criteria for use across appropriate specialties. Engage supplier for support of questions/concerns. Include OR nursing and techs.

PLAN AHEAD
Share criteria for use guidance as well as data to support decision making with key stakeholders. Leverage a physician champion.

FOLLOW-UP FOR FEEDBACK
Create on-going feedback loop for successes and challenges. Routinely evaluate the literature for newly published studies evaluating INFUSE.

Clinical Insights: HealthTrust Physician Advisors

A panel of orthopedic, spine, oral/maxillofacial, and otolaryngology surgeons within our HealthTrust Physician Advisor Network offered the following insights with regard to use of INFUSE Bone Graft within their respective specialties. [6]

Physician Advisor Insights

Ortho/Spine Surgery

- **Ideal patient populations could include revisions with pseudoarthrosis, severe osteoporosis fusions, chronic illnesses, multi-level fusions, Medicare patients, diabetics, smokers, spinal fusions, interbody fusions, posterolateral fusions.**
- **For surgical procedures, utilize for lumbar fusions, anterior lumbar interbody fusion (ALIF), lateral lumbar interbody fusion (LLIF), anterior to psoas (ATP) fusion, posterior spinal fusion (PSF), and multilevel lumbar.**
- **Benefits include successful fusion when compared to other grafts, "protein directing cell differentiation, needs to be away from an open spinal canal"; lower revisions; improved fusion rate. Limitations are caution using in cervical spine (may lead to swelling) and may create bone growth around nerves or undesired sites.**
- **When developing criteria for use, consider patients with fusion difficulties, surgical complexity, patient-specific factors, number of levels fused; "patient risk factors for pseudoarthrosis that make augmentation with INFUSE desirable", "concern for cervical spine surgery," and cost-effectiveness compared to competing products.**
- **Safety concerns include "only use posteriorly in neck [not for anterior cervical discectomy and fusion (ACDF) due to high risk of swallowing issues], increased risk potential if repetitive use in same patient"; cancer patients; "allergy to bovine collagen or immunologic reaction due to prior exposure to Infuse"; and cervical spine surgery.**

Clinical Insights: HealthTrust Physician Advisors (continued)

Physician Advisor Insights

Oral/maxillofacial or Reconstructive Surgery

- Ideal patient populations could include facial trauma related to mandible maxilla and facial skeleton, tibial fractures, and "additional bone augmentation after extensive trauma or bone loss."
- For surgical procedures, "augmenting the mandible and mid face when there is any indication for bone loss," such as dental procedures or facial trauma; "role for augmenting the facial skeleton" as in bone resection for cancer; "may have some use in cosmetic cases for augmenting the zygomatic arch or facial skeleton."
- Benefits include bone growth stimulation, bridging gap between bone and defects, and no need for secondary donor site. Limitations are use in bridging small bony gaps that "do not extend beyond 1 to 2 cm", and not useful for bridging complete bone gaps.
- When developing criteria for use, consider criteria developed for each surgical discipline to determine what extent of bone augmentation is needed.
- A safety concern is infection risk.

Otolaryngology

- Ideal patient populations could include maxilla and mandible reconstruction and radius reconstruction after removal for free flap surgery.
- When developing criteria for use, consider cost, length of time until healed, and durability of the product versus native bone.
- A safety concern is "rejection of materials; strength of materials; weight bearing ability."

Professional Society Statements & Clinical Practice Guidelines

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS)

American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Guidelines (2014) for rhBMP-2 use are available here. [7]

North American Spine Society

North American Spine Society (NASS) [2014] clinical criteria/scenarios for rhBMP-2 use is available for purchase here. [8]

Agency for Healthcare Research and Quality

Agency for Healthcare Research and Quality (AHRQ) Technical Report containing studies evaluating on-label indications for INFUSE Bone Graft are available here. [9]

Clinical Evidence

Numerous studies have assessed INFUSE Bone Graft in a variety of spinal fusions, orthopedic fractures, and oral-maxillofacial applications. A sampling of those studies is included below. Variation is seen in use, dosing, and complications, impacting patient outcomes and safety. [10,11] Of note, many studies are industry-sponsored, and heterogeneity exists across studies. Studies also emphasize risks of adverse events, particularly with off-label use. [12]

A 2020 meta-analysis of 20 randomized controlled trials in 2185 patients compared rhBMP-2 to autologous ICBG. RhBMP-2 was associated with increased fusion rate [odds ratio (OR) 3.79; 95% confidence interval (CI) 1.88-7.63; p=0.0002], less reoperations (OR 0.59; 95% CI 0.43-0.8; p=0.0007), and improved disability scores (mean difference 1.54; 95% CI 0.18-2.89; p=0.03). There was no difference in complications between comparators. [13]

A 2024 retrospective study of 1019 surgeries in 908 patients evaluated INFUSE and bone marrow aspirate for posterior lumbar interbody fusion. The rate for surgery for nonunion was 1.2%. Radiculitis occurred in 42% of patients but was considered transient. Visual analog scale leg and back pain significantly decreased (p<0.001 for both at all timepoints). Functional and health survey scores improved over the course of follow-up (p<0.001 for both at all timepoints).

Clinical Evidence (continued)

Limitations include the following: retrospective, observational, potential for confounders (such as differences or improvements in technique), study involved one surgeon. [14]

A 2016 meta-analysis of 10 randomized controlled trials (industry-sponsored) including 1255 patients evaluated patient factors on efficacy (fusion success) and safety (overall adverse events, device associated adverse events, severe adverse events, or both) of rhBMP-2 versus ICBG in anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), and posterolateral fusion lumbar fusion (PLF). Improved fusion success was seen in patients who were age < 60 years ($p<0.01$), smokers ($p=0.01$), and normal body weight ($p=0.03$). Patients without prior back surgeries had a lower chance of complications ($p<0.01$). Limitations of this study include the heterogeneity among procedures, small sample sizes, potential for confounders, unmasking during treatment and outcomes, and lack of power to determine "subgroup effects." [15]

See Reference section for complete listing of research sources.

Using Yale University Open Data Access of Medtronic Infuse data, a 2013 systematic review and meta-analysis of 13 randomized controlled trials (all industry-sponsored), 47 "intervention series," 31 cohort studies, and 35 case reports/series reported no difference between rhBMP-2 and ICBG in ALIF for fusion rates, success, or adverse event risk. Cancer risk was found to be non-significantly increased; however, the rate of events was minimal, and cases were heterogeneous. [16]

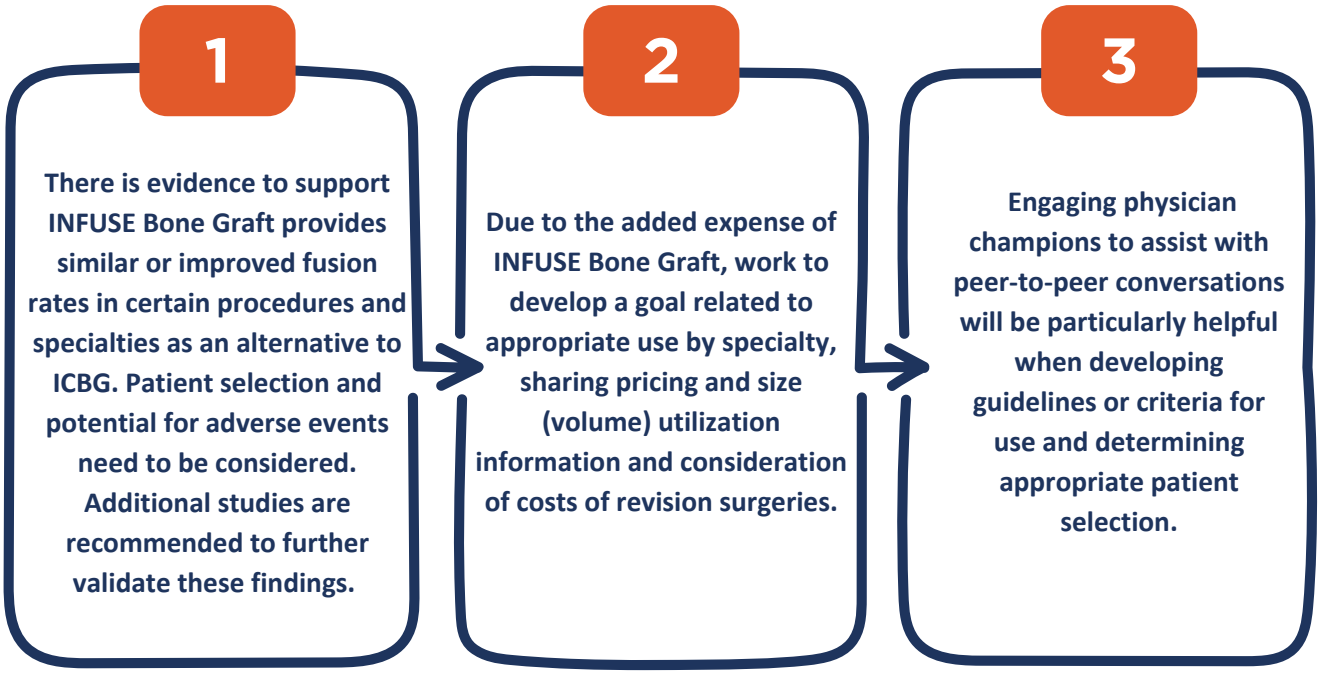
A 2013 meta-analysis by Simmonds et al. of 12 randomized controlled trials (all manufacturer sponsored except for one) and 35 observational studies (on adverse events) evaluated rhBMP-2 for fusion success, pain, and adverse events. Fusion success at 24 months was 12% increased for rhBMP-2 compared to ICBG [relative risk (RR) 1.12; 95% CI, 2%-23%), and pain at 24 months (as measured by the Oswestry Disability Index) was lower for rhBMP-2 compared to ICBG (-3.5% points; 95% CI, -0.49% to -6.47% points). When an adverse event meta-analysis was conducted, pain appeared to be higher at or post-surgery for rhBMP-2 patients (OR 1.78; 95% CI, 1.06-2.95; $p=0.007$), which is different from the results at 24 months. Cancer rates were "more common" for rhBMP-2, but authors determined association to be "inconclusive" due to small event size. Adverse events are based on nonrandomized studies so "findings should be interpreted cautiously" since there is "little information about the comparability of groups." [17]

Clinical Evidence (continued)

A 2011 systematic review of 13 industry-sponsored rhBMP-2 studies, which did not report any adverse events, found an estimated adverse event rate of 10%-50% for rhBMP-2 in spinal fusion. Authors suggest study designs had "potential methodological bias," adverse events that were omitted from reports, "internal inconsistencies," selection bias, and design bias which led to inaccurate and underestimated reporting of adverse events. All fusion types were associated with adverse events, with anterior cervical fusion having "life-threatening events." RhBMP-2 had the same or more adverse events compared to ICBG for posterolateral fusions. [18]

A A 2022 review article by Malham et al. describes recommendations here for spinal indications for which INFUSE may be beneficial such as, spinal fusion (but not anterior cervical fusion), lumbar fusion for degeneration, spinal deformity, and pseudoarthrosis revisions. [7] Patients without successful autograft harvest (in quality or yield), such as those who are elderly, chronic smokers, diabetic, with decreased bone density, with renal or hepatic disease, rheumatoid arthritis, inflammatory bowel disease, Parkinson's disease, and with previous radiotherapy, could also find benefit. [10]

Summary



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