Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Spine Fusion: A Systematic Review and Meta-analysis

Executive Summary

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Introduction

Spinal fusion surgery is a procedure that unites (fuses) two or more vertebral bodies together. It is the most commonly performed surgery for chronic non-specific back pain caused by degenerative conditions,[1] to restrict spinal motion and remove the presumed cause of pain. A variety of fusion techniques are practiced. An interbody fusion, involving removal of a degenerated intervertebral disc and fusion of the adjacent vertebral bodies, can be performed via an anterior (anterior lumbar interbody fusion, ALIF), posterior (posterior lumbar interbody fusion, PLIF), or transforaminal (transforaminal lumbar interbody fusion, TLIF) approach. Posterolateral lumbar fusion (PLF) involves adjacent transverse processes. All techniques use a bone graft and/or bone graft substitute to promote fusion.

Traditionally, spinal fusions are performed by using graft material harvested from the iliac crest. Harvesting bone requires an additional surgery and may be inadequate for long spinal fusions or other difficult cases. Recombinant human bone morphogenetic protein-2, or rhBMP-2, an orthobiologic, is a bone graft substitute that was approved by the U.S. Food and Drug Administration (FDA) in 2002 for use in conjunction with an implant (LT-CAGE™) for single-level ALIF. In December 2003, the FDA approved the use of rhBMP-2 with another implant (INTER FIX™) for similar indications.[2] In clinical practice, rhBMP-2 has primarily been used "off-label" in PLF and TLIF.[3]

Previous systematic reviews have found gaps in the evidence about rhBMP-2, which could have led to misleading conclusions about the balance of effectiveness and harms of rhBMP-2 compared with bone graft.[4, 5] FDA documents summarizing Medtronic-sponsored trials appeared to indicate substantially more adverse events than reported in the journal publications. Observational studies confirmed that serious adverse events can occur with rhBMP-2 use in cervical spine fusion[6-9] and a case series questioned its safety in off-label lumbar fusion.[10] In June 2008, the FDA issued a public health notification of life-threatening complications associated with off-label use of rhBMP-2 in cervical spine fusion—swelling of the neck and throat resulting in compression of the airway and other structures.[11]

To better understand the evidence on the effectiveness and harms of rhBMP-2, the Yale University Open Data Access (YODA) Project commissioned two independent centers to conduct systematic reviews of rhBMP-2, based on published as well as unpublished data for both FDA-approved and off-label uses. As part of this project, the manufacturer of INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, Medtronic Inc., the sole manufacturer of devices involving rhBMP-2 for spinal fusion, agreed to release all of the individual patient data (IPD) and relevant documents for studies of rhBMP-2 that it funded. The Oregon Evidence-based Practice Center was selected as one of the review centers. The primary aims of this report are 1) to estimate effectiveness and harms of rhBMP-2 in spinal fusion in a systematic review, using individual patient data (IPD) when available, and 2) to assess reporting biases in published articles of industry-sponsored studies.

Methods

We used four sources of data: 1) Medtronic IPD, related protocols, and data dictionaries; 2) Medtronic internal documents; 3) documents from the FDA web site; and 4) a broad-based literature search to identify a) additional studies on rhBMP-2 and b) publications related to Medtronic-sponsored studies. For aim 1, we used data from sources 1, 2 and 4(a), and for aim 2, we compared the journal publications of Medtronic-sponsored studies to other sources.

For data sources 1 and 2, the YODA Project provided de-identified patient-level data, protocols, data dictionaries, and Medtronic internal reports for all 17 Medtronic-funded studies of rhBMP-2 in spinal fusion completed or terminated by December 2011. The internal reports included summaries of study data and brief adverse event case histories.

For data sources 3 and 4, we searched MEDLINE® (1996 to August 2012), Embase®, the Cochrane Library® (third quarter 2012), Scopus, ClinicalTrials.gov, and the FDA web site, and manually searched reference lists.

For aim 1, two reviewers independently assessed each article for eligibility. For effectiveness and harms, we included controlled clinical trials and cohort studies of rhBMP-2 in spinal fusion. For harms, we also included uncontrolled intervention series of patients receiving rhBMP-2, case series, and case reports. We excluded studies that combined results of rhBMP-2 with other bone morphogenetic proteins, unless we could determine rhBMP-2 was predominantly used. For aim 2, we identified publications in peer-reviewed journals that reported results from one or more Medtronic trials.

Two reviewers independently evaluated the quality of all included studies based on predefined criteria, and disagreements were resolved by consensus. For Medtronic-funded studies, quality assessment was based on information from trial protocols and internal reports. One investigator abstracted patient and study characteristics and results, and a second reviewed abstracted data for accuracy.

For outcomes related to effectiveness, we included overall success, fusion, neurological success pain, disability, SF-36, and return to work. We applied consistent definitions and recalculated effectiveness outcomes using IPD. Overall success and fusion were determined using multiple criteria; all had to be satisfied for a case to be classified as a success. In the primary analysis, patients meeting some criteria but missing data for others were classified as failures, and patients without data for any criteria were excluded. Harms of rhBMP-2 included overall adverse events, and specific adverse events, e.g., mortality, additional surgery, infection, dysphagia, heterotopic bone formation, subsidence, leg or back pain retrograde ejaculation, urinary retention and cancer.

Data syntheses were stratified by spinal area (lumbar, cervical) and surgical approach (e.g., ALIF, PLF) for all outcomes except cancer and death, for which we combined all surgical approaches. We performed meta-analysis of IPD for ALIF and PLF, and results of published results if studies included in a category were similar enough to produce a meaningful combined estimate. We adapted methods developed by the Agency for Healthcare Research and Quality[12] to rate the strength of evidence for each outcome.

We assessed publication and outcome reporting biases and quality of reporting[13] by comparing journal publications with corresponding study protocols, reports, and data dictionaries provided by Medtronic. We used a previously published protocol to classify publications as primary or secondary and to categorize potential sources of reporting bias.[14, 15]

Results

Study Selection

Comprehensive literature searches identified 14,697 citations. For key questions 1 and 2, we included 13 randomized controlled trials (RCTs), 12 Medtronic trials (1,879 subjects), and one trial sponsored by Norton HealthCare.[16] We excluded one small Medtronic trial because it was

stopped after recruiting only three patients. The study identification number for each Medtronic study could be found in Table 1. In 11 of the 12 included Medtronic-sponsored trials and in the Norton HeathCare-sponsored trial, spinal fusion with rhBMP-2 was compared with spinal fusion with iliac crest bone graft (ICBG). The other Medtronic study (Study 10) compared fusion with rhBMP-2 with implantation of the MAVERICK™ artificial disc.

Table 1. Medtronic study identification

Study Number	Trial Name	Surgical Approach	Reference
1	INFUSE®/LT-CAGE® Pilot	ALIF	Boden et al., 2000[17]
2	INFUSE®/LT-CAGE® Pivotal	ALIF	Burkus et al., 2002[18]
3	INFUSE®/ LT-CAGE® Lap Pivotal	ALIF	Burkus et al., 2003[19]
4	INFUSE®/ Bone Dowel Pilot	ALIF	Burkus et al., 2002[20]
5	INFUSE®/ Bone Dowel Pivotal	ALIF	Burkus et al., 2005[21]
6	INFUSE®/ INTER FIX™ PLIF	PLIF	Haid et al., 2004[22]
7	INFUSE®/ CORNER STONE® ACDF Pilot	ACDF	Baskin et al., 2003[23]
8	INFUSE®/MASTER GRAFT® Pilot	PLF	Dawson et al., 2009[24]
9	INFUSE®/ INTER FIX™ ALIF Pilot	ALIF	Unpublished
10	MAVERICK™ Disc Pivotal	ALIF	Gornet et al, 2011[25]
11	INFUSE®/ TELAMON PEEK PLIF Pilot	Circumferential PLIF	Unpublished
12	rhBMP-2/BCP US Pilot	PLF	Boden et al., 2002[26]
13	rhBMP-2/BCP Canada Pivotal	PLF	Unpublished
14	AMPLIFY™ (rhBMP-2/ CRM) Pivotal	PLF	Dimar et al., 2009[27]
15	rhBMP-2/ CRM 2-level Pilot	PLF	Unpublished
16	rhBMP-2/BCP Mexico Pilot	PLF	Unpublished

ACDF = Anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion

In addition to the RCTs, we included 31 cohort studies and 80 uncontrolled studies (47 intervention series and 33 case series or case reports) of patients who received rhBMP-2 to promote spinal fusion. Four intervention series were prospective Medtronic studies.

The randomized trials generally sought to determine whether rhBMP-2 is as good as ICBG in achieving overall success and solid fusion, and in reducing pain and disability associated with spinal disease, though the published articles analyzed most data as if they were superiority trials. These trials also conducted the assessments of safety required for FDA approval as a new device. Most cohort studies sought to evaluate fusion and identify specific adverse events associated with spinal fusion and to compare the frequency of these adverse events between patients fused with rhBMP-2 and patients fused with autograft and/or allograft. The majority of intervention series sought to determine the rate of fusion success after successful spinal fusion surgery, or both safety and efficacy of rhBMP-2 use, and about a quarter of the intervention series specifically sought to determine the rate of adverse events.

Study Quality

Most trials used similar methods for randomization and allocation concealment, and randomization in the pivotal trials and the larger pilot trials appeared to be satisfactory. While

there were some baseline differences in patient characteristics between those receiving ICBG and rhBMP-2, we did not detect a pattern favoring rhBMP-2.

The main risks for bias were lack of blinding of surgeons, patients, and outcome assessors (except for radiologic endpoints). Except in one study, there was no pre-specified algorithm on how to handle missing data. At 24 months, nine of the 12 randomized trials had follow-up rates over 90% in both groups. The proportion of lost-to-follow-up was much higher after 24 months in the few studies with longer follow up.

The quality of ascertainment varied across outcomes. Effectiveness outcomes (e.g., pain, function, fusion) were generally ascertained with well-designed questionnaires or scales. For harms, the studies used broad classifications for many adverse events, and events were generally not actively elicited using specific symptom questionnaires or objective tests. For example, for retrograde ejaculation, it was unclear how the outcome was defined or whether investigators asked about specific symptoms. In addition, study investigators determined whether or not the adverse event was implant or surgical procedure associated, which is subjective and prone to bias given assessor knowledge of the patient's treatment group. Cancer was not a pre-specified endpoint and only captured by voluntary reporting. Local effects, such as inflammation, ectopic bone formation, or osteolysis, were seldom reported.

Most observational studies were retrospective. The main risks for bias were unclear comparability of groups at baseline or difference in baseline characteristics, unclear blinding of outcome assessors, and failure to adjust for potential confounding variables and baseline differences.

Applicability

The Medtronic trials applied similar eligibility criteria and enrolled similar populations within each surgical approach. Most of the Medtronic-sponsored studies were small. Eleven of the 16 studies enrolled a total of less than 100 patients and 9 of the 16 enrolled less than 50 patients. Two off-label uses had exceptionally sparse data (ACDF and PLIF), making it very difficult to evaluate findings, especially less common adverse events, or to assess applicability.

Patients had discogenic back and/or leg pain, usually single-level disease, with ≤ Grade 1 spondylolisthesis, preoperative Oswestry Disability Index (ODI) scores ≥ 30 or 35, had not responded to conservative treatment for 6 months, were <40% over their ideal weight, and had not recently used tobacco. The mean age of patients in most trials was 40-60, and both genders were well-represented.

Some exclusion criteria were obesity, alcohol or drug abuse, autoimmune disease, osteoporosis, and conditions requiring treatment with steroids. For assessing applicability in trials with strict eligibility criteria, it is important to know the numbers of patients who did not qualify for the trial, and the specific reasons they did not. We could not find this information in the journal articles or in documents Medtronic provided.

Unfortunately, the observational studies were not especially useful in helping us evaluate the effectiveness of rhBMP-2 in broader populations. Most observational studies were small, and provided little information on patient characteristics.

Benefits and Harms

Anterior Lumbar Interbody Fusion in Lumbar spine

We included 13 studies using rhBMP-2 in anterior lumbar interbody fusion (ALIF), including 6 Medtronic RCTs (5 fair quality and 1 poor quality), four poor quality cohort studies

[28-31] and four intervention series, including one sponsored by Medtronic. Five RCTs compared rhBMP-2 with ICBG, and the other one compared rhBMP-2 with artificial disk replacement. The ALIF trials constituted the main body of evidence concerning INFUSE™ Bone Graft, the product approved by FDA.

Based on IPD meta-analysis of the five Medtronic RCTs (n=465), there was moderate strength of evidence of no consistent differences between rhBMP-2 and ICBG in overall success and fusion. At 24 months, the average overall success rate was 61% for the rhBMP-2 group and 53% for the ICBG group. There were no differences between rhBMP-2 and ICBG in overall success at 6 months (Risk Ratio [RR] 1.18, 95% CI 0.93 to 1.50), 12 months (RR 1.12, 95% CI 0.95 to 1.33), and 24 months (RR 1.19, 95% CI 0.99 to 1.42). Fusion rates ranged from 60% to 100% at 24 months. RhBMP-2 was associated with higher radiographic fusion versus ICBG at 6 months (RR 1.10, 95% CI 1.02 to 1.19, I^2=0%); and similar likelihood of fusion at 12 months (RR 1.09, 95% CI 0.95 to 1.24, I^2=29%) and 24 months (RR 1.05, 95% CI 0.88 to 1.24, I^2=76%). The results of fusion from cohort studies were generally consistent with results from RCTs.

Similarly, results from the meta-analysis of the five RCTs indicated generally moderate strength of evidence of no consistent differences between rhBMP-2 and ICBG in neurological success, ODI success, back and leg pain and other effectiveness outcomes. The one exception was that, on average, the SF-36 physical component summary score was approximately 3 points higher for patients in the rh-BMP-2 group at 3, 6, 12 and 24 months, though the magnitude of the difference was small, failing to meet the typical criteria for a clinically meaningful difference.[32]

The occurrence of adverse events was common. At 4 weeks, 38% of patients in the rhBMP-2 group and 45% of patients in the ICBG group had experienced at least one adverse event and at 24 months, about 80% of patients in both groups had experienced at least one adverse event. There was moderate strength of evidence that the proportions of patients experiencing at least one adverse event were not significantly different between rhBMP-2 and ICBG groups through 4 weeks (RR 0.84, 95% CI 0.61 to 1.17) and through 24 months (RR 0.96, 95% CI 0.85 to 1.09). There was also moderate strength evidence of no difference between groups in the risk of experiencing an adverse event classified as "serious" by study investigators (RR 1.12, 95% CI 0.72 to 1.74 at 4 weeks; RR 0.94, 95% CI 0.67 to 1.33 at 24 months). At 4 weeks, 8% of patients in the rhBMP-2 group and 9% of patients in the ICBG group had experienced at least one serious adverse event, and at 24 months, about 35% of patients in both groups had experienced at least one serious adverse event. In addition, there was no difference in risk of adverse events classified as "device-related" by the study investigators (RR 1.44, 95% CI 0.57 to 3.67) at 24 months. The proportion of adverse events judged to be device-related was low (rhBMP-2 7% vs. ICBG 4%).

Similarly, we did not detect any significant difference between rhBMP-2 and ICBG groups on any specific adverse events (e.g., infection, possible lumbar radiculitis, neurological and spinal events). The trial data for specific adverse events were sparse, along with potential poor ascertainment, making it impossible to make any definitive conclusions for specific adverse events. For retrograde ejaculation and urogenital problems, there was a higher rate in the rhBMP-2 group compared to the ICBG group but the differences were not statistically significant and confidence intervals were wide. One cohort study[30] also reported higher rates of retrograde ejaculation in the rhBMP-2 group, though the difference was significant compared to the control group with rhBMP-2 (5/69 vs. 1/174, P = 0.0025). Overall, the strength of evidence is low. For subsidence, the trial data also indicated an insignificantly increased risk of retrograde ejaculations, and the direction of effect was consistent across trials and observational studies.

While the estimates are imprecise, the condition was probably more consistently ascertainable and clearly defined than some other adverse events, and the strength of evidence is moderate.

Posterolateral Fusion in Lumbar Spine

We included 20 studies to evaluate the benefits and harms in posterlateral fusion (PLF). Five of these studies were RCTs comparing rhBMP-2 with ICBG (four fair quality and one poor quality), four sponsored by Medtronic (Studies 8, 12-14) and one by Norton HealthCare. Three of the Medtronic-sponsored RCTs used a higher dose and concentration of rhBMP-2 than used in ALIF trials. The RCT sponsored by Norton HealthCare did not report dosage. In addition, we included 7 cohort studies (2 fair quality and 5 poor quality) reported in eight publications[33-40] and seven intervention series, two (Studies 15 and 16) sponsored by Medtronic and five by others,[41-45] and one case series.[46] The Medtronic-sponsored posterolateral fusion trials constitute the main body of evidence about higher dosages and concentrations of rhBMP-2, including AMPLIFY, than that used in the ALIF trials.

Similar to ALIF, meta-analysis based on IPD (4 RCTs, *n*=722) provided moderate strength evidence of no consistent difference between rhBMP-2 and ICBG in overall success and fusion from 6 months through 24 months. For overall success, rhBMP-2 had significantly higher rates at 6 months (RR 1.34, 95% CI 1.10 to 1.64), but not at 12 months (RR 1.07, 95% CI 0.93 to 1.25) or 24 months (RR 1.05, 95% CI 0.91 to 1.21). At 24 months, the rate of overall success ranged from 40 to 60% in both groups. Similar to overall success, rhBMP-2 had significantly higher rates at 6 months (1.37, 95% CI 1.19 to 1.59) but not at 12 months (RR 1.29, 95% CI 0.94 to 1.78) and 24 months (RR 1.16, 95% CI 0.96 to 1.41). The fusion rate at 24 months ranged from 70% to 90% in the ICBG group and 86% to 93% in the rhBMP-2 group. Heterogeneity was present (I^2=86% and 76% at 12 and 24 months, respectively) and could not be attributed to differences in factors such as age, gender, number of levels fused, smoking status, or diabetes. The additional trial[16] also found no difference in fusion rates at 24 months (rhBMP-2 86% vs. ICBG 71%; RR 1.12, 95% CI 0.98 to 1.29).

For other effectiveness outcomes, our IPD meta-analysis of the four trials (n=722) also provided generally moderate strength of evidence that there was no consistent difference in neurological success, ODI score, back and leg pain scores, SF-36, and return to work between the rhBMP-2 group and the ICBG group at any time point from 6 weeks to 24 months.

For longer followup, limited IPD was available from two Medtronic trials at 48 months (Study 13 and 14); and from one Medtronic trial at 60 months (Study 14). Overall success and fusion were significantly greater with rhBMP-2 at 48 months, but not at 60 months.

As in ALIF trials, the occurrence of adverse events was also common in PLF. About 50% of patients had experienced at least one adverse event at 4 weeks and over 80% at 24 months. There was moderate strength of evidence of no difference between rhBMP-2 and ICBG in risk of experiencing at least one adverse event at 4 weeks (RR 0.93, 95% CI 0.66 to 1.31) and through 24 months (RR 1.02, 95% CI 0.95 to 1.10). There was also no difference between groups in risk of experiencing a serious adverse event (RR 0.89, 95% CI 0.67 to 1.18 at 4 weeks; RR 0.96, 95% CI 0.83 to 1.11). At 4 weeks, about 20% of patients in either group had experienced at least one serious adverse event, and at 24 months, the proportion was about 50%. In addition, there was no difference between rhBMP-2 and ICBG in the likelihood of experiencing an adverse event classified as "device-related" by the study investigators at 24 months, and the event rate was low (6% versus 5%, RR 1.36, 95% CI 0.57 to 3.23).

For specific adverse events, we found similar rates for rhBMP-2 and ICBG at 4 weeks and 24 months, but estimates were frequently imprecise, precluding strong conclusions. The only

exception was that the rhBMP-2 group had increased risk of back and leg pain through 4 weeks, though heterogeneous events (e.g., radiculopathy, Baker's cyst, arthritic knee pain, or ankle pain) were included and may be unrelated to fusion surgery.

Results from cohort studies[33-40] and intervention series[41-45, 47, 48] appeared consistent with the randomized trials, though few studies[37, 38, 40, 43] reported specific adverse events.

Other Approaches in Lumbar Spine

Evidences for other surgical approaches for comparative benefit and harms are limited. We included only one small Medtronic-sponsored RCT for the PLIF approach, and all other evidence for PLIF/TLIF and the circumferential approaches is from low-quality observational studies. Cohort studies usually showed no significant differences in fusion rates and occasionally other effectiveness outcomes between rhBMP-2 and other bone graft alternatives, but the strength of evidence was usually low or insufficient.

For harms, cohort studies usually showed similar rates of overall complications between rhBMP-2 and other bone graft alternatives, and concerns over increased risk of heterotopic bone formation and radiculitis were raised. Strength of evidence was usually low or insufficient, and data from cohort and intervention studies provided estimates of rates from actual practice.

Cervical Spine Fusion

For anterior cervical spine fusion, we included one small, fair quality, randomized trial sponsored by Medtronic, six cohort studies, two rated fair quality[6, 7] and four rated poor quality,[8, 9, 28, 49] and seven intervention series.[9, 50-56]

The one RCT (*n*=33) showed no differences between rhBMP-2 and ICBG in likelihood of overall success, fusion, and other benefit outcomes, and three cohort studies also found no clear differences in effectiveness.[8, 9, 28] The evidence was low or insufficient.

For harms, IPD data from the one RCT indicated that rhBMP-2 was associated with greater risk of adverse events than ICBG at 24 months (45 adverse events in 18 patients vs. 13 adverse events in 15 patients; Rate Ratio 2.88, 95% CI 1.30 to 6.41). A large, fair quality cohort study (n=27,067) found rhBMP-2 associated with increased risk of complications in the immediate postoperative period (Odds Ratio [OR] 1.43, 95% CI 1.12 to 1.70).[6] The strength of evidence was low.

Moderately strong evidence indicated a higher rate of dysphagia with rhBMP-2 compared with controls. While the small trial found no difference in rates of dysphagia between rhBMP-2 and ICBG groups up to four weeks since surgery, one large cohort study found increased risk associated with rhBMP-2 (OR 1.63; 95% CI 1.30 to 2.05) [6] and smaller cohort studies (total *n*=111,3) were consistent with these results.[7-9, 49] The intervention series studies reported 5% to 60% of patients developed dysphagia, with differences in dysphagia definitions.[51, 53-56] The large cohort study also found low strength evidence of increased wound complications (OR 1.67, 95% CI 1.10 to 2.53).[6]

In posterior cervical spine fusion, there were no controlled trials of rhBMP-2, and we included four retrospective cohort studies (n=3,233), one fair quality[6] and three poor quality;[57-59] and two intervention series (total *n*=82).[60 61] There was insufficient evidence to evaluate the comparative effectiveness, and the cohort studies provided low strength evidence of no difference in rates of overall adverse events with and without rhBMP-2.

Cancer and Death

Five Medtronic-sponsored trials with IPD (Studies 2, 4, 5, 10, 14) reported at least one cancer through 24 months and were included in our meta-analysis. We found a significantly increased risk of cancer associated with the use of rhBMP-2 compared to the ICBG group at 24 months (RR 3.45, 95% 1.98 to 6.00 and absolute difference 1.9 percentage points, 95% CI 0.5 to 3.2), with a number needed to harm of 53 (95% CI 31 to 200). However, the cancers in the meta-analysis included many different types of malignancies. Fewer studies provided data at 48 months. While the rhBMP-2 group still showed a higher risk, the association was attenuated and no-longer significant (four studies; RR 1.82, 95% CI 0.84 to 3.95). Excluding non-SEER cancers resulted in similar estimates to those including non-SEER cancers (RR 2.92 through 24 months, 95% CI 1.75 to 4.87 and RR 1.92 through 48 months, 95% CI 0.86 to 4.32). The total number of cancers included was 23 at 24 months, and 27 at 48 months; the strength of evidence was low.

There was no difference between rhBMP-2 and ICBG in risk of death through 24 months (nine trials, RR 0.67, 95% CI 0.28 to 1.63—Studies 2, 4, 6-10, 13-14) or 48 months (four trials, RR 0.65, 95% CI 0.33 to 1.30—Studies 4, 10, 13-14), but the event rates were low and estimates of RR were imprecise.

Quality of Reporting

Nine of the 12 included Medtronic trials were published in medical journals as individual trials.[17, 18, 20, 22-24, 26, 27, 62] One trial was partly described in an article that analyzed two trials together.[21]

Overall success was the primary study endpoint for six published Medtronic-sponsored trials (Studies 2, 3, 5, 8, 10, and 14) but only two of the primary publications (for Study 8 and Study 10) reported results for overall success.[24, 62] Fusion was listed as a primary outcome or primary effectiveness outcome in ten Medtronic-sponsored studies (Studies 2, 3, 4, 5, 6, 7, 8, 12, 14, and 16) and was reported in all nine primary publications.

Reporting of Effectiveness

There was important bias in the way the results of the ALIF studies reported effectiveness outcomes. In 2002, the FDA approved rhBMP-2 with the LT-Cage in ALIF based on three premarketing studies (Studies 1, 2, and 3).[63] By 2004, at least 12 articles and reviews reporting results from these studies had been published in major orthopedic journals.[17-19, 64-71] In contrast with reports to the FDA, many of these articles presented the results of the pivotal trials as demonstrating better fusion rates than ICBG. For example, the primary publication for Study 2 reiterated high fusion rates (94.5% vs. 88.7%) in the abstract, results, and conclusion sections, while failing to mention that the difference was not statistically significant in the abstract and results sections.[18]

In 2003, Burkus and colleagues published a *post hoc* "integrated analysis" that promoted the idea that rhBMP-2 would have superior outcomes compared with ICBG with sufficient sample size.[19] The authors combined the rhBMP-2 groups from Study 2 and Study 3 and compared them with a control group that combined the ICBG arm of Study 2 (*n*=136) with an older, unrelated, unpublished series of patients (*n*=266) who underwent laparoscopic surgery with the LT-CAGE.[19] However, in its report to the FDA of Study 2, Medtronic chose not to combine the results of Study 2 and Study 3 since the overall success rates were higher in the rhBMP-2 arm of Study 3 than in the rhBMP-2 arm of Study 2. Also, according to an internal Medtronic report, surgeons in the unrelated series were likely less skilled with the new laparoscopic cage technique, as evidenced by longer operative times, higher blood loss, and longer hospital stays. [72]

The authors did not mention these concerns or the previous decision of not conducting an integrated analysis, and concluded that rhBMP-2 "had statistically superior outcomes" for these outcomes and for fusion rates in the "integrated analysis."[19] In 2004, in another journal, they stated "…the outcomes represent typical results from a wide variety of surgeons with different degrees of experience…."[69]

Two Medtronic studies of rhBMP-2 used bone dowels, an off-label lumbar application (Studies 4, 5). The larger, pivotal bone dowel trial (Study 5) was terminated early and published only in an article that combined the pilot and pivotal trials, representing them as "a two-part, prospective, randomized, multicenter study" with "two sequential phases." It reported that "fusion rates were significantly better in the study group ($p<0.001$)" without mentioning early termination,[65] as did two additional articles by the same author.[21, 73]

In posterolateral fusion, the published article reported higher overall success rates than we observed based on our IPD analysis (Study 8),[24] or reported significantly higher fusion rate in the rhBMP-2 group, (Study 14, 96% vs. 89%, $P=0.014$)[27] which was not seen in our IPD analysis (90% vs. 90%). Some of the differences may be due to our classification of patients with partial data as failures in IPD, although it is not clear why this would differentially affect the rhBMP-2 group in Study 14.

Reporting of Adverse Events

As a previous review has noted,[4] there was serious selective reporting and underreporting of adverse events in the published articles for both rhBMP-2 and ICBG groups, especially in the Medtronic trials published early. The actual rates of adverse events were much higher than reported. For example, for Study 2, Burkus et al.[18, 25] reported only 11 intraoperative vascular events (6 rh-BMP-2, 5 ICBG), six retrograde ejaculation events (not by rhBMP-2 versus ICBG groups, but by surgical approach of transperitoneal versus retroperitoneal) and eight adverse events related to the iliac crest graft site at 24 months. However, IPD indicated 315 adverse events in the rhBMP-2 group and 274 adverse events in the autograft group two years after surgery. Instead, articles simply stated either "no unanticipated device-related adverse events"[18, 20, 22, 23] or no adverse event directly related or attributable to rhBMP-2.[17, 26, 69] Some publications sought to emphasize "donor site hip pain," which was assessed only in the control group patients and only on the side of the iliac crest operation. On the contrary, Medtronic provided the FDA with complete, even exhaustive information about total adverse events and serious adverse events. For the two most recently published trials,[25, 27] underreporting appeared much less of an issue and all adverse events during operation and at 24 months were completely reported.

Conclusions

In spinal fusion, rhBMP-2 and ICBG appear to be similarly effective when used in ALIF and PLF, though the current evidence does not allow definitive conclusions regarding the effectiveness in other surgical approaches. The occurrence of adverse events and the risks for any adverse event were similar with and without rhBMP-2. We found some evidence of rhBMP-2 associated with important specific harms but estimates for comparative risk of specific adverse events were frequently imprecise and outcome ascertainments were poor, preventing strong conclusions. Our analysis underscores the need for more definitive evidence about harms before rhBMP-2 became widely used.

Evidence of reporting bias in the published articles of industry-sponsored trials is substantial. The availability of IPD from the manufacturer-sponsored trials allowed a more

thorough evaluation of both benefits and harms that was not possible only with published papers, and reduced the problem of publication and reporting biases. Complete reporting of adverse events is imperative in published trials.

Even with IPD from 12 trials, the evidence base is small within each surgical approach and there was no randomized trial truly independent of the manufacturer. More research is needed to provide more reliable estimates of risk of cancer and other adverse events and to identify patient populations in which use of rhBMP-2 may be beneficial, such as cases where use of bone graft alone is associated with a high risk of pseudoarthrosis. Based on the currently available evidence, it is difficult to identify clear indications for rhBMP-2 in spinal fusion.

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Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Spine Fusion: A Systematic Review and Meta-analysis

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Yale Open Data Access (YODA) Project or Medtronic.

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Contents

INTRODUCTION

Spinal fusion surgery is a procedure that unites (fuses) two or more vertebral bodies together. A variety of fusion techniques are practiced. An interbody fusion, involving removal of a degenerated intervertebral disc and fusion of the adjacent vertebral bodies, can be performed via an anterior (anterior lumbar interbody fusion, ALIF), posterior (posterior lumbar interbody fusion, PLIF), or transforaminal (transforaminal lumbar interbody fusion, TLIF) approach.[1] Posterolateral lumbar fusion (PLF) involves adjacent transverse processes. All techniques use a bone graft and/or bone graft substitute to promote fusion. Fusion can be performed with or without supplemental hardware (instrumentation), such as plates, screws, or cages, which serve as an internal splint when the bone graft heals.

Spinal fusion surgery is used in conditions associated with spinal instability. It is the most commonly performed surgery for chronic non-specific back pain caused by degenerative conditions,[1] and its purpose is to restrict spinal motion and remove the presumed cause of pain. Spinal fusion is one of the most rapidly growing procedures in the United States; from 1997 to 2009 the rate doubled from 7 to 15 per 10,000 population.[2]

Traditionally, spinal fusions are performed by using graft material harvested from the iliac crest. Harvesting bone requires an additional surgery and may be inadequate for long spinal fusions or other difficult cases. Recombinant human bone morphogenetic protein-2 (rhBMP-2), an orthobiologic, was developed as a bone graft substitute. In the late 1990s, several animal model studies indicated that rhBMP-2 promotes bone growth.[3] In the early 2000s, industry-sponsored human trials confirmed the effect of this protein in bone-growth induction, with the advantage of not requiring a bone graft harvest, a procedure associated with pain and other complications. These early trials reported that rhBMP-2 was associated with higher fusion rates than iliac crest bone graft (ICBG) in anterior lumbar interbody fusion (ALIF), and reported no adverse events attributable to rhBMP-2.[4, 5] In 2002, the U.S. Food and Drug Administration (FDA) approved the use of rhBMP-2 in conjunction with a metal implant for single-level spinal fusion surgery using the ALIF approach (commercial name: INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device; Medtronic, Memphis, TN). In December 2003, the FDA approved the use of rhBMP-2 with another implant (INTER FIX™; Medtronic, Memphis, TN) for similar indications.[6]

Around the time of and after the FDA approval, publications based on additional industry-sponsored clinical trials reported beneficial effects of rhBMP-2 in spinal fusion procedures that were not approved by the FDA, again reporting no device-related adverse events.[7-9] These publications, as well as promotional material, emphasized two potential advantages of rhBMP-2 compared with bone grafts: "fast" or "accelerating" fusion, and avoidance of iliac crest donor-site complications.[5, 8-10] Use of rhBMP-2 increased from 0.7% of spinal fusion surgeries in 2002 to 25% in 2006.[11] While the FDA approval was for ALIF in conjunction with lordotic tapered cages (LT-CAGE™; Medtronic, Memphis, TN), the majority of clinical use has been "off label" in PLF or TLIF.[12]

In 2010, a systematic review conducted for the Centers for Medicare and Medicaid noted that, in the trials conducted by Medtronic to obtain premarketing approval for rhBMP-2, information about its potential harms was sparse.[13] In 2011, a review that compared FDA documents with journal publications found that gaps in the information published in journals could have led to misleading conclusions about the balance of benefits and harms of rhBMP-2 compared with bone graft.[14] FDA documents summarizing Medtronic-sponsored trials appeared to indicate substantially more adverse events than reported in the journal publications and documented adverse events such as subsidence, infection, urinary retention, and early back and

[1] A glossary and list of abbreviations and acronyms used in this report appear after the reference list.

leg pain that were not reported in the published industry-sponsored trials.[14] Observational studies confirmed that serious adverse events can occur with rhBMP-2 use in cervical spine fusion[11, 15-17] and a case series questioned its safety in off-label lumbar fusion.[18] In July 2008, the FDA issued a public health notification of life-threatening complications associated with off-label use of rhBMP-2 in cervical spine fusion—swelling of the neck and throat resulting in compression of the airway and other structures.[19] The FDA required Medtronic Sofamor Danek to include boxed warnings for the INFUSE® Bone Graft and INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device products (Appendix A).

To better understand the evidence on the benefits and harms of rhBMP-2, Yale University Open Data Access (YODA) Project commissioned two independent centers to conduct systematic reviews of rhBMP-2, based on published as well as unpublished data for both FDA-approved and off-label uses. As part of this project, Medtronic, Inc., (Medtronic), the sole manufacturer of devices involving rhBMP-2 for spinal fusion, agreed to release all of the individual patient data (IPD)—the data for each study participant included in a trial (as opposed to study level aggregated data)—and relevant documents for studies of rhBMP-2 that it funded. The Oregon Evidence-based Practice Center was selected as one of the review centers. The primary aims of this report are 1) to estimate the benefits and harms of rhBMP-2 for spinal fusion using all available data and 2) to assess reporting biases in published articles of industry-sponsored studies. The current report only covers evidence in spinal fusion. While rhBMP-2 has been approved for other indications, tibial fractures[20] and maxillofacial and dental regenerative uses,[21] these applications were not addressed in this review.

METHODS

Scope and Key Questions

Yale University provided preliminary aims to the two review teams for discussion and comment. Based on feedback from the review teams, a set of reconciled aims were developed to ensure the same scope between the two teams (Appendix B). Key Questions to guide this review were formulated by investigators at the Oregon Evidence-based Practice Center based on the reconciled aims:

> **Key Question 1:** What are the benefits of rhBMP-2 compared with alternatives when used in spinal fusion?
>
> **Key Question 2:** What are the harms of rhBMP-2 compared with alternatives when used in spinal fusion?
>
> **Key Question 3:** What are the reporting biases in published articles of industry-sponsored studies?

For Key Questions 1 and 2, as described in more detail below, we conducted a systematic review, including assessment of the quality and potential for bias in the design, conduct, and reporting of each study. We stratified studies and reported our findings by surgical site (lumbar, cervical, thoracic) and approach (e.g., anterior, posterolateral) except for selected outcomes (e.g., death and cancer) and assessments (e.g., applicability). When appropriate, we conducted meta-analyses of rhBMP-2 versus autograft for effectiveness and harms outcomes. For Medtronic studies, we used IPD exclusively to assess benefits and harms. For other studies, we used data from journal publications.

For Key Question 3, as described in more detail below, we compared the journal publications of Medtronic-sponsored studies to other sources and adapted a previously published protocol to

classify publications as primary or secondary and to categorize potential sources of reporting bias.[22, 23] For binary outcomes, such as fusion and reoperation, we examined how the results of a meta-analysis based on IPD compared with those of an analysis based only on publicly available reports and journal articles.

The following criteria applied to all studies considered for inclusion in Key Questions 1 and 2, whether identified through literature searching or through materials from the manufacturer.

Inclusion Criteria

To be eligible, studies had to meet all of the following criteria:

1. *Patients:* Humans with deformity, instability, or degeneration of the spine or with presumed discogenic back pain (with or without leg pain).
2. *Interventions and Comparators:* Any rhBMP-2 containing devices (e.g., INFUSE®), including products approved outside the United States (e.g., InductOs®), versus any control or no control group. We excluded studies of human bone morphogenetic protein 7 (rh-BMP-7, OP-1) or other non rhBMP-2 bone morphogenetic proteins. We included studies of different bone morphogenetic proteins if they reported results for rhBMP-2 separately or if we could determine rhBMP-2 was predominantly used.
3. *Outcomes:* For outcomes related to effectiveness, we included overall success (as defined in the study protocols), fusion, neurological status, pain and functional status variables (e.g., disability, functional health such as SF-36, return to work). Harms of rhBMP-2 included overall adverse events, and specific adverse events (e.g., mortality, additional surgery, infection, inflammation, dysphagia, heterotopic bone formation, osteolysis, subsidence, leg or back pain, neurological complications [e.g., retrograde ejaculation, urinary retention] and cancer).
4. *Time Points:* We included all follow-up time points. Long-term outcomes were defined as those measured more than two years after the surgery.
5. *Design:* We included controlled clinical trials and cohort studies to evaluate benefits. We also recorded fusion rates from studies that followed a group that underwent surgery, but lacked a control group (intervention series). We also included case series/case reports if the reports were in a special population underrepresented in other studies, such as children. For harms, we included controlled clinical trials, cohort studies, case-control studies, intervention series, case series, and case reports.
6. *Other:* Only English-language studies were included.

Data Sources

To address these Key Questions, we used four sources of data: 1) Medtronic IPD, related protocols, and data dictionaries; 2) Medtronic internal reports; 3) documents from the FDA web site, and 4) a broad-based literature search to identify a) additional studies on rhBMP-2 and b) publications related to Medtronic-sponsored studies.

For data sources 1 and 2, the YODA Project provided de-identified patient-level data, protocols, data dictionaries, and Medtronic internal reports for all 17 Medtronic-funded studies of rhBMP-2 in spinal fusion completed or terminated by December 2011. The list of documents we received for each study is provided in Appendix C. The internal reports included summaries of study data and brief adverse event case histories. We also received 1,229 MedWatch adverse event reports submitted to the FDA between July 2003 and July 2012.

For data sources 3 and 4, we searched Ovid MEDLINE® (1996 to August 2012), Elsevier Embase® (1996 to August 2012), the Cochrane Database of Systematic Reviews® (third quarter 2012), the Cochrane Central Register of Controlled Trials® (third quarter 2012), the Database of Abstracts of Reviews of Effects (1996 to third quarter 2012), Health Technology Assessment (1996 to Third Quarter 2012), and Sciverse Scopus® (1995 to third quarter 2012) using terms for rhBMP-2. (See Appendix D for search strategies.) Limits included a date limit (1996-present) and a study subject limit to humans. Electronic database searches were supplemented by hand searches of reference lists of included studies and reviews. We searched ClinicalTrials.gov (U.S. National Institutes of Health), International Clinical Trials Registry Platform (World Health Organization), the Current Controlled Clinical Trials, and the U.S. Food and Drug Administration web sites for study protocols and additional patient data. In addition, we searched the U.S. Food and Drug Administration Center for Devices and Radiological Health (CDRH) and the European Medicines Agency's European Public Assessment Reports web sites for filings and scientific reviews.

All citations were imported into an electronic database (Endnote® v.X4). For Key Questions 1 and 2, two reviewers independently assessed titles and abstracts of citations identified from literature searches using the criteria listed above. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by two independent reviewers. Disagreements were resolved by consensus.

For trials referred to in abstracts, we searched Google Scholar, ClinicalTrials.gov, and material received from Medtronic for additional information about study design, conduct, and results. If additional information was available to assess the eligibility, quality, and final results of the study, we included it in our review. If not, we noted the results reported in the abstract but did not include the study in the systematic review or meta-analysis.

Data Abstraction and Calculation

We abstracted the following data from published studies and reports: type of trial and trial length; inclusion and exclusion criteria; interventions; numbers enrolled, analyzed, withdrawn and lost to follow-up; baseline characteristics; results for each outcome; and funding source. Data abstraction for each study was completed by two reviewers; the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness against the original articles.

We abstracted adverse events from a random sample of 200 MedWatch reports, and searched all MedWatch reports with key terms associated with serious adverse events (cancer, died, tracheo, arrest, and expired). When a report had one of these keywords, we read the complete report and recorded the results in a database.

For effectiveness outcomes, we considered "overall success" (see definition below), fusion, pain, functional status (measured by scales such as the Oswestry Disability Index [ODI] score), neurologic status, SF-36, and return to work. Harms of rhBMP-2 included overall adverse events and specific adverse events (e.g., mortality, additional surgery, infection, dysphagia, heterotopic bone formation, osteolysis, subsidence, leg or back pain, neurological complications [e.g., retrograde ejaculation, urinary retention], and cancer).

Definitions and Calculations of Endpoints for Individual Patient Data

We obtained individual patient data from 17 Medtronic studies. The data were provided as SAS® datasets. (See Appendix E for detailed information about SAS datasets provided by Medtronic.) Each study had two sets of data: raw and derived. The raw data were transcribed directly from the case report forms (CRF) and the derived data were calculated from the raw data.

We used the study protocols and ClinicalTrials.gov entries to determine prespecified primary outcomes. In nine studies, the primary effectiveness measure was "overall success" (at 24 months); fusion was the primary endpoint in the remainder. IPD also included information on pain, ODI, neurologic status, SF-36, and return to work. Most of these outcomes were derived from raw data. Studies differed slightly in how they specifically defined these outcomes. To reduce variation in outcome measures as a source of heterogeneity, we recoded and recalculated all effectiveness endpoints (except for return to work) from the raw data by applying consistent definitions. These definitions were based on those from the Medtronic protocols; Appendix F contrasts the definitions used in our IPD analysis versus Medtronic protocols and journal publications.

Medtronic provided data on adverse events as derived datasets. For three trials (Studies 2, 8 and 14 – see study identification numbers in Table 1) we used the case histories provided with the internal reports submitted to FDA to verify the counts of adverse events in the derived datasets. We found no inconsistency between the two data sources and relied on the derived datasets for all other trials. We also compared the IPD on adverse events with those presented in the internal reports and found them to be consistent. Therefore, we obtained overall and specific adverse events directly from derived datasets (no recalculation) based on Medtronic categorization, except for urinary retention, wound infection, wound dehiscence, and possible lumbar radiculitis, which we identified by reviewing case histories in internal reports. These outcomes were not prespecified outcomes in the trials or in the case histories. In the primary analysis, we defined "possible radiculitis" as 1) back pain plus leg, thigh, or buttock pain or weakness (unilateral or bilateral); 2) adverse events described as "sciatica" or "radiculopathy;" or 3) back and/or leg pain with use of epidural steroids or surgery for radiculopathy (e.g., discectomy, laminectomy). We excluded cervical/arm symptoms, numbness/paresthesias without weakness or pain, just back pain, just leg pain, and pain attributed to trauma. Further, since the case histories only provided limited information to classify cases, we applied three alternative definitions of radiculitis (Appendix F) in sensitivity analyses.

Table 1. Medtronic study identification

Study Number	Trial Name	Surgical Approach	Reference
1	INFUSE®/LT-CAGE® Pilot	ALIF	Boden et al., 2000[4]
2	INFUSE®/LT-CAGE® Pivotal	ALIF	Burkus et al., 2002[5]
3	INFUSE®/ LT-CAGE® Lap Pivotal	ALIF	Burkus et al., 2003[24]
4	INFUSE®/ Bone Dowel Pilot	ALIF	Burkus et al., 2002[7]
5	INFUSE®/ Bone Dowel Pivotal	ALIF	Burkus et al., 2005[8]
6	INFUSE®/ INTER FIX™ PLIF	PLIF	Haid et al., 2004[25]
7	INFUSE®/ CORNER STONE® ACDF Pilot	ACDF	Baskin et al., 2003[9]
8	INFUSE®/MASTER GRAFT® Pilot	PLF	Dawson et al., 2009[26]
9	INFUSE®/ INTER FIX™ ALIF Pilot	ALIF	Unpublished
10	MAVERICK™ Disc Pivotal	ALIF	Gornet et al, 2011[27]
11	INFUSE®/ TELAMON PEEK PLIF Pilot	Circumferential PLIF	Unpublished
12	rhBMP-2/BCP US Pilot	PLF	Boden et al., 2002[28]
13	rhBMP-2/BCP Canada Pivotal	PLF	Unpublished
14	AMPLIFY™ (rhBMP-2/ CRM) Pivotal	PLF	Dimar et al., 2009[29]
15	rhBMP-2/ CRM 2-level Pilot	PLF	Unpublished
16	rhBMP-2/BCP Mexico Pilot	PLF	Unpublished

ACDF = Anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion

In the manufacturer's trial protocol, leg and back pain were assessed by measuring pain intensity on a 0-10 scale at each follow-up point. Leg and back pain were also recorded as adverse events in the derived adverse event datasets. We analyzed back and leg pain as a score on a numerical rating scale. Separately, we analyzed back and leg pain when it was reported as an adverse event. More detailed information on how outcome measures were derived and harms were categorized is provided in Appendix G.

Management of Missing Data

Overall success and fusion were each a composite outcome based on multiple criteria; all criteria had to be satisfied to classify a case as a success (Appendix F). For these outcomes, we performed three analyses based on different assumptions for missing values and partial data. In our primary analysis, patients meeting some criteria but missing data for others were conservatively classified as failures, since the patient is available for evaluation (not missing) but there was inadequate evidence to prove that all criteria had been met. Patients without data for any criteria were excluded. We also performed two sensitivity analyses: in one, patients with missing data for some or all criteria were excluded; in the other, such patients were included as failures. For other binary effectiveness outcomes, patients with missing data were excluded in the primary analysis but included as failures in the sensitivity analysis. For adverse events, all patients were included since we analyzed cumulative adverse events from the time of surgery.

Quality Assessment

For Medtronic-funded studies, quality assessment was based on information from trial protocols and internal reports. Otherwise, we used journal articles, ClinicalTrials.gov reports, and other available information to assess the quality (risk of bias) of each study. We adapted criteria for quality from the Cochrane Back Review Group[30] and the U.S. Preventive Services Task Force[31] (Appendix M). For randomized trials, we assessed randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; reporting and assessment of dropouts; handling of incomplete data; the use of intent-to-treat analysis; and ascertainment, timing, and reporting of outcomes.[30] We used data dictionaries and protocols for additional information regarding how well each endpoint was ascertained and how it was recorded in study data sheets. For cohort studies, we assessed selection methods to create an inception cohort and to ascertain exposures, potential confounders, methods to reduce bias (such as masking outcome assessors), and the appropriateness of statistical methods to adjust for confounding.[31] We used applicable cohort study criteria to rate the quality of intervention series (defined as a longitudinal study that enrolled a group of patients undergoing a surgical procedure with rhBMP-2 but without a control group). Individual studies were rated "good," "fair," or "poor" quality using standard definitions.[32]

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results. *Fair-quality* studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses—the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Poor-quality studies have a serious or "fatal" flaw or combination of flaws in design or analysis, or large amounts of missing information. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under

investigation. We did not exclude studies rated poor-quality *a priori*, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Applicability Assessment

We recorded factors important for understanding the applicability of studies, such as the study's criteria for eligibility, population characteristics, and whether the treatment received by the intervention and control groups were reasonably representative of standard practice.[33] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as "high" or "low") because applicability may differ based on the user of this report.

Data Synthesis and Analysis

For journal articles and internal reports, we constructed evidence tables showing the study characteristics, quality ratings, and reported results (Appendix M). The trials evaluated a variety of surgical approaches, particularly for lumbar degenerative disc disease. We stratified data synthesis of benefits and harms (except for cancer and death) by the following categories of surgical sites/approaches: ALIF, PLF, PLIF, TLIF, anterior cervical discectomy and fusion (ACDF), posterior cervical spine fusion, the circumferential approach defined as an interbody fusion with posterior fixation, and thoracic spine. Within ALIF, we analyzed a trial that compared fusion with rhBMP-2 versus artificial disc replacement (no bone graft or fusion)[27] separately from trials that compared fusion with rhBMP-2 versus fusion with iliac crest autograft. Different surgical approaches were expected to affect benefits and harms differently and/or to be associated with different harms. After consultation with two spine surgeons regarding which comparisons would be clinically meaningful, we decided it would be inappropriate to combine studies across surgical approaches. Such stratification also nearly coincided with stratification based on rhBMP-2 dosage, resulting in an analysis of studies with low-dose rhBMP-2 (ALIF) separate from those with higher dose of rhBMP-2 (PLF).

For all outcomes, the primary analyses focused on time periods up to 24 months, since all of the Medtronic randomized control trials had follow-up data to 24 months. For harms, we aggregated data into two periods for Medtronic trials:

1. Operative and up to four weeks postoperative
2. Up to 24 months postoperative

For the outcomes cancer and death, meta-analyses were performed by combining across all surgical approaches because these outcomes were rare and not believed to necessarily be affected by the surgical approaches. We excluded preexisting cancers from all cancer analyses.

We also analyzed three controlled trials (one ALIF, and two PLF) that provided data longer than 24 months. For cancer and death we analyzed the cumulative number of events up to 24 and 48 months. Cancer events were very sparse after 48 months so we only conducted a sensitivity analysis by combining data up to 48 months and after 48 months, instead of a separate analysis for cancers occurring after 48 months.

Meta-analysis

We conducted meta-analysis of studies similar enough to produce a meaningful combined estimate. Otherwise, studies were synthesized qualitatively. As mentioned above, in deciding which studies to combine, we considered the surgical approach, surgical site, carrier, concentration, and dose of rhBMP-2. We also performed tests of statistical heterogeneity.

Among trials, only the ALIF and PLF approaches provided adequate data for meta-analyses. We had access to IPD for all of the ALIF trials and for all but one PLF trial.[34] Therefore our meta-analyses were primarily based on IPD and we qualitatively compared the results from the one PLF trial with IPD results.

In addition, to qualitatively compare the results in publications to those of our primary meta-analysis, we conducted a separate meta-analysis of published results for selected discrete outcomes (e.g., fusion). We also combined results from cohort studies in a meta-analysis if enough data were available.

For the draft version of this report, we conducted meta-analyses using a two-step approach. In response to the comments from the reviewers of the draft report and from the journal editors of the manuscript based on this report,[35] we performed meta-analyses using a mixed effects model, when appropriate, and reported those results in the main text of this report. The mixed effects model has the theoretical advantage of providing a better way to handle missing data.[36] When it was not appropriate to use the mixed effects model, we reported results from the two-step approach as explained below. The methods and results from the two-step approach for ALIF and PLF trials through 24 months are presented in Appendix H.

Methods for Individual Patient Data Meta-analyses

To assess benefits and harms for ALIF and PLF approaches through 24 months, for continuous outcomes, we used a linear mixed effects model to obtain a combined mean difference between rhBMP-2 and control groups after adjusting for baseline values and individual study effects.[37] We assumed random treatment effects and heterogeneous residual variance across included studies. For common binary outcomes, we used a generalized linear mixed effects model assuming random treatment effects and binomial distribution with log link to obtain a combined risk ratio (RR). For rare binary outcomes, we used a generalized linear fixed effects model assuming binomial distribution with log link. We fitted a separate model for each time point. When the generalized linear model with log link could not produce a combined estimate due to ill-fitting data, we provided combined estimates from a two-step approach (Appendix H).

We assessed statistical heterogeneity using the estimated between-study variance from the mixed effects model.[37] We evaluated baseline age, sex, smoking status, diabetes status, previous back surgery, and employment status as potential sources of heterogeneity. For all meta-analyses, we also performed sensitivity analyses by excluding poor quality studies (Study 1 for ALIF, n=10 included in the meta-analysis; Study 12 for PLF, n=16 included in the meta-analysis) and studies utilizing a lower rhBMP-2 concentration for PLF (Study 8, n=46), and by excluding graft-site-related adverse events in analyses of overall adverse events. These meta-analyses caused minimal changes in estimates. Sensitivity analyses using alternative definitions of overall success and fusion based on different assumptions for missing values also produced similar results. Results of these sensitivity analyses are not separately reported. In most meta-analysis, we did not find significant heterogeneity. We only noted the cases when heterogeneity was substantial. For outcomes with a forest plot, we presented study level estimates with the combined estimate from the mixed effects model unless specified otherwise.

For cancer, we performed sensitivity analyses by excluding events not reportable to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Program (skin cancers with low propensity to metastasize). We also performed a sensitivity analysis by including all zero-event trials in the meta-analysis as a combined "pseudo-trial" with an assumption of no cancers in the rhBMP-2 group and one cancer in the control group. The above meta-analyses for continuous, common, and rare binary outcomes were performed using PROC

MIXED, PROC NLMIXED, and PROC GENMOD respectively, using SAS® software 9.2 (SAS Institute Inc., Cary, NC, USA).

To assess benefits and harms for ALIF and PLF beyond 24 months, the number of studies with available data was too small to reliably and consistently estimate the random treatment effects using the mixed effects model. As in cases in which the generalized linear model with log link could not produce a combined estimate due to ill-fitting data, we analyzed the data using a two-step approach (Appendix H).

Meta-analysis of Results from Publications

For published results, meta-analysis was conducted for selected discrete outcomes including fusion and additional surgery. For fusion, we used a random effects model similar to the second step of the model used in the two-step approach (Appendix H). For the outcome of additional surgery, which was rare, we used a generalized linear fixed effects model assuming binomial distribution with log link.

Grading the Strength of Evidence

For each surgical approach, compared with iliac crest bone graft, we rated the evidence about the following outcomes: overall success, fusion, neurological success, ODI success, ODI score, SF-36, pain score, additional surgeries, and selected adverse events (Appendix I).

We adapted methods developed by the Agency for Healthcare Research and Quality (Table 2)[38] to rate the strength of each body of evidence. Specifically, for each group of studies, we assessed the aggregate risk of bias, consistency, directness, and precision of the evidence.[38] For rating a body of observational studies, we also considered whether there was a dose-response association or a large effect size, and whether plausible confounders would be likely to change the direction or magnitude of the effect.[38]

It should be noted that the implication or application of evidence grades depends on the decision-making context.[39]

Table 2. Definitions of the grades of overall strength of evidence

Grade	Definition
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 the 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 the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Assessment of Reporting and Related Biases

Reporting bias refers to incomplete or inaccurate reporting of study outcomes and encompasses publication bias, outcome reporting bias, multiple publication bias, location bias, language bias, time lag bias, citation bias, and others (e.g., ghostwriting, misrepresentation of facts, reframing). We assessed certain reporting biases and quality of reporting of Medtronic studies by comparing journal publications with corresponding study protocols, reports, and data dictionaries provided by Medtronic. Assessments of reporting bias were based on articles published in peer-reviewed journals or their supplements. We excluded articles from "throwaway" journals,[40] promotional material, and information from commercial web sites. We did not assess location bias or language bias, and also excluded types of bias that could not be

adequately assessed using the materials we received from Medtronic (e.g., ghostwriting, case history adjudication).

We identified the primary outcomes for each study from the study protocols, statistical analysis plan, protocol amendments, and entries in ClinicalTrials.gov. We noted when we could not identify prespecified primary outcomes from these sources. We determined the publication status of each trial and selected one published report as the main study report using the following order of priority: a full-length study report in a stand-alone article, a detailed letter to the editor that reported study results, a review using results from the included trial, or a pooled analysis using results from the included trial.[22] If there was more than one paper on a study trial in the same order of priority category, we used the earlier paper. If we were in doubt as to whether a publication represented data from a Medtronic trial, we queried Yale University who queried Medtronic. We used the same criteria to identify disagreements between protocol and publication as Vedula and colleagues.[22] Specifically, we considered that there was a disagreement between the outcome in the published trial and the study protocol when: 1) a new primary outcome not mentioned in the protocol was introduced in the published report, 2) the report did not distinguish between primary and secondary outcomes although they were distinguished in the protocol, 3) an outcome described as "primary" in the protocol or an internal report was described as a secondary outcome in the publication, and 4) a protocol-specified primary outcome was not described in the published report.

We compared results from IPD meta-analysis and published trials and noted discrepancies for primary and secondary outcomes. For adverse events, we compared information from IPD with the corresponding publications for specific adverse events (e.g., retrograde ejaculation) and for total adverse events.

Funding Source

This project was funded by a research subcontract to Oregon Health & Science University under a sponsored research agreement between Yale University and Medtronic, Inc. Yale served as the intermediary for data and information requests to Medtronic and managed the peer review of the draft report. Medtronic provided comments on the draft version of this report, but had no influence over the selection of evaluators, conduct of these analyses, the release of the results, the publication of these findings, or how we responded to their comments.

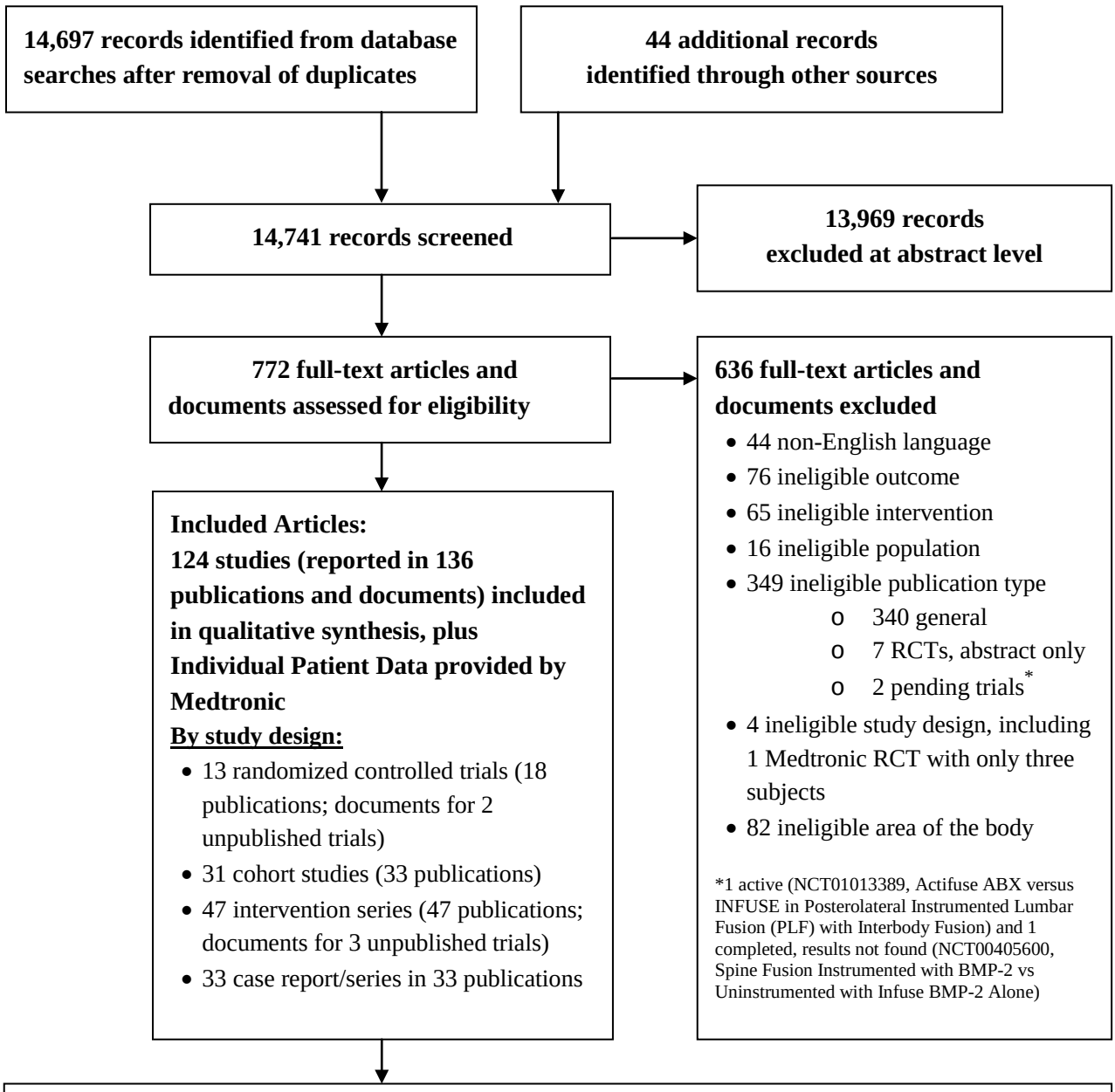
RESULTS

Effectiveness and Harms of rhBMP-2 in Lumbar, Cervical, and Thoracic Spine Surgery (Key Questions 1 and 2)

Study Selection

Figure 1 shows the flow of study selection for Key Questions 1 and 2. A total of 13 randomized trials were included: 12 Medtronic trials (1,879 subjects), and one trial of instrumented PLF plus rhBMP-2 versus ICBG in patients over 60 years of age (102 subjects) that was sponsored by Norton HealthCare.[34] We excluded one small Medtronic trial because it was stopped after recruiting only three patients. Included articles are listed in Appendix J and excluded articles are listed in Appendix K. Evidence tables for included studies appear in Appendix M.

Figure 1. Literature flow diagram



Included studies by approach and study design (sponsorship, approach if applicable):

	ALIF	PLF	Anterior Cervical	Other
Trials	6 (Medtronic)	4 (Medtronic) 1 (Other)	1 (Medtronic)	1 (Medtronic, PLIF)
Cohorts	4 (Other)	7 (Other)	6 (Other)	14 (Other)
Intervention Series	1 (Medtronic) 3 (Other)	2 (Medtronic) 5 (Other)	7 (Other)	1 (Medtronic, PLIF) 28 (Other)

ALIF = anterior lumbar interbody fusion; PLF = posterolateral lumbar fusion; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial

We identified seven abstracts that reported on studies that were described as "randomized trials" but did not clearly correspond to a journal publication.[41-47] One of these was registered in ClinicalTrials.gov and compared instrumented versus noninstrumented fusion with rhBMP-2.[44] Three abstracts described a study or studies similar to Medtronic Study 13, but we could not determine with certainty whether they reported the same trial.[41-43] Two other trials compared rhBMP-2 with other products (Silicated Calcium Phosphate, or b-TCP+BMA).[46, 47] Finally, an abstract that appeared in 2009 reported a trial of "infuse BMP" (sic) versus silicate substituted calcium phosphate (Actifuse) in ACDF.[45] This trial reported worse swallowing outcomes in patients who received rhBMP-2 as measured by a mean swallowing score (1.44 for BMP versus 0.79 for Actifuse, p=0.0002) and the need for steroid treatment (34.1% versus 14.0%).

In 11 of the 12 included Medtronic-sponsored trials and in the Norton HeathCare-sponsored trial, spinal fusion with rhBMP-2 was compared with spinal fusion with ICBG. The other Medtronic study (Study 10) compared fusion with rhBMP-2 with implantation of the MAVERICK™ artificial disc (Medtronic; Memphis, TN). In most cases, a metal interbody cage or metal fixation system was also employed. However, in two trials (Studies 4 and 5), both the rhBMP-2 group and the ICBG groups utilized an allograft bone dowel in which either rhBMP-2 or ICBG was placed prior to implantation.

In addition to the RCTs, we included 31 cohort studies, 80 uncontrolled studies (47 intervention series and 33 case series or case reports) of patients who received rhBMP-2 to promote spinal fusion (Appendix M). Medtronic provided IPD for four prospective intervention series (Studies 3, 11, 15, and 16). Medtronic did not provide data on an intervention series completed in June 2012, that evaluated rhBMP-2 used with another device in cervical degenerative disc disease.[48]

Study Quality

Medtronic internal documents provided useful information for assessing the internal validity, ascertainment of outcomes, and reporting of the Medtronic randomized trials.

Study Design

Most trials used similar methods for randomization and allocation concealment. While descriptions of these methods were incomplete in journal articles, protocols and data summaries provided to the FDA in Medtronic internal documents suggest that randomization in the pivotal trials and the larger pilot trials was satisfactory (Table 3). There were some potentially important baseline differences between randomized groups in some studies. For example, in Study 2 a higher proportion of patients in the rhBMP-2 group worked before surgery (47% vs. 37%) and had diabetes (4% vs. 0.7%) than did those in the ICBG group. However, the pattern of these differences did not consistently favor the rhBMP-2 groups, and the FDA did not appear to identify discordant results among investigator sites.

Table 3. Included Medtronic studies of recombinant human bone morphogenetic protein-2 (rhBMP-2)

IDE Clinical Trial Name (Study #) Study, Year (Reference)	Study Design	Sample Size, n		rhBMP-2 Conc. (mg/cc) Dose (mg) Carrier	Baseline Characteristics							Quality
		I	C		Mean Age, years	Male, *n* (%)	Diabetes, *n* (%)	Smoking, *n* (%)	Prior Back Surgery, *n* (%)	Work before surgery, *n* (%)	Duration of Followup, months	
Anterior lumbar interbody fusion												
INFUSE®/ LT-CAGE® Pilot (Study 1) Boden, 2000[4]	RCT	11	3	1.5 3.9-7.8 ACS	I: 42.5 C: 40.2	I: (5) 46% C: (2) 67%	I: 0 C: 0	I: (1) 9% C: (1) 33%	I: (5) 46% C: 0	I: (6) 55% C: (2) 67%	24	Poor
INFUSE®/ LT-CAGE® Pivotal (Study 2) Burkus, 2002[5]	RCT	142	136	1.5 4.2-8.4 ACS	I: 43.3 C: 42.3	I: 78 (55%) C: 68 (50%)	I: 6 (4%) C: 1 (0.7%)	I: 47 (33%) C: 49 (36%)	I: 54 (38%) C: 55 (40%)	I: 67 (47%) C: 50 (37%)	I: 72 C: 24	Fair
INFUSE®/ LT-CAGE® Lap Pivotal (Study 3) Burkus, 2003[24] *	IS	134		1.5 4.2-8.4 ACS	I: 42.4	I: 57 (43%)	I: 3 (2%)	I: 40 (30%)	I: 33 (25%)	I: 70 (53%)	72	Fair
INFUSE®/ Bone Dowel Pilot (Study 4) Burkus, 2002[7]	RCT	24	22	1.5 8.1-11.7 ACS	I: 41.5 C: 45.6	I: 8 (33%) C: 10 (46%)	I: 2 (8%) C: 1 (5%)	I: 8 (33%) C: 6 (28%)	I: 11 (46%) C: 7 (32%)	I: 11 (46%) C: 9 (41%)	48	Fair
INFUSE®/ Bone Dowel Pivotal (Study 5) Burkus, 2005[8] †	RCT	55	30	1.5 8.1-11.7 ACS	I: 39.7 C: 42.1	I: 24 (44%) C: 9 (30%)	I: 0 C: 1 (3%)	I: 18 (33%) C: 11 (37%)	I: 18 (33%) C: 10 (33%)	I: 36 (66%) C: 16 (53%)	24	Fair
INFUSE®/ INTER FIX™ ALIF Pilot (Study 9) Unpublished	RCT	25	20	1.5 8.4-16.8 ACS	I: 45.9 C: 44.9	I: 11 (44%) C: 9 (45%)	I: 0 C: 1 (5%)	I: 10 (40%) C: 6 (30%)	I: 11 (44%) C: 7 (35%)	I: 12 (48%) C: 13 (68%)	24	Fair
MAVERICK™ Disc Pivotal (Study 10) ‡ Gornet, 2011[27]	RCT	172	405	1.5 4.2-12.0 ACS	I: 40.2 C: 39.9	I: 86 (50%) C: 205 (50.6%)	Not measured	I: 56 (32.6%) C: 117 (28.99%)	I: 48 (27.9%) C: 115 (28.4%)	I: 96 (55.8%) C: 248 (61.2%)	84	Fair

IDE Clinical Trial Name (Study #) Study, Year (Reference)	Study Design	Sample Size, n		rhBMP-2 Conc. (mg/cc) Dose (mg) Carrier	Baseline Characteristics							Quality
		I	C		Mean Age, years	Male, *n* (%)	Diabetes, *n* (%)	Smoking, *n* (%)	Prior Back Surgery, *n* (%)	Work before surgery, *n* (%)	Duration of Followup, months	
Posterior lumbar fusion												
rhBMP-2/BCP Mexico Pilot § (Study 16) Unpublished	IS	I1: 7 I2: 8	8	2.23.0 15.0-40.0 BCP	I1: 53.9 I2: 41.7	I1: 1 (14%) I2: 4 (52%)	I1: 0 I2: 0	I1: 0 I2: 0	I1: 0 I2: 0	I1: 2 (29%) I2: 3 (38%)	12	Fair
rhBMP-2/BCP US Pilotıı (Study 12) Boden, 2002[28]	RCT	I1: 11 I2: 11	5	2.1 42.0 BCP	I1: 50.1 I2: 57.6 C: 52.9	I1: 6 (55%) I2: 3 (27%) C: 2 (40%)	I1: 1 (9%) I2: 0 C: 2 (40%)	I1: 2 (18%) I2: 0 C: 1 (20%)	I1: 2 (18%) I2: 3 (27%) C: 0	I1: 6 (55%) I2: 6 (55%) C: 0	24	Poor
rhBMP-2/BCP Canada Pivotal (Study 13) Unpublished	RCT	99	98	2.1 42.0-63.0 BCP	I: 53.0 C: 53.0	I: 35 (36%) C: 48 (49%)	I: 2 (2%) C: 6 (6%)	I: 29 (30%) C: 26 (26%)	I: 19 (19%) C: 20 (20%)	I: 20 (20%) C: 24 (24%)	24 or 48**	Fair
INFUSE®/ MASTER GRAFT® Pilot (Study 8) Dawson, 2009[26]	RCT	25	21	1.5 12.0 ACS	I: 55.9 C: 56.9	I: 10 (40%) C: 9 (43%)	I: 0 C: 3 (14%)	I: 6 (24%) C: 5 (24%)	I: 6 (24%) C: 6 (28%)	I: 7 (28%) C: 9 (43%)	24	Fair
AMPLIFY™ (rhBMP-2/ CRM) Pivotal (Study 14) Dimar, 2009[29]	RCT	239	224	2.0 40.0 CRM	I: 53.2 C: 52.3	I: 108 (45.2%) C: 95 (42.4%)	I: 17 (7.1%) C: 27 (12.1%)	I: 63 (26.4%) C: 59 (26.3%)	I: 73 (30.5%) C: 62 (27.7%)	I: 83 (34.7%) C: 92 (41.1%)	60	Fair
rhBMP-2/ CRM 2-level Pilot (Study 15) Unpublished	IS	29		2.0 40.0 CRM	I: 53.9	I: 15 (52%)	I: 3 (10%)	I: 12 (41%)	I: 7 (24%)	I: 13 (45%)	36	Poor
Posterior lumbar interbody fusion												
INFUSE®/ INTER FIX™ PLIF (Study 6) Haid, 2004[25]	RCT	34	33	1.5 4.2-8.4 ACS	I: 46.3 C: 46.1	I: 17 (50%) C: 15 (46%)	I: 1 (3%) C: 1 (3%)	I: 18 (53%) C: 15 (46%)	I: 12 (35%) C: 13 (40%)	I: 9 (27%) C: 15 (46%)	24	Fair

IDE Clinical Trial Name (Study #) Study, Year (Reference)	Study Design	Sample Size, n		rhBMP-2 Conc. (mg/cc) Dose (mg) Carrier	Baseline Characteristics							Quality
		I	C		Mean Age, years	Male, *n* (%)	Diabetes, *n* (%)	Smoking, *n* (%)	Prior Back Surgery, *n* (%)	Work before surgery, *n* (%)	Duration of Followup, months	
Circumferential posterior lumbar interbody fusion												
INFUSE®/ TELAMON PEEK PLIF Pilot (Study 11) Unpublished	IS	30	N/A	1.5 8.4 ACS	I: 51.0	I: 12 (40%)	I: 2 (7%)	I: 8 (27%)	I: 14 (47%)	I: 9 (30%)	36	Poor
Anterior cervical discectomy and fusion												
INFUSE®/ CORNER STONE® ACDF Pilot (Study 7) Baskin, 2003[9]	RCT	18	15	1.5 0.6-1.2 ACS	I: 51.3 C: 47.1	I: 8 (44%) C: 7 (47%)	I: 0 C: 0	I: 5 (28%) C: 7 (47%)	I: 1 (6%)** C: 0**	I: 12 (67%) C: 9 (60%)	24	Fair

ACDF = anterior cervical discectomy and fusion: ACS = absorbable collagen sponge; ALIF = anterior lumbar interbody fusion; BCP = biphasic calcium phosphate; C = comparator group (ICBG or artificial disc); CRM = compression resistant matrix; ICBG = iliac crest bone graph; I = investigational group (rhBMP-2 group); IDE = investigational device exemption; IS = intervention series; N/A = not applicable; PEEK = polyetheretherketone; PLF = posterolateral lumbar fusion; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial; rhBMP-2 = recombinant human bone morphogenic protein-2; US = United States

* Study 3 data not published independently. Burkus, 2003[24] contains pooled data from Studies 3 and 2. Patients underwent laparoscopic ALIF in this study; patients in the other ALIF studies underwent laparoscopic surgery except for 4 patients in the rhBMP-2 group of Study 1.

† Study 5 data not published independently. Burkus, 2005[8] contains pooled data from Studies 4 and 5.

‡ Comparator is an artificial disc, not ICBG.

§ The Mexico pilot study was an intervention series with two cohorts.

‖ I1 = rhBMP-2 without internal fixation, I2 = rhBMP-2 + TSRH (Texas Scottish Rite Hospital) pedicle screw instrumentation, C: autograft + TSRH

¶ 100 patients (including both intervention and control group) were followed for 24 months (rhBMP-2 vs. ICBG, using CD horizon spinal system) and 97 patients were followed for 48 months (rhBMP-2 vs. ICBG, using TSRH spinal system).

** Prior *neck* surgery

In the Medtronic-supported trials and intervention series, the main risks for bias were inability to blind surgeons or patient to treatments, and lack of blinding of outcome assessment for all endpoints except fusion. Assessment or adjudication of most effectiveness and adverse event outcomes could have been influenced by knowledge of the patient's treatment. For example, for "overall success," a composite measure that included fusion, pain scores, neurological status, no additional surgery procedure classified as "failure," and the lack of "serious adverse event classified as implant associated or implant/surgical procedure associated," is based on a blinded, detailed assessment of fusion as well as several unblinded measures of varying rigor. In particular, determinations of whether or not the adverse event was implant or surgical procedure associated is subjective and prone to bias given the assessor's knowledge of the patient's treatment group.

Most trials were described as noninferiority or equivalence studies in study objectives. Statistical analysis plan and margins of noninferiority for primary outcome were available for pivotal trials and appeared reasonable. However, sample size calculations in most trials were not based on a noninferiority or equivalence design and most outcomes in the published trials were analyzed as endpoints from superiority trials. No published pivotal trials analyzed data using a Bayesian approach as specified in the protocols.

Except in one trial,[29] there was no prespecified algorithm on how to handle missing data. For example, it was not clear how a composite outcome was determined if some but not all criteria were missing. The primary analysis in the published industry-sponsored trials seemed to use the observed data instead of using intent-to-treat analysis—i.e., data missing at a particular measurement time were simply excluded from the analyses. At 24 months, 9 of the 12 randomized trials had follow-up rates over 90% in both groups. The proportion of lost to follow-up was much higher after 24 months in the few studies with longer follow up. In the study that had a prespecified missing data algorithm (Study 14), the protocol stated that the reason to use the observed data is that intent-to-treat analysis is not conservative for a noninferiority trial; however, as mentioned above, the published article analyzed most outcomes as if they were from superiority trials.

Most observational studies were retrospective and small. The main risks for bias for cohort studies were unclear comparability of groups at baseline, differences in baseline characteristics, unclear blinding of outcome assessors, and failure to adjust for potential confounding variables and baseline differences.

Ascertainment of Study Endpoints

Individual patient data are most valuable for endpoints that are ascertained consistently and measured accurately. The quality of ascertainment varied for different endpoints. Effectiveness outcomes seemed to be ascertained reliably using well-designed questionnaires. For example, to assess neurological endpoints, investigators used a comprehensive neurological status scale measuring different neurological functions and, in some protocols, were instructed to be thorough and vigilant in their assessments.

For harms, a broad classification was used for many adverse events (e.g., cardiovascular or urogenital adverse events), and events were generally not actively elicited using specific symptom questionnaires or objective tests. For events like retrograde ejaculation or urinary retention, patients do not always volunteer information, and it was unclear how such outcomes were defined or whether investigators asked about specific symptoms. Cancer was not considered in the protocols as a prespecified endpoint, and was only captured by voluntary reporting through a generic adverse event text field. Such passive reporting of adverse events is associated with under-ascertainment.[49] For back and leg pain, the types of adverse events

included were very heterogeneous (e.g., radiculopathy, Baker's cyst, sacroiliac joint pain, arthritic knee pain, or ankle pain). No trial defined radiculitis, and adverse events consistent with possible radiculitis were variously classified within the same trial as back and leg pain, neurological, or spinal events. We also found very little information in the Medtronic datasets about local effects such as inflammation and ectopic bone formation or on osteolysis and subsidence, which were not systematically ascertained. While it is unrealistic to expect investigators of new devices to predict all adverse events in early trials and design trial protocols to detect them, later trials could have been better designed to collect adverse events data of higher quality.

Major complications, secondary surgical procedures, and some adverse event endpoints, such as wound complications are often clinically evident when they occur and are more likely to have been ascertained reliably. For these outcomes, the quality of ascertainment is less of a threat to validity than incomplete or biased reporting. (We were unable to assess the integrity of case report adjudication because we did not have access to case reports at the investigator site level.)

When an adverse event was detected, investigators were instructed to assess whether it was caused by the device or the surgical procedure. In several of the protocols, investigators were asked to record whether they thought there was a "reasonable possibility" that the adverse event "may have been caused both by the device and the surgical procedure" or whether it was "unrelated" or "undetermined." Because causal relationships between rhBMP-2 and its possible complications were largely unknown, these assessments are likely to be unreliable. The lack of blinding in these assessments is another potential source of bias.

Not many cohort studies evaluated effectiveness outcomes such as fusion and patient reported clinical outcomes such as disability and function. However, some observational studies that were designed specifically to assess adverse events had more reliable or complete ascertainment.[17, 50-54] One large cohort study used ICD-9 codes from large administrative datasets to ascertain serious complications.[11]

Applicability

The Medtronic trials applied similar eligibility criteria and enrolled similar populations within each surgical approach (Table 3). Patients had discogenic back and/or leg pain, usually single-level disease, with ≤ Grade 1 spondylolisthesis, preoperative ODI scores ≥ 30 or 35, had not responded to conservative treatment for 6 months, were <40% over their ideal weight, and had not recently used tobacco. The mean age of patients in most trials was 40-60 years, and both genders were well-represented.

Some exclusion criteria were obesity, alcohol or drug abuse, autoimmune disease, osteoporosis, and conditions requiring treatment with steroids. To determine effects of these and other eligibility criteria on applicability, it is important to know the numbers of patients who did not qualify for the trial, and the specific reasons they did not. We could not find this information in the journal articles or in documents Medtronic provided.

Most of the Medtronic-sponsored studies were small. Eleven of the 16 studies enrolled a total of less than 100 patients, and 9 of the 16 enrolled less than 50 patients. Two off-label uses had exceptionally sparse data (ACDF and PLIF) making it very difficult to evaluate findings, especially less common adverse events, or to assess applicability.

The Medtronic intervention series were typically conducted to evaluate a different surgical procedure (e.g., laparoscopy instead of open surgery) rather than populations different than those evaluated in the randomized trials. Most of them focused on fusion rates but did not report harms.

The largest non-Medtronic observational study reported on 328,468 spinal fusion patients from the 2002-2006 Nationwide Inpatient Sample database, including a broader patient

population than the trials.[11] In this cohort study, patients were 53 years old (Standard Deviation [SD] 14), white (59%), had disc herniation or degenerative disease (73%), and had 1 or 2 levels fused (84%). Both men and women were well represented, as was income level and type of hospital. There were few non-elective admissions (13%) and few fusions greater than 2 levels (15%). Most other cohort studies and case series were retrospective, small, evaluated off-label use, and provided little information on patient characteristics. Most focused on harms and did not report effectiveness outcomes. A few series reported rhBMP-2 use in a special population, such as spinal deformity patients[55] or children.[56-60]

Effectiveness and Harms for Lumbar Spine

Anterior Lumbar Interbody Fusion

Summary Findings

The anterior lumbar interbody fusion trials constitute the main body of evidence about the INFUSE Bone Graft, the product approved by FDA.

- Based on meta-analysis of five randomized controlled trials (*n*=465), there were no consistent differences in effectiveness between rhBMP-2 and ICBG from 6 weeks to 24 months after the time of surgery (strength of evidence: moderate).
  - One exception is that rhBMP-2 was consistently associated with superior SF-36 physical component summary scores from 3 through 24 months, but differences were small (weighted mean difference [WMD] 3.68 on a 0 to 100 scale, 95% confidence interval [CI] 0.86 to 6.49, at 24 months).
  - rhBMP-2 was associated with a small improvement in back pain (WMD 0.74 on a 0 to 10 scale, 95% CI 0.00 to 1.49) and ODI score (WMD 7.35 on a 0 to 50 scale, 95% CI 0.70 to 14.0) at 24 months, but differences were small.
- For adverse events reported in these randomized trials, there were no statistically significant differences between rhBMP-2 and ICBG. Estimates often had more uncertainty than those for effectiveness outcomes.
  - The likelihood of experiencing at least one adverse event or one serious adverse event was similar (strength of evidence: moderate).
  - For wound infection and reoperations, estimates favored rhBMP2, but the differences were not statistically significant and confidence intervals were wide (strength of evidence: low).
  - For retrograde ejaculation, subsidence, and urinary retention, there were signals of increased risk with rhBMP-2. Differences were not statistically significant but favored ICBG, and upper bounds of confidence intervals were high, indicating that the studies did not rule out a high additional risk associated with rhBMP-2.
- Observational studies were generally small and reported fusion and specific adverse results consistent with trials. The exception is subsidence where observational studies reported higher rates using varying outcome definitions.

Overview of Medtronic Trials

The INFUSE Bone Graft consists of synthetic recombinant human bone morphogenetic protein-2 (rhBMP-2) and an absorbable collagen sponge (ACS). We identified 14 studies using the INFUSE Bone Graft in ALIF—including six randomized trials, four cohort studies,[51, 61-63] and four intervention series.[24, 50, 64, 65] Seven of these studies—six randomized trials and one intervention series—were sponsored by Medtronic (Studies 1–5, 9 and 10, Table 4). In five of

the randomized trials, rhBMP-2 was compared with an autograft consisting of bone from the ICBG.[4, 5, 7, 8, 66]

Table 4. Anterior lumbar interbody fusion (ALIF) studies in chronological order

Start Date	IDE # (Study Number)*	Interventions	Sample Size (intervention vs. control)	Publication Date
1996-1997	G950165	Unknown	266 vs. unknown	Not published, data not available.
	G960065 (Study 1)	LT-CAGE: INFUSE vs. Autograft Pilot Study (Open/Laparoscopic)	11 vs. 3	*Spine* 2/1/2000[4]
1998	G960065 (Study 2)	LT-CAGE: INFUSE vs. Autograft Pivotal Trial (Open)	143 vs. 136	*Journal of Spinal Disorders & Techniques* 10/1/2002[5]
1998	G960065 (Study 3)	LT-CAGE: INFUSE Pivotal Intervention Series (Laparoscopic)	134	Not published separately
1998	G970124 (Study 4)	Bone Dowel: INFUSE vs. Autograft Pilot (Open)	24 vs. 22	*Spine* 11/1/2002[7]
1998	(Studies 2, 3, 266)	Combined analysis of 3 studies: LT-CAGE: INFUSE vs. Autograft Pivotal Trial (Open + Laparoscopic) plus one arm of G950165.	--	*Journal of Spinal Disorders & Techniques* 4/1/2003[24] *Orthopedics* 7/1/2004[67] *J Neurosurgery: Spine* 10/1/2004[68]
1999	G980207 (Study 9)	INTER FIX: INFUSE vs. Autograft Pilot (Open)	25 vs. 20	Not published
2000	G970124 (Study 5)	Bone Dowel: INFUSE vs. Autograft Pivotal (Open)	55 vs. 30	Not published separately
2000	G970124 (Studies 4,5)	Bone Dowel: INFUSE vs. Autograft Pilot + Pivotal (Open)	79 vs. 52	*The Journal of Bone and Joint Surgery Am* 6/1/2005[8]
2003	G010354 (Study 10)	LT-CAGE with INFUSE vs. MAVERICK Replacement Disc (Open)	172 vs. 405	*Spine* 12/1/2011[27]

*Numbers in parenthesis refer to studies for which Medtronic provided individual patient data.
IDE = investigational device exemption

In July 2002 the FDA gave premarket approval for the use of the INFUSE Bone Graft for ALIF procedures in patients who had degenerative disc disease at one level from L4-S1. The approval was based on results from the pilot study (Study 1) and two "pivotal" studies: a randomized trial of the rhBMP-2 (INFUSE) graft versus ICBG (Study 2), and a separate series of patients who underwent laparoscopic implantation of the INFUSE Bone Graft (Study 3). The LT-CAGE was used in all patients in Studies 2 and 3. At the time of the approval, the FDA was also aware of four other Medtronic studies of rhBMP-2: three of these evaluated posterolateral fusions and one an ACDF approach.

The purpose of the pivotal trials for INFUSE/LT-CAGE was to demonstrate to the Food and Drug Administration that the rhBMP-2 device was non-inferior to iliac crest autograft when used in a similar setting. After analyzing the results of the pivotal trials, the FDA concluded that patients receiving the investigational device had equivalent fusion, overall success, and pain outcomes compared with the patients receiving autografts.

Later, Medtronic evaluated rhBMP-2 with a previously approved fusion cage design, the INTER FIX threaded fusion device (Study 9, 45 patients) or a bone dowel (Studies 4, 5). Finally,

Medtronic conducted an RCT in which the control arm received the INFUSE®/LT-Cage and the intervention group received an artificial disc (Study 10).

All of the Medtronic trials had similar design features and, for effectiveness outcomes, all trials were rated fair quality except for Study 1, which was rated poor-quality, due to baseline differences and because randomization results were revealed to the patient prior to informed consent to enter the study. Overall, the most important limitation was that patients, surgeons, and, except for radiologists, outcome assessors were not blinded to treatment assignment. Most of the studies were too small for randomization to result in clinically equivalent groups. The methods for randomization seemed satisfactory, but, in the pivotal trial of INFUSE/LT-Cage, a higher proportion of patients in the rhBMP-2 group were employed at baseline (Study 2, 47% vs. 37%). Patients in Study 3, the intervention series consisting of rhBMP-2 patients who underwent a laparoscopic surgical procedure, appeared to be at lower risk of complications than patients in the randomized arms: they had a substantially lower baseline rate of previous back surgery (37.8% vs. 40.4% for Study 2, vs. 24.6% for Study 3) and a lower rate of tobacco users (32.9%, 36.0%, 29.9%.) (Table 3).

Comparative Effectiveness of rhBMP-2 Versus Fusion Without rhBMP-2

Overall success. In reviewing the INFUSE/LT-Cage studies, the FDA concluded that there was a 99.4% chance that the 24-month overall success rate for the investigational groups was equivalent to the 24-month success rate for the control group. While we did not conduct a Bayesian analysis, the results of our meta-analysis of the five RCTs using IPD (Studies 1, 2 4, 5 and 9; n=465 excluding 4 laparoscopic patients in Study 1) are consistent with this conclusion. At 24 months, the average overall success rate was 61% for the rhBMP-2 group and 53% for the ICBG group.

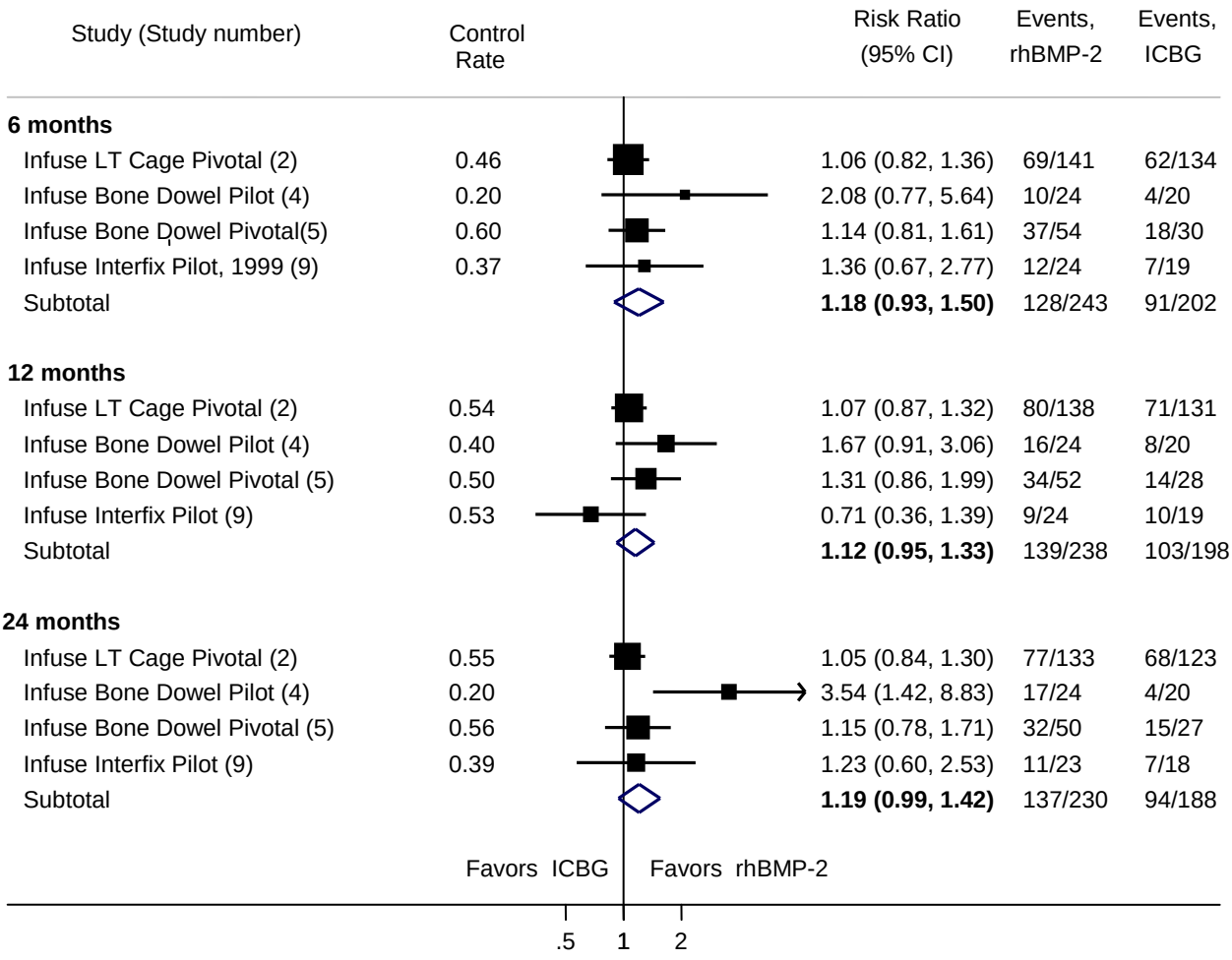
IPD results provided moderate strength of evidence that there were no differences between rhBMP-2 and ICBG in overall success at 6 months (RR 1.18, 95% CI 0.93 to 1.50), 12 months (RR 1.12, 95% CI 0.95 to 1.33), and 24 months (RR 1.19, 95% CI 0.99 to 1.42) (Figure 2).

In the Medtronic-sponsored intervention series of laparoscopic fusion using the INFUSE/LT-Cage, (n=137) (Study 3), the rate for overall success at 24 months was 61% in our analysis, comparable to the rate in rhBMP-2 group with open procedure in Study 2 (58%). Using Medtronic's method, which may have excluded patients that were missing data on one or more components of the overall success measure, the rate was 68%.

Comparative data beyond 24 months was sparse. One RCT (Study 4) showed no significant difference between groups in overall success rate at 48 months (rhBMP-2 9/21 vs. 5/19; RR 1.63, 95% CI 0.66 to 4.00). Studies 2 and 3 provided data in the rhBMP-2 group but not in the ICBG group. In both Study 2 and 3, overall success rates were between 50% and 60% at both time points (38/64 for Study 2 and 38/73 for Study 3 at 48 months; 42/73 for Study 2 and 41/68 for Study 3 at 72 months).

Two small (combined n=60) cohort studies also found no difference between rhBMP-2 plus ICBG or rhBMP-2 plus allograft versus ICBG plus allograft or allograft plus demineralized bone matrix in likelihood of fusion by 24 months.[61, 62] One non-industry sponsored intervention series (n=46) reported 96% of 93 levels fused using rhBMP-2 with a titanium mesh cage.[65]

Figure 2. Comparison of overall success rates in ALIF trials



ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft

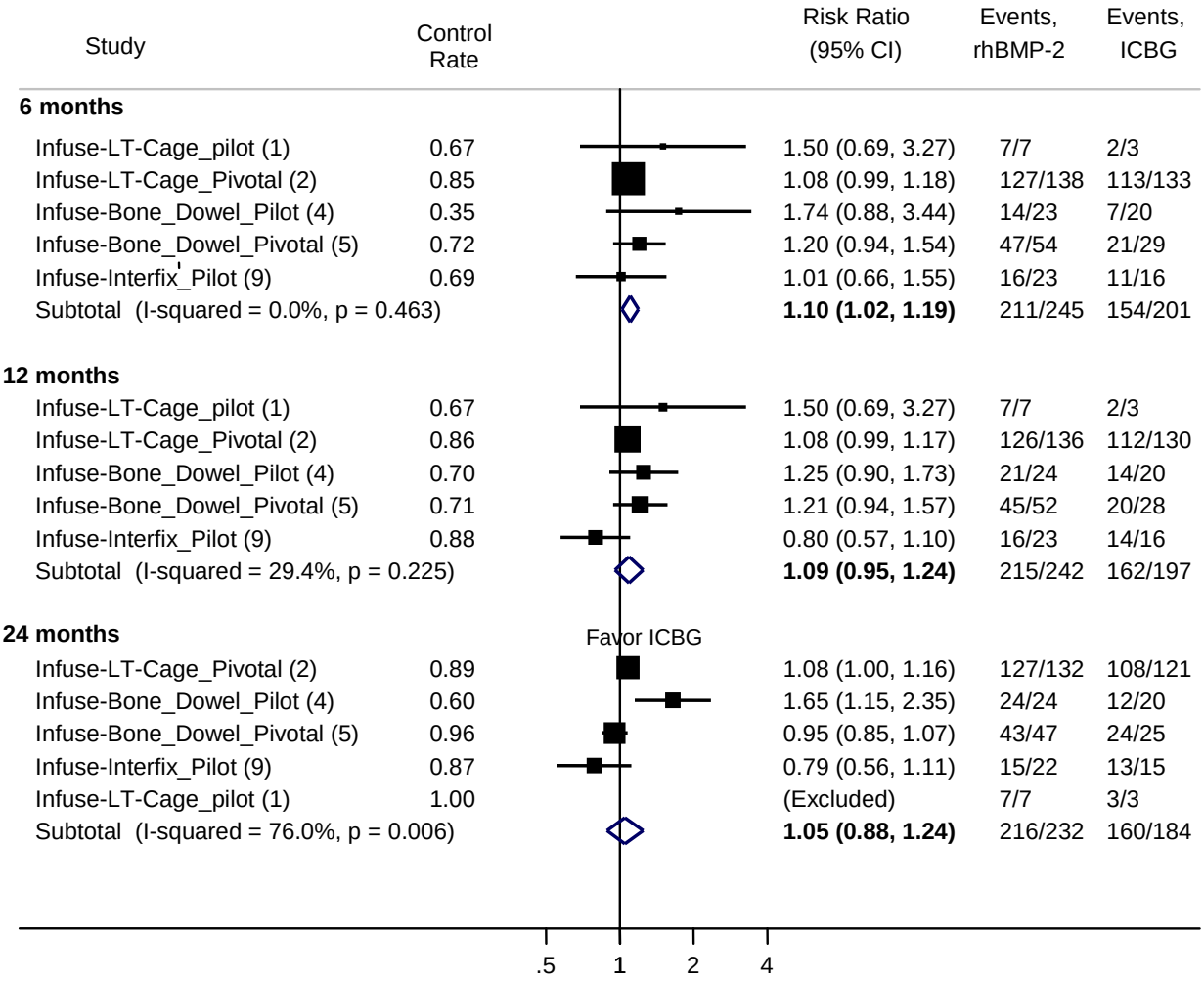
Fusion. In the RCTs of rhBMP-2 versus ICBG (Studies 1, 2, 4, 5, and 9, *n*=465), fusion rates at 24 months ranged from 60 to 100% and were generally similar for both groups (Figure 3). IPD results provided moderate strength of evidence that ALIF with rhBMP-2 was associated with higher radiographic fusion versus ICBG at 6 months (RR 1.10, 95% CI 1.02 to 1.19, I^2=0%); and similar likelihood of radiographic fusion at 12 months (RR 1.09, 95% CI 0.95 to 1.24, I^2=29%) and 24 months (RR 1.05, 95% CI 0.89 to 1.24, I^2=76%). Heterogeneity at 24 months could not be explained by the seemingly "outlying" Study 4. In most cases, estimates of fusion rates using our method were similar to estimates using Medtronic's methods. However, for the laparoscopic series (Study 3), the fusion rate using our method of measurement was 82% at 24 months compared with 93% based on the Medtronic measure.

Three studies (Studies 2, 3, and 4) reported long term fusion data beyond 24 months. Methods for handling of missing data seemed to influence the results of fusion at 48 months. One RCT (Study 4) with fusion data from 37 of 46 patients (80%) at 48 months found rhBMP-2 associated with higher likelihood of fusion than was ICBG (rhBMP-2 18/19 versus ICBG 10/18; RR 1.7, 95% CI 1.1 to 2.6). However, we classified six patients from the ICBG group and one from the rhBMP-2 group as failures due to partial data. In the rhBMP-2 arm of the second RCT (Study 2), at 72 months fusion data was available for 72 patients out of 143 who started the study. Of those, 93% were fused at 72 months. The laparoscopic series (Study 3) reported that 68 of 134 patients who started the study had data at 72 months, and 90% of those patients were fused at 72 months.

Neurological success, disability and other effectiveness outcomes. From 6 weeks through 24 months after surgery, IPD results provided moderate strength of evidence that there were no consistent differences between rhBMP-2 and ICBG in neurological success, ODI score, or most other effectiveness measures (Table 5). The one exception of consistent difference was that, on average, the SF-36 Physical Component Summary score was approximately three points higher for patients in the rhBMP-2 group at 3, 6, 12, and 24 months (WMD 3.68 on a scale of 0 to 100, 95% CI 0.86 to 6.49, at 24 months), but not at 6 weeks. In addition, rhBMP-2 was associated with a small improvement in back pain (WMD 0.74, 95% CI 0.00 to 1.49) and ODI score (WMD 7.35 on a scale of 0 to 50, 95% CI 0.70 to 14.0) at 24 months, the primary time point. The magnitudes of all differences were small.

One RCT (Study 4) showed no significant difference between groups in any of these effectiveness outcomes at 48 months.

Figure 3. Comparison of fusion rates in ALIF trials*



* The results of this figure are based on the two-step approach.
ALIF = anterior lumbar interbody fusion

Table 5. Effectiveness endpoints for ALIF with rhBMP-2 vs. ICBG

Endpoint (Scale)	6 weeks	3 months	6 months	12 months	24 months
	Risk ratio (95% CI) Sample Size, n (Studies)				
Overall success	----	----	1.18 (0.93 to 1.50) 445 (4)	1.12 (0.95 to 1. 33) 436 (4)	1.19 (0.99 to 1. 42) 418 (4)
Fusion	----	----	**1.10 (1.02 to 1.19)**† 446 (5)	1.09 (0.95 to 1.24)† 439 (5)	1.05 (0.88 to 1.24)† 416 (5)
Neurological success	1.02 (0.93 to 1.13) 434 (4)	1.06 (0.97 to 1.16) 442 (4)	1.01 (0.91 to 1.12) 433 (4)	1.04 (0.94 to 1.14) 420 (4)	1.08 (0.98 to 1.19) 400 (4)
ODI success	1.04 (0.83 to 1.29) 442 (4)	1.03 (0.87 to 1.23) 455 (5)	1.09 (0.95 to 1.25) 450 (5)	1.03 (0.92 to 1.15) 436 (5)	1.10 (0.97 to 1.24) 417 (5)
Return to work‡	1.21 (0.71 to 2.05) 211 (4)	0.97 (0.70 to 1.32) 210 (4)	1.02 (0.89 to 1.17) 207 (4)	1.01 (0.90 to 1.14) 201 (4)	1.06 (0.94 to 1.19) 196 (4)
	Weighted mean difference (95% CI) Sample Size, n (Studies)				
ODI (0-50)§	-2.36 (-6.91 to 2.19) 444 (4)	-5.05 (-10.21, 0.10) 461 (5)	-3.79 (-8.69 to 1.11) 456 (5)	-3.74 (-9.09 to 1.60) 441 (5)	**-7.35 (14.00 to -0.70)** 423 (5)
Back pain (0-10)§	0.21 (-0.28 to 0.71) 443 (4)	**-0.57 (-1.06 to -0.09)** 446 (4)	-0.36 (-0.94 to 0.22) 442 (4)	-0.51(-1.18 to 0.16) 426 (4)	**-0.74 (-1.49 to 0.00)** 409 (4)
Leg pain (0-10)§	**-0.57 (-1.12 to -0.02)** 443 (4)	-0.37 (-1.02 to 0.27) 446 (4)	-0.20 (-0.72 to 0.32) 442 (4)	-0.49 (-1.07 to 0.08) 426 (4)	-0.60 (-1.28 to 0.08) 409 (4)
SF-36® PCS (0-100)‖	0.55 -1.02 to 2.11) 356 (3)	**2.91 (0.28 to 5.53)** 374 (4)	**3.00 (0.69 to 5.31)** 449 (5)	**2.94 (0.85 to 5.03)** 440 (5)	**3.68 (0.86 to 6.49)** 421 (5)
SF-36® MCS (0-100)‖	-0.36 (-2.45 to 1.73) 356 (3)	0.74 (-1.34 to 2.83) 374 (4)	-0.33 (-2.24 to 1.59) 449 (5)	-0.56(-2.60 to 1.48) 440 (5)	2.90 (-0.29 to 6.08) 421 (5)

ALIF = anterior lumbar interbody fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2; ODI = Oswestry Disability Index; PCS = physical component summary; MCS = mental component summary

Values in bold font are significant at 0.05 level.

*For ALIF, a total *n*= 465 was included in the analysis, excluding 4 patients who underwent laparoscopic surgery in study 1;

†These combined estimates were obtained using a two-stage approach.

‡Includes only patients who worked before surgery. For ALIF, 221 patients worked before surgery.

§For ODI, back pain, and leg pain, high values represent worse outcomes and a negative difference favors rhBMP-2.

‖For SF-36® PCS and MCS, low values represent worse outcomes and a positive difference favors rhBMP-2.

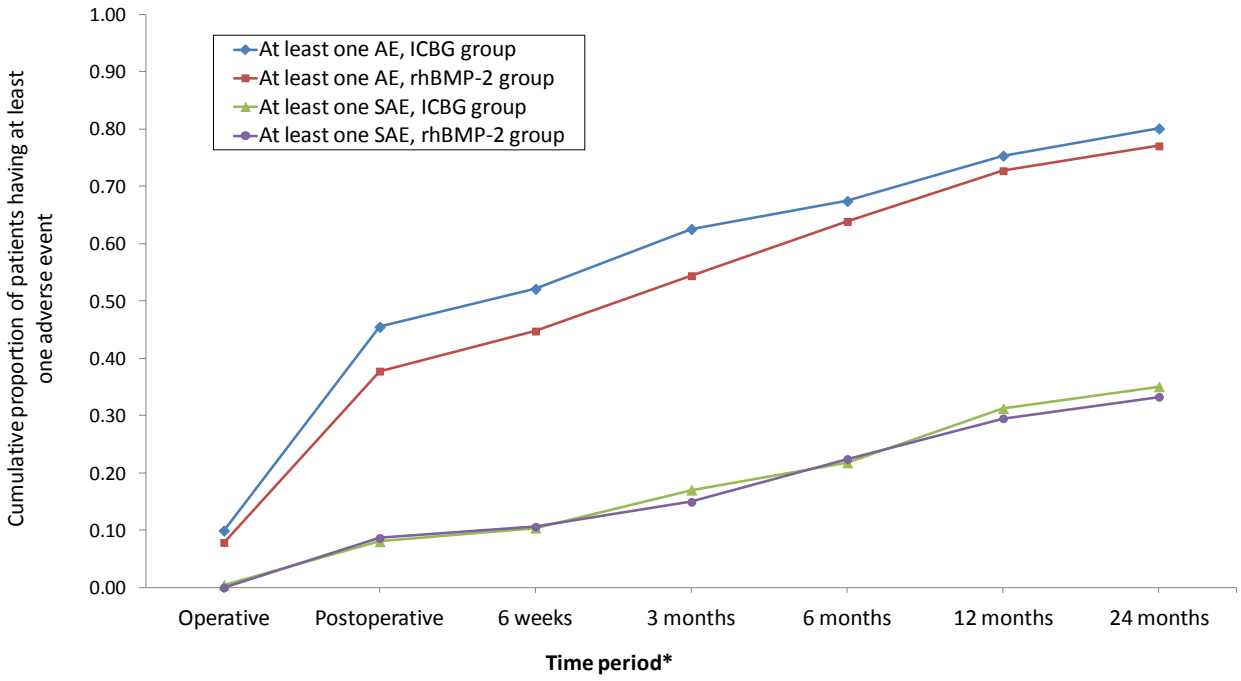
Other comparisons. Medtronic used rhBMP-2 with the LT-Cage as the control group in a trial of the MAVERICK™ Total Disc Replacement (Medtronic, Memphis, TN) (Study 10, *n*=577). In that trial, fusion utilizing rhBMP-2 was associated with worse outcomes than artificial disc replacement for disability, pain, and health at all time periods.[27] Fusion rates for rhBMP-2 at 12 and 24 months were 81% and 79%, lower than the fusion rate in the pivotal trial of rhBMP-2 with the LT-CAGE (Study2, 96%). In the journal article reporting Study 10 [27], the fusion rate for rhBMP with the LT-CAGE was reported to be 100%, which did not appear to include patients with partially missing data.

Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Overall adverse events. The occurrence of adverse events was common. For example, for pivotal Study 2, at 4 weeks, 89 adverse events occurred in the 143 patients in the rhBMP-2 group, and 92 adverse events occurred in the 136 patients in the ICBG group. At 24 months, 315 and 274 adverse events occurred in the rhBMP-2 group and ICBG group, respectively.

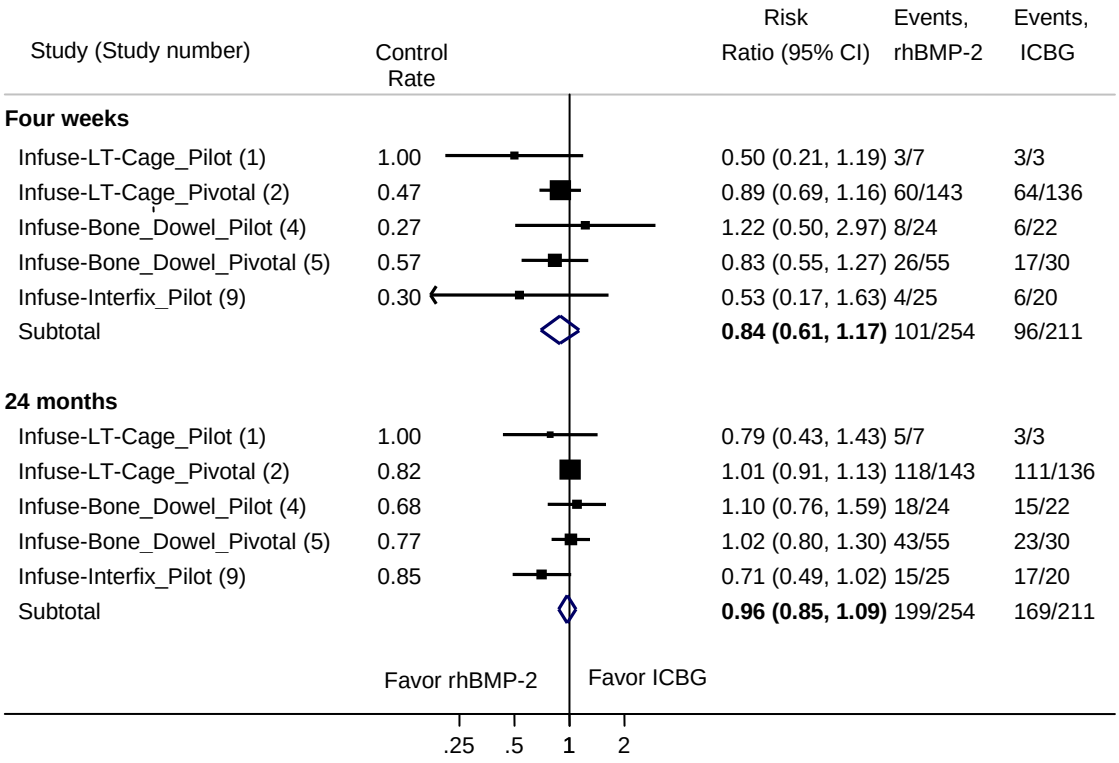
Based on meta-analysis of five RCTs (Studies 1, 2, 4, 5, and 9; *n*=465) the rate of adverse events at 4 weeks was 0.48 per patient in the rhBMP-2 group and 0.65 per patients in the ICBG group. At 24 months, the rates of adverse events were similar in the two groups (1.7 vs. 1.7 per patient). At 4 weeks, 38% of patients in the rhBMP-2 group and 45% of patients in the ICBG group had experienced at least one adverse event (RR 0.84, 95% CI 0.61 to 1.17), and at 24 months, about 80% of patients in both groups had at least one adverse event (RR 0.96, 95% CI 0.85 to 1.09) (Figure 4 – "postoperative" corresponds to 4 weeks; Figure 5).

Figure 4. Cumulative proportion of patients with at least one adverse event (ALIF)



AE = adverse event; ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2; SAE = serious adverse event.
*There was no significant difference between the rhBMP-2 versus ICBG groups at any time point for either outcome.

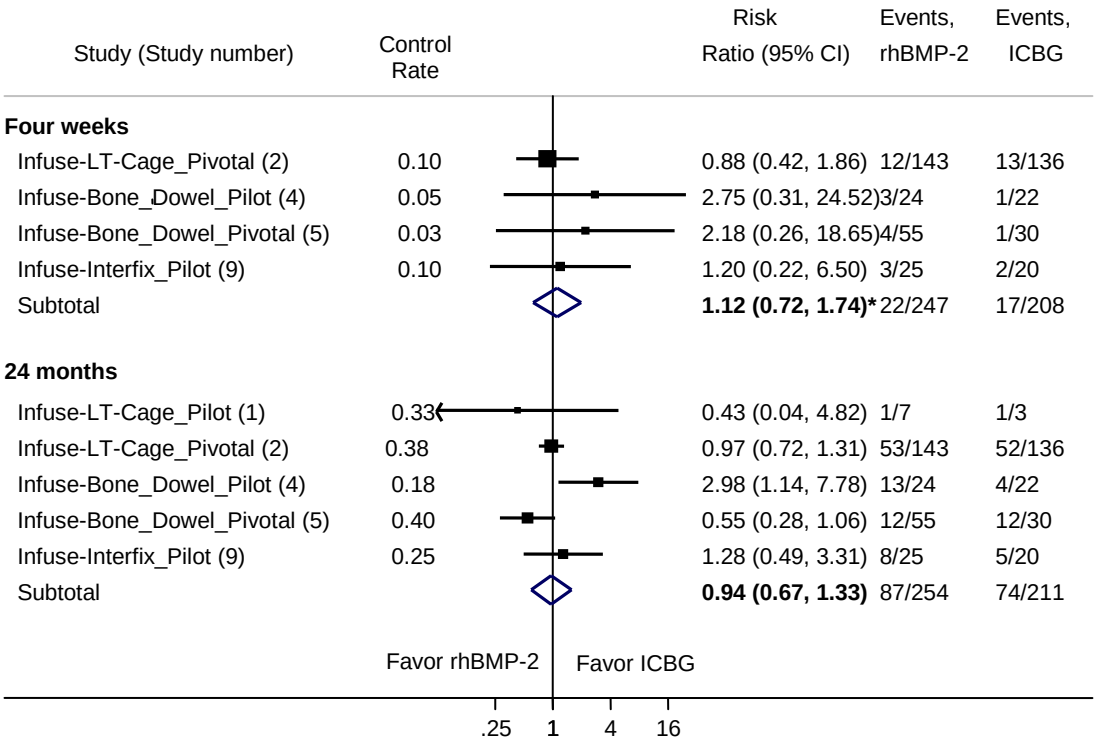
Figure 5. Comparison of proportion of patients having at least one adverse event in ALIF trials



ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft

In the Medtronic-supported trials, no difference between groups was observed in the risk of experiencing an adverse event recorded as “serious” (RR 1.12, 95% CI 0.72 to 1.74 at 4 weeks; RR 0.94, 95% CI 0.67 to 1.33 at 24 months) (Figure 6). At 4 weeks, 8% of patients in the rhBMP-2 group and 9% of patients in the ICBG group had experienced at least one adverse event classified by the original investigators as serious, and at 24 months, about 35% of patients in both groups had at least one such event (Figure 4). In addition, there was no difference in the risk of events classified as “device-related” (RR 1.44, 95% CI 0.57 to 3.67) at 24 months. The proportion of adverse events judged to be device-related by the study investigators was low (rhBMP-2 7% vs. ICBG 4%).

Figure 6. Comparison of proportion of patients having at least one serious adverse event in ALIF trials



*The combined risk ratio (RR) was obtained using a generalized linear fixed effects model with binomial distribution and log link.
ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft

For specific adverse events, we did not find significant differences between groups based on RCTs (Studies 1, 2, 4, 5, and 9). Confidence intervals were frequently wide (Table 6), precluding strong conclusions. Heterotopic bone formation was not reported as a separate adverse event in these studies.

Retrograde ejaculation. The pivotal trial of INFUSE reported five instances of retrograde ejaculation out of 78 males (6%) in the rhBMP-2 group versus one case of retrograde ejaculation out of 68 males (1.5%) in the ICBG group, (RR 2.62, 95% CI 0.28 to 24.6, through 4 weeks; RR 4.36, 95% CI 0.52 to 36.4, through 24 months) (Table 6). Among men who had fusion involving the L5-S1 level (n=110), four cases were reported in the rhBMP-2 group and one in the ICBG group (RR 3.3, 95% CI 0.38 to 29 at 24 months). In the laparoscopic series (Study 3), six males out of 57 developed retrograde ejaculation (11%). In the context of a set of premarketing studies, these findings constitute a safety signal.[69, 70]

A cohort study of patients who had surgery with a retroperitoneal approach involving the L5-S1 level found 7% of 69 rhBMP-2 patients versus 1% of 174 control patients reported retrograde ejaculation (P = 0.0025).[63] One trial (Study 10) compared rhBMP-2 versus artificial disc and found no difference in the risk of retrograde ejaculation with rhBMP-2 at 4 weeks (RR 0.80, 95% CI 0.08, 7.53) or at 24 months (RR 1.19, 95% CI 0.22 to 6.39). The rates of retrograde ejaculation in artificial disc patients were 1.5% (3/205) at 4 weeks and 2.0% (4/205) at 24 months, compared with 1.2% (1/86) and 2.3% (2/86) in patients receiving rhBMP-2 at 4 weeks and 24 months, respectively. These rates are slightly lower than those found in a retrospective

cohort study of 95 patients with postoperative retrograde ejaculation in 7% of rhBMP-2 patients (4/54) and 10% of artificial disc patients (4/41), which was also not significantly different (RR 0.76, 95% CI 0.20 to 2.86).[51]

Based on the evidence from the trials and observational studies, it is likely that rhBMP-2 is associated with an increased risk of retrograde ejaculation. While we are moderately confident in the direction of the effect, because there is more uncertainty about the magnitude of the effect due to a high risk of bias and sparse data as well as some inconsistency among the estimates, we find that the evidence is low strength for this outcome. With respect to the risk of bias, in this case lack of blinding and unsystematic ascertainment and case definition could lead to an underestimate of the effect.

Possible lumbar radiculitis. Based on the results from four RCTs (Studies 2, 4, 5, and 9, *n*=455), there was no difference between rhBMP-2 and ICBG in the risk of possible lumbar radiculitis using the primary definition through 4 weeks (RR 1.02, 95% CI 0.35 to 2.99) and 24 months (RR 1.00, 95% CI 0.71 to 1.39). Applying three alternative definitions for lumbar radiculitis provided similar results.

Urinary retention. While the studies did not accurately ascertain urinary retention events, the IPD analysis point estimate suggests possible increased risk with rhBMP-2 at 24 months, based on four trials (Studies 1, 2, and 5, *n*=378, RR 2.55, 95% CI 0.30 to 21.52). Because the estimate is not precise and ascertainment was inadequate, the strength of this evidence is low in that we have less confidence in the exact magnitude of the estimate.

Wound infection and wound dehiscence. There was no difference in incidences of wound infection (Studies 2, 4, and 5, *n*=410: RR 0.73, 95% CI 0.38 to 1.43, low strength evidence) through 24 months, or in wound dehiscence through 24 months (Studies 1 and 2; *n*=293, rhBMP-2 3/253 vs. 0/139, insufficient strength evidence).

Endplate resorption and subsidence. Subsidence is defined as sinking or settling of the device into bone. One randomized trial reported patients with subsidence at 4 weeks (Study 2, *n*=279, RR 1.43, 95% CI 0.24 to 8.41), while two RCTs reported incidences of subsidence through 24 months (Studies 2, 4, and 5; *n*=364, RR 3.15, 95% CI 0.66 to 14.99). At 24 months, subsidence occurred in 4% of rhBMP-2 and 1% of ICBG patients (Table 6).

Cohort studies tended to report higher rates of subsidence using varying outcome definitions. One small cohort study (*n*=24) reported 70% of 20 levels undergoing fusion with rhBMP-2 and allograft showing >10% graft subsidence versus 6% of 16 levels undergoing fusion with allograft plus demineralized bone matrix.[61] A second cohort reported more aggressive resorption of the graft and endplates in the rhBMP-2 group compared with ICBG but did not report sample sizes (N) or percentages.[62] Additionally, one intervention series (*n*=53) reported 55% subsidence when subsidence was defined as a loss of disc space greater than 2mm.[64]

These studies provide moderate strength evidence; while the estimates are imprecise, the condition was probably more consistently ascertainable and clearly defined than some other adverse events, and the direction of effect was consistent across trials and observational studies.

Additional surgeries. Based on IPD meta-analysis of four trials (Studies 2, 4, 5, and 9, *n*=455), moderate strength evidence suggests there was no difference between rhBMP-2 and ICBG in likelihood of additional surgeries at 24 months (RR 0.81. 95% CI 0.49 to 1.33).

In one cohort study, 33% of 9 patients in the rhBMP-2 plus allograft group required salvage posterior fusion compared with 26% of 27 patients in the ICBG plus allograft group (p=0.67).[62]

Other comparisons. Compared with artificial disc replacement (Study 10, *n*=577), rhBMP-2 was associated with lower risk of neurological events at 4 weeks (RR 0.51, 95% CI 0.33 to 0.97), lower risk of gastrointestinal events at 24 months (RR 0.60, 95% CI 0.37 to 0.96), and greater risk of subsidence at 24 months (RR 2.19, 95% CI 1.09 to 4.42). There was no difference in risk of other adverse events including retrograde ejaculation (see section above).

Table 6. Overall and specific adverse events for ALIF with rhBMP-2 vs. ICBG

Event†	≤ 4 weeks		≤ 24 months	
	Patients with rhBMP-2 vs. ICBG	Risk Ratio (95% CI) Sample Size, *n* (Studies)	Patients with rhBMP-2 vs. ICBG	Risk Ratio (95% CI) Sample Size, *n* (Studies)
Anterior lumbar interbody fusion*				
Overall adverse events				
≥ 1 Adverse event, any type	38% vs. 45%	0.84 (0.61 to 1.17) 465 (5)	77% vs. 80%	0.96 (0.85 to 1.09) 465 (5)
≥ 1 Serious adverse event	9% vs. 8%	1.12 (0.72 to 1.74) 455 (4)	33% vs. 35%	0.94 (0.67 to 1.33) 465 (5)
≥ 1 device-related adverse event	---	----	7% vs. 4%	1.44 (0.57 to 3.67) 465 (5)
Specific adverse events				
Anatomical/technical difficulty	0.9% vs. 3%	0.22 (0.04 to 1.05) 419 (4)	Same as four weeks	
Back and/or leg pain	4% vs. 3%	1.05 (0.31 to 3.62) 455 (4)	26% vs. 24%	1.05 (0.72 to 1.53) 465 (5)
Cardiovascular	2% vs. 4%	0.56 (0.16 to 1.92) 409 (3)	6% vs. 7%	0.84 (0.48 to 1.49) 455 (4)
Gastrointestinal	13% vs. 15%	0.86 (0.54 to 1.36) 465 (5)	17% vs. 19%	0.80 (0.45 to 1.43) 465 (5)
Implant problems	2% vs. 1%	1.07 (0.10 to 11.75) 380 (4)	3% vs. 0.9%	2.43 (0.40 to 14.80) 465 (5)
Infection (all types)	6% vs. 5%	1.10 (0.49 to 2.46) 410 (3)	10% vs. 10%	0.90 (0.35 to 2.32) 455 (4)
Neurological	3% vs. 4%	0.81 (0.29 to 2.27) 409 (3)	16% vs. 14%	1.08 (0.60 to 1.94) 455 (4)
Possible lumbar radiculitis (primary)‡	3% vs. 3%	1.02 (0.35 to 2.99) 455 (4)	23% vs. 24%	1.00 (0.71 to 1.39) 455 (4)
Possible lumbar radiculitis (definition 2)‡	2% vs. 3%	0.49 (0.11 to 2.07) 455 (4)	16% vs. 14%	1.12 (0.73 to 1.74) 455 (4)
Possible lumbar radiculitis (definition 3)‡	3% vs. 3%	0.85 (0.23 to 3.04) 455 (4)	26% vs. 22%	1.18 (0.84 to 1.65) 455 (4)
Possible lumbar radiculitis (definition 4)‡	0.8% vs. 2%	0.35 (0.07 to 1.78) 455 (4)	11% vs. 9%	1.28 (0.58 to 2.82) 455 (4)
Respiratory	2% vs. 3%	0.55 (0.21 to 1.41) 364 (2)	3% vs. 5%	0.45 (0.17 to 1.16) 364 (2)
Retrograde ejaculation	4% vs. 1%	2.62 (0.28 to 24.56) 144 (1)	6% vs. 1%	4.36 (0.52 to 36.40) 146 (1)
Spinal event	0% vs. 2%	0/167 vs. 3/158 325 (2)	12% vs. 11%	0.97 (0. 49 to 1.93) 455 (4)
Subsidence	2% vs. 1%	1.43 (0.24 to 8.41) 279 (1)	4 vs. 1%	3.15 (0.66 to 14.99) 364 (2)

Event†	≤ 4 weeks		≤ 24 months	
	Patients with rhBMP-2 vs. ICBG	**Risk Ratio (95% CI) Sample Size, *n* (Studies)**	**Patients with rhBMP-2 vs. ICBG**	**Risk Ratio (95% CI) Sample Size, *n* (Studies)**
Urogenital	7% vs. 4%	1.96 (0.61 to 6.34) 420 (4)	13 vs. 8%	1.62 (0.73 to 3.59) 420 (4)
Vertebral fracture	1% vs. 0%	2/168 vs. 0/156 324 (2)	Same as four weeks	
Urinary retention‡	---	----	6 vs. 2%	2.55 (0.30 to 21.52) 378 (3)
Wound infection‡	---	----	5 vs. 6%	0.73 (0.38 to 1.43) 410 (3)
Wound dehiscence‡	---	----	1% vs. 0%	3/253 vs. 0/139 293 (2)
Relevant additional surgeries	---	----	11% vs. 13%	0.81 (0.49 to 1.33) 455 (4)

ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2
Values in bold font are significant at 0.05 level.
*For ALIF, a total *n*=465 was included in the analysis, excluding 4 patients who underwent laparoscopic surgery in study 1.
†Categories of adverse events are based on Medtronic datasets, except for those indicated otherwise.
‡Based on individual adverse event case histories in the proprietary reports provided by Medtronic

Posterolateral Fusion

Summary Findings

The Medtronic-sponsored posterolateral fusion trials constitute the main body of evidence about higher dosages and concentrations of rhBMP-2, including AMPLIFY™ (Medtronic, Memphis, TN), than the ALIF trials.

- IPD from four randomized controlled trials (N=722) provided moderate-strength evidence of no consistent significant differences in effectiveness between ICBG and rhBMP-2 at dosages of primarily 40 mg to 63 mg through 24 months. Significant differences were found at one of several time points for selected outcomes, in particular:
  - RhBMP-2 had significantly higher rates in overall success (RR, 1.34; 95% CI 1.10 to 1.64) and fusion (RR, 1.37; 95% CI 1.19 to 1.59) at 6 months.
  - RhBMP-2 was associated with a small improvement in leg pain at 3 months (WMD, 0.44 on a scale of 0 to 10; 95% CI 0.01 to 0.87), and in Physical Component Scale of the SF-36 at 6 months (WMD on a scale of 0 to 100, 1.79; 95% CI 0.27 to 3.31).
- At longer durations of followup, there were small or no difference in overall success and fusion between rhBMP-2 and ICBG, based on limited evidence from trials.
- RhBMP-2 and ICBG had similar rates of overall adverse events and most specific harms through 4 weeks, 24 months, and 48 months (strength of evidence: moderate).
- Evidence from the Medtronic trials was insufficient to assess the potential consequences of ectopic bone formation.
- Results from observational studies seemed consistent with the randomized trials, although few studies reported specific adverse events.

Overview of Included Evidence

We identified five randomized trials (*n*=835), four sponsored by Medtronic (Studies 8, 12-14) and one[34] sponsored by Norton Healthcare (*n*=102). In addition, we identified six non-Medtronic sponsored cohort studies of PLF reported in seven publications,[71-77] one cohort study

of combined posterolateral and posterior lateral interbody fusion,[78] seven intervention series, two sponsored by Medtronic (Studies 15 and 16), and five by others,[79-83] and one case series.[84]

The Medtronic randomized controlled trials compared rhBMP-2 with ICBG, both in conjunction with either the CD HORIZON SPIRE® or TSRH® Spinal Systems (Medtronic; Memphis, TN). The purpose of these trials was to test the feasibility of the investigational device with rhBMP-2 (Study 8), or whether an investigational device with rhBMP-2was non-inferior or equivalent to ICBG (Studies 12-14). The dosage of rhBMP-2 was 12 mg in one trial (Study 8) and ranged from 40 mg to 63 mg in the other three trials (Studies 12-14). Mean age ranged from 53 to 56 years. About 57% of patients were female, 7.6% had diabetes, and 22.2% were tobacco users. The majority of patients had single-level degenerative disease. In one trial (Study 13), 15% of patients were fused at two levels. Patients with previous spine fusion attempts at the involved level were excluded. Eleven patients from one RCT who underwent fusion with rhBMP-2 without instrumentation were excluded from our meta-analysis of IPD (Study 12).

The randomized controlled trial funded by Norton Healthcare included 102 adults over 60 years old.[34] The study compared rhBMP-2/ACS versus ICBG and reported on clinical, radiographic, and economic outcomes, at 2-year follow-up.

While the randomized controlled trials focused on comparing rhBMP-2 with ICBG**,** the cohort studies compared rhBMP-2 plus allograft or local bone to autograft alone,[72, 73] rhBMP-2 plus ICBG to ICBG alone,[75] rhBMP-2 to bone marrow aspirate allograft or autograft,[76] and rhBMP-2 plus ICBG to ICBG plus an implantable spinal fusion stimulator.[77] One trial compared rhBMP-2 versus ICBG at each vertebral level within the same patient (rhBMP-2 on the patient's right side versus ICBG used on the patient's left side).[71]

All randomized trials were rated fair quality except for Study 12, which was rated poor quality due to baseline differences in patient characteristics between groups. The trials were downgraded due to methodological limitations such as unclear blinding of outcome assessors other than radiologists for Medtronic trials, and inadequate description of patient comorbidities.[34] Cohort studies were rated fair quality[71-73] or poor quality[74-78] Methodological limitations involved: enrollment criteria,[71-74, 76] blinding,[71-73, 78] baseline differences between groups,[73, 75-78] and failure to adjust for potential confounding variables.[74-78]

Comparative Effectiveness of rhBMP-2 Versus Fusion Without rhBMP-2

AMPLIFY (Study 14)[29] was the largest RCT assessing the effectiveness and harms of rhBMP-2 using the PLF approach. The FDA executive summary concluded that there was a 99.9 to 100% chance that the 24-month rate for overall success, fusion, ODI score success, and neurologic success for the rhBMP-2 group was noninferior to the ICBG group. Our IPD analysis was not inconsistent with this result, in that we did not find significant differences between the rhBMP-2 and ICBG groups for these outcomes. However, our analysis showed lower fusion and overall success rates for the rhBMP-2 group at 24 months than was reported in the FDA executive summary and the published journal article. In particular, the FDA executive summary reported that the overall success and fusion rate at 24 months was 60.5% and 95.9%, respectively, for the rhBMP-2 group and 55.5% and 89.3% for the ICBG group. The published journal article reported similar fusion rates of 96% versus 89%, with a significantly higher fusion rate in the rhBMP-2 group ($P = 0.014$). Based on our IPD analysis, the overall success and fusion rate at 24 months was similar between the rhBMP-2 group (55.9%, 90.0%) and the ICBG group (56.5%, 89.5%), and we found no significant difference in fusion rate at 24 months ($P = 0.87$). The difference in results may be due to the difference in handling missing data, though it does not explain why only the rates for the rhBMP-2 group are different.

Even though overall success was designed as a safety and efficacy outcome and incorporated criteria for both benefits and harms, unfavorable outcomes still occurred in patients classified as

an overall success (Table 7). In fact, the FDA's executive summary of Medtronic's AMPLIFY™ rhBMP-2 Matrix premarket approval application suggested that overall success needs to be considered in the context of the occurrence of back/leg pain, relationship-undetermined adverse events, and additional surgeries such as reoperations and elective removals. Based on our analysis of IPD data, among those having overall success at 24 months in the rhBMP-2 group, 26.4% had back/leg pain before 24 months and 16.1% had back/leg pain at 24 months. The proportions patients having serious back and/or leg pain before and at 24 months were 8.5% and 1.7%, respectively. Since back and/or leg pain included heterogeneous events that may not have been related to spine surgery, we examined success in the context of the occurrence of radiculitis. Among those having overall success at 24 months in the rhBMP-2 group, 6.8% had radiculitis before 24 months and 7.6% had radiculitis at 24 months. The proportions of patients having serious radiculitis (event severity ≥ 3) before and at 24 months were 1.7% and 2.6%, respectively. In the ICBG group, 18.1% had radiculitis before 24 months and 4.8% had radiculitis at 24 months. The proportions of patients having serious radiculitis before and at 24 months were 3.8% and 1.0%, respectively. Similarly, a considerable proportion of patients classified as an overall success had relationship-undetermined adverse events (Table 7). The results for comparative effectiveness based on all evidence are presented below.

Table 7. Proportion of patients rated as overall successes in AMPLIFY trial, but who still had other negative outcomes*

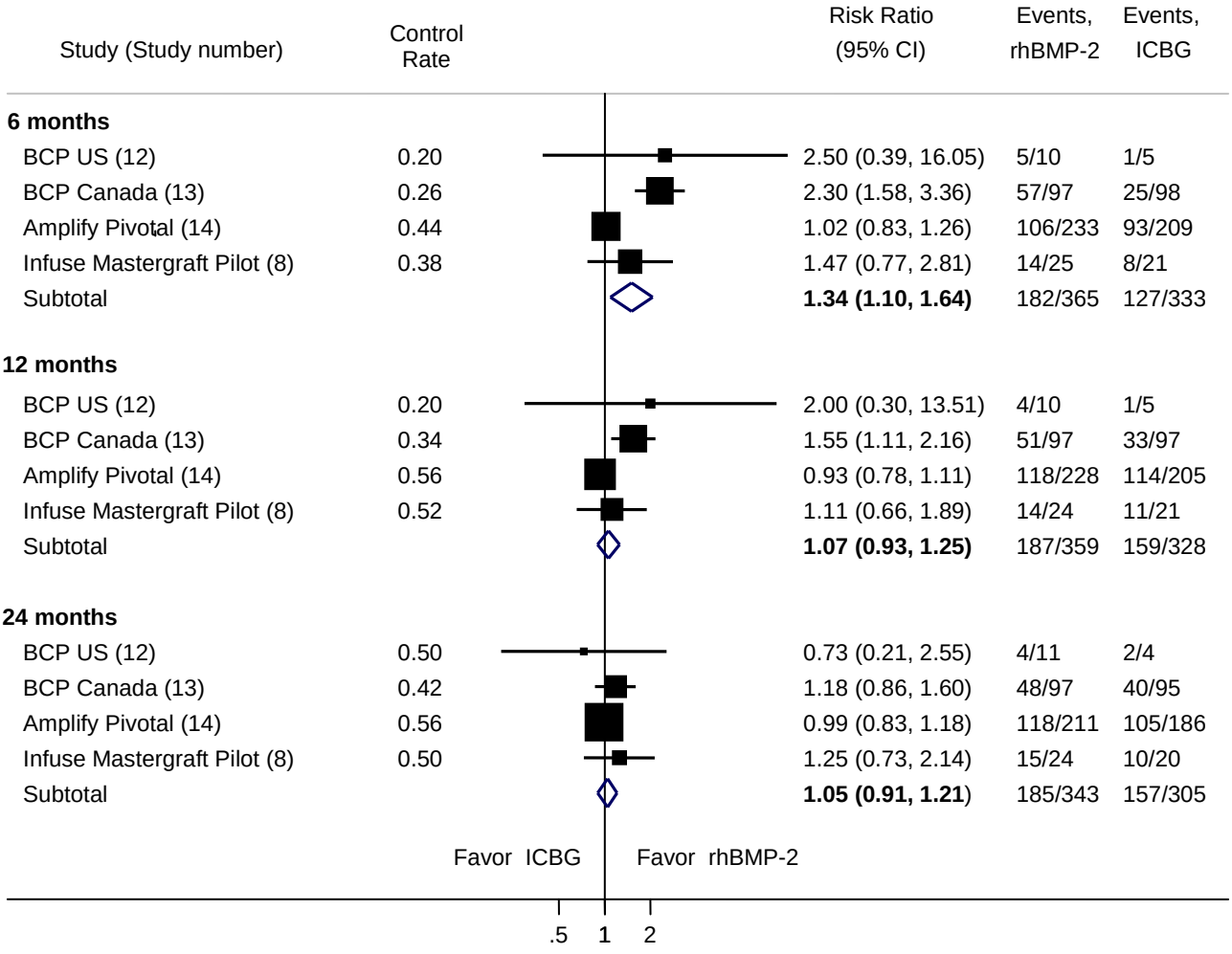
	6 months		12 months		24 months	
	rhBMP-2 (*n*=106)	**ICBG (N=93)**	**rhBMP-2 (N=118)**	**ICBG (N=114)**	**rhBMP-2 (N=118)**	**ICBG (N=105)**
Radiculitis	1.9/2.8	3.2/4.3	4.2/3.4	6.1/12.3	6.8/7.6	18.1/4.8
Serious radiculitis	0.9/0.0	2.2/0.0	0.9/0.0	1.8/6.1	1.7/2.5	3.8/1.0
Back/leg pain	17.9/5.7	8.6/7.5	18.7/9.3	14.0/12.3	26.3/16.1	24.8/13.3
Serious back/leg pain	1.9/0.9	2.2/0.0	1.7/3.4	1.7/0.9	8.5/1.7	3.8/1.9
Relationship-undetermined adverse events	16.0/8.5	11.8/9.7	26.3/7.6	21.1/15.8	32.2/14.4	30.5/10.5
Relationship-undetermined Serious adverse events	0.9/0.0	3.2/0.0	1.7/0.0	5.3/4.4	3.4/1.7	6.7/0.0
Reoperations	–	–	–	–	1.7/0.0	2.9/0.0
Elective removals	–	–	–	–	0.9/0.0	1.0/2.9

* % before each time point/% at each time point

Overall success. Our IPD meta-analysis of the AMPLIFY™ Pivotal RCT, plus the other three Medtronic randomized trials (*n*=722) (Studies 8, 12-14), provided moderate strength of evidence of no consistent difference between rhBMP-2 and ICBG groups in likelihood of overall success (Figure 7) through 24 months. rhBMP-2 had significantly higher rates at 6 months (RR, 1.34; 95% CI 1.10 to 1.64), but not at 12 months (RR, 1.07; 95% CI 0.93 to 1.25) or 24 months (RR, 1.05; 95% CI 0.91 to 1.21). At 24 months, the rate of overall success ranged from 40 to 60% in both groups.

Although the journal publications only reported outcomes up to 24 months, limited IPD was available from two trials at 48 months (Studies 13 and 14) and from one trial at 60 months (Study 14). The overall success rate was 48% in the rhBMP-2 group and 35% in the ICBG group at 48 months. RhBMP-2 was associated with a greater likelihood of overall success at 48 months (RR 1.4, 95% CI 1.04 to 1.8, I^2 = 0.0%), but not at 60 months (RR, 1.2, 95% CI 0.94 to 1.5).

Figure 7. Comparison of overall success rates in PLF trials



PLF = posterolateral lumbar fusion; ICBG = iliac crest bone graft

Fusion. Across all time points, evidence for radiographic fusion was of moderate strength. The fusion rate at 24 months ranged from 70 to 90% in the ICBG group and 86 to 100% in the rhBMP-2 group, and there was no evidence of consistent difference between rhBMP-2 and ICBG groups through 24 months. Similar to overall success, rhBMP-2 had significantly higher rates at 6 months (1.37, 95% CI 1.19 to 1.59) but not at 12 months (RR 1.29, 95% CI 0.94 to 1.78) or 24 months (RR 1.16, 95% CI 0.96 to 1.41) (Figure 8). Heterogeneity was present (I^2=86% and 76% at 12 and 24 months, respectively) and could not be attributed to differences in factors such as age, gender, number of levels fused, smoking status, or diabetes.

Similar to IPD results, one RCT that restricted inclusion to persons 60 years and older (*n*=102) found no significant difference between rhBMP-2 and ICBG in likelihood of fusion at 24 months (86% versus 71%; RR 1.12, 95% CI 0.98 to 1.29).[34] It used a less rigorous definition for fusion success (the presence of either unilateral or bilateral bridging bone) than was used in our meta-analysis.[34]

For long-term results, rhBMP-2 was associated with a greater likelihood of fusion rate at 48 months (RR 1.15, 95% CI 1.04 to 1.27, I^2 = 0.0%), but not at 60 months (RR, 1.08, 95% CI 0.99 to 1.2). The fusion rate was 93% in the rhBMP-2 group and 81% in the ICBG group at 48 months.

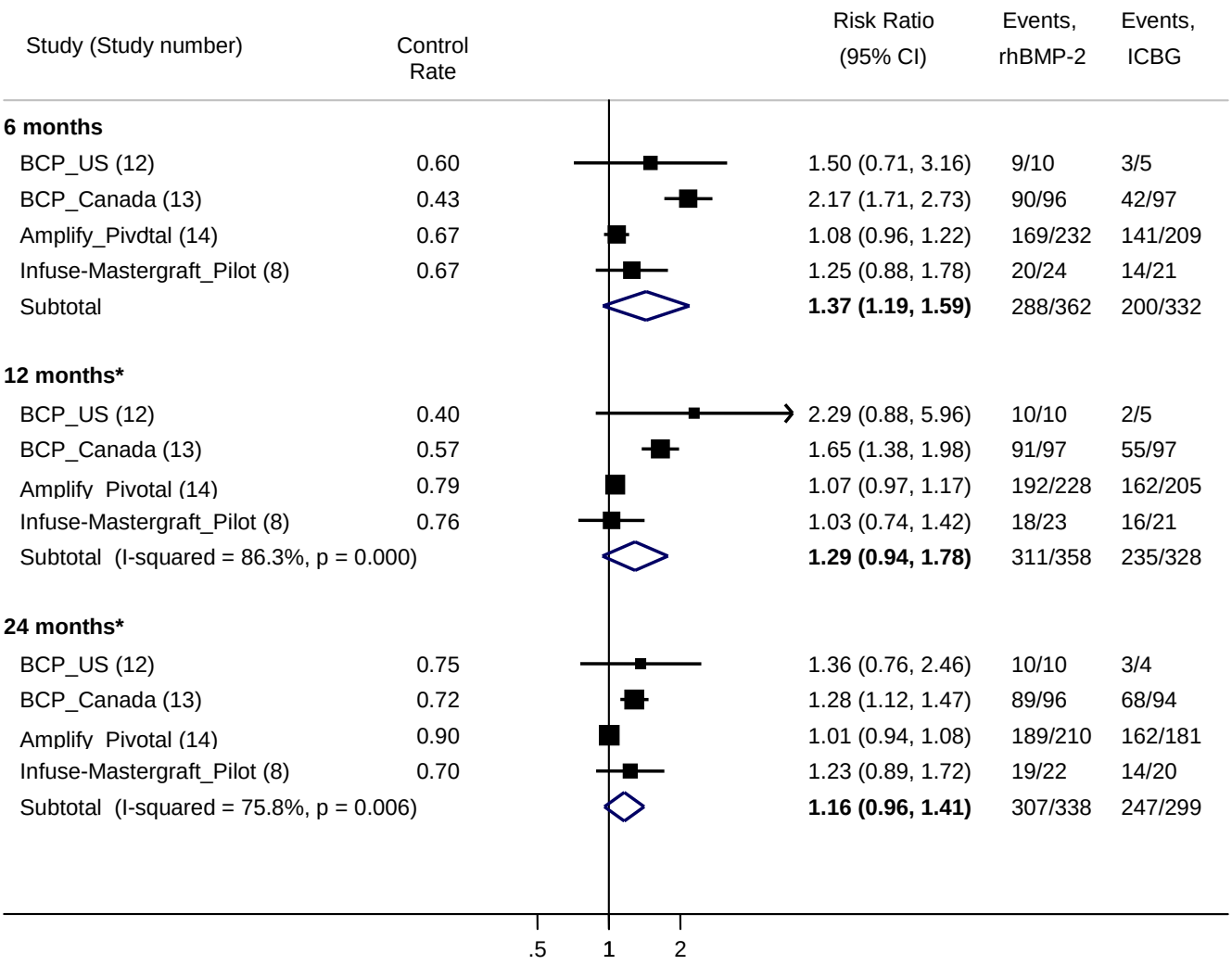
Two cohort studies reported fusion occurred earlier with rhBMP-2 than with autograft/allograft[72, 77] but three studies indicated that by 24 months there was no difference in fusion between groups.[71, 72, 77] The other two cohort studies found increased fusion rates with rhBMP-2 at 24 months[75, 76] but did not report important prognostic baseline patients characteristics[75] or did not control for number of levels fused.[76]

Fusion rates from intervention series were similar to those in the randomized controlled trials and ranged from 80% at 15 months[82] to 95% at 2 years,[79, 83] and 88% at 28.6 months.[80] However, based on IPD analysis from one intervention series with two-level fusion, fusion rates were substantially lower at 6 months (43%), 12 months (48%), and 24 months (69%) (Study 15).

Neurological success, disability and other effectiveness outcomes. For other effectiveness outcomes, our IPD meta-analysis of the four trials (Studies 8, 12-14) provided moderate strength evidence that there was also no consistent difference in neurological success, ODI success, ODI scores, back pain scores, and return to work between the rhBMP-2 group and the ICBG group at any time point up to 24 months (Table 8). SF-36 mental health scores were also not consistently different between the groups, but evidence was of low strength for the 24 month time point due to strong inconsistency, and other time points provide moderate strength evidence for this outcome. Based on moderate strength evidence, rhBMP-2 was associated with a small improvement in leg pain at 3 months (WMD, 0.44; 95% CI 0.01 to 0.87), and in Physical Component Scale of the SF-36 at 6 months (WMD, 1.79; 95% CI 0.27 to 3.31) only.

Additionally, at 48 months, IPD from the two trials (Study 13 and 14) found no difference between rhBMP-2 and ICBG in the likelihood of neurological success (RR 1.03, 95% CI 0.93 to 1.13) or in disability scores (WMD -0.54, 95% CI -5.3 to 4.3). At 60 months, based on IPD from Study 14, there was also no difference in the likelihood of neurological success (RR 0.99, 95% CI 0.90 to 1.08) or in disability scores (WMD -1.4, 95% CI -5.5 to 2.76).

Figure 8. Comparison of fusion rates in PLF trials



*The results are based on the two-step model.
PLF = posterolateral lumbar fusion; ICBG = iliac crest bone graft

Table 8. Effectiveness endpoints for PLF with rhBMP-2 vs. ICBG*

Endpoint (Scale)	6 weeks	3 months	6 months	12 months	24 months
			Risk Ratio (95% CI) Sample Size, *n* (Studies)		
Overall success	----	----	**1.34 (1.10 to 1.64)** 698 (4)	1.07 (0.93 to 1.25) 687 (4)	1.05 (0.91 to 1.21) 648 (4)
Fusion	----	----	**1.37 (1.19 to 1.59)** 694 (4)	1.29 (0.94 to 1.78)† 686 (4)	1.16 (0.96 to 1.41)† 637 (4)
Neurological success	1.03 (0.94 to 1.13) 706 (4)	1.0 (0.93 to 1.08) 705 (4)	1.02 (0.96 to 1.09) † 693 (4)	1.01 (0.95 to 1.07) 683 (4)	1.01 (0.92 to 1.10) 636 (4)
ODI success	1.00 (0.81 to 1.23) 707 (4)	1.03 (0.91 to 1.17) 704 (4)	1.07 (0.98 to 1.17) 693 (4)	1.01 (0.91 to 1.11) 683 (4)	1.01 (0.91 to 1.12) 640 (4)
Return to work‡	1.26 (0.71 to 2.21) 233 (3)	1.09 (0.85 to1.40) 232 (3)	0.87 (0.67 to 1.14) 225 (3)	1.07 (0.96 to 1.19) 227 (3)	1.03 (0.94 to 1.14) 208 (3)
			Weighted mean difference (95% CI) Sample Size, n (Studies)		
ODI (0-50)§	0.74 (-1.68 to 3.17) 718 (4)	-1.97 (-4.36, 0.42) 714 (4)	-2.40 (-4.85 to 0.04) 703 (4)	-2.09(-5.28, 1.10) 694 (4)	-1.98 (-4.86 to 0.90) 650 (4)
Back pain (0-10)§	0.10 (-0.27 to 0.48) 716 (4)	-0.25 (-0.62 to 0.12) 713 (4)	-0.46 (-1.14 to 0.23) 702 (4)	-0.42 (-1.34 to 0.50) 693 (4)	-0.31 (-0.76 to 0.15) 649 (4)
Leg pain (0-10)§	0.23 (-0.21 to 0.66) 715 (4)	**-0.44 (-0.87 to -0.01)** 712 (4)	-0.27 (-0.71 to 0.17) 701 (4)	-0.29 (-0.75 to 0.16) 692 (4)	-0.34 (-0.82 to 0.13) 648 (4)
SF-36® PCS (0-100)‖	-0.10 (-1.15 to 0.96) 709 (4)	0.64 (-0.68 to1.96) 708 (4)	**1.79 (0.27 to 3.31)** 696 (4)	1.83 (-0.19 to 3.85) 689 (4)	1.10 (-0.65 to 2.86) 644 (4)
SF-36® MCS (0-100)‖	0.52 (-0.94 to 1.98) 709 (4)	-0.05 (-1.59 to1.50) 708 (4)	0.06 (-1.48 to 1.60) 696 (4)	-0.50 (-2.56 to 1.57) 689 (4)	0.54 (-3.16 to 4.25) 644 (4)

ODI = Oswestry Disability Index; PCS = physical component summary; MCS = mental component summary; PLF = posterolateral lumbar fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2

Values in bold font are significant at 0.05 level.

*A total *n*=722 was included in the analysis, excluding 11 patients randomized to rhBMP-2 without instrumentation in study 12.

†These combined estimates were obtained using a two-step approach.

‡Includes only patients who worked before surgery (*n*= 241).

§For ODI, back pain, and leg pain, high values represent worse outcomes and a negative difference favors rhBMP-2.

‖For SF-36® PCS and MCS, low values represent worse outcomes and a positive difference favors rhBMP-2.

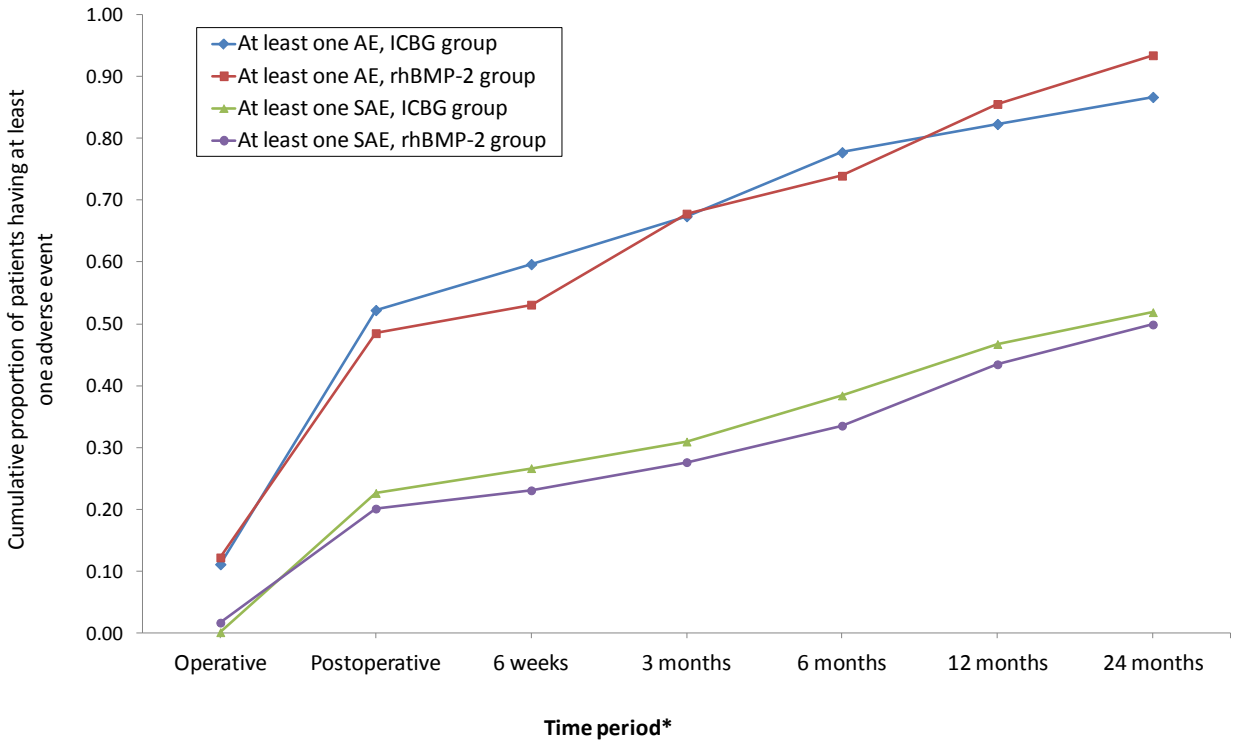
Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Overall adverse events. Based on IPD analysis of four trials (Studies 8, 12-14; *n*=722), the rate of adverse events per patient through 4 weeks was 0.91 in the rhBMP-2 group vs. 0.84 in the ICBG group. The rate was about three events per patient in both groups through 24 months.

About 50% of patients had experienced an adverse event at four weeks and over 80% at 24 months (Figure 9 – "postoperative" corresponds to 4 weeks). There was no difference between rhBMP-2 and ICBG in risk of experiencing at least one adverse event at 4 weeks (RR0.93, 95% CI 0.66 to 1.31) and through 24 months (RR 1.02, 95% CI 0.95 to 1.10) (Figure 10). There was also no difference between groups in the likelihood of experiencing a serious adverse event (RR 0.89, 95% CI 0.67 to 1.18 at 4 weeks; RR 0.96, 95% CI 0.83 to 1.11) (Figure 11). At 4 weeks, about 20% of patients in the rhBMP-2 group and 23% in the ICBG group had experienced at least one adverse event classified by the Medtronic investigators as "serious," and at 24 months, about 50% of patients in both groups had at least one serious adverse event (Figure 9).

At 24 months, there was no difference between rhBMP-2 and ICBG in the likelihood of experiencing an adverse event classified by the Medtronic investigators as "device-related,", and the event rate was low (6% vs. 5%, RR 1.36, 95% CI 0.57 to 3.23).

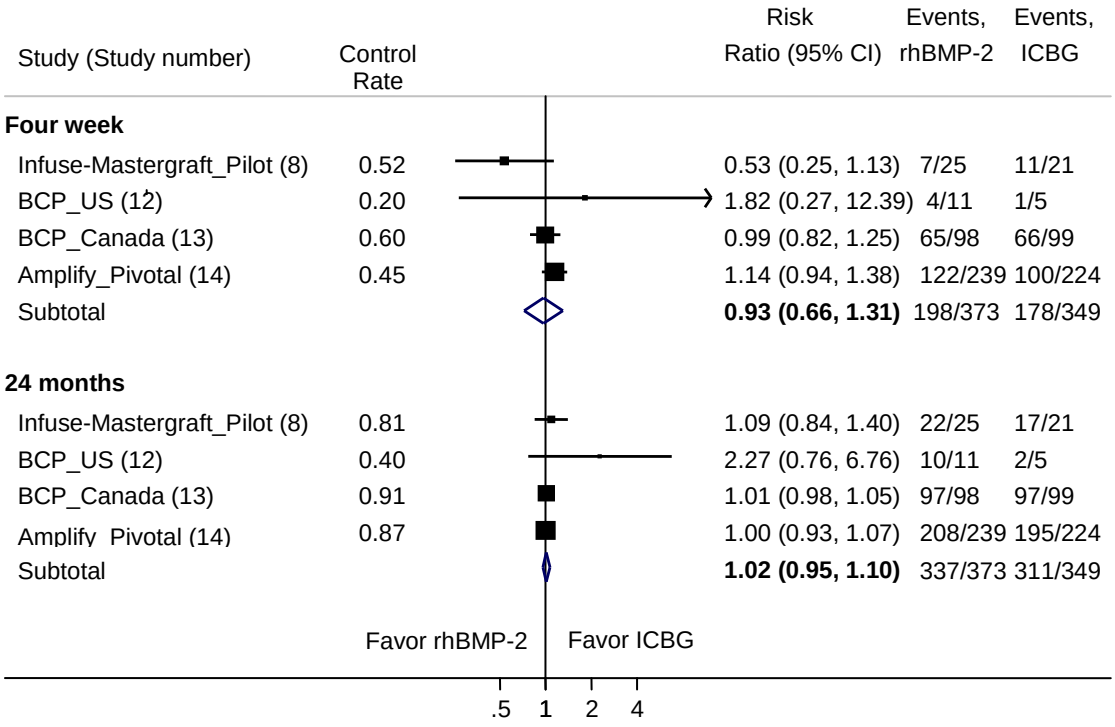
Figure 9. Cumulative proportion of patients with at least one adverse event (PLF)



AE = adverse event; ICBG = iliac crest bone graft; PLF = posterolateral lumbar fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2; SAE = serious adverse event

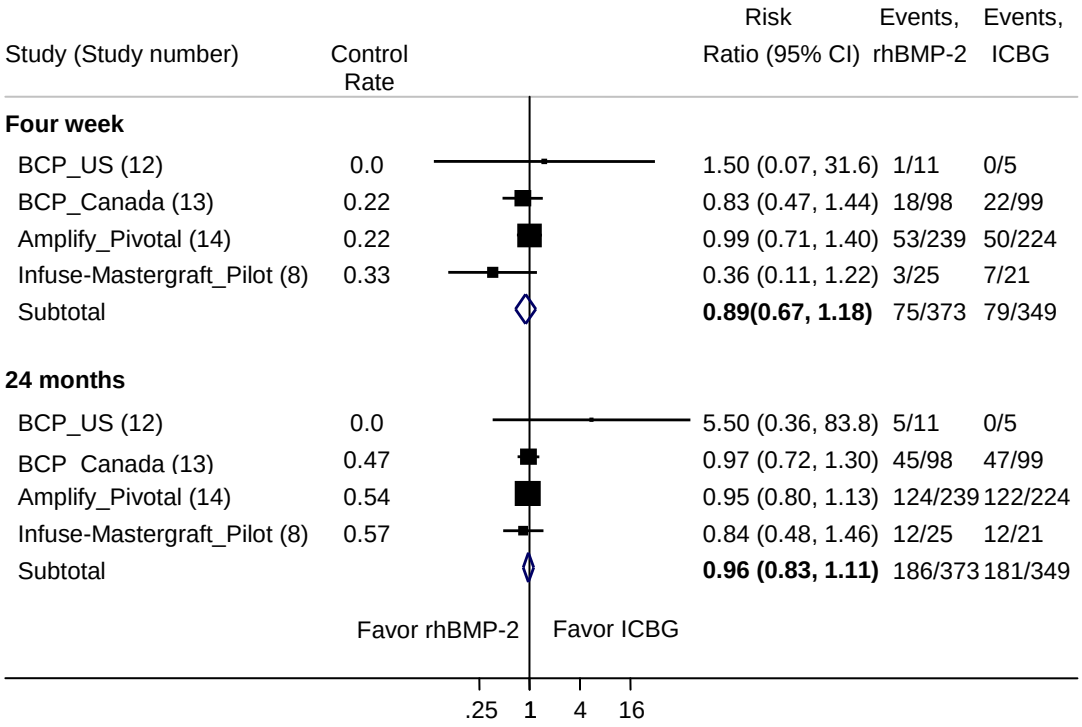
*There was no significant difference between the rhBMP-2 versus ICBG groups at any time point for either outcome and surgery approach.

Figure 10. Comparison of proportion of patients having at least one adverse event in PLF trials



PLF = posterolateral lumbar fusion; ICBG = iliac crest bone graft

Figure 11. Comparison of proportion of patients having at least one serious adverse event in PLF trials



PLF = posterolateral lumbar fusion; ICBG = iliac crest bone graft

Additional surgeries. Based on IPD analysis of four randomized trials (combined *n*=722), moderate strength evidence suggests there was no difference between rhBMP-2 and ICBG in likelihood of additional surgeries at 24 months (12% versus 14%, RR 0.72, 95% CI 0.38 to 1.34). In a small cohort study of 62 subjects with a mean follow-up of 28.4 months, additional surgery rates were also similar (8% versus 10%).[76] The rate of relevant additional surgeries from IPD analysis of one intervention series (Study 15) was 14%.

Specific adverse events. In the Medtronic trials, IPD analysis demonstrated a significant between-groups difference only for back and/or leg pain through 4 weeks, with higher rates in the rhBMP-2 groups (Table 9). However, the types of adverse events classified as back and leg pain were very heterogeneous (e.g., radiculopathy, Baker's cyst, sacroiliac joint pain, arthritic knee pain, or ankle pain) and may not be related to spine surgery. We also found no difference in the risk of possible radiculitis through 4 weeks and 24 months based on the primary definition and the three alternative definitions.

At 4 weeks and 24 months, there was also no statistically significant difference between groups in neurological events. Heterotopic bone formation was not coded as a specific adverse event in any PLF Medtronic study. Because heterotopic bone formation was not specifically coded, it was not possible to correlate excess bone formation with radicular symptoms in IPD.

Table 9. Overall and specific adverse events for PLF with rhBMP-2 vs. ICBG

Event†	≤ 4 weeks		≤ 24 months	
	Patients with rhBMP-2 vs. ICBG	**Risk Ratio (95% CI) Sample Size, *n* (Studies)**	**Patients with rhBMP-2 vs. ICBG**	**Risk Ratio (95% CI) Sample Size, I (Studies)**
Overall adverse events				
≥ 1 Adverse event, any type	48% vs. 52%	0.93 (0.66 to 1.31) 722 (4)	93% vs. 87%	1.02 (0.95 to 1.10) 722 (4)
≥ 1 Serious adverse event	20% vs. 23%	0.89 (0.67 to 1.18) 722 (4)	50% vs. 52%	0.96 (0.83 to 1.11) 722 (4)
≥ 1 device-related adverse event	---	----	6% vs. 5%	1.36 (0.57 to 3.23) 722 (4)
Specific adverse events				
Anatomical/technical difficulty	1% vs. 0%	4/337 vs. 0/323 660 (2)	Same as four weeks	
Back and/or leg pain	8% vs. 4%	**1.83 (1.15 to 2.93)** 706 (3)	49% vs. 42%	1.18 (0.91 to 1.52) 722 (4)
Cardiovascular	14% vs. 14%	0.85 (0.40 to 1.81) 706 (3)	19% vs. 21%	0.90 (0.57 to 1.40) 722 (4)
Dural injury	6% vs. 7%	0.76 (0.55 to 1.04) 722 (4)	6% vs. 8%	0.79 (0.50 to1.23) 722 (4)
Gastrointestinal	7% vs. 10%	0.71 (0.36 to 1.44) 722 (4)	16% vs. 18%	0.88 (0.64 to 1.21) 722 (4)
Implant problems	2% vs. 0.6%	2.83 (0.87 to 9.26) 706 (3)	3% vs. 2%	1.58 (0.58 to 4.29) 706 (3)
Infection (all types)	9% vs. 10%	0.99 (0.57 to 1.73) 706 (3)	18% vs. 19%	0.96 (0.71 to 1.31) 706 (3)
Neurological	5% vs. 3%	1.53 (0.88 to 2.65) 722 (4)	26% vs. 23%	0.97 (0.62 to 1.51) 722 (4)
Possible lumbar radiculitis (primary)‡	3% vs. 2%	1.30 (0.69 to 2.46) 722 (4)	24% vs. 26%	0.95 (0.73 to 1.22) 722 (4)
Possible lumbar radiculitis (definition 2)‡	3% vs. 2%	1.65 (0. 62 to 4.40) 722 (4)	14% vs. 15%	0.90 (0.54 to 1.51) 722 (4)
Possible lumbar radiculitis (definition 3)‡	3% vs. 3%	1.32 (0.73 to 2.38) 722 (4)	24% vs. 26%	0.91 (0.71 to 1.18) 722 (4)
Possible lumbar radiculitis (definition 4)‡	2% vs. 1%	1.54 (0.45 to 5.20) 455 (4)	10% vs. 11%	0.89 (0.42 to 1.87) 455 (4)
Respiratory	4% vs. 3%	1.38 (0.42 to 4.55) 706 (3)	7% vs. 5%	1.44 (0.87 to 2.39) 706 (3)
Spinal event	1% vs. 1%	1.05 (0.21 to 5.17) 676 (3)	9% vs. 10%	0.89 (0.61 to 1.29) 722 (4)
Urogenital	7% vs. 7%	1.03 (0.53 to 2.01) 722 (4)	13% vs. 12%	1.04 (0.60 to 1.82) 722 (4)
Vertebral fracture	2% vs. 0.9%	1.26 (0.23 to 6.94) 660 (2)	1% vs. 1%	0.94 (0.16 to 5.42 660 (2)
Relevant additional surgeries	---	----	12% vs. 14%	0.72 (0.38 to 1.34) 722 (4)

ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2; PLF = posterolateral lumbar fusion.
Values in bold font are significant at 0.05 level.
†Categories of adverse events are based on Medtronic datasets, except for those indicated otherwise.
‡Based on individual adverse event case histories in the proprietary reports provided by Medtronic.
§A total *n*=722 was included in the analysis, excluding 11 patients randomized to rhBMP-2 without instrumentation in study 12.

In longer follow-up beyond 24 months, there was no significant difference for any adverse events at 48 months based on IPD from two trials (Studies13 and 14), and at 60 months based on IPD from one trial (Study 14). The strength of evidence based on the trial data was insufficient for these outcomes at all time periods.

Three cohort studies,[75, 76, 78] one intervention series,[81] and one case series[84] provided limited evidence on specific adverse events. One of these, a small cohort study, reported rates of leg pain within the first 72 hours after surgery.[78] This study combined patients receiving posterolateral fusion and posterior lumbar interbody fusion and reported 25% of 64 rhBMP-2 patients experienced leg pain versus 12.5% of 40 patients in the control group. The other observational studies did not report rates of back and/or leg pain. Results from cohort studies were consistent with the randomized controlled trials in finding no differences between rhBMP-2 and control groups at 24 months in dural injury (ranges, 4 to 5% compared with 0 to 5%),[75, 76] and spinal events (transitional stenosis, 2.5% compared with 0%).[75] The intervention series reported that 7.8% of 1,037 rhBMP-2 patients experienced major surgical complications, 10.2% experienced minor complications, and 0.7% developed new or more severe postoperative radicular symptoms.[81] In the same series, three new onset radiculopathy were reported in 51 patients with dural tear and none from the 51 propensity score matched patients without dural tear.[84]

Posterior Lumbar Interbody Fusion

Summary Findings

- One small randomized trial of PLIF sponsored by Medtronic (*n*=67) generally provided insufficient evidence to make any definitive statements on benefits and harms at any time point.

Overview of Included Evidence

Evidence for the comparative effectiveness of rhBMP-2 or autogenous iliac crest bone graft in PLIF is available from the IPD analysis from one Medtronic trial (Study 6, *n*=67). Patients were randomized to interbody fusion with NOVUS^{TM} LC (Medtronic Sofamor Danek; Memphis, TN) cages containing either rhBMP-2 or ICBG and were followed to 24 months.

This trial was rated fair quality and was downgraded due to methodological limitations that included unclear blinding of outcome assessors other than radiologists and missing data. There were fewer patients enrolled in this study than originally planned after increased posterior bony overgrowth was detected in rhBMP-2 patients which led to a suspension of enrollment. Because this is a single, very small, fair quality study and outcomes are imprecise and consistency cannot be determined, the strength of the evidence is found to be insufficient for all but two outcomes highlighted below.

Comparative Effectiveness of rhBMP-2 Versus ICBG

Table 10 shows the results of the IPD analysis for clinical outcomes at 6 weeks and 3, 6, 12, and 24 months. There were no differences between the groups on overall success, fusion, neurologic success, or any measures of pain or function at any time point. Evidence for fusion is low strength, while the rest is insufficient because of a lack of precision in estimates.

Table 10. Effectiveness endpoints for PLIF with rhBMP-2 vs. ICBG

Outcome	6 weeks	3 months	6 months	12 months	24 months
			Relative risk (95% CI) Sample size		
Overall success	----	----	1.25 (0.70 to 2.23) 64	1.24 (0.68 to 2.24) 61	1.50 (0.80 to 2.81) 62
Fusion	----	----	1.01 (0.79 to 1.28) 63	0.98 (0.75 to 1.27) 60	1.15 (0.86 to 1.54) 61
Neurologic success	0.93 (0.73 to 1.18) 63	1.04 (0.79 to 1.37) 64	1.10 (0.87 to 1.39) 61	1.25 (0.97 to 1.61) 60	0.94 (0.72 to 1.23) 60
ODI success	0.94 (0.48 to 1.85) 64	1.20 (0.79 to 1.81) 65	1.13 (0.76 to 1.67) 63	1.17 (0.75 to 1.81) 60	1.03 (0.71 to 1.51) 59
Return to work*	2.78 (0.86 to 8.94) 24	1.67 (0.66 to 4.20) 24	1.24 (0.83 to 1.86) 23	1.17 (0.94 to 1.44) 23	1.23 (0.80 to 1.87) 22
			Weighted mean difference (95% CI) Sample size		
ODI (0-50)	5.80 (-2.30 to 13.9) 64	-1.22 (-9.37 to 6.93) 65	-1.80 (-10.9 to 7.31) 63	-4.64 (-13.5 to 4.26) 60	1.28 (-8.61 to 11.2) 59
Back pain (0-10)	0.05 (-1.33 to 1.42) 63	-0.33 (-1.68 to 1.02) 64	0.09 (-1.19 to 1.37) 63	-0.53 (-2.00 to 0.95) 60	-0.96 (-2.52 to 0.60) 59
Leg pain (0-10)	-0.48 (-2.14 to 1.17) 63	-0.51 (-2.07 to 1.05) 64	-0.63 (-2.24 to 0.98) 63	-1.20 (-2.90 to 0.51) 60	-0.02 (-1.78 to 1.74) 59
SF-36 PCS (0-100)	3.23 (-0.21 to 6.66) 62	2.41 (-2.24 to 7.06) 64	2.98 (-2.23 to 8.19) 61	3.92 (-2.27 to 10.1) 58	1.30 (-5.21 to 7.82) 56
SF-36 MCS (0-100)	1.84 (-3.03 to 6.71) 62	0.72 (-4.52 to 5.97) 64	0.49 (-5.77 to 6.75) 61	0.86 (-5.73 to 7.45) 58	2.1 (-4.59 to 8.77) 56

*Includes only patients who did not work before surgery
ICBG = iliac crest bone graft; PLIF = posterior lumbar interbody fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2

Comparative Harms of rhBMP-2 Versus ICBG

Overall adverse events. Based on IPD analysis, there were 43 adverse events in the 34 patients in the rhBMP-2 group and 55 in the 33 patients in the ICBG group up to 4 weeks, and the difference was not significant (rate ratio 0.76; 95% CI 0.45 to 1.28). The rates of adverse events were also similar up to 24 months, with 112 adverse events in the rhBMP-2 group and 120 adverse events in the ICBG group (rate ratio 0.91; 95% CI 0.65 to 1.26).

At 4 weeks, 65% of patients in the rhBMP-2 group and 70% of patients in ICBG group had at least one adverse event (RR 0.93; 95% CI 0.66 to 1.30). Up to 24 months, 97% of patients in the rhBMP-2 group and 100% of patients in ICBG group had at least one adverse event. No difference was found at either time point. In contrast, patients in the rhBMP-2 group were less likely to experience at least one serious adverse event compared with the ICBG group at 4 weeks

(12% vs/ 33%; RR 0.35; 95% CI 0.12 to 0.998), though not at 24 months (32% vs. 48%; RR 0.67; 95% CI 0.37 to 1.22).

Specific adverse events. Table 11 shows results of the IPD analysis of specific adverse events in patients fused with rhBMP-2 versus ICBG. There were no differences between treatment groups in the occurrence of any specific adverse by 4 weeks or 24 months. Retrograde ejaculation was not reported as a specific adverse event in Study 6.

Table 11. Specific adverse events for PLIF with rhBMP-2 vs. ICBG

	Patients experiencing adverse events rhBMP-2 (*n*=34) vs. ICBG (*n*=33) RR (95% CI)	
Adverse Event	**≤ 4 weeks**	**≤ 24 months**
Back and/or leg pain	0% vs. 6%; 0/34 vs. 2/33	35% vs. 24% 1.46 (0.68 to 3.10)
Cardiovascular	18% vs. 27% 0.65 (0.26 to 1.62)	18% vs. 30% 0.58 (0.24 to 1.42)
Dural injury	9% vs. 6% 1.46 (0.26 to 8.16)	The same as 4 weeks
Gastrointestinal	21% vs. 24% 0.85 (0.35 to 2.07)	26% vs. 33% 0.79 (0.38 to 1.66)
Infection	9% vs. 12% 0.73 (0.18 to 3.01)	21% vs. 15% 1.36 (0.48 to 3.86)
Neurological	12% vs. 9% 1.29 (0.31 to 5.35)	41% vs. 39% 1.05 (0.58 to 1.87)
Respiratory	0% vs. 6% 0/34 vs. 2/33	The same as 4 weeks
Spinal event	--	15% vs. 15% 0.97 (0.31 to 3.05)
Trauma	0% vs. 3% 0/34 vs. 1/33	21% vs. 15% 1.36 (0.48 to 3.86)
Urogenital	0% vs. 12% 0/34 vs. 4/33	3% vs. 12% 0.24 (0.30 to 2.06)

PLIF = posterior lumbar interbody fusion; ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2

Circumferential Posterior Lumbar Interbody Fusion/Transforaminal Lumbar Interbody Fusion

Summary Findings

- There were no randomized trials of circumferential PLIF/TLIF. Evidence is limited to observational studies.
  - Two small cohort studies (*n*=159) reported no difference between fusion with rhBMP-2 with or without ICBG versus ICBG alone (strength of evidence: low).
  - Evidence on surgery-related complications was insufficient strength to draw conclusions.

- Two cohort studies (n=159) demonstrated non-significantly increased incidence of radiculitis with rhBMP2, with or without local autograft, compared with local or iliac crest bone graft (strength of evidence: low).

Overview of Included Evidence

We found no randomized controlled trials of circumferential transforaminal lumbar interbody fusion. The only comparative evidence available comes from three poor-quality cohort studies (n=202).[85-87] These studies were downgraded due to methodological limitations including: unclear comparability of groups at baseline,[85, 87] unclear blinding of outcome assessors,[85-87] and failure to adjust for potential confounding variables.[85-87] Cohort studies compared rhBMP-2 with ICBG,[87] rhBMP-2 plus local autograft to local autograft plus allograft,[85] or rhBMP-2 plus ICBG or local autograft with ICBG.[86] Mean follow-up ranged from 9 months[86] to 19 months[87] or was unclear.[85]

We also identified 14 published intervention series describing outcomes in patients receiving PLIF or TLIF using rhBMP-2,[52-55, 88-97] one unpublished intervention series for which we were also provided IPD (Study 11), and 15 case reports of adverse events in patients who received circumferential transforaminal or posterior interbody lumbar fusion.[18, 98-111]

Comparative Effectiveness of rhBMP-2 Versus Autograft/allograft

Radiographic fusion. Low strength evidence based on combined data from two cohort studies found no significant difference in fusion between rhBMP-2, with or without autograft, compared with iliac crest autograft (96% in both groups; RR 1.00; 95% CI 0.93 to 1.07).[86, 87]

Compared with the fusion rates for the rhBMP-2 groups in the cohort studies, rates were similarly high for rhBMP-2 based on IPD analysis of the unpublished intervention series (Study 11) at 6 months (90%, 27/30), 12 months (100%, 28/28), and 24 months (96%; 24/25). Rates of fusion for the 13 of 14 published intervention series that reported fusion ranged from 59% [53] to 100% [55, 89, 92, 94, 97] with most in the range of 90 to 100%.

Other benefits. Cohort studies provided no additional evidence on benefits.

Comparative Harms of rhBMP-2 Versus Autograft/allograft

Overall adverse events. One cohort study (n=119) reported no difference between rhBMP-2 and ICBG in the number of patients with any complications (29.1% compared with 45.5%; RR 0.81; 95% CI, 0.60 to 1.03).[87] This evidence is insufficient strength due to poor study quality, lack of ability to assess consistency of findings, and lack of precision.

IPD analysis of one intervention series (Study 11; n=30) found the proportion of patients with any adverse event at 4 weeks was 53% and at 24 months was 97%. The proportion of patients with any serious adverse event was 13% and 37% at 4 weeks and 24 months, respectively.

Radiculitis. Low strength evidence based on combined data from two cohort studies (*n*=162) found higher incidence of radiculitis with rhBMP-2, with or without local autograft, compared with local or iliac crest bone graft (13% versus 2%; RR 3.74; 95% CI 0.74 to 18.90) but this difference was not significant.[85, 87]

Based on IPD analysis of one intervention series (Study 11; *n*=30), 13% had radicular symptoms associated with fusion with rhBMP-2. However, rates of radicular pain observed in four published intervention series studies were lower, ranging from 2%[95] to 3%.[54, 88, 93] We also identified one case report of radiculopathy beginning approximately 4 weeks postoperatively in a 27-year-old male who underwent L4-L5 TLIF.[104] Magnetic resonance imaging revealed a fluid collection compressing the right L4 nerve root requiring decompression, which resolved the radiculopathy.

Other harms. Rates of additional harms reported in one cohort study were low and did not differ significantly between rhBMP-2 and ICBG: vertebral osteolysis (5.8% versus 0), dural injury (4.7% versus 0), lumbar infection (3.5% versus 6.1%), ectopic bone formation (2.3% versus 0), and lumbar hematoma (1.2% versus 3%).[87]

Compared with the rates for rhBMP-2 in cohort studies, rates for rhBMP-2 in intervention series were similar for dural injury (3.3% in Study 11 and 1.2 to 4.7% in three other intervention series),[91, 92, 95] infection (6.7% through 4 weeks and 10% through 24 months in Study 11 and 0 to 3.5% in three other intervention series),[54, 95, 97] ectopic or heterotopic bone formation (3 to 6.3%),[93, 95] and lumbar hematoma (2.1%).[95] However, for vertebral osteolysis, rates in intervention series ranged widely, from 3 to 85%.[52, 53, 90, 93] Although back and/or leg pain were not reported in the cohort studies, we noted that back and/or leg pain was the most frequent category of adverse events reported based on IPD analysis of the Medtronic intervention series (Study 11) (23.5%).

We also identified nine cases of heterotopic ossification/ectopic bone formation,[18, 98, 100] associated with symptomatic neural compression, nine cases of symptomatic vertebral osteolysis,[99, 102, 106, 109] and one case each of pseudoarthrosis,[105] Charcot arthropathy,[101] inflammatory cyst formation,[110] and acute renal insufficiency, supraventricular tachycardia, and confusion[103] associated with rhBMP-2. There was also one case of cauda equina syndrome after the sealant used to protect against radiculitis when rhBMP-2 is used in conjunction with a TLIF expanded.[111]

Circumferential Anterior Lumbar Interbody Fusion

Summary Findings

- There were no randomized trials of circumferential ALIF. Evidence is limited to observational studies; we were not able to make any definitive statements on effectiveness and harms (strength of evidence: insufficient).

Overview of Included Evidence

Our literature search identified no randomized trials for this fusion technique. There were also no individual patient data available. Three small, poor quality cohort studies (combined *n*=190) provided the only comparative data on benefits and harms.[10, 112, 113] The first (*n*=55) compared rhBMP-2 with ICBG in patients undergoing long spinal deformity surgery;[113] the second (*n*=60) compared rhBMP-2 with ICBG and/or rib autograft (local autograft was used in three cases) in patients needing extension of previous idiopathic scoliosis fusion to the sacrum;[112]

and the third (n=75) compared rhBMP-2 plus allograft with allograft alone in 1-3 level fusion.[10] Studies were downgraded due to methodological limitations such as: surgeries not performed during same time frame,[113] baseline differences between groups or information on important characteristics missing,[10, 112] unclear blinding,[113] and failure to adjust for potential confounders.[10, 112, 113]

Three intervention series also provided information on fusion and adverse events.[114-116] In the first (n=32), patients undergoing single-level fusion received rhBMP-2 with a titanium cage and either a spinous process plate (CD HORIZON SPIRE; Medtronic Sofamor Danek, Memphis, TN) fixation in 21 cases or bilateral pedicle screw fixation in 11 cases;[116] in the second (n=130), rhBMP-2 was used in conjunction with local bone graft with or without allograft with a mean of 3.2 levels fused;[114] and the third (n=50) used rhBMP-2 combined with a fresh frozen femoral ring allograft in one- or two-level fusion.[115] Additionally, three case reports provided information on heterotopic bone formation[117, 118] or bone resorption.[119]

Strength of the evidence for all outcomes was found to be insufficient due primarily to methodological limitations, lack of precision, and for some outcomes lack of ability to determine consistency with other study findings.

Comparative Effectiveness of rhBMP-2 Versus Fusion Without rhBMP-2

Radiographic fusion. In patients undergoing spinal deformity surgery due to scoliosis, fusion was reported in 96% of 23 rhBMP-2 patients versus 72% of 32 ICBG patients at 2 years (p=0.057).[113] Although patient characteristics were similar in the two groups, there were differences in surgical approach (40% paramedian retroperitoneal in the ICBG group versus 100% in the rhBMP-2 group). Also different were the number of vertebrae fused anteriorly, with an average of 7.1 in the ICBG group versus 3.9 in the rhBMP-2 group.

In a second cohort of patients undergoing extension of previous scoliosis fusion to the sacrum, fusion was reported in 89% of 36 patients receiving rhBMP-2 versus 79% of 24 patients in the ICBG/rib group at 2 years, which was not significant (P-value not reported).[112] Differences in grading fusion existed between raters in 49% of patients. Whenever there was a difference between fused and not fused, a consensus was reached by averaging the ratings.

The third cohort reported 100% of 45 patients receiving rhBMP-2 plus allograft fused at 2 years versus 89% of 30 patients who received allograft alone, which was statistically significant (p<0.001).[10] Diagnoses included degenerative disc disease, spondylolisthesis, and degenerative scoliosis and were reported to be similar between groups but the percentage of patients within each diagnosis by group was not given.

Fusion rates in intervention series ranged from 86 to 94%, depending on the observer grading the radiographs (n=50)[115] to 100% (combined n=162).[114, 116] However, follow-up in one study was short, in some cases as short as 1 month, with a mean of 4.9 months for patients receiving rhBMP-2 in conjunction with minimal access spinal techniques and pedicle screws.[116]

Disability. Two cohort studies included ODI scores as outcomes[10, 112] and one included the Scoliosis Research Society forms SRS-22 and SRS-30.[112] One found no difference in improvement between groups on either disability measure at any time point,[112] while the other found rhBMP-2 associated with greater improvement in ODI scores at 6 months, but not at 12 or 24 months, when compared with the control group ($p<0.001$ at 6 months, p-values for 12 and 24 months were not reported).[10]

Pain. One cohort study evaluated pain using a numerical rating scale and found that rhBMP-2 was associated with improvements in pain scores at 6 months but not at 12 or 24 months ($p<0.001$ at 6 months, p-values for 12 and 24 months were not reported).[10]

Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Total adverse events. There were no significant differences in complication rates between groups reported in the three cohort studies.[10, 112, 113] One study reported 25 total adverse events, with 18 complications in 36 patients in the rhBMP-2 group and 17 complications in 24 patients in the control group ($p=0.181$).[112] The second reported two complications in 45 patients receiving rhBMP-2 versus one in 30 control patients.[10] The third reported one perioperative complication in the 23 rhBMP-2 patients and zero in the 32 ICBG patients.[113] Additionally, a single intervention series reported a 12% complication rate in 50 patients receiving rhBMP-2 in one- or two-level fusion.[115]

Urinary retention. A single instance of urinary retention was reported in one patient in an intervention series of 50 patients.[115]

Wound infection. A single deep wound infection was reported in both groups of one cohort study, representing 3% of patients in the rhBMP-2 arm versus 4% of patients in the control arm.[112]

Wound dehiscence. One cohort study reported one superficial wound dehiscence out of 30 patients in the control group (3%) versus none in 45 rhBMP-2 patients.[10]

Endplate resorption and subsidence. There was one case report of osteoclastic stimulation leading to back and buttock pain.[119]

Heterotopic bone formation. One cohort study reported no ectopic bone formation,[10] and two case reports of heterotopic bone formation within the abdomen following circumferential fusion with ALIF have been reported.[117, 118]

Reoperations. Rates of repeat surgeries for revision, supplemental fixation, hardware removal, and reoperations for other wound-related reasons were not different in two cohort studies, 6% of 36 patients in the rhBMP-2 group versus 13% of 24 patients in the autograft group[112] and 0% out of 45 in the rhBMP-2 group versus 13% out of 30 patients in the control group.[10]

Other Complications. One cohort study reported that 1 patient out of 23 in the rhBMP-2 group developed acute tubular necrosis following surgery.[113] This was attributed to the intraoperative use of Aprotinin.

Circumferential Axial Lumbar Interbody Fusion

Summary Findings

- Evidence is limited to two small observational studies and is insufficient strength for all outcomes.

Overview of Included Evidence

We identified no randomized axial lumbar interbody fusion trials, a single matched cohort study (n=99),[120] and one intervention series (n=12).[121] The cohort study matched 45 patients in one hospital who received rhBMP-2 with 54 patients in a second hospital in a different city who did not receive rhBMP-2.[120] All patients underwent L5-S1 fusion. This cohort study was rated poor quality due to methodological limitations including: failure to describe the fusion material used in the patients who did not receive rhBMP-2, failure to describe the factors on which the patients were matched, unclear blinding of outcome assessors, and missing information on prognostic characteristics such as smoking status and comorbidities. The intervention series consisted of adults with lumbar degenerative scoliosis with a mean of 3.5 (range 2 to 8) levels fused.[121]

Comparative Effectiveness of rhBMP-2 Versus Fusion Without rhBMP-2

Radiographic fusion. Based on the cohort study results, there was no significant difference in overall fusion rates between patients who did and did not receive rhBMP-2 (p=0.27).[120] The rate of fusion was 96% in the rhBMP-2 group and 93% in the group without rhBMP-2. The intervention series did not report fusion results.[121]

Pain. In the cohort study, at the 24-month postoperative follow up, there was no difference in mean visual analog scores (VAS) (7.5, 95% CI -1.8 to 7.7) between the two groups, despite a significant difference in preoperative VAS scores (-8.4, 95% CI -1.4 to -0.2).[120]

Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Adverse events. In the cohort study, one infection developed in each group.[120] Both infections were due to the supplemental instrumentation which resulted in removal of pedicle screws in seven (15.5%) patients in the rhBMP-2 group and two (3.7%) patients in the control group, due to complaints of persistent pain and tenderness at the site of the screws. Additionally, one patient in each group underwent extension of fusion from L5-S1 to L4-L5.

In the intervention series, three patients had thigh dysathesias postoperatively and one patient was noted to have transient quadriceps weakness.[121]

Mixed Lumbar Spine Fusion

Summary Findings

- Compared with fusion without rhBMP-2, fusion with rhBMP-2 was associated with a lower risk of repeat fusion (strength of evidence: moderate).
- There was low strength evidence for no difference in total complications or wound complications between fusion with rhBMP-2 or without rhBMP-2.

Overview of Included Evidence

Four cohort studies, three fair quality[11,122,123] and one poor quality,[124] provided evidence on the harms of rhBMP-2 when used in various lumbar fusion types. One study used a health insurance claims database,[122] a second used data from the Nationwide Inpatient Sample,[11] a third used Veterans Affairs clinic records,[124] and the fourth used data from a tertiary referral spine trauma center.[123] These studies included various surgical approaches (e.g., use of an interbody device, circumferential fusion, posterior approach, transforaminal approach) in a combined analysis. Although two of these cohort studies did not specify the BMP used (rhBMP-2 or rhBMP-7), due to the restrictions imposed on the use of rhBMP-7 by the Humanitarian Use Device of not more than 4,000 cases per year, most of the surgeries reported would have used rhBMP-2.[11, 122] However, since the outcomes of rhBMP-2 may differ based on surgical approach, the applicability of the results from these studies to any particular surgical approach is unclear. Studies were downgraded due to methodological limitations such as baseline differences between groups,[123, 124] unclear blinding of outcome assessors,[11, 122-124] and failure to adjust for potential confounding variables.[124]

Comparative Effectiveness and Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Repeat fusion. Two cohort studies (N=6,142) provided moderate strength evidence for repeat fusion surgery.[122, 123] Use of rhBMP-2 was associated with a significantly lower risk of repeat fusion surgery at 1 year (2.3% compared with 3.4%; adjusted odds ratio, 0.66; 95% CI 0.47 to 0.94).[122] Compared with rhBMP-2 use in circumferential fusion, risk of repeat fusion was higher with rhBMP-2 use in posterolateral fusion (adjusted odds ratio, 2.12; 95% CI 1.29 to 3.47), but similar with interbody fusion (adjusted odds ratio, 1.50; 95% CI 0.97 to 2.32).[122] A second cohort study also found a lower risk of repeat fusion with rhBMP-2 (41/947, 4.3%) compared to demineralized bone matrix (40-306, 13.1%, p<0.001) and autograft (22/145, 15.2%, p<0.001).[123]

Renal insufficiency. Based on a poor quality retrospective review of New York Harbor Health Care System Manhattan Veterans Affairs computerized clinic records, 12.5% of patients developed transient renal insufficiency after fusion with rhBMP-2 (3/24) compared with no cases in 125 patients who did not receive rhBMP-2 (P = 0.006).[124] Interbody cage placement was used in 70% in the rhBMP-2 group and 30% in the non-rhBMP-2 group (P = 0.001). This evidence is insufficient strength due to the methodological limitations of the study, the lack of ability to determine consistency with other studies, the indirectness of the outcome measure, and low precision of the estimate.

Other complications. Based on low strength evidence from data from the Nationwide Inpatient Sample database (n=36,807), there was no significant difference between fusion surgery with or without rhBMP-2 in total complications (adjusted odds ratio, 1.03; 95% CI 0.95 to 1.12), wound complications (adjusted odds ratio, 0.93; 95% CI 0.80 to 1.08), or other complications (adjusted odds ratio, 1.05; 95% CI 0.95 to 1.15).[11]

Other studies. One case series reported 17 children successfully fused using rhBMP-2 at various fusion levels ranging from the occiput to L4 with both posterior or anterior and posterior approaches.[125] Other studies of rhBMP-2 did not analyze data in a usable manner.[126, 127]

Effectiveness and Harms for Cervical Spine

Anterior Cervical Spine Fusion

Summary Findings

- No differences in effectiveness outcomes were found.
- Based on IPD analysis of one small randomized trial (n=33) and three small cohort studies (n=135), there were no differences between rhBMP-2 and ICBG or autograft/allograft in likelihood of fusion, improvements in disability, arm pain, or neck pain (strength of evidence: low).
- Adverse events rates were greater with rhBMP-2 than with the control. One large cohort study (n=27,067) and four smaller cohort studies (n=1113) reported increased dysphagia/dysphonia (strength of evidence: moderate) and the large cohort study reported increased wound-related complications with rhBMP-2 (strength of evidence: low).

Overview of Included Evidence

One Medtronic sponsored randomized trial with IPD (Study 7), six cohort studies,[11, 15-17, 61, 128] and seven intervention series[17, 50, 129-134] provided evidence for effectiveness and harms.

The randomized trial was small (*n*=33) and rated fair quality. The intervention group (*n*=18) for the pilot RCT received an ACDF using rhBMP-2 with a CORNERSTONE-SR™ (Medtronic; Memphis, TN) Allograft Ring and an ATLANTIS™ Anterior Cervical Plate (Medtronic; Memphis, TN). The control group (*n*=15) received the same surgery except that iliac crest autograph bone was used in lieu of rhBMP-2. Ten intervention patients and eight control patients had surgery to fuse one level, whereas the remaining patients had two-level arthrodesis. The patients were followed for 24 months. This RCT was downgraded due to methodological limitations including: missing data, and uncertain blinding of outcome assessors other than radiologists.

Three cohort studies were rated fair quality[11,15,128] and three poor quality.[16,17,61] Studies were downgraded due to methodological limitations including: lack of information on prognostic baseline characteristics such as comorbidities and smoking status,[15-17, 61, 128] lack of blinding information on outcome assessors,[11, 15-17, 61, 128] and failure to control for potential confounding variables.[16, 17, 61] One cohort study compared rhBMP-2 plus allograft with ICBG (*n*=66);[16] a second compared rhBMP-2 plus allograft with allograft plus demineralized bone matrix (*n*=23);[61] a third compared rhBMP-2 plus PEEK cages with allograft plus demineralized bone matrix (*n*=46).[17] Additionally, seven intervention series reported fusion and/or adverse events.[17, 50, 129-134]

Comparative Effectiveness of rhBMP-2 Versus Fusion with Autograft/Allograft

Radiographic fusion. Low strength evidence, based on one small trial and three small cohort studies, does not indicate important differences in fusion rates between rhBMP-2 and controls using various forms of autograft or allograft. Based on IPD analysis of one randomized trial (Study 7), patients in the rhBMP-2 group experienced a similar likelihood of fusion versus ICBG at 3, 6, 12, and 24 months with fusion rates in the rhBMP-2 group between 81 and 94% and between 73 and 100% in the ICBG group (Table 12). Three small cohort studies (combined *n*=135)[16,17,61] reported fusion outcomes. One cohort study (*n*=23) reported 100% fusion with rhBMP-2 plus allograft versus 92% with allograft plus demineralized bone matrix,[61] a second (*n*=46) reported 100% with rhBMP-2 plus PEEK cages versus 96% with allograft plus demineralized bone matrix,[17] and a third (*n*=66) reported 94% fused with rhBMP-2 plus allograft versus 97% with ICBG.[16] Overall, there was no difference in fusion between the rhBMP-2 and no rhBMP-2 groups based on the three cohort studies (RR 1.04, 0.96 to 1.12). Fusion rates were also reported in six intervention series ranging from 89 to 100%, comparable to the one RCT and cohort studies.[50, 129-131, 133, 134]

Table 12. Effectiveness endpoints for anterior cervical spine fusion with rhBMP-2 vs. ICBG

Percent of Events (n/N): rhBMP-2 vs. ICBG					
Outcome (scale)	**6 weeks**	**3 months**	**6 months**	**12 months**	**24 months**
Overall success	----	---	67% (12/18) vs.. 85% (11/13)	80% (12/15) vs. 64% (9/14)	71% (10/14) vs. 77% (10/13)
Fusion	----	---	94% (15/16) vs. 92% (12/13)	93% (14/15) vs. 86% (12/14)	92% (11/12) vs. 100% (12/12)
Neurologic success	78% (14/18) vs. 93% (14/15)	94% (17/18) vs. 93% (14/15)	89% (16/18) vs. 100% (13/13)	93% (14/15) vs. 86% (12/14)	100% (14/14) vs. 92% (12/13)
NDI success	89% (16/18) vs. 8%7 (13/15)	88% (15/17) vs. 93% (14/15)	89% (16/18) vs. 92% (12/13)	93% (14/15) vs. 93% (13/14)	93% (13/14) vs. 92% (12/13)
Return to work	58% (7/12) vs. 67% (6/9)	83% (10/12) vs. 100% (9/9)	92% (11/12) vs. 100% (8/8)	100% (10/10) vs. 100% (9/9)	100% (8/8) vs. 100% (8/8)
	Weighted mean difference (95% CI) sample size				
NDI (0-50)	-0.21 (-11.47 to 11.06) 33	-3.44 (-16.19 to 9.30) 32	-1.64 (-11.72 to 8.45) 30	3.22 (-9.73 to 16.16) 29	-4.66 (-16.94 to 7.62) 27
Neck pain (0-10)	-2.04 (-5.56 to 1.47) 33	-1.03 (-4.90 to 2.83) 32	0.15 (-3.30 to 3.59) 30	-2.55 (-6.43 to 1.33) 29	-2.92 (-6.26 to 0.41) 27
Arm pain (0-10)	0.14 (-4.23 to 4.52) 33	-0.28 (-5.32 to 4.77) 32	1.67 (-1.56 to 4.89) 30	2.21 (-2.08 to 6.50) 29	0.82 (-3.46 to 5.09) 27
SF-36 PCS (0-100)	0.89 (-6.23 to 8.00) 32	1.01 (-6.23 to 8.24) 30	1.45 (-7.49 to 10.40) 26	-1.84 (-9.55 to 5.85) 28	2.48 (-6.64 to 11.61) 26
SF-36 MCS (0-100)	1.71 (-6.16 to 9.57) 32	7.75 (-1.42 to 16.93) 30	3.93 (-3.62 to 11.48) 26	6.20 (-1.22 to 13.62) 28	5.13 (-4.13 to 14.39) 26

NDI = Neck Disability Index; MCS = Mental Component Summary; PCS = Physical Component Summary

Overall success, neurological success and NDI success. Evidence was insufficient to draw conclusions concerning rhBMP-2's effect on overall success, neurological success, Neck Disability Index (NDI) success, SF-36 physical and mental component summary scores, and return to work (Table 12).

Disability, neck and arm pain, return to work, physical and mental health. Based on IPD analysis of a single randomized trial (Study 7), there were no differences between rhBMP-2 versus ICBG in disability, neck pain, or arm pain Table 12). Two cohort studies (combined *n*=112) also found no differences between rhBMP-2 plus PEEK cages or allograft versus ICBG or allograft plus DBM and on neck disability, neck pain, and arm pain scores, but did not report quality-of-life or return-to-work outcomes.[16, 17] The strength of this evidence is low, with low precision and moderate risk of bias.

Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Overall adverse events. In a large cohort study (*n*=27,067), the use of rhBMP-2 was associated with an increased risk of any complication immediate postoperative (OR 1.43, 95% CI 1.12 to 1.70) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, medical comorbidities, levels fused, primary payer, and geographic location of hospital.[11] This increase was primarily due to increased dysphagia/dysphonia and wound-related complications.

Based on IPD analysis of one randomized trial (Study 7), more adverse events were reported in the rhBMP-2 group (45 in 18 patients) versus the ICBG group (13 in 15 patients) over the 24 months of followup (Rate Ratio 2.88, 95% CI 1.30 to 6.41), although there was no difference between groups in the first 4 weeks after surgery (Rate Ratio 1.83, 95% CI 0.58 to 5.79).[9] The strength of this evidence is low, based primarily on the large cohort study.

Dysphagia. Moderately strong evidence indicates a higher rate of dysphagia and related outcomes with rhBMP-2 compared with controls. While the small trial (Study 7) found no statistically significant difference in rates of dysphagia between groups (one patient in the rhBMP-2 group [6%] and two patients in the ICBG group [13%] experienced dysphagia [difficulty swallowing] and/or dysphonia [hoarseness]) up to four weeks since surgery, five cohort studies found significantly increased risk with rhBMP-2. A large cohort study found the use of rhBMP-2 was associated with an increase in dysphagia and/or dysphonia, (OR 1.63; 95% CI 1.30 to 2.05) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, medical comorbidities, levels fused, primary payer, and geographic location of hospital.[11]

A second cohort study (*n*=234) reported 28% of patients in the rhBMP-2 group experienced clinically significant neck swelling versus 4% in the control group (p<0.0001).[15] In this study, there was a significant increase in complications due to prevertebral swelling associated with rhBMP-2 use compared to no rhBMP-2 use (OR 10.1; 95% CI 3.8 to 26.6) after adjustment for age, combined anterior/posterior surgery, surgery level, plating, myelopathy, number of levels fused, smoking status, prior anterior surgery, and gender, although this study was not able to control for dose of rhBMP-2 used. Another cohort (*n*=775) reported a significant increase in dysphagia (*P*=0.001) and in respiratory failure (*P* =0.001) related to the use of rhBMP-2 after adjustment for covariates.[128] Two other cohort studies also found increased neck swelling

complications associated with rhBMP-2 use, but these studies did not control for potential confounding variables.[16, 17] Five intervention series reported 5% to 60% of patients with dysphagia depending on how dysphagia was defined.[130-134]

Wound complications. Low strength evidence suggests there is a significantly increased risk of wound complications associated with rhBMP-2. In a large cohort study, use of rhBMP-2 was associated with increased wound complications (OR 1.67, 95% CI 1.10 to 2.53) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, medical comorbidities, levels fused, primary payer, and geographic location of hospital.[11] Wound complications included infection, dehiscence, seroma, and hematoma.

In the randomized trial (Study 7), two patients in the rhBMP-2 group experienced wound complications (one patient experienced self-limiting wound drainage and one experienced wound swelling that necessitated a return to the operating room for incision and drainage of the wound) versus none in the ICBG group.

Heterotopic bone formation. The randomized trial (Study 7) reported two patients in the rhBMP-2 group (11%) and one patient in the control group (7%) demonstrated bone formation immediately anterior to segments adjacent to the treated level, which was visible on the 12-month postoperative radiographs.

Two intervention series also reported excess interbody bone formation in 13% of 24 patients,[135] and excessive bone growth into the foramina or spinal canal in 68% of 22 patients.[129] However, heterotopic bone formation was not associated with neurological sequelae in either of these studies.

This evidence was found to be insufficient strength due to imprecision and lack of ability to assess consistency of findings, given evidence is limited to a very small trial.

Endplate resorption and subsidence. One cohort study found early lucencies and subsidence at 12 months postoperatively in 33% of 18 levels fused with rhBMP-2 plus allograft compared with no instances of lucencies and subsidence in 0 of 22 levels fused with allograft and DBM.[61] The incidence of endplate resorption was 100% of 34 patients in one intervention series,[50] while another reported moderate or severe endplate resorption in 57% of 38 levels fused, with 39% having lucencies in the PEEK grafts larger than 3mm at 15 months postoperatively.[129] There was no mention of association between endplate resorption, subsidence, lucencies, and increased neurological symptoms in any of these studies. This evidence is considered insufficient strength due to methodological limitations of this study to assess the outcomes, lack of ability to assess consistency with other studies, and low precision.

Additional surgeries. A pooled estimate of four cohort studies (n=369) indicates low strength of evidence that there is no significantly increased risk of additional surgeries associated with rhBMP-2 (RR 3.84, 95% CI 0.56 to 26.5).[15-17, 61] The randomized trial reported one patient in the rhBMP-2 group required surgical intervention at an adjacent level, unrelated to the first surgery, necessitating the removal of the anterior plate.[9] One additional surgery, due to swelling, was necessary in the rhBMP-2 group based on IPD analysis. However, this patient did not require surgical revision, hardware removal, or supplemental fixation. No additional surgeries were reported with ICBG.

Other complications. Based on MedWatch data provided by the manufacturer, six deaths were reported in the immediate postoperative period in patients who had cervical fusion, no cases of cancer, and eight required tracheotomy (four who had anterior cervical fusion and four with less specific cervical fusion). One cohort study reported increased 90-day mortality associated with cervical spine fusion with rhBMP-2 (p=0.047).[128]

Posterior Cervical Spine Fusion

Summary Findings

- We found insufficient evidence to evaluate effectiveness of rhBMP-2 in posterior cervical spine fusion.
- Based on four cohort studies (*n*=3,233) there was no difference in adverse events between fusion with rhBMP-2 and fusion without rhBMP-2 immediately postoperative and at later time points (strength of evidence: low).
- Based on one cohort study (*n*=2,869) there was no difference in wound complications when using rhBMP in posterior spinal fusion (strength of evidence: low).
- Two cohort studies provided low strength evidence of no increase in dysphagia or dysphonia associated with rhBMP or rhBMP-2.

Overview of Included Evidence

There were no published RCTs and no individual patient data (IPD) involving rhBMP-2 in posterior cervical fusion identified in this review. Four retrospective cohort studies (*n*=3,233), one fair quality[11] and three poor quality;[136-138] two intervention series (*n*=53);[139, 140] and (*n*=29) three case reports[141-143] provided data on benefits and harms. Studies were downgraded due to methodological limitations such as baseline differences between groups,[136, 138] unclear blinding of outcome assessors,[11, 137] differential loss to followup,[138] and failure to adjust for potential confounding variables.[136-138]

Additionally, several case reports/case series[56-60] reported fusion and/or adverse events associated with use of rhBMP-2 in the pediatric population.

Comparative Effectiveness of rhBMP-2 Versus Fusion Without rhBMP-2

Evidence on effectiveness outcomes was insufficient, with only one small poor quality cohort study with low to moderate precision, depending on specific outcome. A small retrospective cohort study of 204 patients with degenerative cervical spinal conditions found that patients receiving rhBMP-2 were more likely to have a successful fusion than those who did not (100% versus 88%, respectively, p=0.01) but also more likely to experience recurrent neck pain (48% versus 29%, p=0.003) during the 24-month follow-up period.[138] There were no differences between groups on improvement in Nurick myelopathy and American Spinal Injury Association (ASIA) scores. There was no adjustment for potentially confounding variables. In a small intervention series, 100% of 53 patients achieved fusion by 24 months postoperatively.[139] A second intervention series reported 26 of 29 patients experienced successful fusion with rhBMP-2.[140]

Effectiveness of rhBMP-2 in Posterior Cervical Spine Fusion in Children

Evidence in children was insufficient, with only five case reports/case series reporting the use of rhBMP-2 in posterior cervical spine fusion in children.[56-60] One case series involved 48 children, average age 11 (range 3-18), who received rhBMP-2 to facilitate occipitocervical

decompression and fusion to treat congenital and acquired defects such as Chiari malformation, Klippel-Feil syndrome, odontoideum, Down syndrome, and basilar invagination.[58] All patients achieved successful fusion in an average of 6.7 months (range 4-14 months).

Cases of 14 children ranging from 19 months-14 years of age with craniosynostosis, Down syndrome with craniovertebral instability, and trauma-induced cervical spinal instability were reported to have successful fusions using rhBMP-2.[56, 57, 59, 60]

Comparative Harms of Fusion With rhBMP-2 and Fusion Without rhBMP-2

Total adverse events. Low strength evidence indicates no increased risk of overall adverse events with rhBMP-2. A cohort study of 2,869 patients reported no increased risk of complications associated with the use of rhBMP-2 in posterior cervical spine fusion in the immediate postoperative period (OR1.03, 95% CI 0.73 to 1.44) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, comorbidities, levels fused, primary payer, and geographic location of hospital.[11] The remaining three cohort studies also reported no differences in frequency of adverse events associated with the use of rhBMP-2 compared with no rhBMP-2 use, but did not control for confounding factors (RR 0.80, 0.43 to 1.49).[136-138]

Dysphagia. Low strength evidence from two cohort studies found no increased risk of dysphagia associated with the use of rhBMP or rhBMP-2 in posterior cervical fusion.[11, 138]

Neck swelling. There are four cases of substantial posterior cervical swelling after fusion with rhBMP-2 reported in the published literature.[141-143] Symptoms typically began several days postoperatively (range 3 days to 2 weeks) and involved compression of the spinal cord, neurological decline, and need for urgent surgical intervention. All four patients survived.

Wound complications. Low strength evidence, based on three cohort studies, indicated no increased risk of wound complications associated with rhBMP-2 use. Three cohort studies (n=2,869, 204, and 77) found no increased risk of wound complications.[11, 136, 138] The largest study reported on wound complications, including infection, dehiscence, seroma, and hematoma (OR 1.11, 95% CI 0.60 to 2.05) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, comorbidities, levels fused, primary payer, and geographic location of hospital.[11] The smaller study reported only wound dehiscence (p=0.37) and hematoma rates (p=0.94).[138] A very small cohort study (n=77) reported more wound complications requiring treatment in the rhBMP-2 group (15% vs. 3%), but given the small sample size, this difference was not significant (P=0.11).[136] One superficial wound infection was reported out of 53 patients receiving rhBMP-2 in an intervention series.[139]

Reoperations. No difference in reoperation rates was found between rhBMP-2 use and non-use (P =0.36) in a small cohort study (n=204).[138] Because this is based on a single, small, poor quality observational study this evidence is considered insufficient strength.

Harms of rhBMP-2 in Posterior Cervical Spine Fusion in Children

A case series involving 48 children, average age 11 (range 3-18 years), who received rhBMP-2 to facilitate occipitocervical decompression and fusion to treat congenital and acquired defects such as Chiari malformation, Klippel-Feil syndrome, odontoideum, Down syndrome, and

basilar invagination, reported six complications felt to be a result of rhBMP-2 and which had never been experienced by the study's senior author prior to introduction of rhBMP-2 into the practice. [58] There were five instances of postoperative seroma formation and one of excessive ectopic bone formation. Two of the seroma patients developed symptoms due to compression of the brainstem requiring emergency reoperation. Both survived. This evidence is insufficient strength due to methodological concerns.

Benefits and Harms for Thoracic Spine

Summary Findings

- Evidence is unavailable for the benefits of rhBMP-2 in thoracic fusion (strength of evidence: insufficient).
- Based on one cohort study (*n*=3,257) fusion with or without rhBMP-2 is associated with similar rates of complications (strength of evidence: low).

Overview of Included Evidence

We found no eligible studies with evidence on the potential benefits of rhBMP-2 in thoracic fusion. Limited evidence on harms came from a subgroup of 3,257 thoracic patients from the fair-quality Nationwide Inpatient Sample database cohort study,[11] a case series of 10 patients,[144] and two case reports.[145] The cohort study was downgraded due to unclear blinding of outcome assessors.[11] Although one cohort study did not specify whether rhBMP-2 or rhBMP-7 was used, based on the restriction imposed on the use of rhBMP-7 by the Humanitarian Use Device to 4,000 uses per year, most of the fusion surgeries would have used rhBMP-2.

Comparative Harms of rhBMP-2 Versus Fusion Without rhBMP-2

Low strength evidence suggests that there is no significant difference between fusion surgery with or without rhBMP-2 in any complications (adjusted odds ratio, 1.05; 95% CI 0.83 to 1.32), wound complications (adjusted odds ratio, 0.78; 95% CI 0.53 to 1.17), or other complications (adjusted odds ratio, 1.27; 95% CI 0.98 to 1.66) after adjustment for age, race, sex, income, elective admission, teaching hospital, revision surgery, diagnosis, comorbidities, levels fused, primary payer, and geographic location of hospital.[11]

A case series of 10 patients[144] and a report of two cases[145] provided additional non-comparative evidence on harms. Clinically significant pleural effusion occurred in four of 10 patients following thoracic spinal fusion using rhBMP-2.[144] No adverse events were reported following use of rhBMP-2 in posterior-only pedicle screw-based instrumented spinal fusion involving the thoracic spine in a 17-year-old boy and a 30-year-old male, both with type-1 neurofibromatosis.[146]

Overall Cancer and Death

Summary Findings

- Based on meta-analysis of five trials (*n*=1450), risk of cancer was significantly higher at 24 months in the rhBMP-2 group versus the control group (RR 3.45; 95% CI 1.98to 6.00) with a 1.9% absolute risk increase (95% CI 0.5 to 3.2%; number needed to harm [NNH] = 53). The difference was not statistically significant at 48 months (RR 1.82; 95% CI 0.84 to 3.95) (strength of evidence: low).

- There was no significant difference in death rate between the rhBMP-2 and the control groups at 24 and 48 months (strength of evidence: low).

Cancer

Five Medtronic-sponsored trials with IPD (Studies 2, 4, 5, 10, 14; *n*=1450) reported at least one cancer through 24 months and were included in our meta-analysis (see Table 13 for detailed information about cancer events—the included cancer types were very heterogeneous). One pre-existing cancer (renal cancer) in the rhBMP-2 group in Study 8 and another pre-existing cancer (pancreatic cancer) in the rhBMP-2 group in Study 13 were excluded from the analysis. Compared with the control group, there was low strength evidence that rhBMP-2 was associated with a 1.9% increase in the absolute risk of cancer (95% CI 0.5 to 3.2; NNH=53, 95% CI 31 to 200) with an RR of 3.45 (95% 1.98 to 6.00) (Figure 12). The effect of dosage was unclear: 10 of 17 cancers in the rhBMP-2 group occurred in the AMPLIFY trial (Study 14), but another high-dose study (Study 13) had no cancers in the rhBMP-2 group (*n*=98). It was also unclear whether under-reporting played a role.

To assess the potential impact of the seven Medtronic trials with zero cancers in both treatment groups (sample sizes 14 to 197), we performed a sensitivity analysis by considering these trials as a combined "pseudo-trial" (*n*=429) and included it in the meta-analysis by conservatively assuming that no cancer occurred in the rhBMP-2 group and one cancer occurred in the control group. The sensitivity analysis showed a 1.3% (95% CI 0.2 to 2.4; NNH=77, 95% CI 42 to 500) absolute increase in cancer risk associated with rhBMP-2 (RR 2.90; 95% CI 1.19 to 7.08). Three non-SEER cancers (one basal cell carcinoma and two squamous cell carcinomas) occurred in the rhBMP-2 group and zero occurred in ICBG group during the 24-month period. When these three cases were excluded, the association between rhBMP-2 and increased cancer risk remained significant (RR 2.92; 95% CI 1.75 to 4.87).

At 48 months, four trials (Studies 4, 10, 13, 14; *n*=1183) provided IPD data on cancer risk for the meta-analysis. The rhBMP-2 arm of the INFUSE-LT-Cage Pivotal trial (Study 2) had three additional cancers at 48 months, but was not included in the analysis since there were no follow-up data for the ICBG group. Based on the four trials with follow-up data in both groups, there was no statistically significant difference in cancer risk between rhBMP-2 and the control groups (RR 1.82; 95% CI 0.84 to 3.95). One non-SEER cancer (one squamous cell carcinoma) occurred in the ICBG group and no non-SEER cancers occurred in the rhBMP-2 group between 24 months and 48 months. Results were similar when the four non-SEER cancers (three from the rhBMP-2 group up to 24 months and one from ICBG group between 24 and 48 months) were excluded from the 48-month analysis (RR 1.92; 95% CI 0.86 to 4.32).

After 48 months, one additional patient developed cancer in the rhBMP-2 group in one trial (Study 13) at 72 months and two additional patients developed cancers in the control group (artificial disc) in one trial (Study 10) at 60 months. The sensitivity analysis including cancers through 48 months and these three additional cancer patients after 48 months showed no difference in cancer risk between rhBMP-2 and control groups (RR 1.69; 95% CI 0.94 to 3.03).

Additionally, two cohort studies[124, 147] provided evidence of cancer. One of them included 125 patients (24 rhBMP-2, 101 ICBG) undergoing lumbar and lumbosacral fusion. Four cancers occurred in the rhBMP-2 group within 24 months after surgery, and eight cancers occurred in the rhBMP-2 group between 3 to 63 months after the surgery. The results (RR 2.10; 95% CI 0.69 – 6.41) were consistent with those from the Medtronic RCTs, but the difference was not significant.

A retrospective cohort study using U.S. Medicare claims data assessed the association between the use of BMP during lumbar spinal fusion surgery with subsequent risk of pancreatic cancer specifically.[147] The results were not reported separately by rhBMP-2 and rhBMP-7; however, due to the restrictions imposed on the use of rhBMP-7 by the Humanitarian Use Device of not more than 4,000 cases per year, most of the surgeries reported would have used rhBMP-2. The study did not find an increased risk (adjusted HR=0.70, 95% CI 0.34-1.45) for pancreatic cancer. The study was sponsored by Wyeth, the manufacturer of rhBMP-2, and the mean follow-up of the BMP group (1.04±0.73 years) was shorter than the non-BMP group (1.46±0.86 years). The study population was older than the patients included in the RCTs, with a mean age of 75 years old.

Among the four Medtronic intervention series, only Study 3 reported a single case of breast cancer at 36 months and a single non-SEER cancer (squamous cell carcinoma) at 72 months.

The strength of this evidence is considered low due to moderate risk of bias and low precision. Additionally, the cancers identified were very heterogeneous.

Table 13. Cancer occurrence at 24 and 48 months in randomized trials*

	Patients Receiving rhBMP-2				Patients Receiving ICBG or Artificial Disc		
	Number of Cancers	**Time Period from Surgery, months**	**Type of Surgery**	**rhBMP-2 Dose, mg**	**Number of Cancers**	**Time Period from Surgery, months**	**Type of Surgery**
Cancers up to 24-month followup							
Basal cell carcinoma†	2	1.5, 3	PLF	40	0	---	---
Breast	2	24	ALIF	4.2-8.4;8.1-11.7	1	3	ALIF
Carcinoid	1	24	ALIF	4.2-12	0	---	
Colon	0	---	---	---	1	6	PLF
Larynx	1	6	PLF	40	0	---	---
Liver	1	6	ALIF	4.2-12	0	---	---
Lung	1	6	PLF	40	0	---	---
Melanoma	1	24	ALIF	4.2-12	0	---	---
Lymphoma	1	24	PLF	40	2	12, 24	PLF, AD
Ovarian	1	12	PLF	40	0	---	---
Pancreatic	2	12	ALIF, PLF	4.2-8.4;40	0	---	
Prostate	1	12	PLF	40	1	3	AD
Squamous cell carcinoma†	2	12, 24	PLF	40	0	---	---
Stomach	1	24	PLF	40	0	---	---
Thyroid	1	12	ALIF	8.1-11.7	1	24	AD
Total cancers up to 24 months	18 (in 17 patients; total *n*=633 patients)				6 (in 6 patients; total *n*=817 patients)		

	Patients Receiving rhBMP-2				Patients Receiving ICBG or Artificial Disc		
	Number of Cancers	**Time Period from Surgery, months**	**Type of Surgery**	**rhBMP-2 Dose, mg**	**Number of Cancers**	**Time Period from Surgery, months**	**Type of Surgery**
Cancers occurring between 24- and 48-month follow-ups‡							
Breast	0	---	---	---	1	36	PLF
Leukemia	1	36	PLF	40	0	---	---
Melanoma	2	36, 48	PLF, ALIF	40, 4.2-8.4	0	---	---
Merkle cell carcinoma	0	---	---	---	1	36	AD
Prostate	1	36	PLF	40	1	48	PLF
Squamous cell† carcinoma	0	---	---	---	1	48	PLF
Thyroid	1	36	PLF	40	1	48	PLF
Uterine	0	---	---	---	1	36	AD
Total cancers up to 48 months§	20 (in 16 patients; total *n*=483 patients)				11 (in 11 patients; *n*=700 patients)		

ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2; PLF = posterolateral lumbar fusion; AD = artificial disc.

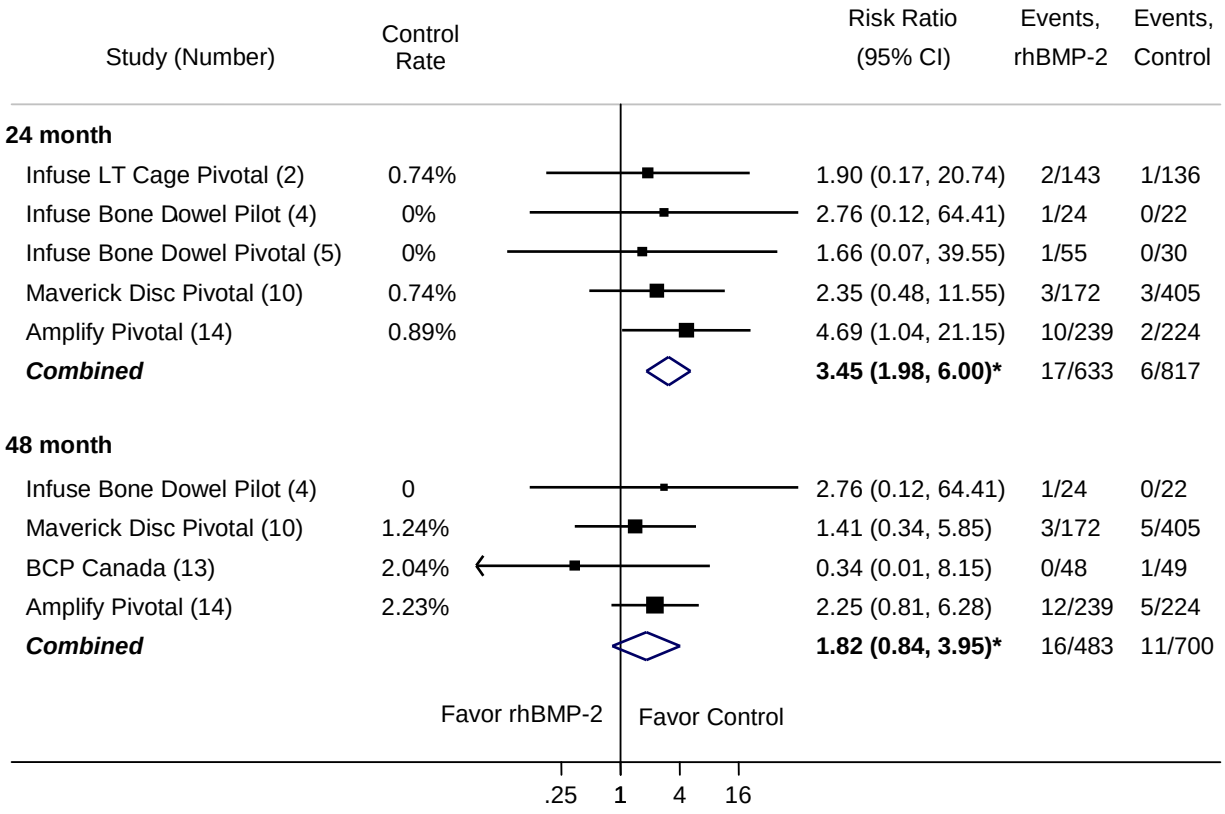
* Does not include 1 pancreatic cancer and 1 renal cancer that were discovered during the study but determined to exist prior to the study.

† Non-SEER cancers (for which data is not reportable by the Surveillance, Epidemiology and End Results [SEER] Program, National Cancer Institute)

‡ Does not include cancers occurring after 48 months of followup or cancers occurring in rhBMP-2 arms of studies without a control arm (intervention series or when only the rhBMP-2 arm experienced continued followup); additional cancers reported in these rhBMP-2 patients were 1 each—colon cancer, breast cancer, squamous cell carcinoma, thyroid cancer, testicular cancer—and 2 basal cell carcinomas. Does not include 1 thyroid cancer and 1 leukemia in the control arms of studies after 48 months.

§ Total from studies following patients up to 48 months, excluding patients for whom only 24-month data were available.

Figure 12. Comparison of cancer risk between the rhBMP-2 and ICBG groups



*The combined risk ratio (RR) was obtained using a generalized linear fixed effects model with binomial distribution and log link without correction for zero events. The RR from each study was estimated, when there is zero event, by adding a continuity correction of 0.5, for illustrative purposes.
ICBG = iliac crest bone graft; rhBMP-2 = recombinant human bone morphogenetic protein-2

Death

Nine Medtronic RCTs provided adequate data to be included in a meta-analysis of death at 24 months (Studies 2, 4, 6-10, 13-14). There was low strength of evidence of no significant difference in mortality between rhBMP-2 and the control groups (RR 0.67; 95% CI 0.28 to 1.63). Four Medtronic RCTs (Studies 4, 10, 13-14) were included in the meta-analysis at 48 months and the results were similar (RR 0.65; 95% CI 0.33 to 1.30).

MedWatch Forms

Summary Findings

We received 1,229 MedWatch adverse event reports submitted to the FDA between July 2003 and July, 2012.

Most of the forms concerned TLIF, PLF, and ACDF.

- Occurrence of cancer did not play a role in the forms we examined.
- Most of the patients who died had undergone cervical spine fusion.
- TLIF was associated with leg pain, fluid collection, and heterotopic bone formation.

Overview of Included Evidence

Medtronic provided us with 1,229 MedWatch reports concerning rhBMP-2 spanning a period of 8 years from July 2003 to July 2012. Many of these reports were responses Medtronic provided to published articles, abstracts, or presentations, and are referred to here simply as publications. We were primarily interested in the MedWatch forms about patients not already reported in studies.

We initially searched the MedWatch data files for words we thought would provide the highest yield of important reports. We chose: “died,” “expired,” “arrest,” “cancer” and the prefix “tracheo”. This yielded 45 hits of which four were duplicates.

Of the 17 hits for cancer, six MedWatch reports were in response to a publication. Of the remaining 11, one was actually a lipoma and 10 were due to a pre-existing cancer. Of the 10 due to a pre-existing cancer, there was one report of cancer growth accelerating following fusion surgery. Of the 14 hits for died/expired, three did not involve a death and three were in response to a publication. Of the remaining eight, five were in the postoperative period of patients who had ACDF or other cervical spine fusion. Of the remaining three hits, one was a postoperative PLF patient, one was a postoperative posterior fusion with screws, and one was an operative PLIF patient who went into cardiac arrest during the surgery. Of the 11 hits for “tracheo”, three were in response to a publication, one involved mandible surgery, and the remaining were patients having ACDF or other cervical spine fusion. All of the three hits for cardiac and/or respiratory arrest were captured in the “died” and “expired” searches.

Out of concern that our limited ability to search the MedWatch data files might have caused us to miss other deaths, cancers, or other important events, we reviewed 200 random MedWatch forms. Of these 200 forms, 93 (46.5%) were in response to a publication. The surgical approaches most often involved were TLIF (44 total hits with 18 in response to a publication), PLF (23 total hits with 11 in response to a publication), and ACDF (20 hits with 15 in response to a publication). Only information on the three approaches that received the most MedWatch forms are discussed here, as data on other approaches is too sparse to be meaningful.

Of the 26 TLIF hits not involving a publication, 12 involved new, worsening, or recurrent pain in the legs, 10 involved a fluid collection or cyst formation, six involved heterotopic

ossification or unexpected bone growth, and 17 involved another surgery. Of the 12 PLF hits not involving a publication, five involved pain, three involved a seroma formation, one involved the Guillain-Barre syndrome, one involved a compression fracture, and one involved ectopic bone formation. Of the five ACDF hits not involving a publication, one person died, three involved swelling, one involved difficulty breathing, and one involved a hematoma.

In review, occurrence of new cancer did not play a role in the forms we examined, most of the patients who died had cervical fusion, and TLIF was associated with leg pain, fluid collections, and heterotopic bone formation.

Publication and Reporting (Key Question 3)

Nine of the 12 included Medtronic trials were published in medical journals as individual trials (Table 14).[4, 5, 7, 9, 25, 26, 28, 29, 148] One trial was partly described in an article that analyzed two trials together (Table 14).[8] One of the four Medtronic intervention series (Study 3) was presented in publications that combined the data with data from other studies.[24, 149] Results of another intervention series (Study 16) was not formally published but mentioned in a publication[150] that did not present details of the design or analysis. The other two intervention series (Studies 11 and 15) were not published.

Summary results from four of the trials (Studies 1, 2, 8, and 14) and one intervention series (Study 3) are available to the public from the FDA.[151-153] For the other eight trials, no reports of results were available from the FDA. No study results were available from ClinicalTrials.gov.

Table 14. Publication of Medtronic-sponsored studies of rhBMP-2 for spinal fusion

Primary Publication, Year*	Label	Medtronic study name (study number)	N	Results Available from FDA?	Primary Outcome Measure
Anterior lumbar interbody fusion trials					
Boden 2000[4]	On-label	INFUSE®/LT-CAGE® Pilot RCT (Study 1)	14	Yes	Fusion
Burkus 2002[5]	On-label	INFUSE®/LT-CAGE® Open Pivotal RCT (Study 2)	279	Yes	Overall success
Published in combined analysis only Burkus 2003[24]	On-label	INFUSE®/LT-CAGE® Laparoscopic Pivotal intervention series (Study 3)	134	Yes	Overall success
Unpublished	On-label	INFUSE®/INTER FIX™ ALIF Pilot RCT (Study 9)	45	No	Fusion, ODI Neurological status
Burkus 2002[24]	Off-label	INFUSE®/Bone Dowel Pilot RCT (Study 4)	46	No	Fusion, Disc height, ODI, Neurological status, Implant AEs, Surgery for implant AEs, Permanent AEs
Published in combined analysis only Burkus 2005[8]	Off-label	INFUSE®/Bone Dowel Pivotal RCT (Study 5)	85	No	Overall success
Gornet 2011[27]	On-label†	MAVERICK™ Disc Pivotal RCT (Study 10)	577†	No	Overall success
Posterolateral fusion trials					
Dawson 2009[26]	Off-label	INFUSE®/MASTERGRAFT® Pilot RCT (Study 8)	46	Yes	Overall success
Boden 2002	Off-label	rhBMP-2/BCP US Pilot RCT (Study12)	27	No	Fusion, ODI
Unpublished	Off-label	rhBMP-2/BCP Canada Pivotal RCT(Study13)	197	No	Fusion, ODI
Dimar 2009[29]	Off-label	AMPLIFY™ (rhBMP-2/CRM) Pivotal RCT (Study 14)	463	Yes	Overall success
Unpublished	Off-label	rhBMP-2/ CRM 2-level Pilot intervention series (Study 15)	29	No	Overall Success
Unpublished ‡	Off-label	rhBMP-2/BCP Mexico Pilot intervention series (Study 16)	15	No	Fusion§
Posterior lumbar interbody fusion trial					
Haid 2004[25]	Off-label	INFUSE®/INTER FIX™ PLIF RCT (Study 6)	67	No	Fusion, ODI, Neurological status
Circumferential posterior lumbar interbody fusion trial					
Unpublished	Off-label	INFUSE®/ TELAMON PEEK PLIF Pilot intervention series (Study 11)	30	No	Overall Success
Anterior Cervical Spine Fusion Trial					
Baskin 2003[9]	Off-label	INFUSE®/CORNERSTONE® ACDF Pilot RCT (Study 7)	33	No	Fusion, NDI, Neurological status

*Includes references for journal publication(s) and publicly available FDA reports, if applicable.
†Control arm (n=172) is on-label, intervention arm (n=450) is off-label.
‡This study is partially published in McKay 2002.[150]
§This is based on the registered protocol in ClinicalTrials.gov.
FDA = U.S. Food and Drug Administration; N = no; NDI = Neck Disability Index; ODI = Oswestry Disability Index

Primary Study Endpoints

Overall success was the primary study endpoint for six published Medtronic-sponsored trials (Studies 2, 3, 5, 8, 10, and 14) but only two of the primary publications reported results for overall success.[26, 27] In one of these two trials there was no statistically significant difference between rhBMP-2 and iliac crest bone graft for overall success.[26] In the other, results favored the artificial disc intervention group[27] over rhBMP-2. In studies where overall success was not reported in the primary journal publication, IPD analysis indicated no differences between groups in overall success (Table 15).

Fusion was listed as a primary outcome or primary effectiveness outcome in ten Medtronic-sponsored studies (Studies 2, 3, 4, 5, 6, 7, 8, 12, 14, and 16) and was reported in all nine primary publications (Table 15), although in five of the nine studies, no p-values for fusion were given or results were not provided for all three time points (6, 12, and 24 months).

We also identified several trials with multiple publications (studies 2, 3, 4, 5, and 14). Details on publication bias and other issues for effectiveness and harms can be found below by relevant surgical approach.

Table 15. Comparison of individual patient data analysis with published data in Medtronic-sponsored studies of rhBMP-2

IDE Clinical Trial Name, Design, (Study #) (References*)	Sample Size, *n*		Overall Success, 24 Months					Fusion, 24 Months					Cumulative Number of Adverse Events up to 24 Months			
			IPD Results			Published Results†		IPD Results			Published Results†		IPD Results‡		Published Results†§	
	I	C	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2	ICBG	rhBMP-2	ICBG
Anterior lumbar interbody fusion – on-label use																
INFUSE®/LT-CAGE® Pilot (1) Boden, 2000[4] RCT/Poor	11	3	NA	NA	NA	NA	NA	11/11 (100%)	3/3 (100%)	1.00	11/11	2/3	20	7	6	2
INFUSE®/LT-CAGE® Pivotal (2) Burkus, 2002[5] RCT/Fair	143	136	77/133 (58%)	68/123 (55%)	1.05 (0.84, 1.30)	NR	NR	127/132 (96%)	108/121 (89%)	1.08 (1.00,1.16)	120/127 (94.5%)	102/115 (88.7%)	315	274	6	13
INFUSE®/ LT-CAGE® Lap Pivotal (Study 3) Burkus, 2003[24] ‖ IS/Fair	134		70/115 (61%)	NA	NA	NR	NA	93/114 (81.6%)	NA	NA	81/86 (94.2%)	NA	264	NA	NR	NA
INFUSE®/ INTER FIX™ ALIF Pilot (Study 9) Unpublished RCT/Fair	25	20	11/23 (48%)	7/17 (41%)	1.16 (0.57, 2.36)			15/22 (68%)	13/15 (87%)	0.79 (0.56, 1.11)			28	25		
MAVERICK™ Disc Pivotal (Study 10) Gornet, 2011[27] RCT/Fair**	172	405	58/139 (42%)	233/371 (63%)	0.64 (0.53, 0.77)	57/103 (55.3%)	230/313 (73.5%) p<0.001	107/136 (79%)	NA	NA	100%††	NA	449	1,139	407	982
Anterior lumbar interbody fusion – off-label use																
INFUSE®/ Bone Dowel Pilot RCT (Study 4) Burkus, 2002[7]	24	22	17/24 (71%)	4/20 (20%)	3.54 (1.42, 8.83)	NR	NR	24/24 (100%)	12/20 (60%)	1.65 (1.15,2.35)	24/24 (100%)	13/19 (68.4%)	40	24	0	0
INFUSE®/ Bone Dowel Pivotal (Study 5) Burkus, 2005[8] ¶	55	30	33/50 (66%)	15/27 (56%)	1.19 (0.80, 1.76)	NR	NR	43/47 (91%)	24/25 (96%)	0.95 (0.85,1.07)	NSR	NSR	95	76	0	0

IDE Clinical Trial Name, Design, (Study #) (References*)	Sample Size, *n*		Overall Success, 24 Months					Fusion, 24 Months					Cumulative Number of Adverse Events up to 24 Months			
			IPD Results			Published Results†		IPD Results			Published Results†		IPD Results‡		Published Results†§	
	I	C	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2	ICBG	rhBMP-2	ICBG
Posterior lumbar interbody fusion – off-label use																
INFUSE®/ INTER FIX™ PLIF RCT (Study 6) Haid, 2004[25]	34	33	15/31 (48%)	10/31 (32%)	1.50 (0.80, 2.81)	NR	NR	25/31 (81%)	21/30 (70%)	1.15 (0.86, 1.54)	92.3%††¶¶	77.8%†† NS	112	120	29	35
INFUSE®/ TELAMON PEEK PLIF Pilot IS (Study 11) Unpublished	30		13/25 (52%)	NA	NA		NA	24/25 (96%)	NA	NA			103	NA		NA
Posterior lumbar fusion – off-label use																
rhBMP-2/BCP Mexico Pilot IS (Study 16) Unpublished ‡‡	I1: 7 I2: 8		NA	NA	NA			NA	NA	NA			8 ‖‖	NA		NA
rhBMP-2/BCP US Pilot RCT (Study 12) §§ Boden, 2002[28]	I1: 11 I2: 11	5	I1: 4/11 (36%) I2: 4/10 (40%)	2/4 (50%)	I1 vs. C: 0.73 (0.21, 2.55)	NR	NR	I1: 10/10 (100%) I2: 9/10 (90%)	3/4 (75%)	I1 vs. C: 1.36 (0.76, 2.46)	I1: 11/11 (100%) I2: 9/9 (100%)	2/5 (40%)	44	5	4	0
rhBMP-2/BCP Canada Pivotal RCT (Study 13) Unpublished	99	98	48/97 (49%)	40/95 (42%)	1.18 (0.86, 1.60)			89/96 (93%)	68/94 (72%)	1.28 (1.12, 1.47)			345	330		
INFUSE®/ MASTER GRAFT® Pilot RCT (Study 8) Dawson, 2009[26]	25	21	15/24 (63%)	10/20 (50%)	1.25 (0.73, 2.14)	17/21 (81%)	11/20 (55%) p=0.345	19/22 (86%)	14/20 (70%)	1.23 (0.89, 1.72)	18/19 (95%)	14/20 (70%) p=0.174	70	59	2	3

IDE Clinical Trial Name, Design, (Study #) (References*)	Sample Size, *n*		Overall Success, 24 Months					Fusion, 24 Months					Cumulative Number of Adverse Events up to 24 Months			
			IPD Results			Published Results†		IPD Results			Published Results†		IPD Results‡		Published Results†§	
	I	C	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2 (%)	ICBG (%)	RR (95% CI)	rhBMP-2 (%)	ICBG (%)	rhBMP-2	ICBG	rhBMP-2	ICBG
AMPLIFY™ (rhBMP-2/ CRM) Pivotal RCT (Study 14) Dimar, 2009[29]	239	224	118/211 (56%)	105/186 (56%)	0.99 (0.83, 1.18)	NR	NR	189/210 (90%)	162/181 (90%)	1.01 (0.94, 1.08)	186/194 (96%)	151/169 (89%) p=0.014	758	673	603	579
rhBMP-2/ CRM 2-level Pilot IS (Study 15) Unpublished	29		12/26 (46%)	NA	NA		NA	18/26 (69%)	NA	NA		NA	97	NA		NA
Anterior cervical discectomy and fusion – off-label use																
INFUSE®/ CORNER STONE® ACDF Pilot (Study 7) Baskin, 2003[9] RCT/Fair	18	15	10/12 (83%)	10/12 (83%)	1.00 (0.70, 1.43)	NR	NR	11/12 (92%)	12/12 (100%)	0.92 (0.77, 1.09)	10/10	10/10	45	13	2	1

ACDF = anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; C = comparator group (ICBG group); CI = confidence interval; CRM = compression resistant matrix; I = investigational group (rhBMP-2 group); ICBG = iliac crest bone graft; IDE = investigational device exemption; IPD =Individual patient data; IS = intervention series; NA = not applicable; NR = not reported; NS = not significant; NSR = not separately reported; PEEK = polyetheretherketone; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial; rhBMP-2 = recombinant human bone morphogenetic protein-2; US = United States.

* The primary study publication is referenced in the table. Study results are also reported in the following publications—Study 1: Khan, 2002,[154] McKay, 2002, [150] Poynton, 2002,[155] Sandhu, 2003;[156] Study 2: McKay, 2002,[150] Burkus, 2003,[24] Sandhu, 2003 [156], Burkus, 2004 [68], Burkus, 2004 [67], Burkus, 2005 [157]; Study 3: Kleeman, 2001 [158], Khan, 2002,[154] McKay, 2002 [150], Poynton, 2002 [155], Sandhu, 2003 [156], Burkus, 2004 [68], Burkus, 2004 [67], Burkus, 2005 [157], Medtronic [159]; Study 4: Khan, 2002.[154] McKay, 2002 [150], Sandhu, 2003 [156], Burkus, 2004 [68], Burkus, 2005 [8], Burkus, 2005 [157], Burkus 2006, [160], Study 5: Burkus, 2004 [68], Burkus, 2005 [8], Burkus, 2005 [157], Burkus, 2006 [160]; Study 6: : McKay, 2002 [150], Poynton, 2002 [155], Sandhu, 2003 [156], Burkus, 2005 [157]; Study 7: McKay, 2002 [150], Study 8: Burkus, 2004 [68]; Study 8: Burkus, 2004 [68], Burkus, 2005 [157]; Study 12: Sandhu, 2003 [156]; Study 16: McKay, 2002 [150], Burkus, 2005 [157].

† For unpublished studies, cells are blank.

‡ More information about the type and number of specific adverse effects can be found in Appendix L. These numbers do not include non-union and non-union pending.

§ The type and number of specific adverse effects reported by each journal publication can be found in Table 16.

‖ Study 3 data not published independently. Burkus, 2003 [24] contains pooled data from Studies 3 and 2.

¶ Study 5 data not published independently. Burkus, 2005 [8] contains pooled data from Studies 4 and 5.

** The comparison group in this study received artificial disc, not ICBG. Discrepancy in numbers between published trial and IPD partially due to an updated Medtronic data set provided to the authors.

†† n not reported; results reported only as percentages.

‡‡ The Mexico pilot study was an intervention series with two cohorts.

§§ I1 = rhBMP-2 without internal fixation; I2 = rhBMP-2 + TSRH (Texas Scottish Rite Hospital) pedicle screw instrumentation; C = autograft + TSRH. This study only followed patients for 12 months, so there were no data at 24 months.

‖‖ The cumulative number of adverse events up to 12 months.

¶¶ The table in this publication reports a slightly higher percentage (97.3%).

Lumbar Spinal Fusion

Reporting of Effectiveness

There was important bias in the way the results of the ALIF studies reported effectiveness outcomes. Overall success was the primary effectiveness endpoint in Study 2, 3, 5 and 10 and the rate of overall success was in the range of 50 to 60% based on our IPD analysis. Only the published article for Study 10[27] reported the results for overall success that the rhBMP-2 group had lower rate (55.3%, 57/103) than the artificial disc group (73.5%, 230/313; $P < 0.001$).

Since the FDA's approval of rhBMP-2 with the LT-CAGE based on Studies 1-3, by 2004, at least 12 articles and reviews reporting results from these studies had been published in major orthopedic journals.[4, 5, 24, 67, 68, 150, 154-156, 158, 161] Despite the findings of equivalence—accepted by Medtronic, the study investigators, and the FDA—many of these articles presented the results of the pivotal trials as demonstrating better fusion rates than ICBG. For example, the primary publication for Study 2 reiterated high fusion rates (94.5% vs. 88.7%) in the abstract, results, and conclusion sections, but the abstract and results failed to mention that the difference was not statistically significant.[5] Another publication reported results for one site in Study 3 (22 of the 137 subjects), stating a 100% rate of fusion and "improvement in back pain, leg pain, and function", which did not represent the overall results for the study (Table 15, Study 3).[158] Seven other Medtronic-supported articles that referred to Study 3 cited this article instead of the overall results.[8, 9, 24, 25, 67, 68, 157]

In 2003, Burkus and colleagues published a *post hoc* "integrated analysis" that promoted the idea that rhBMP-2 would have superior outcomes compared with ICBG with sufficient sample size.[24] The investigators argued that, because Study 2 had demonstrated a trend toward faster fusion with INFUSE, an analysis with a larger sample size would be able to show INFUSE's unequivocal superiority over ICBG in ALIF. Three of the four authors of this paper were also authors of the publication of the pivotal Study 2, in which they published pain success rates (74.6% in the rhBMP-2 group versus 78.7% in the autograft group at 2 years); leg pain (6.3 versus 6.3); back disability (23.9 versus 23.8); patient satisfaction (81.2% versus 80.4%); and fusion rates that did not differ between the two groups.[5]

Despite the overall finding that fusion rates and most patient-centered outcomes for rhBMP-2 and ICBG were equivalent in the pivotal study, the authors combined the rhBMP-2 groups from Study 2 and Study 3 and compared them with a control group that combined the ICBG arm of Study 2 (n=136) with an older, unrelated, unpublished series of patients (n=266) who underwent laparoscopic surgery with the LT-CAGE.[24] Using a statistical method to adjust for baseline differences and for open versus laparoscopic technique, the authors concluded that rhBMP-2 "had statistically superior outcomes" for fusion rates and for ODI scores, Physical Component Summary (PCS) scores, and Pain Index of the SF-36 scale. In 2004, in another journal, they stated, "the outcomes represent typical results from a wide variety of surgeons with different degrees of experience…"[67]

There are three problems with the validity of this approach. First, the 266 patients represent historical controls, an approach that often has a very high risk of bias because of differences in surgical technique, proficiency, and other aspects of care that improve over time. In fact, Medtronic was aware that the surgeons in the earlier study were likely less skilled at laparoscopic ALIF than the surgeons in the later Study 3. In internal documents, Medtronic compared mean operative time, blood loss, and hospital stay in the two laparoscopic series: "The values in the current laparoscopic INFUSE Bone Graft/LT-CAGE device clinical trial are lower in all three

categories. This may be attributable to increased surgeon experience with laparoscopic interbody fusion procedures."[159] (p. 2077) In the publications, the authors did not mention this concern and concluded that rhBMP-2 "had statistically superior outcomes" for these outcomes (shorter operative times, less blood loss, and shorter hospital stays).

Second, patients and outcomes in the rhBMP-2 arms of Study 2 and Study 3 were not comparable. In its report to the FDA of Study 2, Medtronic chose not to combine the results of the open RCT with the laparoscopic INFUSE study since the overall success rates were higher in the rhBMP-2 laparoscopic arm than in the rhBMP-2 arm of the trial of open ALIF. As noted above, there were important baseline differences between these groups that could be associated with the better surgical outcomes in the laparoscopic group. Medtronic wrote that combining them would have "bolstered the overall success results of the investigational group." Instead, they focused on presenting data arising from the open RCT only and stated that such "manner of presentation has the most scientific appeal" and "is the sternest test for the investigational group."[162] (p.751)

A third problem with the integrated analysis concerns conducting analyses when one already knows the results. The FDA specifically advises: "To avoid producing potentially biased results, decisions on how data will be analyzed should be done prospectively, before results are known."[163] The integrated analysis takes an open ALIF RCT which showed no significant difference in rates of fusion between INFUSE versus ICBG, and added to that a laparoscopic intervention series of INFUSE, which was known to have better results than the open RCT, and added to that a laparoscopic ICBG arm known to have worse results than the laparoscopic INFUSE arm. The practice of *post-hoc* inclusion of groups of patients with known results renders the results meaningless.

The publications do not discuss these limitations or the fact that Medtronic had previously decided not to conduct an integrated analysis of this type. Publication of this analysis in three separate journals appeared to serve no scientific purpose and suggested a publication strategy that aimed to emphasize better fusion rates rather than the actual results of equivalent effectiveness measured by overall success.

Two Medtronic studies of rhBMP-2 used bone dowels, an off-label lumbar application (Table 15, Studies 4, 5). In 2002, Burkus and colleagues reported that 24 out of 24 patients (100%) receiving rhBMP-2 achieved fusion at 24 months compared with 13 out of 19 in the control group (68%) (Table 15, Study 4).[7] The larger, pivotal bone dowel trial (Study 5) was terminated early. Study 5 was published only in an article that combined the pilot and pivotal trials, representing them as "a two-part, prospective, randomized, multicenter study" with "two sequential phases." It reported that "fusion rates were significantly better in the study group ($p<0.001$)" without mentioning early termination,[68] as did two additional articles by the same author.[8, 160] In our analysis, fusion rates for Study 5 were 91% for rhBMP-2 vs. 95% for ICBG (Table 15, Study 5).

In posterolateral fusion, although 24-month overall success was the protocol-defined primary endpoint in two randomized controlled trials (Studies 8 and 14), results for this outcome were only published for the smaller of the two trials (Study 8).[26] Overall success rates were higher in the published report (81% [17/21] for rhBMP-2 compared with 55% [11/20] for ICBG; P = 0.345) than we observed based on our IPD analysis (63% [15/24] compared with 50% [10/20] RR 1.25; 95% CI 0.73 to 2.14). Unpublished 24-month overall success rates for the larger trial (Study 14) were 56% (118/211) in the rhBMP-2 group and 56% (105/186) in the ICBG group based on our IPD analysis (RR 0.99; 95% CI 0.83 to 1.18). Also, based on out IPD analysis from Study 14, rhBMP-2 and ICBG did not differ in rates of overall success (56 % vs. 56%) and fusion (90% vs. 90%). In contrast, the journal publication and FDA summary reported that use of rhBMP-2 resulted in a higher fusion rate (96% vs. 89%, P = 0.014).[29, 153]

For posterior lumbar interbody fusion, there is only one Medtronic-sponsored trial (Study 6) and the published effectiveness results[25] were consistent with our IPD results. The abstract of the journal article for Study 6[25] highlighted that, at 24 months, fusion rate of the rhBMP-2 group was higher than the control's (92.3% versus 77.8%), but did point out that the difference is not statistically significant.

Reporting of Adverse Events

As a previous review noted,[14] there was serious selective reporting and underreporting of adverse events in the published articles for both rhBMP-2 and ICBG groups, especially in the Medtronic trials published early. While each trial collected data on adverse events from multiple categories (> 10), no or only very few selected harms were reported in the published articles (Tables 15 and 16). The actual rates of adverse events were much higher than reported. For example, for Study 2, Burkus et al.[5] reported only 11 intraoperative vascular events (6 rh-BMP-2, 5 ICBG), six retrograde ejaculation (not by rhBMP-2 versus ICBG groups, but by surgical approach of transperitoneal versus retroperitoneal) and eight adverse events related to iliac crest graft site at 24 months. However IPD indicated 315 adverse events in the rhBMP-2 group and 274 adverse events in the autograft group two years after surgery. As another example, although infection is an important complication that was listed on the adverse event reporting form and probably ascertained accurately, infection rates were reported in only two of nine pertinent publications (Table 17). In addition, in all trials the published articles reported no device-related adverse events. Though the ascertainment of this adverse event was problematic, as discussed earlier in the results section, it was a pre-defined outcome based on the trial protocol and occurred in both groups (Table 18). Instead, articles simply stated either "no unanticipated device-related adverse events" [5, 7, 9, 25] or no adverse event directly related or attributable to rhBMP-2.[4, 28] On the contrary, Medtronic provided the FDA with complete, even exhaustive information about total adverse events and serious adverse events.

Some publications sought to emphasize "donor site hip pain" which was assessed only in the control group patients and only on the side of the iliac crest operation. The primary publication for Study 2, the pivotal trial for on-label use in ALIF, represented the hip pain scores in the rhBMP-2 group as zeroes even though hip pain was not measured in that group (Figure 1 of Burkus, 2002).[5]

In December, 1999 (prior to FDA approval of rhBMP-2 for use in ALIF), Medtronic suspended enrollment in Study 6 because of ectopic bone formation in some patients,[164] potentially leading to radiculopathy from nerve root impingement. In March, 2002, Medtronic requested FDA permission to terminate the study. The same year, Medtronic sponsored a supplement in the journal *Spine* in which review articles were published along with conclusions from an "international panel of experts" that included outside experts, investigators associated with Medtronic, and Medtronic employees. Two articles in the supplement discussed the concern about ectopic bone formation in Study 6. While noting that large randomized trials were needed to establish the safety of rhBMP-2 in off-label procedures, the supplement argued that ectopic bone formation, and complications it might cause, were due to poor technique.[150, 155] No data from Study 6 were presented to support this argument. The international panel stated "when used properly, BMPs currently appear to be extremely safe for spine fusion".[165]

After Study 6 was terminated, an article published in 2004[25] reported data on ectopic bone formation (rhBMP-2 24/34 vs. ICBG 4/33, $p<0.001$) for the first time. Despite the small sample, the authors emphasized the lack of association between ectopic bone formation and leg pain and gave an incomplete account of the reasons for study termination.[14, 166]

For the two most recently published trials,[27, 29] underreporting appeared much less of an issue and all adverse events during operation and at 24 months were completely reported. For example, the journal publication of Study 10 reported that 7% of rhBMP-2 patients had a serious adverse event that was "possibly device-related".[27] The Dimar publication provided detailed summary of adverse events in Study 14.[29] The main difference between our IPD analysis and the published data for this trial related to second surgery events. The analyses in the published report only included revisions, nonelective removals and supplemental fixations, resulting in significantly lower second surgery rates for rhBMP-2 than for ICBG (8% compared with 16%; p=0.015). However, when elective removal and reoperation were included in the IPD analysis, the difference was not significant (rh-BMP-2: 36 events in 34 patients; ICBG, 57 events in 43 patients; $P = 0.15$).

Anterior Cervical Spinal Fusion

There is only one Medtronic-sponsored trial (Study 7) of rhBMP-2 in anterior cervical spinal fusion, and the published article reported results on all three primary effective outcomes: fusion, NDI and neurological status.[9] There were two effectiveness outcomes showing a discrepancy between published results and our IPD analysis. Improvement in NDI and arm pain were reported as greater in the rhBMP-2 group compared with the ICBG group (p=0.03 for both comparisons) in the published study, while the IPD analysis demonstrated no difference between groups. This difference was likely due to data analysis methods used. The published results did not adjust for the baseline score imbalance appropriately. With appropriate adjustment in the IPD analysis using ANCOVA, we found no difference. In all other efficacy outcomes examined, the published results agreed with the IPD analysis.

For harms, the published article did not report any adverse events other than the three cases of heterotopic bone formation in the section of radiographic outcomes.[9] IPD analysis of the trial demonstrates increased rate of overall adverse events associated with rhBMP-2 use, which is consistent with the findings of a large cohort study.[11] Data on specific adverse events from the small trial is too sparse for any definite conclusions. In this case, the cohort studies provided better evidence for adverse events.

Table 16. Comparison of reported adverse events in published trials versus adverse events in the IPD up to 24 months

Author Trial	Surgical Approach	Number of Patients		Number of Adverse Events and Additional Surgery* Reported by Published Study		Number of Adverse Events and Additional Surgery* Based on IPD†		Was Graft Site Adverse Event Reported?	Author Comments on Comparison of Harms
		rhBMP-2	Control	rhBMP-2	Control	rhBMP-2	Control		
Boden, 2000[4] INFUSE- LT-CAGE Pilot	ALIF	11	3	Adverse events: 6 (1 ileus and delay in gait training, 1 wound dehiscence, 1 low back pain and 3 trauma) Additional surgeries: 0	2 (1 ileus and delay in gait training, 1 urinary retention) 0	20 0	7 (1)	No	There were few clinically relevant adverse events. None was directly related to the cage or graft material.
Burkus, 2002[5] INFUSE- LT-CAGE Pivotal‡	ALIF	143	136	Adverse events: 6 (6 intraoperative vascular Additional surgeries: (11)	13 (5 intraoperative vascular, 8 graft side related) (14)	315 17 (13)	274 17 (14)	Yes, 8 events	There were no unanticipated device-related adverse events in either treatment group.
Burkus, 2002[7] INFUSE- Bone Dowel Pilot	ALIF	24	22	Adverse events: 0 Additional surgeries: (1)	0 4(3)	40 1	24 4(3)	No	No unanticipated adverse events that were related to the use of INFUSE occurred.
Burkus, 2005[8] INFUSE- Bone Dowel Pivotal	ALIF	55	30	Adverse events: 0 Additional surgeries: (1)	0 (4)	95 4(2)	76 5(5)	No	No comment.
Gornet, 2011[27] MAVERICK Disc Pivotal§	ALIF	172	405	Adverse events: 153 of 172 had at least one AE, complete reporting of AE in a table Additional surgeries: 15(12)	345 of 405 had at least one AE, reported all AEs in a table 15+22(15)¶	449 events occurred in 151‖ patients 15(12)	1139 events occurred in 345 patients 34(15)	Not applicable	Overall adverse event rates for the two treatment groups showed no statistical difference
Haid, 2004[25] INFUSE – INTER FIX PLIF	PLIF	34	33	Adverse events: 29 (19 Neurological, 10 bone formation outside the disc space with leg pain increase) Additional surgeries: 6(3)	35 (1 cardiovascular, 20 neurological, 2 graft side related, 12 bone formation outside the disc space with leg pain increase) 6(3)	112 4(2)	120 1(0)	Yes, 2 events	No unanticipated device-related adverse events occurred in either treatment group.

Author Trial	Surgical Approach	Number of Patients		Number of Adverse Events and Additional Surgery* Reported by Published Study		Number of Adverse Events and Additional Surgery* Based on IPD†		Was Graft Site Adverse Event Reported?	Author Comments on Comparison of Harms
		rhBMP-2	Control	rhBMP-2	Control	rhBMP-2	Control		
Baskin, 2003[9] INFUSE – Cornerstone ACDF Pilot	ACDF	18	15	Adverse events: 2 ectopic bone formation, as part of radiographic outcomes Additional surgeries: (1)	1 ectopic bone formation, as part of radiographic outcomes 0	45 2(1)	13 0	No	There were no unanticipated device-related adverse events in either treatment group.
Dawson, 2009[26] INFUSE – Mastergraft Pilot	PLF	25	21	Adverse events: 2 (1 durotomy, 1 wound infection) Additional surgeries: (2)	3 (1 durotomy, 1 wound infection, 1 graft side related) (2)	70 3(3)	59 3(2)	No	No comment.
Boden, 2002[28] INFUSE – 2/BCP US pilot	PLF	11 + 11	5	Adverse events: 4 (1 leg pain, 1 back pain, 2 hematoma), all led to second surgery Additional surgeries: (4)	0 0	44 5(5)	5 0	No	There were no complications attributable to the rhBMP-2/BCP or TSRH internal fixation.
Dimar, 2009[29] INFUSE – 2/BCP Amplify Pivotal	PLF	239	224	Adverse events: 209 of 239 has at least one AE, complete reporting of AE in a table Additional surgeries: (20)	198 of 224 has at least one AE, complete reporting of AE in a table (36)	758 events occurred in 208 patients 34(20)	673 events occurred in 195 patients 43(31)	Yes, 17 events	No significant differences between the study groups for all event categories, except for graft site related events. No adverse event specifically attributed to use of rhBMP-2 matrix in the study group identified.

ACDF = anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; BCP = biphasic calcium phosphate; IPD =Individual patient data; PLF = posterolateral lumbar fusion; PLIF = posterior lumbar interbody fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2

*For additional surgery, the numbers in parenthesis are the number of subjects with at least one revision, removal, supplemental fixation. The numbers not in parenthesis are the number of subjects with at least one revision, elective and non-elective removal, supplemental fixation and reoperation.

†The specific adverse events can be found in Appendix L

‡Six cases of retrograde ejaculation were reported, but not by intervention groups

§ The comparison group is artificial disc, not ICBG

‖ This number is different from the published study because Medtronic sent an updated dataset.

¶ Fifteen subjects had revision, removal and supplemental fixation, and 22 patients had reoperations; there could be overlap between the two groups.

Table 17. Infection at 24 months

Study Number	Study	Approach	Number Enrolled rhBMP-2 vs. Control	IPD Numbers rhBMP-2 vs. Control	Published Numbers rhBMP-2 vs. Control
1	INFUSE/LT-CAGE Pilot RCT	ALIF	11 vs. 3 (4 BMP lap patients not analyzed)		Not Reported
2	INFUSE/LT-CAGE Open Pivotal RCT	ALIF	143 vs. 136	1.1 (.61, 2.1)	Not Reported
3	INFUSE/LT-CAGE Lap Pivotal 1-Arm	ALIF	134	19 events in 17 patients	Not Reported
4	INFUSE Bone Dowel Pilot RCT	ALIF	24 vs. 22	0.31 (.01, 7.2)	Not Reported
5	INFUSE Bone Dowel Pivotal RCT	ALIF	55 vs. 30	0.91 (.23, 3.5)	Not Reported
6	INFUSE INTER FIX RCT	PLIF	34 vs. 33	1.4 (.48, 3.9)	Not Reported
7	INFUSE/CONRNERSTONE Pilot RCT	ACDF	18 vs. 15	4 vs. 0	Not Reported
8	INFUSE MASTER GRAFT Pilot RCT	PLF	25 vs. 21	0.84 (.24, 3.0)	Not Reported
9	INFUSE INTERFIX Pilot RCT	ALIF	25 vs. 20	2.4 (.10, 56)	Not Published
10	MAVERICK Disc Pivotal RCT	ALIF	172 vs. 405	1.2 (.60, 2.3)	12 vs. 24 patients
11	INFUSE/TELAMON Instrument 1-Arm	PLIF/ Circumferential	30		Not Published
12	rhBMP-2/BCP US Pilot RCT	PLF	22 vs. 5 (11 rhBMP-2 only patients not analyzed)		Not Reported
13	rhBMP-2/BCP Canada Pivotal RCT	PLF	98 vs. 99	1.5 (.82, 2.6)	Not Published
14	AMPLIFY rhBMP-2/CRM Pivotal RCT	PLF	239 vs. 224	0.81 (.55, 1.2)	39 vs. 45 patients
15	rhBMP-2/CRM 2-Level Pilot 1-Arm	PLF	29		Not Published
16	rhBMP-2/BMP Mexico Pilot	PLF	15		Not Published
17	INFUSE/CORNERSTONE Pivotal RCT	ACDF	2 vs. 1	Excluded	Not published

ACDF = Anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; CRM = compression resistant matrix; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial; rhBMP-2 = recombinant human bone morphogenetic protein-2

Table 18. Individual patient data on device-related adverse events and device-related serious adverse events as defined by Medtronic

Study Number	Study	Approach	Number Enrolled rhBMP-2 vs. Control	IPD Numbers for Device-related AE rhBMP-2 vs. Control	IPD Numbers for Device-related Serious AE rhBMP-2 vs. Control
1	INFUSE/LT-CAGE Pilot RCT	ALIF	11 vs. 3 (4 rhBMP-2 lap patients not analyzed)	1 vs. 2	0 vs. 1
2	INFUSE/LT-CAGE Open Pivotal RCT	ALIF	143 vs. 136	11 vs. 5	5 vs. 0
4	INFUSE Bone Dowel Pilot RCT	ALIF	24 vs. 22	1 vs. 0	0 vs. 0
5	INFUSE Bone Dowel Pivotal RCT	ALIF	55 vs. 30	2 vs. 1	2 vs. 0
6	INFUSE INTER FIX RCT	PLIF	34 vs. 33	3 vs. 0	2 vs. 0
7	INFUSE/CONRNERSTONE Pilot RCT	ACDF	18 vs. 15	0 vs. 0	0 vs. 0
8	INFUSE MASTER GRAFT Pilot RCT	PLF	25 vs. 21	2 vs. 0	2 vs. 0
9	INFUSE INTERFIX Pilot RCT	ALIF	25 vs. 20	2 vs. 1	1 vs. 1
10	MAVERICK Disc Pivotal RCT	ALIF	172 vs. 405	16 vs. 18	
12	rhBMP-2/BCP US Pilot RCT	PLF	22 vs. 5 (11 rhBMP-2 only patients not analyzed)	0 vs. 0	0 vs. 0
13	rhBMP-2/BCP Canada Pivotal RCT	PLF	98 vs. 99	8 vs. 2	3 vs. 1
14	AMPLIFY rhBMP-2/CRM Pivotal RCT	PLF	239 vs. 224	13 vs. 14	11 vs. 10

ACDF = Anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion; RCT = randomized controlled trial; rhBMP-2 = recombinant human bone morphogenetic protein-2

DISCUSSION

Summary of Results

Effectiveness

Most evidence about the effectiveness and safety of rhBMP-2 came from premarketing randomized trials sponsored by Medtronic. These trials were designed to obtain marketing approval from the FDA for the use of rhBMP-2 in spinal fusion. The studies generally sought to determine whether rhBMP-2 is as good as ICBG in achieving overall success and solid fusion, and in reducing pain and disability associated with spinal disease, though the published articles analyzed most data as if they were superiority trials. These trials also conducted the assessments of safety required for FDA approval as a new device. Intervention series sponsored by Medtronic were conducted according to protocols that were similar to those of the RCTs. Most of these intervention series sought to demonstrate that rates of fusion and adverse events were similar to those observed in the rhBMP-2 arm of the trials.

Additional evidence about fusion and safety came from cohort studies. The majority sought to identify specific adverse events associated with spinal fusion surgery and to compare the frequency of these adverse events between patients fused with rhBMP-2 and patients fused with autograft and/or allograft. In addition, a few intervention series, conducted independently of Medtronic, reported rates of fusion success and adverse events associated with rhBMP-2 use in actual practice. About a quarter of intervention series specifically sought to determine the rate of adverse events.

Our analysis of IPD found that, for ALIF and PLF, overall success rates were generally similar between rhBMP-2 and ICBG groups. Although 7 of the 10 published manufacturer-sponsored trials[5, 7, 8, 25, 26, 28, 29] reported higher fusion rates in the rhBMP-2 group at 24 months, sometimes without statistical significance, we did not find consistently significantly increased fusion rate in our meta-analysis. Rather, the use of rhBMP-2 generally resulted in similar fusion rates compared with the use of ICBG in lumbar spinal fusion, regardless of surgical approach, through 24 months of follow-up, except for an increase in fusion rate associated with rhBMP-2 at 6 months for ALIF and for PLF. Results from cohort studies for fusion usually were consistent with the IPD results. Similarly, despite greater improvements in ODI score and pain often reported in the published trials,[5, 7, 8, 25, 26, 28, 29] we found that for most other outcomes for benefits (ODI score, pain, and neurological success) patients generally had similar results in the two treatment groups through 24 months. The exceptions were that rhBMP-2 patients undergoing ALIF showed consistently better SF-36 PCS scores from 3 months through 24 months, and rhBMP-2 was associated with better back pain scores and ODI score at 24 months in ALIF. However, the magnitude of differences was small, at about a 2- to 3-point increase for SF-36 PCS on a 0-100 scale, a seven-point increase for ODI on a 0-50 scale, and about a half- to three-quarter point change in pain on a 0-10 scale. None of these differences meet typical criteria for a clinically meaningful difference.[167] In addition, we did multiple tests at multiple time points for multiple outcomes without adjusting for multiple comparison. Some of the differences we saw at selected time points may be due to chance. This applies to outcomes related to both benefits and harms, including cancer. We emphasized results with a consistent pattern for effectiveness outcomes and pointed out all significant results at the primary 24-month time point.

Only three RCTs (one ALIF–Study 4 and two PLF–Studies 13 and 14) provided comparative evidence for follow-up longer than 24 months. The ALIF study is small and did not show a difference in fusion rates between rhBMP-2 and ICBG groups. For PLF, at 48 months, patients in the rhBMP-2 group showed a significant 15% relative increase in fusion rates.

Cancer

We found a significantly increased risk of cancer associated with the use of rhBMP-2 compared with ICBG through 24 months (NNH 53, 95% CI 31 to 200). Fewer studies provided data at 48 months. While the rhBMP-2 group still showed a higher risk, the association was attenuated and no longer statistically significant. Excluding non-SEER cancers resulted in similar estimates to those including non-SEER cancers through 24 and 48 months. However, the cancers in the meta-analysis included many different types of malignancies. The strength of this evidence is low because sample size and event rates were low (the total number of subjects with cancer is 23 at 24 months, and 27 at 48 months) and, cancer events were underreported since, according to Medtronic, they "were captured only by voluntary reporting via the non-descript AE text field".[168] Animal studies do not suggest that rhBMP-2 is carcinogenic,[155] but BMPs are expressed by and promote the growth of some cancers.[169-171] The development of cancer within 2 to 4 years also argues for a pro-oncogenic mechanism.

We had insufficient data to examine particular cancers in detail, and other evidence about rhBMP-2 and cancer is sparse. We only found two additional cohort studies.[124, 147] One cohort study [124] found a non-significantly increased cancer risk with rhBMP-2, which was consistent with the trials; the other specifically assessed pancreatic cancers and did not find increase risk, though the mean length of follow-up of the BMP group was only one year.

Other Adverse Events

For anterior cervical spinal fusion, there was only one small RCT with 33 patients and it did not provide robust evidence for any specific adverse event. Our finding that use of rhBMP-2 was associated with increased adverse events, in particular, wound complications and dysphagia or dysphonia compared with ICBG was based on observational studies that were conducted independent of Medtronic.[11] These same studies formed the basis of a 2008 FDA Public Health Notification regarding risks of rhBMP-2 in cervical fusion.[19] Another large cohort study confirmed that BMP fusions were associated with more overall complications (5.8% versus 2.4%; $P < 0.001$) and more wound infections (2.1% versus 0.4%; $P < 0.001$) than were fusions without rhBMP-2.[172] However, this cohort study was not included in our review, because it was not clear how many patients received rhBMP-2 and how many patients received rhBMP-7.

In lumbar spine fusion, based on Medtronic data, the overall risk of adverse events recorded in the RCTs were similar in rhBMP-2 use compared with the use of ICBG. However, the premarketing studies we used in our meta-analysis were not an adequate means of determining whether rhBMP-2 was associated with an increased risk of serious adverse events. Our analysis underscores the need for more definitive evidence about harms before rhBMP-2 became widely used.

Estimates of risk ratios in the IPD meta-analysis for implant problems, subsidence, urogenital events, and retrograde ejaculation suggested increased risk with rhBMP-2 compared with ICBG, but the confidence intervals for risk ratios were wide, and differences were not statistically significant. Cohort studies and intervention series of serious adverse events from lumbar fusion

were small and methodologically weaker relative to the large-scale cohort studies of the risks of anterior cervical fusion.

Radiculitis was not defined in any trial and adverse events consistent with possible radiculitis were variously classified within the same trial as back and leg, neurological, or spine adverse events. We reclassified events that appeared consistent with radiculitis and found no difference in risk based on multiple definitions, however, we only had limited information based on the brief adverse event history in the Medtronic internal documents.

In summary, there were safety signals in the Medtronic studies. Nevertheless, there has been a lack of well-designed, adequately-powered studies that specifically aimed to systematically assess harms using adequate ascertainment methods. The Medtronic studies provided insufficient evidence that rhBMP-2 was as safe as ICBG.

Quality of Studies

All but two industry-sponsored small randomized trials were rated fair quality. Most of the Medtronic trials were satisfactorily randomized with adequate concealment of allocation. The poor quality trials revealed the randomized assignment to patients prior to obtaining informed consent or exhibited baseline differences. However, there was no evidence to indicate that outcome assessment was blinded other than fusion by radiologists, and this potentially leads to biases for the more subjective outcomes such as neurological success (which includes testing a patient's motor and sensory functions and reflexes).

Effectiveness outcomes such as the SF-36 for physical and mental health and the ODI for functional capabilities were assessed using validated instruments. Ascertainment of adverse events is less rigorous. Study protocols did not describe how adverse events were identified. A typical adverse event form listed a few general adverse events, such "urogenital," with examples given in parenthesis, such as retrograde ejaculation and urinary retention without using specific symptom questionnaires or objective tests. It is not clear whether patients were asked about specific adverse events; whether patients were asked only general, open-ended questions about adverse events; or if adverse events were noted only if the patient spontaneously reported them. If patients were asked about these conditions, it is not clear what specific questions were asked and whether these questions were standardized across outcome assessors. There was no evidence to indicate that adverse events were adequately ascertained, and potentially, adverse events may not have been fully reported by patients. However, the recorded adverse events were generally consistent with the patient adverse event histories in the final report. And, while first evaluations of rhBMP-2 could not be expected to fully anticipate what adverse events to expect, better data collection forms could have been designed over time for later trials.

Handling of missing data is another concern regarding the internal validity of industry-sponsored trials. In general the protocols did not specify how missing data would be handled. Only observed data appeared to be analyzed in the published trials. We conducted several sensitivity analyses with different assumptions about missing data and found that the published results occasionally showed greater benefits in the rhBMP-2 group compared with results from IPD meta-analysis.

An additional measurement issue concerns the ascertainment and reporting of pain and morbidity associated with iliac crest bone graft harvesting. Based on our meta-analysis and review of the literature, we found little difference in effectiveness outcomes (e.g., fusion, disability, pain, mental health) between fusions with rhBMP-2 versus ICBG. Therefore, the primary argument for use of rhBMP-2 lies in reduction in pain and morbidity associated with

harvesting bone from the iliac crest. Since the industry-sponsored trials only assessed pain in the bone graft harvest site in the control group and only on the side of graft harvest, preventing comparative evaluation with the rhBMP-2 group, none of the trials provided sufficient evidence to effectively argue for the use rhBMP-2 in spinal fusion. The reduced morbidity associated with no iliac crest bone harvesting may be beneficial to older adults, but this has not been proven.[173]

Carragee et.al.[14] raised the concern about study design bias against the control groups. In particular, for the PLF approach, there were three major deviations from the usual recommended practices: no facet preparation, discarding local bone graft, and no bone graft augmentation with low autogenous bone graft volumes. Dimar et al.[174] responded to the concerns that discarding local bone graft was for a cleaner study design; mean volume of bone graft used was not low and the one patient with low volume of bone graft had successful fusion at 12 and 24 months. In our analysis of PLF trials, one trial exhibited a low control fusion rate of 43% at 6 months (Study 13) compared with other PLF trials with a control rate of over 60%. However, we do not have relevant information, such as surgical protocols, to evaluate these potential design biases. Further, the success of fusion surgery depends on many factors such as skill and experience of the individual surgeon; patient expectations and comorbidities; the amount of bone, bone graft extenders, and bone graft substitutes used; postoperative instructions provided to the patient and their compliance with instructions; and other unmeasurable factors. The above issues may be only some of the factors that contribute to the success of fusion.

Significance of IPD and Reporting Bias

Meta-analysis of IPD has been considered the gold standard of meta-analysis.[175] For both on-label and off-label indications, journal publications selected analyses and results that favored rhBMP-2 over ICBG. Compared with other reviews,[13, 176] the availability of IPD from the manufacturer sponsored trials allowed a more thorough evaluation of both benefits and harms that is not possible only with published papers, and reduced the problem of publication and reporting biases. Disregarding the trial terminated early with only three subjects (Study 17), IPD provided additional data on two RCTs (Study 9 and Study 13) and three interventional series (Studies 11, 15 and 16), data unavailable in the published literature.

Moreover, while the published studies were more likely to provide information on statistically significant results only at selected time points, with IPD, we were able to examine all outcomes from all time points for the manufacturer-sponsored trials. For example, the outcome "overall success" was defined in 15 of 17 Medtronic studies with IPD, and specified as primary outcomes in 9 studies, but reported in only 2 of 10 published studies.[26, 27] The availability of IPD allowed us to calculate this outcome for 15 studies at all follow-up time points where it was defined.

The availability of IPD enabled us to identify several other biases in reporting on the effectiveness of rhBMP-2. Major publications aimed to give the reader the impression that rhBMP-2 was more effective than ICBG by emphasizing results that were incomplete or not statistically significant and publicizing *post hoc* analyses that had serious flaws and misrepresented the results of the trials. Journal practices regarding sponsored supplements, trial registration, and conflict of interest disclosure may have contributed to publication of an incomplete and sometimes misleading evidence base.[40, 177, 178]

Even though the ascertainment of specific serious adverse events remained a problem and the availability of IPD cannot compensate for flawed data collection or sparse data, the availability of IPD helped with assessing the comparative harms of rhBMP-2 versus ICBG and

provided a more complete picture on the profile of benefits versus harms. In their review, Carragee et al. demonstrated underreporting of adverse events in publications of five studies (three on-label and two off-label) for which the FDA had made summary results public.[14] Our study demonstrates that there was also underreporting of adverse events for more on- and off-label uses with results not previously available to the public. Such underreporting and practice could affect the spine surgeons' ability to evaluate the balance between the benefits and harms of using rhBMP-2 and prevent informed consent. However, underreporting appeared much less of an issue for the two most recently published trials,[27, 29] and all adverse events during operation and at 24 months were reported in the journal articles.

IPD data improved the quality of the meta-analyses in other important ways. First, trials varied in their definitions of outcomes, but with IPD, we were able to recalculate the outcomes based on a consistent definition. Second, for all continuous outcomes, we were able to adjust for potential baseline imbalances. Only the two most recent trials adjusted for potential baseline imbalance while comparing the rhBMP-2 and control groups,[27, 29] and none reported the adjustment mean differences that could be used in study-level meta-analyses. In other studies, baseline imbalance produced a biased estimate of mean difference and generated false significant results. For example, Baskin et al.[9] reported superior improvement in neck disability and arm pains scores in the rhBMP-2 group, but this improvement became insignificant after adjusting for baseline difference.

Lastly, IPD allowed us to better handle missing data. For example, overall success and fusion are based on multiple criteria and yet trial protocols did not define how to handle cases where patients were missing criteria data. With IPD, we could make assumptions about partial missing data to calculate more than one version of the variables and using sensitivity analyses check the impact of "missingness" on the robustness of results. On the other hand, IPD analysis requires substantially more time and resources than a regular meta-analysis based on study level data, especially, as in this case, where all derived variables were required to be recalculated from raw data.

Usefulness of Other Manufacturer-provided Documents

Along with IPD, we also received trial protocols and internal reports, many of which the manufacturer had submitted to the FDA. In addition to providing definitions of outcome variables, the protocols were very helpful for assessing the quality of the trials. Incomplete or inadequate reporting of methods may result in downgrading of study quality even though a study was conducted properly. Trial protocols provide more complete information to evaluate the adequacy of randomization and allocation concealment, specification of primary versus secondary outcomes, and reporting bias. In fact, the trial protocols and the internal reports provided all the necessary information for assessing the quality of the Medtronic studies. The internal reports also provided brief case histories for adverse events that were helpful in two ways: 1) they helped us to cross check the adverse event data in the derived dataset; and 2) they allowed us to parse out more specific adverse events that were aggregated into categories with other adverse events in the IPD supplied by Medtronic (e.g., urinary retention was aggregated into urogenital) and evaluate adverse events that were not predefined in the studies (e.g., possible lumbar radiculitis).

The protocols and internal reports were essential to assess whether journal publications were consistent with what Medtronic reported to the FDA. As described earlier, some of the analyses reported in publications were not included in reports to the FDA. With respect to effectiveness

data, information that was crucial for assessing the validity of analyses was reported to the FDA but was omitted in journal publications. We also found that adverse events identified in the trials had been thoroughly reported in the Medtronic internal documents to the FDA, even though they were underreported in journal articles.

MedWatch reports were helpful in cases where the manufacturer responded to the published literatures' reports of death or other AEs in the MedWatch reports. For example, in an article by Yaremchuck, eight individuals having cervical spine fusion required tracheotomy.[128] We initially excluded this study because we could not determine if this was rhBMP-2 or rhBMP-7. The manufacturer response in the MedWatch reports allowed us to confirm the use of rhBMP-2 and include this paper. However, in general, MedWatch reports were not very useful in assessing the harms of rhBMP-2. Based on data from the Nationwide Inpatient Sample database,[11] a 20% sample of US community hospitals, 17,495 spine fusions were performed using BMP in 2006 alone, while over the past 10 years, only 1,229 MedWatch reports were filed, representing a very small sample compared with the potential cases of rhBMP-2 use. Importantly, it is not possible to determine the representativeness of the adverse events experienced with rhBMP-2 in general use. MedWatch reports can be useful for identifying rare adverse events not described in cohort studies and RCTs. However, in our MedWatch analysis, we did not find new rare or alarming adverse events.

Limitations

Study Sponsorship

We planned to assess the association between estimates of effectiveness and harm and study sponsorship, but we did not find adequate data to assess such associations in this review. Industry sponsorship is a potential source of bias in study outcomes[179, 180] and industry-sponsored studies often have more favorable outcomes than do studies not sponsored by industry.[181, 182] However, because nearly all evidence from RCTs in this review came from manufacturer-sponsored RCTs, we were unable to compare this evidence with evidence from non-industry-sponsored studies. Only one RCT (n=102) was not manufacturer sponsored,[34] but its authors were actively involved in other manufacturer-sponsored trials. Unfortunately, there were no RCTs with a funding source truly independent of the manufacturer that could provide comparison to the results of manufacturer sponsored RCTs. If we look at the results from RCTs compared with cohort studies, while there is no fundamental difference between the two sets of results, the assessment was completely confounded by study design.

Sparse Data

Even with IPD on 1,879 patients, from 12 trials, the evidence base is small within each surgical approach. Only two pivotal trials each were available for meta-analyses of ALIF and PLF, and one ALIF pivotal trial terminated early before all planned subjects were recruited. For both ALIF and PLF, the results suggested that rhBMP-2 may be associated with higher fusion rates, but it is only statistically significant at the interim 6 months. Similarly for harms, the results suggested that rhBMP-2 may be associated with higher implant displacement, subsidence, urogenital events, and retrograde ejaculation, but we were unable to draw definite answers for these outcomes either. The problem may be more serious for adverse events given the poorer ascertainment. Additionally, there has been no prospective, well-designed, adequately-powered study specifically aimed to assess important harms using adequate ascertainment methods. On a

related note, while limited evidence on comparative effectiveness and harms of rhBMP-2 were available from less than 2,000 patients of RCTs, tens of thousands of spine fusions were performed using rhBMP-2. For example, for anterior cervical spine fusion, the only RCT included 33 patients in two treatment groups, which was too small to detect any specific adverse event. However, in 2006 alone, 2,299 anterior cervical fusions with BMP were performed, based on a national sample of 20% of U.S. community hospitals.[11]

A few large cohort studies assessed complication rates associated with BMP use in routine care.[11, 147, 172] However, the use of rhBMP-2 and rhBMP-7 was not separated due to the setup of billing codes in a manner to allow us to evaluate the association with rhBMP-2 only. We could only include the results from two cohort studies[11, 147] as they were U.S. studies and few, if any, cases of rhBMP-7 use are likely. rhBMP-7 was a Humanitarian Use Device (HUD) indicated for revision posterolateral lumbar spinal fusion in the U.S.,[183] and there was a HUD-imposed restriction allowing treatment of fewer than 4,000 individuals per year.[184]

Assessment of Dosage Effect

There was also insufficient information to adequately evaluate the effects of dose on risk of harms. Eleven Medtronic studies (Studies 1-11) used rhBMP-2 at a concentration of 1.5mg/mL, with total doses ranging from 0.6-16.8 mg. Higher and unapproved concentrations of rhBMP-2 (2.0-3.0 mg/mL) were used in five of the six PLF studies, with total doses ranging from 15.0-63.0 mg. We did separate analyses for ALIF trials and PLF trials so the trials using low dosage rhBMP-2 were evaluated separately from trials using higher dosage, however, determining the effects of rhBMP-2 dosage was not possible due to differences in surgical approach, rhBMP-2 carrier, and fusion hardware.

Materials to Assess Reporting Bias

Although we had unusual access to protocols and documents submitted by the manufacturer to the FDA, other information, such as operative notes and internal correspondence, might have helped assess the extent of design and reporting bias. Internal correspondence is essential to evaluate selective analysis reporting, ghostwriting, time lag bias, and misrepresentation of facts.[23] Finally, we did not receive case report forms and, therefore, were not able to evaluate the integrity of adverse event adjudication. We do know that protocols called for an independent Data Safety Monitoring Board, which included two physicians who were not study investigators, and either a biostatistician or an epidemiologist.

Future Research and Conclusions

We found substantial evidence of reporting bias, no evidence that rhBMP-2 is more effective than ICBG in spinal fusion, and some evidence of an association with important harms. Despite data collection limitations for effectiveness outcomes, mainly lack of blinding, rhBMP-2 appeared to be at least as effective as ICBG. The quality of harms data was much worse due to both poor ascertainment and lack of blinding, preventing any strong conclusion. Journal articles should require complete adverse events reporting in order to present a balanced picture of benefits and harms. Based on the currently available evidence, it is difficult to identify clear indications for rhBMP-2 in spinal fusion.

Future research is needed to provide reliable estimates on risk of cancer and other specific adverse events such as retrograde ejaculation, osteolysis, subsidence, heterotopic bone formation, and radiculitis. It will be important to determine the best effective dose of rhBMP-2 to balance

benefits with potential harms, and to identify patient populations in which use of rhBMP-2 may be beneficial, such as cases where use of bone graft alone is associated with a high risk of pseudoarthrosis or in children with certain congenital and acquired spinal defects. Meta-regression using the IPD could help to clarify how the benefits and harms differ by patient characteristics and comorbidities.

Results from the large database would be more helpful if patients using rhBMP-2 could be distinguished from patients using rhBMP-7. Use of large prospective cohort or open label trials, where patients are given true informed consent with rigorous and completed ascertainment of pre-defined outcomes, along with statistical techniques to reduce bias and confounding (such as propensity score) could provide better results for the comparative harms of rhBMP-2.

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ABBREVIATIONS AND ACRONYMS

ACDF	anterior cervical discectomy and fusion
ACS	absorbable collagen sponge
ALIF	anterior lumbar interbody fusion
ASIA	American Spinal Injury Association
BCP	biphasic calcium phosphate
CI	confidence interval
CRF	case report form
CRM	compression resistant matrix
FDA	U.S. Food and Drug Administration
HUD	Humanitarian Use Device
ICBG	iliac crest bone graft
IDE	investigational device exemption
IPD	individual patient data
IS	intervention series
NDI	Neck Disability Index
ODI	Oswestry Disability Index
NNH	number needed to harm
PEEK	polyetheretherketone
PLIF	posterior lumbar interbody fusion
PLF	posterolateral lumbar fusion
RCT	randomized controlled trial
rhBMP-2	recombinant human bone morphogenetic protein-2
RR	risk ratio
SD	standard deviation
SEER	Surveillance Epidemiology and End Results Program, National Cancer Institute
TLIF	transforaminal lumbar interbody fusion
TSRH	Texas Scottish Rite Hospital
VAS	visual analog score
WMD	weighted mean difference
YODA	Yale Open Access Data Project

GLOSSARY

This glossary defines terms as they are used in reports produced by the Oregon Evidence-based Practice Center, Drug Effectiveness Review Project, at Oregon Health & Science University. Additional definitions specific to this report have been defined using available medical dictionaries and other resources. Definitions may vary slightly from other published definitions.

ACDF (anterior cervical discectomy and fusion): A surgical procedure performed to remove a herniated or degenerative disc in the cervical (neck) spine and then fuse together the vertebrae above and below the disc space. The surgical approach for this type of procedure is from the front, through the throat area.

ACS (absorbable collage sponge): surgical sponge made of collagen; used to fill surgical space and as a carrier for *rhBMP-2*.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

ALIF (anterior lumbar interbody fusion): A surgical procedure wherein a disc space within the lower back is fused by inserting a bone graft and/or spinal implant (e.g. cage) directly into the disc space. Termed *anterior* because the spine is approached through the abdomen (the front).

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Allograft: A graft in which transplanted cells, tissues, or organs are sourced from a genetically non-identical member of the same species (as opposed to *autograft*, below).

ANCOVA (analysis of covariance): A statistical test that compares one variable in 2 or more groups taking into account (or to correct for) variability of other variables, called covariates.

Applicability: see *External validity*

Arthrodesis: The artificial induction of joint ossification between two bones via surgery, which is done to relieve intractable pain in a joint which cannot be managed by other treatments.

ASIA(American Spinal Injury Association)Score: The overall score is based on a motor and a sensory score. The motor score is based on the examination of 10 key-muscles on each side. For each movement, force is measured and assigned a coefficient from 0 (absence of muscle contraction) to 5. The sensory score is established after studying tact and prick sensitivity on a key point in each of 28 dermatomes on each side. Absence of sensitivity is quoted: 0, the hypo or the hyperesthesia: 1 and normal sensitivity: 2.

ATLANTIS Anterior Cervical Plate System: A ratcheting plate featuring segments that translate under compression, but maintain their position under tension. This system is intended for use in temporary stabilization of the anterior cervical spine (C2-T1) during the development of spinal fusions.

Autograft: A tissue graft transferred from one part of the patient's body to another part (as opposed to *allograft*, above).

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

BMP (Bone Morphogenetic Protein): Belongs to the TGF-β superfamily of proteins and plays an important role in the development of bone and cartilage.

Bone Dowel: An interbody device used for fusing or reconstructing bones.

Boxed warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Bridging trabeculae: Any of the fine spicules forming a network in cancellous bone crossing a fracture site.

C1-C7 (cervical vertebrae): The seven vertebrae, numbered top (C1) to bottom (C7), immediately inferior to skull and that allow for neck and head movement.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case report: A study reporting observations on a single patient.

CD Horizon Legacy Spinal System: Consists of rods, hooks, and screws for implantation in the spine to correct the abnormal curvature and is made out of titanium or stainless steel implantable grade metal.

Cervical: Relating to the top part of the spine that is composed of the seven vertebrae of the neck and the discs that separate them.

Clinically significant: A result that is large enough to affect a patient’s disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study uses data from records to evaluate exposures and outcomes that occurred in the past.

CI (confidence interval): The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used . If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

CT Scan (computerized axial tomography): A radiographic technique that produces an image of a detailed cross section of tissue.

DDD (degenerative disc disease): Degeneration of the intervertebral disc that often leads chronic low back pain that sometimes radiates to the hips, pain in the buttocks or thighs while walking, and/or sporadic tingling or weakness through the knees.

Demineralized bone matrix: Allograft bone that has had the inorganic mineral removed, leaving behind the organic collagen matrix.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Dysphagia: Medical term for the symptom of difficulty swallowing.

Dysphonia: Difficulty in speaking, usually evidenced by hoarseness.

Ectopic bone: Bone which develops in abnormal or out of place sites.

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Facet : A (synovial) joint between the superior articular process of one vertebra and the inferior articular process of the vertebra directly above it.

Femoral ring allograft: A manufactured, uniform, wedge–shaped, allograft. Generally used in ALIF approach procedures.

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Harms: See *Adverse event*

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

Heterotopic ossification: A nonmalignant overgrowth of bone outside of the skeleton.

Hydroxyapatite crystal: A calcium phosphate complex that is the primary mineral component of bone.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

ICBG (Iliac Crest Bone Graft): A surgical procedure that replaces missing bone with material from the patient's iliac crest.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

INFUSE: Name under which rhBMP-2 is marketed in the U.S by Medtronic. INFUSE comes in kits of varying sizes that include rhBMP-2 and absorbable collagen sponges.

InductOs: Name under which rhBMP-2 is marketed in Eurpope. InductoOs comes in kits of varying sizes that include the active substance, rhBMP-2 (dibotermin alfa in the U.K.), a solvent, and collagen sponges.

Inter Fix threaded fusion device: Consists of a hollow, perforates, metallic cylinder and endcap and is available in a variety of diameters. Use is indicated for spinal fusion procedures at one level from L2-S1. To be used with autogenous bone graft and implanted via an open anterior approach.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Intervertebral foramina: Apertures within every pair of vertebrae that allow for the passage of the spinal nerve root, dorsal root ganglion, the spinal artery of the segmental artery, and communicating veins to body.

Instrumentation: Utilizes surgical procedures to implant titanium, titanium-alloy, stainless steel, or non-metallic devices into the spine. Instrumentation provides a permanent solution to spinal instability. Medical implants are specially designed and come in many shapes and sizes. Typically these include rods, hooks, braided cable, plates, screws, and interbody cages. Cages are simply structures that support bones (either between bones or in place of them) while new bone growth occurs through and around them.

IPD (individual patient data): The raw data for each study participant included in a trial, as opposed to aggregate data.

L1-L5 (Lumbar Vertebrae): The five vertebrae, numbered top (L1) to bottom (L5), between thoracic and sacral vertebrae that allow for flexion and extension, moderate lateral flexion (sidebending), and a small degree of rotation.

Lamina: two broad plates, extending dorsally and medially from the pedicles, fusing to complete the roof of the vertebral arch.

Laminectomy: A spine operation to remove the portion of the vertebral bone called the lamina and also, commonly, the spinous process, overlying ligaments and muscles, and connective tissue.

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

LT Cage lumbar tapered fusion device: A small, hollow, threaded, tapered cylinder that is intended to restore the degenerated disc space to its original height. For use specifically with *INFUSE*.

Lumbar: Pertaining to the lower back area between T12 vertebra and the sacrum.

MAVERICK: An artificial invertebral disc manufactured by Medtronic.

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Nurick Scale: A six-grade system (0-5) based on the “difficulty in walking”.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Oswestry Disability Index: One of the principal condition-specific outcome measures used in the management of spinal disorders, commonly used in patients with low back pain. There are 10 questions that are designed in a way that to realize how the back or leg pain is affecting the patient's ability to manage in everyday life.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Ossification: Formation of or conversion into bone or a bony substance.

Osteoblasts: A cell from which bone develops; a bone-forming cell.

Osteoclast: A large multinucleate cell found in growing bone that “chews” bone and that resorbs bony tissue, as in the formation of canals and cavities

Osteolysis: The degeneration and dissolution of bone caused by disease, infection, or ischemia

Osteomyelitis: Refers to a bone infection, almost always caused by a bacteria. Over time, the result can be destruction of the bone itself.

Outcome: The result of care,treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person that can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Pedicle screws: A form of spinal fusion instrumentation. Pedicle screws are used as anchor points placed on consecutive spinal segments to connect a rod in order to fixate a segment of spine.”

PEEK (polyetheretherketone) Cage: An interbody cage made of a semicrystalline thermoplastic with excellent mechanical and chemical resistance properties that are retained to high temperatures. Can be packed with bone graft material.

PLIF (posterior lumbar interbody fusion): A surgical procedure wherein a disc space within the lower back is fused by inserting a bone graft and/or spinal implant (e.g. cage) directly into the disc space. Termed *posterior* because the spine is approached from the back.

PLF (posterior lumbar fusion): A surgical procedure wherein a disc space within the lower back is fused by approaching the spine through from the back. Differentiated from *PLIF* because there is no *interbody* implant directly into the disc space.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Pseudoarthrosis: A pathological entity characterized by a nonosseous union of bone fragments of a fractured bone due to inadequate immobilization leading to existence of the 'false joint' that gives the condition its name.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Radiculitis: Inflammation of a spinal nerve root, especially of the portion of the root that lies between the spinal cord and the spinal canal, which results in pain and hyperesthesia.

Radiographic fusion: Appearance of a continuous bond between adjacent vertebral segments (see also *radiolucency*).

Radiolucency: The ability of materials of relatively low atomic number to allow most x-rays to pass through them, producing dark images on x-ray film.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Resorption: The loss of substance or bone by physiologic or pathologic means, such as the reduction of the volume and size of the residual ridge of the mandible or maxillae.

Retrograde ejaculation: Ejaculation in which the discharged seminal fluid travels up toward the bladder instead of outside the body through the urethra.

Retroperitoneal: A surgical exposure created by going behind the abdominal cavity. In this approach, the peritoneal sac of the abdomen is mobilized (made free from other tissue) and retracted laterally (to the side). The peritoneum is dissected away from the great vessels and the anterior spine is exposed without entering the abdominal cavity.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

rhBMP-2: Plays an important role in the development of bone and cartilage and is an osteogenic *BMP* (as is rhBMP-7) that has been demonstrated to induce osteoblast differentiation in a variety of cell types.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

S1-S5 (sacral vertebrae): Five vertebrae, numbered top (S1) to bottom (S5), that are fused together by mid 20s to form the large triangular bone at the base of the spine know as the *sacrum*.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Safety signal: Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.[2]

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Scoliosis, idiopathic: An abnormal condition characterized by a lateral curvature of the spine. It is the most common type of scoliosis.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are in relationship to uncertain decisions or assumptions about the data and the methods that were used.

SF-36 Health Survey: A 36 question general health survey that provides a summary assessment physical and mental health. Also PCS (Physical Component Summary), MCS (Mental Component Summary).

[2] Guideline on Good Pharmacovigilance Practices (GVP). Annex I – Definitions. London: European Medicines Agency; February 20, 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123202.pdf

SPIRE stabilization system, CD Horizon: It is a fixation device, or plate, that may be attached to the spinous processes, providing the potential for spinal stability through a less-invasive surgical approach. It is utilized in addition to pedicle screws.

Spondylolisthesis: The partial forward dislocation of one vertebra over the one below it, most commonly the fifth lumbar vertebra over the first sacral vertebra.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Subsidence: Sinking or settling in a bone.

T1-T12 (thoracic vertebrae): The 12 vertebrae, numbered top (T1) to bottom (T12), between lumbar and cervical vertebrae and which have surfaces that articulate with the ribs.

Titanium mesh cage: Cage made of titanium, created as a substitute for bone graft. Can be filled with bone graft.

TLIF (transforaminal lumbar interbody fusion): A surgical procedure in which a disc space within the lower back is fused by inserting a bone graft and/or spinal implant (e.g. cage) directly into the disc space to limit movement between the bones and reduce pain.

TSRH Spinal system: Consists of a variety of shapes and sizes of rods, hooks, screws, cross connectors, staples, plates, and connecting components, as well as implant components from other Medtronic spinal systems, which can be rigidly locked into a variety of configurations, with each construct being tailor-made for the individual case.

Urinary Retention: The inability or difficulty to completely void the urinary bladder.

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g., 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g., hemoglobin A1c values).

VAS (visual analog scale) scores: Helps assess the impact that your shoulder pain has had on your daily life in the past four weeks.

Vertebral column (spine): The column usually consisting of 24 articulating vertebrae (cervical, thoracic, and lumbar) and 9 fused vertebrae in the sacrum and the coccyx that houses and protects the spinal cord in its spinal canal.

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

X^2*:* Chi square statistic. It is used to investigate whether distributions of categorical variables differ from one another.

Appendix A. Boxed Warnings[1-3]

Product	Boxed Warnings
INFUSE® Bone Graft	Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of INFUSE Bone Graft in tibial fracture, 9/149 (6.0%) patients treated with INFUSE Bone Graft and 1/150 (0.7%) patients treated without exposure to rhBMP-2 developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects. The safety and effectiveness of INFUSE Bone Graft in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk. Women of childbearing potential should be advised not to become pregnant for one year following treatment with INFUSE Bone Graft.
InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device	Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, 2/277 (0.7%) patients treated with INFUSE Bone Graft component and 1/127 (0.8%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects. The safety and effectiveness of InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk. Women of childbearing potential should be advised not to become pregnant for one year following treatment with InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

1. Medtronic Sofamor Danek. Boxed Warning for INFUSE® Bone Graft. 2004.
2. Medtronic Sofamor Danek. InFUSE(TM) Bone Graft/LT-CAGE TM Lumbar Tapered Fusion Device. 2002.
3. Medtronic Sofamor Danek. INFUSE® Bone Graft for Certain Oral Maxillofacial and Dental Regenerative Uses. 2007.

Appendix B. Reconciled Aims

Rigorous systematic review and evidence synthesis to determine the safety and effectiveness of rhBMP-2. The project should address the following aims:

1. Identify all relevant studies, across all uses and sponsor (i.e., Medtronic sponsored and others).
2. Determine the questions that were addressed by these studies.
3. Evaluate the quality of the studies. Assess the risk of bias associated with the design, conduct, and reporting of each clinical study, including those identified via the systematic review and those provided by Medtronic, and, if present, how bias may have affected assessment of effectiveness and harms.
    a. Assessment of study design and conduct should include evaluation of internal validity, methods used to ascertain outcomes and other policies and procedures for data collection, as well as, the integrity of case report form (CRF) adjudication.
    b. Assessment of study reporting should include selective publication and selective reporting.
    c. Summary of these findings should include
        i. what conclusions can be drawn by assessing the full body of data and what gaps in knowledge remain, taking into account results from the evaluation of quality and risk of bias, and
        ii. an assessment of applicability of these studies.
4. Conduct meta-analyses from studies identified via the systematic review, if appropriate and using patient-level data, if possible. If not appropriate there should be another approach to summarizing the data. The analysis should consider the following:
    a. For effectiveness, meta-analysis should consider patient-centered outcomes (i.e., quality of life and functional status), as well as surrogate outcomes (i.e., fusion as determined by radiography).
    b. For safety, meta-analysis should include all harms described in the Request for Proposal.

Appendix C. List of Study Documents Provided by Medtronic*

Medtronic Trial (Study number)	Study Protocol	Radiographic Review	Statistical Plan	Final Report	Final Antibody Report	Major Protocol Deviation List	Other Documents
INFUSE®/LT-CAGE® Pilot RCT (1)	●			● Volumes 1, 2	●		
INFUSE®/LT-CAGE® Pivotal RCT (2)	●	●	●	● Volume 1†	● in Final Report		PMA CSR
INFUSE®/LT-CAGE® Lap Pivotal IS (3)	●	●	●	● Volume 2†	● in Final Report		PMA CSR
INFUSE®/Bone Dowel Pilot RCT (4)	●			●	●		
INFUSE®/Bone Dowel Pivotal RCT (5)	●	●	●	●	●		
INFUSE®/Interfix® PLIF RCT (6)	●	●	●	●	● in Final Report		
INFUSE®/Cornerstone® ACDF Pilot RCT (7)	●	●		●	● in Final Report		
INFUSE®/Mastergraft® Pilot RCT (8)	●	●		●	● in Final Report		
INFUSE®/Interfix® ALIF Pilot RCT (9)	●	●		●	● in Final Report		
Maverick_Disc_Pivotal (10)	●	●	●	● Volumes 1-4	●		
INFUSE®/Telamon® IS (11)	●	●		●	● in Final Report		Explanted Device Analysis
BMP/BCP_US RCT (12)	●	●		●	● in Final Report		
BMP/BCP_Canada RCT (13)	●	●	●	●	● in Final Report		Explanted Device Analysis
Amplify® Pivotal RCT (14)	●	●	●	● Parts A, B	●	● in PMA CSR	PMA CSR, Appeal Presentation, Explanted Device Analysis
BMP/CRM 2-Level IS (15)	●	●		●	● in Final Report		

BCP Mexico IS (16)	●	●		●			
INFUSE®/Cornerstone® ACDF Pivotal RCT (7)	●	●	●	●	● in Final Report		

PMA = premarket approval; CSR = clinical study report

*Additional documents provided by Medtronic:

Cancer Report
Cancer Table
3rd Party Review Plan and Appendices 1-2, 29 August 2011
3rd Party Review Plan and Appendices 1-3, 09 August 2011
Use of Second Surgery Failure and Serious Adverse Events (SAE), 30 August 2011
Documentation for Adverse Event (AE) Case History Narrative
File Folder Structure LT-Cage Pilot
Medical Device Report Data Description
Medtronic rhBMP-2 I De-identification Determination, 12 September 2011
Adverse Event Reports for MAVERICK IDE Study, Note to File—MAV AE Explanation
Adverse Event Tables for INFUSE/LT CAGE IDE Study, 09 September 2011, Note to File—LY CAGE AE Table Explanation
Summary Document, 25 August 2011 – Summary Information on Medtronic Clinical Trials
Summary Medtronic rhBMP-2 I Statistical De-Identification Determination, 08 December 2011
Summary Medtronic rhBMP-2 I Statistical De-Identification Determination, 12 September 2011
Medical Device Reports, 100+ individual documents
Various Document Indexes for each study and the cancer report

†Medtronic combined reports for study 2 and study 3 to the Food and Drug Administration; the final report for study 2 is volume 1 and the final report for study 3 is volume 2.

Appendix D. Search Strategies

Searches were repeated in June and August 2012 to identify additional citations.

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to December Week 4, 2011>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 09, 2012

1	Bone Morphogenetic Protein 2/	3737
2	Bone Morphogenetic Proteins/	9745
3	bone morphogen$ protein-2.ti,ab.	2737
4	bone morphogen$ protein-ii.ti,ab.	5
5	bone morphogen$ protein2.ti,ab.	3
6	human recombinant BMP-2.ti,ab.	8
7	human recombinant BMP2.ti,ab.	2
8	recombinant human BMP-2.ti,ab.	146
9	recombinant human BMP2.ti,ab.	15
10	recombinant human bone morphogen$ protein-2.ti,ab.	793
11	recombinant human bone morphogenetic protein-2.rn.	749
12	BMP.ti,ab.	10098
13	BMPs.ti,ab.	2953
14	BMP-2.ti,ab.	3108
15	BMP-ii.ti,ab.	6
16	BMP2.ti,ab.	1373
17	rhBMP-2.ti,ab.	1106
18	rhBMP2.ti,ab.	62
19	rhBMP.ti,ab.	1230
20	rhBMPs.ti,ab.	34
21	rh-BMP.ti,ab.	62
22	hrBMP-2.ti,ab.	2
23	hr-BMP.ti,ab.	3
24	(infuse adj10 bone$).ti,ab.	36

25	InductOS.ti,ab.	3
26	Dibotermin alfa.ti,ab.	2
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	15572
28	27 and humans/	6856
29	27 not (humans/ or animals/)	1010
30	28 or 29	7866
31	limit 30 to yr="1996 -Current"	7484

Database: Elsevier Embase <January 09, 2012>
Search Strategy

1	'bone morphogenetic protein 2'/de	5,457
2	'bone morphogenetic protein'/de	8,773
3	'recombinant bone morphogenetic protein 2'/de	1,498
4	'bone morphogenetic protein 2':ab,ti	2,763
5	'bone morphogenic protein 2':ab,ti	211
6	'bone morphogenetic protein ii':ab,ti	4
7	'bone morphogenetic protein2':ab,ti	6
8	'human recombinant bmp-2':ab,ti	12
9	'human recombinant bmp2':ab,ti	3
10	'recombinant human bmp-2':ab,ti	164
11	'recombinant human bmp2':ab,ti	13
12	'recombinant human bone morphogenetic protein-2':ab,ti	857
13	'recombinant human bone morphogenic protein-2':ab,ti	28
14	bmp:ab,ti	10,979
15	'bmps':ab,ti	3,131
16	'bmp-2':ab,ti	3,357
17	'bmp-ii':ab,ti	7
18	'bmp2':ab,ti	1,540
19	'rhbmp-2':ab,ti	1,266
20	'rhbmp2':ab,ti	71
21	'rhbmp':ab,ti	1,412
22	'rhbmps':ab,ti	40
23	'rh-bmp':ab,ti	77
24	'hrbmp-2':ab,ti	4
25	'hr-bmp':ab,ti	3
26	infuse NEAR/10 bone	99
27	inductos:ab,ti	7
28	inductos:tn	33
29	'dibotermin alfa':ab,ti	4

30	'dibotermin alfa':tn	3
31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	18,712
32	#31 and (1996:py or 1997:py or 1998:py or 1999:py or 2000:py or 2001:py or 2002:py or 2003:py or 2004:py or 2005:py or 2006:py or 2007:py or 2008:py or 2009:py or 2010:py or 2011:py or 2012:py) and [embase]/lim	15,170
33	#31 and (1996:py or 1997:py or 1998:py or 1999:py or 2000:py or 2001:py or 2002:py or 2003:py or 2004:py or 2005:py or 2006:py or 2007:py or 2008:py or 2009:py or 2010:py or 2011:py or 2012:py) and 'human'/de and [embase]/lim	6,480
34	#31 and (1996:py or 1997:py or 1998:py or 1999:py or 2000:py or 2001:py or 2002:py or 2003:py or 2004:py or 2005:py or 2006:py or 2007:py or 2008:py or 2009:py or 2010:py or 2011:py or 2012:py) and [embase]/lim not ('nonhuman'/de or 'animal model'/de or 'animal cell'/de or 'animal tissue'/de or 'human'/de)	1,602

Database: Ovid EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2011>, Cochrane Database of Systematic Reviews <2005 to December 2011>, Database of Abstracts of Reviews of Effects <4th Quarter 2011>, Health Technology Assessment <4th Quarter 2011>
Search Strategy:

1	bone morphogen$ protein-2.ti,ab.	37
2	recombinant human BMP-2.ti,ab.	1
3	recombinant human bone morphogen$ protein-2.ti,ab.	36
4	BMP.ti,ab.	67
5	BMPs.ti,ab.	9
6	BMP-2.ti,ab.	12
7	BMP2.ti,ab.	3
8	rhBMP-2.ti,ab.	49
9	rhBMP.ti,ab.	60
10	(infuse adj10 bone$).ti,ab.	9
11	Dibotermin alfa.ti,ab.	1
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	127
13	limit 12 to yr="1996 -Current" [Limit not valid in DARE; records were retained]	123

Database: Sciverse Scopus <01/11/2012>
Search Strategy:

(TITLE-ABS-KEY**({bone morphogen* protein*}** or **bmp** or **bmp-2** or **{BMP 2}** or **bmp-ii** or **{BMP ii}** or **bmpii** or **rhbmp** or **rhbmp-2** or **rhbmp2** or **{rhBMP 2}** or **rhbmp-ii** or **rhbmpii** or **{rhBMP ii}** or **rh-bmp** or **rh-bmp-2** or **rh-bmp2** or **{rh-BMP 2}** or **rh-bmp-ii** or **rh-bmpii** or **{rh-BMP ii}** or **hrbmp** or **hrbmp2** or **hrbmp-2** or **{hrBMP 2}** or **hrbmp-ii** or **hrbmpii** or **{hrBMP ii}** or **hr-bmp** or **{hr-BMP 2}** or **hr-bmp-2** or **hr-bmp2** or **hr-bmp-ii** or **hr-bmpii** or **{hr-BMP ii}** or **infuse** W/10 **bone** or **inductos** or **{dibotermin alfa}))** and SUBJAREA**(medi)** and PUBYEAR > **1995 (3,948)**

Database: clinicaltrials.gov <01/11/2012>
Search Strategy:

"bone morphogenetic protein*" or BMP* or rh-BMP* or “Infuse Bone” or "Dibotermin alfa" or InductOS | Closed Studies | received from 01/01/1996 to 01/11/2012 (63)

Database: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)**,** http://apps.who.int/trialsearch/AdvSearch.aspx <01/11/2012> (38)
Search Strategy:

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bone morphogenetic protein or bone morphogenic protein or BMP or rhBMP or rhBMP-2 or rhBMP2 or rhBMP-ii or rhBMPii or rh-BMP or rh-BMP-2 or rh-BMP2 or rh-BMP-ii or rh-BMPii or hrBMP or hr-BMP or hr-BMP-2 or hr-BMP2 or hr-BMP-ii or hr-BMPii or INFUSE Bone or Infuse Bone or InductOS or INDUCTOS or dibotermin alfa or Dibotermin Alfa AND date = 01/01/1996-11/01/2012

Database: Current Controlled Clinical Trials (ISRCTN Register)**,** http://www.controlled-trials.com/isrctn/ <01/11/2012> (10)
Search Strategy:

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bone morphogenetic protein or bone morphogenetic proteins or bone morphogenic protein or bone morphogenic proteins or BMP or BMPs or rhBMP or rhBMPs or rhBMP-2 or rhBMP2 or rhBMP 2 or rhBMP-ii or rhBMPii or rh-BMP or rh-BMPs or rh-BMP-2 or rh-BMP2 or rh-BMP-ii or rh-BMPii or hrBMP or hrBMPs or hrBMP-2 or hrBMP2 or hrBMP-ii or hr-BMP or hr-BMPs or hr-BMP-2 or hr-BMP2 or hr-BMP-ii or hr-BMPii or Infuse Bone or InductOS or dibotermin alfa

Appendix E. List of SAS Data Sets Provided by Medtronic*

Table E-1a. Study 1: INFUSE®/LT-CAGE® Pilot—Raw Data

SAS Data Set	Variable Information	Time Points
PREOP1	Patient enrollment demographics, patient qualification for study, pre-operative medical data	Enrollment
PREOP2	Neurological/ functional status (reflexes, sensory, motor, straight leg raise), Oswestry questionnaire (10 questions)	Pre-operative
PREOP3	SF-36 (36 questions)	Pre-operative
SURGERY	Surgery data	Time of surgery
POSTOP6W	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	6 weeks
POSTOP3M	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	3 months
POSTOP6M	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	6 months
POSTOP12M	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	12 months
POSTOP24M	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	24 months
POSTOP36M	Postoperative date (medical, work), neurological/functional status (reflexes, sensory, motor, straight leg raise, pain), Oswestry questionnaire (10 questions), SF-36 (36 questions)	36 months
RADREV	Radiographic review- pre-operative radiographs (type of x-ray, other imaging, measurements, disc space)	Pre-operative
RADREV6W	Radiologic review – CT (bone formation, comments)	6 week
RADREV3M	Radiologic review – CT (bone formation, comments)	3 months
RADREV6M	Radiologic review – CT (bone formation, comments)	6 months
RADREV12	Radiologic review – CT (bone formation, comments)	12 months
RADREV24	Radiologic review – CT (bone formation, comments)	24 months
RADREVOT	Radiologic review – CT (bone formation, comments)	Other

* Medtronic also provided additional data on dates of collecting blood specimens for antibody and dates of collecting radiographic data, which did not provide actual data on patient outcomes and were not separately accounted for here.

Table E-1b. Study 1: INFUSE®/LT-CAGE® Pilot—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12 and 24months when events occurred
D_SURG2	All additional surgeries	3, 12 and 24 months when events occurred
D_TRT	Patient and treatment dataset	NA

Table E-2a. Study 2: INFUSE®/LT-CAGE® Pivotal—Raw Data

SAS Data Set	Variable Information	Time Points
DISCHARGE	Hospital discharge data	Discharge
ENROLL	Patient demographic characteristics at enrollment	Enrollment
NEURO	Neurological status (sensory, motor, reflexes, straight leg raise)	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
OWESTRY	Oswestry disability score (10 questions)	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
PAIN	Back and leg pain, Hip pain at donor site	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
POSTDATA	Postoperative data (comorbidities, return to work, etc)	1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only
PREOP	Pre-operative data (health characteristics)	Pre-operative
QUALIF	Patient qualifications for study	Enrollment
RADREVCT	Radiologic data - CT	6 and 12 months
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
SURGERY	Surgery data	Time of surgery

SAS Data Set	Variable Information	Time Points
SURVEY	Patient survey (medical characteristics, work status, satisfaction)	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
TRADREV	Radiologic review (disc measurements, implant characteristics, radiolucent lines, evidence of bridging bone)	Pre-operative , 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only– data were very sparse at 36 months.

Table E-2b. Study 2: INFUSE®/LT-CAGE® Pivotal—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12, 24 for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only when events occurred
D_ALLSUC	Overall success variable and its components	1.5, 3, 6, 12, 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
D_FUSION	Fusion success (overall success, failure, second surgery failure)	6, 12, 24 months postop for rhBMP-2 and ICBG group, and 48 and 72 months postop for rhBMP-2 only.
D_IVDH	Disc height success status	Pre-operative, postoperative, 1.5, 3, 6, 12, 24 months postop for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
D_NEURO	Neurological success variable and its components	Pre-operative, 1.5, 3, 6, 12, 24 for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24 for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
D_PAIN	Back, leg, and hip pain; change from pre-op; success	Pre-operative, 1.5, 3, 6, 12, 24 for rhBMP-2 and ICBG group, and 36, 48 and 72 months postop for rhBMP-2 only.
D_SF-36	SF-36 health survey scores and success variables	Pre-operative, 1.5, 3, 6, 12, 24 for rhBMP-2 and ICBG group,

SAS Data Set	Variable Information	Time Points
		and 36, 48 and 72 months postop for rhBMP-2 only.
FAILURE	Second surgery failures	1.5, 6, 12, 24 for rhBMP-2 and ICBG group, and 48 and 72 months postop for rhBMP-2 only when events occurred.
SAE	Serious device or device/surgery related adverse events	1.5, 6, 12, 24 for rhBMP-2 and ICBG group, and 36 and 48 months postop for rhBMP-2 only when events occurred.
D_SURG2	All additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, for rhBMP-2 and ICBG group, and 48 and 72 months postop for rhBMP-2 only when events occurred.
D_TRT	Patient and treatment dataset	

Table E-3a. Study 3: rhBMP-2/ACS/LT-Lap IS—Raw Data

SAS Data Set	Variable Information	Time Points
DISCHARGE	Hospital discharge data	Discharge
ENROLL	Patient demographic characteristics at enrollment	Enrollment
NEURO	Neurological status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, 48 and 72 months postoperative
OWESTRY	Oswestry disability score (10 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, 48 and 72 months postoperative
PAIN	Back and leg pain, Hip pain at donor site	Pre-operative, 1.5, 3, 6, 12 and 24, 48 and 72 months postoperative
POSTDATA	Postoperative data (comorbidities, return to work, etc)	1.5, 3, 6, 12 and 24, 48 and 72 months postoperative
PREOP	Pre-operative data (health characteristics)	Pre-operative
QUALIF	Patient qualifications for study	Enrollment
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, 48 and 72 months postoperative
SURGERY	Surgery data	Time of surgery

SAS Data Set	Variable Information	Time Points
SURVEY	Patient survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12 and 24 months postop for rhBMP-2 and ICBG group, and 48 and 72 months postoperative for rhBMP-2 only.
TRADREV	Radiologic review (disc measurements, stability, implant characteristics, radiolucent lines, evidence of bridging bone)	Pre-operative, surgery/discharge, 1.5, 3, 6, 12 and 24, other, 48 and 72 months postoperative

Table E-3b. Study 3: rhBMP-2/ACS/LT-Lap IS—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12, 24, 48, and 72 months
D_ALLSUC	Overall success variable (Oswestry success, neurological success, fusion success, failure and failure due to serious adverse event, overall success)	1.5, 3, 6, 12, 24, , 48, 72 months
D_FUSION	Fusion success (overall success, failure, second surgery failure)	6, 12, 24, , 48, 72 months
D_IVDH	Disc height success status	Pre-operative, discharge, 1.5, 3, 6, 12, 24, other, 48, 72 months
D_NEURO	Neurological success variable and its components	Pre-operative, 1.5, 3, 6, 12, 24, 48, 72 months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 48, 72 months
D_PAIN	Back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, 48, 72 months
D_SF-36	SF-36 health survey scores and success variables	Pre-operative, 1.5, 3, 6, 12, 24, 48, 72 months
FAILURE	Second surgery failures and time period	1.5, 3, 6, 12 and 24months when events occurred
SAE	Serious device or device/surgery related adverse events and time period	1.5, 3, 6, and 24months when events occurred
D_SURG2	All additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, 48, and 72 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-4a. Study 4: rhBMP-2/ACS/Allograft Bone Dowel Pilot RCT—Raw Data

SAS Data Set	Variable Information	Time Points
DISCHARGE	Hospital discharge data	Discharge
ENROLL	Patient demographic characteristics at enrollment	Enrollment
NEURO	Neurological status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, and 48 months postoperative
OWESTRY	Oswestry disability score (10 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and 48 months postoperative
PAIN	Back and leg pain, hip pain at donor site	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12 and 24, and 48 months postoperative
POSTDATA	Postoperative data (comorbidities, return to work, etc)	1.5, 3, 6, 12 and 24, and 48 months postoperative
PREOP	Pre-operative data (health characteristics)	Pre-operative
QUALIF	Patient qualifications for study	Enrollment
RRPOST	Radiographic review (disc space, bridging bone characteristics, stability, radiolucent lines)	Surgery/ discharge, 1.5, 3, 6, 12, 24, and 48 months
RRPRE	Radiographic review – pre-operative radiographs (type of x-rays, measurements, disc space)	Pre-operative
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and 48 months postoperative
SURGERY	Surgery data	Time of surgery
SURVEY	Patient survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12 and 24, and 48 months postoperative

Table E-4b. Study 4: rhBMP-2/ACS/Allograft Bone Dowel Pilot RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Pre-operative, surgery/discharge, 1.5, 3, 6, 12, 24, 48 months when events occurred
D_ALLSUC	Overall success variable (Oswestry success, neurological success, fusion success, failure, overall success)	1.5, 3, 6, 12, 24, 48 months
D_FUSION	Fusion success (overall success, failure, second surgery failure)	6, 12, 24, 48 months

SAS Data Set	Variable Information	Time Points
D_IVDH	Disc height success status	Pre-operative, surgery/discharge, 1.5, 3, 6, 12, 24, 48 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative,1.5, 3, 6, 12, 24, 48 months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 48 months
D_PAIN	Back and leg pain, hip pain, change from pre-op, success	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 48 months
D_SF-36	SF-36 health survey scores, success variables, and change from pre-operative	Pre-operative, 1.5, 3, 6, 12, 24, other, 36, 48, 72 months
FAILURE	Second surgery failures and time period	12, 24, 48 months when events occurred
SAE	Serious device or device/surgery related adverse events and time period	12, 24, 48 months when events occurred
D_SURG2	All additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, 48 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-5a. Study 5: rhBMP-2/ACS/Allograft Bone Dowel Pivotal RCT—Raw Data

SAS Data Set	Variable Information	Time Points
ACCOUNT	Patient accountability (reasons for missed follow-up, lost to follow-up status)	1.5, 3, 6, 12 and 24 months postoperative
BLPAIN	Back and Leg Pain Questionnaire (two back pain and two leg pain questions with scales)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/ discharge, 1.5, 3, 6, 12 and 24, and other months postoperative
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative

SAS Data Set	Variable Information	Time Points
OSWESTRY	Oswestry questionnaire (10 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
PORADREV	Radiologic Review (measurements, implant related AEs, fusion fracture, stability, appearance of radiolucent lines, radiographs, CT)	Surgery/ discharge, 1.5, 3, 6, 12 and 24, and other months postoperative
POSTDATA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24, and other months postoperative
PREOPDATA	Pre-operative data (health characteristics)	Pre-operative
PRRADREV	Radiologic Review Pre-operative Radiographs (x-ray type, measurements)	Pre-operative
QUALIFIC	Patient Qualification (qualifications and eligibility for study)	Pre-operative
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
SURGERY	Surgery Data	Surgery
SURVEY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative

Table E-5b. Study 5: rhBMP-2/ACS/Allograft Bone Dowel Pivotal RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, surgery/ discharge, 1.5, 3, 6, 12, 24, and other months when events occurred
D_ALLSUC	Overall success variable (Oswestry success, neurological success, fusion success, failure, overall success)	Pre-operative, , 1.5, 3, 6, 12, 24, and other months
D_FUSION	Fusion success (overall success, failure, second surgery failure)	,,6, 12, 24, months
D_DISC	Disc height success	1.5, 3, 6, 12, 24 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, and other months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, and other months
D_PAIN	Back and leg pain, hip pain, change from pre-op, success	Pre-operative, surgery/discharge, 1.5, 3, 6, 12, 24, and other months

SAS Data Set	Variable Information	Time Points
D_SF-36	SF-36 health survey scores, success variables, and change from pre-operative	Pre-operative1.5, 6, 12, 24, and other months
FAILURE	Second surgery failures	12, 24 months when events occurred
SAE	Data set for serious device or device/surgery related adverse events	12, 24 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	3, 6, 12, 24 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-6a. Study 6: rhBMP-2/ACS/LC-Posterior IDE Study RCT—Raw Data

SAS Data Set	Variable Information	Time Points
BLPAIN	Back and Leg Pain Questionnaire (two back pain and two leg pain questions with scales)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/ discharge, 1.5, 3, 6, 12 and 24, and other months postoperative
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postop
POSTOPDA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24, and other months postoperative
POSTOS	Postoperative Oswestry Questionnaire (10 questions)	1.5, 3, 6, 12 and 24, and other months postoperative
POSTRADR	Radiologic Review (type of x-rays and imaging, measurements, radiographs and CT scans done)	Surgery/ discharge, 1.5, 3, 6, 12 and 24, and other months postoperative
POSTSURV	Postoperative Patient Survey (medication use and satisfaction)	1.5, 3, 6, 12 and 24, and other months postoperative
PREOPDAT	Pre-operative data (health characteristics)	Pre-operative
PREOS	Pre-operative Oswestry Score (10 questions)	Pre-operative
PRERADRE	Radiologic Review Pre-operative Radiographs (type of x-rays and imaging, measurements, disc space)	Pre-operative

SAS Data Set	Variable Information	Time Points
PRESURV	Pre-operative Patient Survey (medication use and work status)	Pre-operative
QUALIFIC	Patient Qualification (qualifications and eligibility for study)	Pre-operative
SF-36	Health Status Questionnaire (SF 36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postop
SURGERY	Surgery Data	Surgery

Table E-6b. Study 6: rhBMP-2/ACS/LC-Posterior IDE Study RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset of AE: (period of occurrence, category, severity, device relatedness of all adverse events)	Operative/Postoperative, 1.5, 3, 6, 12, 24, and other months when events occurred
D_ALLSUC1	Derive primary "overall success" variable (Oswestry success, neurological success, fusion success, failure, *serious, permanent AE*, overall success)	6, 12, 24 months
D_ALLSUC2	Derive primary "overall success" variable (Oswestry success, neurological success, fusion success, failure, *serious device related or device/surgical associated AE*, overall success)	6, 12, 24 months
D_FUSION	Fusion success (overall success)	6, 12, 24 months
D_IVDH	Disc height success	Pre-operative, 1.5, 3, 6, 12, 24 months
D_NEURO	Neurological success components dataset (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, and other months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, and other months
D_PAIN	Dataset of back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, and other months
D_SF-36	Dataset for SF-36 health survey scores and success variables (change from pre-operative)	Pre-operative, 1.5, 3, 6, 12, 24, and other months
FAILURE	Dataset second surgery failures	12, 24 months when events occurred
SAE1	Dataset for serious permanent adverse events	6months when events occurred
SAE2	Dataset for serious device or device/surgery related adverse events	12 and 24 months when events occurred

SAS Data Set	Variable Information	Time Points
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, and other months when events occurred
D_TRT	Study patient and treatment	NA

Table E-7a. Study 7: rhBMP-2/ACS/SR/Bone Plate IDE Study—Raw Data

SAS Data Set	Variable Information	Time Points
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/ discharge, 1.5, 3, 6, 12 and 24 postoperative
NAPAIN	Neck & Arm Pain Questionnaire (two neck pain and two arm pain scales)	Pre-operative, 1.5, 3, 6, 12 and 24 postoperative
NEURO	Neurological Status (reflexes, motor, sensory)	Pre-operative, 1.5, 3, 6, 12 and 24 postoperative
POSTOPDA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24 months postoperative
POSTOS	Postoperative Neck Disability Index (13 sections)	1.5, 3, 6, 12 and 24 months postoperative
POSTSURV	Postoperative Patient Survey (medication use and satisfaction)	1.5, 3, 6, 12 and 24 months postoperative
PREOPDAT	Pre-operative data (health characteristics)	Pre-operative
PREOS	Pre-operative Neck Disability Index (13 sections)	Pre-operative
PRESURVE	Pre-operative Patient Survey (medication use and work status)	Pre-operative
QUALIFIC	Patient Qualification (qualifications and eligibility for study)	Pre-operative
RADREV	Review of Radiographs (measurements, evidence of bridging bone, fusion status, evidence of graft and/or hardware problems)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12 and 24 months postop
SF-36	Health Status Questionnaire (SF 36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24 months postop
SURGERY	Surgery Data	Surgery
USAGE	Implant Usage	Surgery

Table E-7b. Study 7: rhBMP-2/ACS/SR/Bone Plate IDE Study—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset of AE: (period of occurrence, category, severity, device relatedness of all adverse events)	Surgery/ discharge, 1.5, 3, 6, 12, 24, and other months when events occurred
D_ALLSUC	Derive primary "overall success" variable (NDI neurological, fusion, and overall success)	6, 12, 24 months
D_FUSION	Fusion success (overall success)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, and other months
D_NEURO	Neurological success components dataset (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24 months
D_NDI	NDI score, change from pre-operative variable for score and success	Pre-operative, 1.5, 3, 6, 12, 24 months
D_SF-36	Dataset for SF-36 health survey scores and success variables (change from pre-operative)	Pre-operative, 1.5, 3, 6, 12, 24 months
D_PAIN	Dataset of back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24 months
D_SURG2	A SAS dataset of all additional surgeries	Surgery/ discharge, 6, 12, 24, and other months when events occurred
D_TRT	Study patient and treatment	NA

Table E-8a. Study 8: INFUSE™/ MasterGraft™/CD HORIZON® Spinal System-Pilot Study RCT—Raw Data

SAS Data Set	Variable Information	Time Points
ACCOUNT	Patient accountability (reasons for missed follow-up)	Variable: 1.5, 3, 6, 12 and 24, 36 postoperative
BLPQ	Back and Leg Pain Questionnaire (two back pain and two leg pain questions)	Pre-operative, 1.5, 3, 6, 12, 24 and 36months postoperative
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPQ	Hip (donor site) Pain Questionnaire (2 questions)	Surgery/ discharge, 1.5, 3, 6, 12 and 24, 36 months postoperative

SAS Data Set	Variable Information	Time Points
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, 36months postop
OSW	Oswestry Questionnaire (10 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, 36months postoperative
PSTD	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24, 36months postoperative
PRED	Pre-operative data (health characteristics)	Pre-operative
QUAL	Patient Qualification (inclusion/exclusion criteria)	Pre-operative
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, 36months postoperative
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12 and 24, 36months postop
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12 and 24, 36months postop

Table E-8b. Study 8: INFUSE™/ MasterGraft™/CD HORIZON® Spinal System-Pilot Study RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, surgery/ discharge, 1.5, 3, 6, 12, 24, and 36 months when events occurred
D_ALLSUC	Overall success variable (Oswestry success, neurological success, fusion success, failure, overall success)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
D_FUSION	Fusion success (overall success, failure, second surgery failure)	6, 12, 24 and 36 months
D_HIP		Surgery/discharge, 1.5, 3, 6, 12, 24 and 36 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from preop for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
D_OSW	Oswestry score,change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
D_PAIN	Back and leg pain, hip pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
D_SF-36	SF-36 health survey scores, success variables, and change from pre-operative	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months

SAS Data Set	Variable Information	Time Points
FAILURE	Second surgery failures	Variable: 1.5, 12, 24 and 36 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Variable: Operative, postoperative, 1.5, 3, 6, 12, 24 and 36 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-9a. Study 9: rhBMP-2/ACS/LC IDE Study RCT—Raw Data

SAS Data Set	Variable Information	Time Points
BLPAIN	Back and Leg Pain Questionnaire (two back pain and two leg pain questions with scales)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postop
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/ discharge, 1.5, 3, 6, 12 and 24 months postoperative
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
POSTOPDA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24, and other months postoperative
POSTOS	Postoperative Oswestry Questionnaire (10 questions)	1.5, 3, 6, 12 and 24, and other months postop
POSTSURV	Postoperative Patient Survey (medication use and satisfaction)	1.5, 3, 6, 12 and 24, and other months postoperative
PREOPDAT	Pre-operative data (health characteristics)	Pre-operative
PREOS	Pre-operative Oswestry Score (10 questions)	Pre-operative
PRESURVE	Pre-operative Patient Survey (medication use and work status)	Pre-operative
PRERADREV	Radiologic Review Pre-operative Radiographs (measurements, disc space)	Pre-operative
QUALIFIC	Patient Qualification (inclusion/ exclusion criteria)	Pre-operative
RADREV	Radiologic Review (measurements, stability, implant problems, radiolucent lines, CT results)	Surgery/ discharge, 1.5, 3, 6, 12 and 24 months postoperative

SAS Data Set	Variable Information	Time Points
SF-36	Health Status Questionnaire (SF 36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24, and other months postoperative
SURGERY	Surgery Data	Surgery

Table E-9b. Study 9: rhBMP-2/ACS/LC IDE Study RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset of AE: (period of occurrence, severity, device relatedness)	Variable: Operative, Postoperative, 1.5, 3, 6, 12, 24, and other months when events occurred
D_ALLSUC	Derive primary "overall success" variable (Oswestry success, neurological success, fusion success, failure, serious permanent AE, overall success, serious device or device/surgical related AE)	6, 12 and 24 months
D_FUSION	Fusion success dataset (overall success)	6, 12 and 24 months
D_IVDH	Disc height success dataset	Surgery/discharge, 1.5, 3, 6, 12 and 24months
D_NEURO	Neurological success components dataset (motor, sensory, reflexes, and straight leg scores, change from preop for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24 and othermonths
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24 and other months
D_PAIN	Dataset of back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24 and other months
D_SF-36	Dataset for SF-36 health survey scores and success variables (change from pre-operative)	Pre-operative, 1.5, 3, 6, 12, 24 and other months
FAILURE	Dataset second surgery failures	1.5, 12, 24 and other months when events occurred
SAE1	Dataset for serious permanent adverse events	1.5,24 and other months when events occurred
SAE2	Dataset for serious device or device/surgery related adverse events	1.5 and 24 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 24, and other months when events occurred
D_TRT	Study patient and treatment	NA

Table E-10a. Study 10: MAVERICK™ Total Disc Replacement-Pivotal Study RCT—Raw Data

SAS Data Set	Variable Information	Time Points
ACCT	Patient accountability (reasons for missed follow-up)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
BLPQ	Back and Leg Pain Questionnaire (two back pain and two leg pain questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
DSCH	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENRL	Patient Enrollment (patient demographics)	Enrollment
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
OSW	Oswestry Questionnaire (10 questions)	Pre-operative`, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
PRED	Pre-operative data (health characteristics)	Pre-operative
PSTD	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
QUAL	Patient Qualification (inclusion/exclusion criteria)	Pre-operative
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months and unscheduled
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months

Table E-10b. Study 10: MAVERICK™ Total Disc Replacement-Pivotal Study RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months when events occurred
D_ALLSUC	Derive primary overall success variable (Oswestry, neurological, disc height success, failure, serious AE, overall success)	3, 6, 12, 24, 36, 48, 60, 84 months
D_FUSION	Fusion success (overall success and other indicators)	6, 12, 24, 36, 48, 60, 84 months

SAS Data Set	Variable Information	Time Points
D_IVDH	Disc Height success dataset	3, 6, 12, 24, 36, 48, 60, 84 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from preop for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
D_OSW	Oswestry score,change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
D_PAIN	Back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
D_SF-36	SF-36 health survey scores, success variables, and change from preop	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 84 months
FAILURE	Second surgery failures	3, 6, 12, 24, 36, 60, 84 months when events occurred
D_SAE	Dataset for serious device or device/surgery associated AE	3, 6, 12, 24, 36, months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72, 84 and other months when events occurred
D_TRT	Study patient and treatment	NA

Table E-11a. Study 11: TELAMON P™ Implant/INFUSE™ Bone Graft/CD HORIZON® Spinal System-Pilot Study IS—Raw Data

SAS Data Set	Variable Information	Time Points
ACCT	Patient accountability (reasons for missed follow-up)	3, 6, 12, 24, 36, and 48 months
BLPQ	Back and Leg Pain Questionnaire (two back pain and two leg pain questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
DSCH	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENRL	Patient Enrollment (patient demographics)	Enrollment
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 36, and 48 months
OSW	Oswestry Questionnaire (10 questions)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 36, and 48 months
PRED	Pre-operative data (health characteristics)	Pre-operative
PSTD	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12, 24, 36, and 48 months

SAS Data Set	Variable Information	Time Points
QUAL	Patient Qualification (inclusion/exclusion criteria)	Pre-operative
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 36, and 48 months
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months

Table E-11b. Study 11: TELAMON P™ Implant/INFUSE™ Bone Graft/CD HORIZON® Spinal System-Pilot Study IS—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12, 24, 36, and 48 months when events occurred
D_ALLSUC	Derive primary overall success variable (Oswestry, neurological, disc height success, failure, serious AE, overall success)	3, 6, 12, 24, 36, and 48 months
D_FUSION	Fusion success (overall success and other indicators)	6, 12, 24, 36, and 48 months
D_IVDH	Disc Height success dataset	3, 6, 12, 24, 36, and 48 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from preop for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
D_OSW	Oswestry score,change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
D_PAIN	Back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
D_SF-36	SF-36 health survey scores, success variables, and change from preop	Pre-operative, 1.5, 3, 6, 12, 24, 36, and 48 months
FAILURE	Second surgery failures	36 months when events occurred
D_SAE	Dataset for serious device or device/surgery associated AE	24 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	3, 6, 12, 24 and 36 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-12a. Study 12: rhBMP-2/BCP/TSRH Spinal System IDE Study RCT—Raw Data

SAS Data Set	Variable Information	Time Points
BLPAIN	Back and Leg Pain Questionnaire (two back pain and two leg pain questions with scales)	Pre-operative, 1.5, 3, 6, 12 and 24 months postoperative
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/ discharge, 1.5, 3, 6, 12 and 24 months postoperative
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12and 24 months postoperative
POSTDATA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12 and 24 months postoperative
POSTOS	Postoperative Oswestry Questionnaire (10 questions)	1.5, 3, 6, 12and 24 months postoperative
POSTSURV	Postoperative Patient Survey (medication use and satisfaction)	1.5, 3, 6, 12 and 24 months postoperative
PREOPDAT	Pre-operative data (health characteristics)	Pre-operative
PREOS	Pre-operative Oswestry Score (10 questions)	Pre-operative
PRESURVE	Pre-operative Patient Survey (medication use and work status)	Pre-operative
QUALIFIC	Patient Qualification (inclusion/ exclusion criteria)	Pre-operative
RADREV	Radiologic Review (measurements, stability, implant problems, radiolucent lines, CT results)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24 and other months postoperative
SF-36	Health Status Questionnaire (SF 36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12and 24 months postoperative
SURGERY	Surgery Data	Surgery
USAGE	Device Usage	Surgery

Table E-12b. Study 12: rhBMP-2/BCP/TSRH Spinal System IDE Study RCT—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset of AE: (period of occurrence, severity, device relatedness)	Variable: operative, postoperative, 1.5, 3, 6, 12 and 24 months when events occurred
D_ALLSUC	Derive primary “overall success” variable (Oswestry,	6, 12 and 24 months

SAS Data Set	Variable Information	Time Points
	neurological, fusion success, failure, overall success)	
D_FUSION	Fusion success dataset (overall success)	6, 12 and 24 months
D_NEURO	Neurological success components dataset (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12 and 24 months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12 and 24 months
D_PAIN	Dataset of back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12 and 24 months
D_SF-36	Dataset for SF-36 health survey scores and success variables (change from preop)	Pre-operative, 1.5, 3, 6, 12 and 24 months
FAILURE	Dataset second surgery failures	12and 24 when events occurred.
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 6, 12, and 24 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-13a. Study 13: rhBMP-2/BCP/TSRH Spinal System-Canada—Raw Data

SAS Data Set	Variable Information	Time Points
BLPAIN	Back and Leg Pain Questionnaire (two back pain and two leg pain questions with scales)	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 postoperative
DISCHARG	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENROLL	Patient Enrollment (patient demographics)	Enrollment
HPAIN	Hip Pain (pain severity and occurrence)	Surgery/Discharge, 1.5, 3, 6, 12, 24, other months, 48, 72 months postop
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
POSTDATA	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
POSTOS	Postoperative Oswestry Questionnaire (10 questions)	1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
POSTSURV	Postoperative Patient Survey (medication use and satisfaction)	1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative

SAS Data Set	Variable Information	Time Points
PREOPDAT	Pre-operative data (health characteristics)	Pre-operative
PREOS	Pre-operative Oswestry Score (10 questions)	Pre-operative
PRESURVE	Pre-operative Patient Survey (medication use and work status)	Pre-operative
QUALRMB	Patient Qualification – Arm B (include/ exclude criteria)	Pre-operative
QUALIFIC	Patient Qualification (inclusion/ exclusion criteria)	Pre-operative
RADREV	Radiologic Review (measurements, bridging bone, implant problems, radiolucent lines)	Surgery/Discharge, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
SF-36	Health Status Questionnaire (SF 36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
SURGERY	Surgery Data	Surgery
USAGARMB	Device Usage (Arm B)	Surgery
USAGE	Device Usage	Surgery

Table E-13b. Study 13: rhBMP-2/BCP/TSRH Spinal System-Canada—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset of AE: (period of occurrence, severity, device relatedness)	Operative, postoperative, 1.5, 3, 6, 12, 24, 48, 72 months postoperative when events occurred
D_ALLSUC	Derive primary “overall success” variable (Oswestry and fusion success, failure, trial indicator, overall success)	Pre-operative, 1.5, 3, 6, 12, 24, 48, 72 months postoperative
D_FUSION	Fusion success dataset (overall success, trial indicator)	6, 12, 24, 48 and 72 months postoperative
D_NEURO	Neurological success components dataset (motor, sensory, reflexes, and straight leg scores, change from preop for all, success status all, trial indicator)	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
D_OSW	Oswestry score, change from pre-op, and success, trial indicator	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
D_PAIN	Dataset of back and leg pain, change from pre-op, success, trial indicator	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative
D_SF-36	Dataset for SF-36 health survey scores and success variables (change from preop)	Pre-operative, 1.5, 3, 6, 12, 24, other months, 48, 72 months postoperative

SAS Data Set	Variable Information	Time Points
FAILURE	Dataset second surgery failures	12, 24 and 48 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Operative, Postoperative, 1.5, 3, 6, 12, 24, 48 and 72 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-14a. Study 14: rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study—Raw Data

SAS Data Set	Variable Information	Time Points
ACCT	Patient accountability (reasons for missed follow-up)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
BLPQ	Back and Leg Pain Questionnaire (two back pain and two leg pain questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
DSCH	Hospital Discharge (orthosis, discharge date, patient classification, AE between surgery and discharge)	Discharge
ENRL	Patient Enrollment (patient demographics)	Enrollment
HPQ	Hip (Donor) Site Pain Questionnaire	Surgery/ discharge, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
NEURO	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
OSW	Oswestry Questionnaire (10 questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
PRED	Pre-operative data (health characteristics)	Pre-operative
PSTD	Postoperative Data (health characteristics, work status)	1.5, 3, 6, 12, 24, 36, 48 and 60 months
QUAL	Patient Qualification (inclusion/exclusion criteria)	Pre-operative
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months

Table E-14b. Study 14: rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Operative, postoperative, 1.5, 3, 6, 12, 24, 36, 48 and 60 months when events occurred
D_ALLSUC	Derive primary overall success variable (Oswestry, neurological, fusion success, failure, serious AE, overall success)	Pre-operative, 6, 12, 24, 36, 48, 60, 72 months
D_FUSION	Fusion success (overall success and other indicators)	Pre-operative, 6, 12, 24, 36, 48, 60, 72 months
D_HIP	Disc Height success dataset	Surgery/discharge, 1.5, 3, 6, 12, 24, 36, 48, 60 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72 months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72 months
D_PAIN	Back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72 months
D_SF-36	SF-36 health survey scores, success variables, and change from pre-operative	Pre-operative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72 months
FAILURE	Second surgery failures	1.5, 3, 6, 12, 24, 36, 48, 60months when events occurred
D_SAE	Dataset for serious device or device/surgery associated AE	Surgery/discharge, 1.5, 3, 6, 12, 24, 36, 60 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 1.5, 3, 6, 12, 24, 36, 48, 60, 72 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-15a. Study 15: rhBMP-2/CRM/CD HORIZON® Spinal System-2-Level Pilot—Raw Data

SAS Data Set	Variable Information	Time Points
BLPQ	Back and Leg Pain Questionnaire (two back pain and two leg pain questions)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
CONT	Patient Contact (reason for missed follow-up)	6, 12, 24 and 36 months
DISP	Patient Disposition (Withdrawls and terminations)	24 months

SAS Data Set	Variable Information	Time Points
DSCH	Hospital Discharge	Discharge
ENRL	Patient Enrollment (patient demographics)	Pre-operative
NEUR	Neurological Status (motor, sensory, reflexes, straight leg raise)	Pre-operative, , 1.5, 3, 6, 12, 24 and 36 months
OSW	Oswestry Questionnaire (10 questions)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
PRED	Pre-operative data (health characteristics)	Pre-operative
QUAL	Patient Qualification (inclusion/ exclusion)	Pre-operative
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12, 24and 36 months
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12, 24 and 36 months

Table E-15b. Study 15: rhBMP-2/CRM/CD HORIZON® Spinal System-2-Level Pilot—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	Period of occurrence, category, severity, device relatedness of all adverse events	Pre-operative, Postoperative, 1.5, 3, 6, 12, 24, 36 months when events occurred when events occurred
D_ALLSUC	Derive primary overall success variable (Oswestry, neurological, fusion success, failure, serious AE, overall success)	6, 12, 24, 36 months
D_FUSION	Fusion success (overall success and other indicators)	6, 12, 24, 36 months
D_NEURO	Neurological success (motor, sensory, reflexes, and straight leg scores, change from pre-operative for all, success status all)	Pre-operative, 1.5, 3, 6, 12, 24, 36 months
D_OSW	Oswestry score, change from pre-op, and success	Pre-operative, 1.5, 3, 6, 12, 24, 36 months
D_PAIN	Back and leg pain, change from pre-op, success	Pre-operative, 1.5, 3, 6, 12, 24, 36 months
D_SF-36	SF-36 health survey scores, success variables, and change from pre-operative	Pre-operative, 1.5, 3, 6, 12, 24, 36 months

SAS Data Set	Variable Information	Time Points
FAILURE	Second surgery failures	6 and 24 months when events occurred
D_SAE	Dataset for serious device or device/surgery associated AE	6 and 24 months when events occurred
D_SURG2	A SAS dataset of all additional surgeries	Postoperative, 1,5, 3, 12, 24 and 36 months when events occurred
D_TRT	Study patient and treatment	NA

Table E-16a. Study 16: rhBMP-2/BCP database - Bmp BCR (Mexico)—Raw Data

SAS Data Set	Variable Information	Time Points
PREOP1	Patient Enrollment (demographic information), Patient Qualification (inclusion/exclusion) and Pre-operative Data (medical data)	Pre-operative
PREOP2	Neurological Status (reflexes, sensory, motor, straight leg), Neuro/Functional Status, Oswestry Questionnaire (10 questions)	Pre-operative
PREOP3	SF 36 (36 Questions)	Pre-operative
SURGERY	Surgery Data	Surgery
HOSPITAL	Hospital Discharge (orthosis, complications)	Discharge
POSTOP6W	Postoperative (medical data), Neurological Status (reflexes, sensory, motor, straight leg), Neuro/Functional Status, Oswestry Questionnaire (10 questions), SF 36 (36 Questions)	1.5 months
POSTOP3M	Postoperative Data (medical data), Neurological Status (reflexes, sensory, motor, straight leg), Neuro/Functional Status, Oswestry Questionnaire (10 questions), SF 36 (36 Questions)	3 months
POSTOP6M	Postoperative Data (medical data), Neurological Status (reflexes, sensory, motor, straight leg), Neuro/Functional, SF 36 (36 Questions)Oswestry Questionnaire (10 questions)Status	6 months
POSTOP12	Postoperative Data (medical data) , Neurological Status (reflexes, sensory, motor, straight leg), Neuro/Functional, SF 36 (36 Questions)Oswestry Questionnaire (10 questions)Status	12 months
RADREV	Radiographic Review (type of x-rays, measurements, evidence of fusion, evidence of implant problems)	Surgery/ discharge, 1.5, 3, 6, 12 months

Table E-16b. Study 16: rhBMP-2/BCP database - Bmp BCR (Mexico)—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset for all the adverse events (time point, study cohort)	Operative, postoperative , 1.5, 3, 6, 12 months when events occurred
D_SURG2	A SAS dataset for all the additional surgeries	6 months when events occurred

Table E-17a. Study 17: INFUSE/CORNERSTONE-SR/ATLANTIS ACP-PIVOTAL STUDY—Raw Data

SAS Data Set	Variable Information	Time Points
ABDY	Blood specimens for antibody	Pre-operative, 1.5, 3, 6 and 12 months
ACCT	Patient Accountability (reason for lack of follow up)	6 and 12months
DSCH	Hospital Discharge (orthosis, AE)	Discharge
ENRL	Patient Enrollment (demographics)	Pre-operative
HPQ	Hip (donor site) pain questionnaire	Surgery/ discharge, 1.5, 3, 6, 12 and 24 months
NAPQ	Neck and arm pain questionnaire (2 questions neck, 2 arm)	Pre-operative, 1.5, 3, 6, 12 and 24 months
NDI	Neck Disability Index (10 questions)	Pre-operative, 1.5, 3, 6, 12 and 24 months
NEUR	Neurological Status (motor, sensory)	Pre-operative, 1.5, 3, 6, 12 and 24 months
PRED	Pre-operative Data (medical questions)	Pre-operative
PSTD	Postoperative Data (brace use, return to work)	1.5, 3, 6, 12 and 24 months
QUAL	Patient Qualification (inclusion/ exclusion)	Pre-operative
RDAT	Radiologic Data	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12 and 24 months
RREV	Radiologic Review (implant problems, bridging bone, radiolucent lines)	Pre-operative, surgery/ discharge, 1.5, 3, 6, 12 and 24 months
SF-36	Health status questionnaire (SF-36 – 36 questions)	Pre-operative, 1.5, 3, 6, 12 and 24 months
SURG	Surgery Data	Surgery
SUVY	Patient Survey (medical characteristics, work status, satisfaction)	Pre-operative, 1.5, 3, 6, 12 and 24 months

Table E-17b. Study 17: INFUSE/CORNERSTONE-SR/ATLANTIS ACP-PIVOTAL STUDY—Derived Data

SAS Data Set	Variable Information	Time Points
D_AE	A SAS dataset for all the adverse events (time point, device related, severity, treatment group)	Postoperative, 3 and 24 months when events occurred
D_SURG2	A SAS dataset for all the additional surgeries	24 months when events occurred
D_TRT	Study patient and treatment dataset	NA

Appendix F. Outcome Variable Definitions/Criteria from Medtronic Protocols Compared with Those in Published Studies and Individual Patient Data Analysis for Comparative Effectiveness and Harms

Outcome Variable	**Surgical Approach** (Study Number)	**Medtronic Protocol Definition/Criteria**	**Published Studies*** **Definition/Criteria**	**Individual Patient Data Analysis in This Review Definition/criteria**
Overall success	ALIF/PLIF /PLF (2, 3, 4, 5, 6, 8, 9, 12, 13, 14; not defined in Study 1)	All of the following criteria need to be satisfied: Fusion Improvement in the ODI for low back pain (ODI success) Maintenance or improvement in neurologic status (neurologic success) No serious adverse event classified as implant- or implant/surgical-associated No additional surgical procedure classified as "failure"	Only reported for Study 8, which used the same definition as the Medtronic protocol.	Same definition as Medtronic protocol except for a minor difference in Study 8: In Study 8, definition of ODI success differed slightly. (See definition for ODI success below.) In primary analysis, patients had to satisfy all criteria; patients with data for some but not all criteria were categorized as failures. In sensitivity analyses, we categorized patients with data for some but not all criteria as missing and excluded them from the analysis.
	Artificial disc (Maverick) (10)	Same as ALIF/PLF (see above), except: Fusion not a criterion Disc height is a criterion that postoperative disc height at each visit after 6 weeks was no more than 2mm shorter than postoperative disc height at 6 weeks	Same definition as Medtronic protocol	
	ACDF (7)	Same as ALIF/PLF (see above), except: Success based on improvement in NDI	Definition not reported	
Fusion	ALIF (1)	Bone growing continuously through the cage and connecting with vertebral bodies above and below through at least one cage,	Presence of continuous trabecular bone growth through both of the cages	Same definition as Medtronic protocols, except: If data from a CT scan were available, they were used first. If data from CT scan were not available but data from radiographs were available, radiographs data were used. In primary analysis, patients had to satisfy all criteria; patients with data for some but not all criteria were categorized as failures. In sensitivity analyses, we categorized patients with data for some but not all criteria as missing and excluded them from the analysis.

Outcome Variable	**Surgical Approach** (Study Number)	**Medtronic Protocol Definition/Criteria**	**Published Studies*** **Definition/Criteria**	**Individual Patient Data Analysis in This Review Definition/criteria**
	ALIF/PLIF/ Artificial disc rhBMP-2 arm (2, 3, 4, 5, 6, 9,10)	All criteria must be met: 1) Evidence of continuous trabecular bone growth connecting the vertebral bodies and/or through either one or both implants; 2) Absence of radiolucency covering >50% of implant 3) Translation of ≤ 3mm and angulation of <5 degrees. Fusion assessed primarily with radiographs. CT scans used as a secondary method.	In addition to criteria used in the Medtronic protocols, patients who underwent a secondary surgery were considered as failed fusion in published studies (Study 2, combined analysis of Studies 2 and 3, Study 4, combined analysis of Studies 4 and 5, Study 6), and evidence of continuous trabecular bone growth was assessed generally using a CT scan. Study 6 used both CT and radiographs.	
	PLF (8, 12, 13, 14)	All criteria must be met: 1) Evidence of continuous trabecular bone growth connecting the transverse processes ; 2) Absence of radiolucent lines through the fusion mass; 3) Translation of ≤ 3mm and angulation of <5 degrees. Fusion assessed primarily with radiographs. CT scans used as a secondary method.	Same definition as Medtronic protocols: Study 8 used both CT and radiographs but did not say how they were used for assessing bridging trabecular bone. Study 12 and 14 used radiographs and CT scans as specified in the protocols.	
	ACDF (7)	All criteria must be met: 1) Evidence of bridging bone 2) Absence of radiolucency covering >50% of superior or inferior surface of graft 3) Translation of ≤ 3mm and angulation of <4 degrees. Radiographs and CT scans used to assess fusion.	Same definition as Medtronic protocol (The published study also used both CT and radiographs but did not say how they were used for assessing bridging trabecular bone.)	
ODI success	ALIF/PLIF /PLF, artificial disc (2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14)	At least a 15-point improvement in ODI score for back pain at each visit postoperatively compared with pre-operative index score (FDA's recommendation; a 15-point improvement is clinically meaningful based on Copay, 2008¶) Study 8 used a 15% improvement instead of a 15-point increase. Not defined in the protocol of Study 1	Studies 1 and 12: at least 15% improvement Study 10: at least 15-point improvement Other studies reported results with improvement of at least 15% (Studies 2 and 8), or at least 20% (Study 8), or at least 15 points (Studies 4 and 6) without explicitly defining success, or only reported actual scores (combined analysis of Studies 2 and 3, and 4 and 5).	Same definition as Medtronic protocols, except: For Study 8, an increase of at least 15 points in ODI score was used (to be consistent with definitions used in all other studies).
	ACDF (7)	At least a 15-point improvement in NDI score for neck pain at each visit postoperatively compared with pre-operative index score (FDA's recommendation; a 15-point improvement is clinically meaningful based on Copay, 2008¶)	Same definition as Medtronic protocol	Same definition as Medtronic protocol

Outcome Variable	Surgical Approach (Study Number)	Medtronic Protocol Definition/Criteria	Published Studies* Definition/Criteria	Individual Patient Data Analysis in This Review Definition/criteria
Neurologic success	ALIF/PLIF /PLF, artificial disc **(**2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14; not defined in Study 1)	Four neurologic tests evaluated motor function, sensory function, deep tendon reflexes, and sciatic tension signs (straight-leg raise). A score was developed for each test. Studies 2, 3, 5, 6, 9, 12, and 13: the scores of the four tests were totaled and an overall score was expressed as a percentage of the maximum possible score. A neurologic success was defined as a postoperative overall score no more than 10% worse than the pre-operative overall score. Studies 4, 8, 10, 14: neurologic success was defined as having the same or better score in all four tests compared to pre-operative score.	Not defined in Study 1; mean score reported. Studies 2, 4, 6,10: used the same definition as the Medtronic protocols. Combined analysis of Studies 2 and 3, combined analysis of Studies 4 and Studies 5, 8, 14: neurologic success was not reported, neither were the mean scores. Study 12: scores not reported; outcome briefly mentioned.	Used definition from Medtronic protocols for studies 4, 8, 10, 14 for all studies.
	ACDF (7)	Same as ALIF/PLF for Studies 2, 3, 5, 6, 9, 12, and13 (see above), except: Sensory symptoms and the foraminal compression test were used in the place of sciatic tension signs.	Neurologic status of the patients was determined by evaluating two neurologic tests: motor and sensory function. Neurologic success was based on demonstrated maintenance or improvement in both tests.	Same as above, except: The four neurologic tests were motor function, sensory function, reflexes, and sensory symptoms; plus the foraminal compression test.
Surgical procedure "failure"	ALIF/PLIF /PLF, artificial disc (2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14)	*Surgical procedure classified as a failure when any of the following occurred:* Supplemental fixation Device removal‡ Revision §	Combined analysis of Studies 4 and 5, Study 8 and 10: Same definition as Medtronic protocols. For Study 6: a second spinal surgery at the same level All other published studies: Not reported.	Same definition as Medtronic protocols
SF-36	(All studies)	Standard definition†	Standard definition†	Standard definition†
Back or leg pain	ALIF/PLIF /PLF (2, 3, 4, 5, 6, 8, 9, 12, 13, 14)	Sum of rating scores on intensity and duration of back or leg pain, both on a scale of 0 to 10. Back and leg pain not separately measured in Study 1	Same definition as Medtronic protocols	Only rating score on intensity of back or leg pain on a scale from 0 to 10 was used.
	Artificial disc (10)	Multiplication of rating scores (0-10) on intensity and duration of back or leg pain	Same definition as Medtronic protocol	Only rating score on intensity of back or leg pain on a scale from 0 to 10 was used.
Neck or arm pain	ACDF (7)	Sum of rating scores on intensity and duration of neck or arm pain, both on a scale of 0 to 10	Same definition as Medtronic protocol	Only rating score on intensity of neck or arm pain on a scale from 0 to10 was used.
Adverse event	(All studies)	No definition in protocols; "adverse event" listed in the data collection forms	Sparsely reported; as defined in Medtronic datasets	As defined in Medtronic datasets

Outcome Variable	Surgical Approach (Study Number)	Medtronic Protocol Definition/Criteria	Published Studies* Definition/Criteria	Individual Patient Data Analysis in This Review Definition/criteria
Device-related adverse event	(All studies)	Reasonable possibility that the adverse event may have been caused by the implant(s) or by device and surgical procedure, as determined by Study investigators	Only reported in Study 10 and 14; as defined in Medtronic datasets	As defined in Medtronic datasets
Serious adverse event	(All studies)	For events defined in the WHO Recommendations for Grading of Acute and Subacute Toxic Effects, any adverse event with severity 3 or 4. For events not defined by the WHO Toxicity Scale, any adverse event if it limits the patient's ability to perform routine activities despite symptomatic therapy, if it results in the need to remove the implant, or if the patient is at immediate risk of death.	Only reported in Study 10, defined as WHO Grade 3 or 4 adverse event	Serious adverse events categorized as: An adverse event with a severity score of 3 or 4, based on Medtronic categorization of severity in Medtronic datasets.
Relevant additional surgeries	(All studies)	Not specifically defined what is "relevant" but classified additional surgeries as: supplemental fixation, device removal, revision and re-operation	Study 1: not reported. All other studies reported secondary/additional surgeries as classified in Medtronic protocols. Study 14 compared second surgeries including revision, non-elective removal, and revision only. Elective removal and reoperation was excluded.	Relevant additional surgery: Supplemental fixation Device removal Revision Re-operation Based on classification in Medtronic datasets
Possible lumbar radiculitis	ALIF/PLIF /PLF (1, 2, 4, 5, 6, 8, 9,12, 13, 14)	Not defined as an outcome	Not defined as an outcome	Primary definition: back pain plus any leg or buttock pain or weakness (includes pain described as sciatica, radiculopathy or radicular pain, use of epidural steroids or decompression surgery). Sensitivity analysis looked at other definitions. Definition 2 similar to primary definition except back pain not required. Leg numbness and nerve root injections also included as indicating possible radiculitis. Definition 3 same as definition 2 except that any type of back and leg pain was included (e.g., osteoarthritis). Definition 4 defined possible lumbar radiculitis simply as back and/or leg pain with the use of epidural steroids or decompression surgery.

ACDF = anterior cervical discectomy and fusion; ALIF = anterior lumbar interbody fusion; CT = computed tomography; FDA = U.S. Food & Drug Administration; NDI = Neck Disability Index (Vernon); ODI = Oswestry Disability Index/Oswestry Low Back Pain Disability Questionnaire; PLF = posterolateral lumbar fusion; PLIF = posterior lumbar interbody fusion; WHO = World Health Organization.

* Studies 9 and 13 were not published.

† Standard definition for Medical Outcomes Study 36-ltem Short Form Health Survey (SF-36) was used for all studies in all sources. [Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute; 1994.]

¶ Copay AG, Glassman SD, Subach BR, et al. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. Spine J. 2008 Nov-Dec;8(6):968-74. PMID: 18201937

‡ Studies 7, 8 and 14 used non-elective device removal.

§ Studies 6, 9, 12, and 13 used revision after two weeks of surgery. For revisions within two weeks of surgery, Medtronic determined whether or not these events were failures on a case-by-case basis, with input from FDA.

Appendix G. Individual Patient Data Raw Data Calculation

Medtronic provided two sets of individual patient data (IPD): raw and derived. The raw data were those transcribed directly from the case report form (CRF) and the derived data were calculated from the raw data. For example, SF-36 comprises 36 questions in CRF. The raw data contained information about answers of the 36 questions and the derived data had information about the calculated scores of mental health and physical health components based on the 36 questions.

In this review, the effectiveness measures included overall success, fusion, neurological success, Oswestry Disability Index (ODI) success, ODI score, back and leg pain for lumbar spine (or neck and arm pain for cervical spine), mental health and physical health components of SF-36 and return to work. Except for return to work, all other effectiveness measures were derived measures in Medtronic protocols. We recalculated or recoded all these derived measures from the raw individual patient data, based on the following:

1. The criteria to define overall success, fusion, neurological success and ODI score success, while similar across most trials, were not consistent across all trials. We applied a consistent definition across all trials for each of these outcomes.
2. If a patient had an additional surgery that was device or surgery related, it was categorized as a second surgery failure. In the Medtronic derived datasets, all data after second surgery failure were either treated as missing or replaced by using last observation carrying forward.

   However, Medtronic datasets provided raw data for these patients after second surgery failure. We calculated all measures based on these observed data, which reflected the actual status for these patients after second surgery failure. Applying the principle of intention to treat, we used these calculated data in our analysis.
3. Derived measures were not provided in two of the Medtronic trials, and needed to be calculated.

The outcome definitions used in our IPD analysis are presented in Appendix F. In our calculation of derived effectiveness measures, we tried to use more stringent criteria. In particular:

1. Fusion was defined by the satisfaction of all three criteria: evidence of bridging trabeculae, no evidence of motion as defined by no more than 3mm difference in translation and less than 5° difference in angular motion between flexion and extension, and no evidence of radiolucency surrounding greater than 50% of either device (ALIF, PLIF and ACDF), or no evidence of a radiolucency line (PLF) based on surgical approach. For evidence of bridging trabeculae, since most patients have CT scans, we used data from CT scans first and only used data from radiographs when CT scans are not available.

   The radiographic reviews should be completed by two independent, blinded radiologists. If there is a disagreement, a third radiologist would break the tie. In our calculation, we found that patients may have data on some, but not all three criteria, or may have information from only one radiologist, or that two radiologists did not agree on fusion status but there is no information of review on the third radiologist.

To account for the varying patterns of partial data and missing data, we calculated multiple versions of fusion. In the primary analysis, if a patient had partial missing data, it was classified as a fusion failure. This was a more stringent definition, given that the patient was available for evaluation but the available data were not adequate to show successful fusion. In the sensitivity analysis, we used this measure for primary analysis. The second version we treated patients with partial missing data as missing for the fusion outcome, and therefore they were excluded from the analysis. We also conducted another sensitivity analysis by treating patients with any missing data as fusion failures.

2. Neurological success was evaluated based on a comprehensive neurological scale within four domains: motor, sensory, reflexes, and straight leg raise. Postoperative neurological success was defined by improvement or maintenance on all four domains compared to pre-operative score.

3. Postoperative ODI score improvement (ODI success) was defined as a 15-point decrease in disability score compared to pre-operative score.

4. Overall success was defined by meeting all of the following five conditions: i) fusion; ii) ODI success; iii) neurological success; iv) no serious adverse event classified as device associated or device/surgical procedure associated; v) no additional surgical procedure classified as a "failure."

   Again, we found that patients may have data on some, but not all five conditions and we calculated multiple versions of overall success. In the primary analysis, the primary analysis version of fusion was used for the first condition, and if a patient had partial missing data, it was classified as a failure for overall success. In the sensivitity analysis, the sensitivity analysis version of fusion was used for the first condition, and if a patient had partial missing data, it was classified as missing for overall success and excluded from the analysis. Again, we also conducted another sensivity analysis by treating as failures patients for whom any data was missing.

5. For leg and back pain for lumbar spine, or arm or neck pain for cervical spine, a numerical rating scale from 0 to 10 was used to measure both pain intensity and duration. The Medtronic derived variables either added the two scales together, as in most trials, or multiplied the two scales together, to produce a composite score. In our assessments, it was not very interpretable to use a numerical rating scale of 0 to 10 to evaluate pain duration, and it has not been a standard measure to assess pain. Therefore, we only used pain intensity on a 0 to 10 scale as the pain measure.

For harms and second surgeries, only derived data were provided. We checked the accuracy of adverse events in the derived datasets against the brief case history of adverse events in the manufacture final reports for three trials (Studies 2, 8 and 14). We found no inconsistency between the two data sources and relied on the derived datasets for all other trials. We also compared the IPD data on adverse events to those presented in the detailed study reports and found them to be generally consistent. In the manufacture's trial protocol, leg pain and back pain were assessed by measuring pain intensity and duration on a 0-10 scale at each follow-up point. Leg and back pain was also recorded as an adverse event in the derived adverse event datasets. We analyzed both pain intensity (as an effectiveness outcome) and a leg and back pain event (as an adverse event) based on the way the manufacturer measured the two variables.

The dataset for harms listed each adverse event (AE), the period that the AE occurred, the severity of the AE classified by Medtronic based on World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects on a scale from 1 to 4, and whether the AE was device and/or surgical related classified by Medtronic. Based on these derived data, for each trial, we calculated the number of AEs for each patient and the number of patients for each of the following categories: i) having at least one AE; ii) having at least one serious AE (severity ≥ 3); iii) having at least one device-related AE; and iv) having at least one major additional surgery (e.g., revision, elective or non-elective removal of one or more components of the original device and supplemental fixation, reoperation at the involved level that does not remove, modify or add any components). These categories were used to assess overall AE. For specific AEs, the number of patients with each specific AE was calculated. In all calculations, non-unions or pending unions, which were included in the derived datasets for harms, were excluded from the harm analysis since fusion was considered as an effectiveness outcome. For all AE assessment, we aggregated the data into two time periods: 4 weeks and 24 months. The former period included data from operative and 0 - 4 weeks postoperative to characterize short term AE and the latter period included data up to 24 months to characterize long term AE.

Appendix H. Two-Step Model and Results

Meta-analysis using two-step approach

For ALIF and PLF trials with IPD, we conducted meta-analysis using a two-step approach.[1] In the first step, for each study, we calculated aggregated study-level estimates for each outcome. In the second step, we combined the estimates from different studies.

Step One: Calculating study-level estimates from individual patient data

For continuous outcomes (ODI score, pain and SF-36), we used the mean difference as the effect measure, and we conducted an analysis of covariance (ANCOVA) to estimate the mean difference between the two treatment groups using postoperative scores while adjusting for the baseline preoperative score for each study (The summary data was provided in Appendix L.) For binary outcomes, the risk ratio (RR) was used as the primary effect measure. When the combined estimate was statistically significant and the control rates were similar across studies, an absolute risk difference was also calculated to aid in clinical interpretation of results. For the number of adverse events, a Poisson regression model was first used to estimate a rate ratio to compare the treatment groups for each study and then this rate ratio was combined in the meta-analysis.

Step Two: Pooling across studies

When feasible, we pooled the study level estimates to obtain summary estimates of effects using standard meta-analysis methods for study-level data. We assessed the presence of statistical heterogeneity among the studies with standard χ^2 tests and the magnitude of heterogeneity with the I^2 statistic.[2] The trials were combined using a random effects model [3] to account for variation among studies. We used a random effects model except in the case of outcomes with rare events, where a fixed effects model (Mantel-Haenszel method with no continuity correction) was used. A fixed effects model provides better combined estimates even for rare event in the presence of heterogeneity.[4] Rates and proportions from the rhBMP-2 or control group, when necessary, were also combined using a random effects model.

Within each surgical approach appropriate for meta-analysis, the number of trials was too small to use meta-regression to evaluate the effect of study-level variables.[5] We performed sensitivity analysis by excluding poor quality studies, studies that utilized a lower rhBMP-2 concentration (posterolateral fusion), and graft site related adverse events in the analysis of harms. In addition, we meta-analyzed the manufacture derived effectiveness outcome variables in IPD datasets as one more sensitivity analysis. Sensitivity analyses produced similar results in general.

Results of Meta-analysis using two-step approach

Results of effectiveness and harms for ALIF and PLF trials through 24 months based on the two-step approach are presented below (Table I-1 and Table I-2), and results from longer follow-up are presented in the main text. Results of effectiveness and harms for ALIF and PLF trials through 24 months in the main text are based on the mixed effects model.

References

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Table H-1. Effectiveness Endpoints for ALIF and PLF with rhBMP-2 vs. ICBG Based on Two-step Approach Through 24 Months*

Outcome Scale	6 weeks	3 months	6 months	12 months	24 months
ALIF†					
			Relative risk (95% CI) **I^2 %** **Sample Size, *n* (Studies)**		
Overall success	----	----	1.13 (0.93 to 1.37) 0.0 445 (4)	1.14 (0.89 to 1.45) 26.9 436 (4)	1.28 (0.89 to 1.83) 56.2 418 (4)
Fusion	----	----	**1.10 (1.02 to 1.19)** 0.0 446 (5)	1.09 (0.95 to 1.24) 29.4 439 (5)	1.05 (0.88 to 1.24) 76.0 416 (5)
Neurological success	1.01 (0.94 to 1.08) 0.0 434 (4)	1.00 (0.92 to 1.09) 37.8 442 (4)	0.98 (0.91 to 1.06) 0.0 433 (4)	1.01 (0.94 to 1.09) 0.0 420 (4)	1.04 (0.96 to 1.13) 0.0 400 (4)
ODI success	1.19 (0.79 to 1.78) 49.6 442 (4)	1.02 (0.86 to 1.21) 8.8 455 (5)	1.06 (0.95 to 1.19) 0.0 450 (5)	1.02 (0.83 to 1.26) 48.4 436 (5)	1.08 (0.95 to 1.22) 0.0 417 (5)
Return to work§	1.21 (0.73 to 1.98) 0.0 211 (4)	1.02 (0.70 to 1.47) 48.7 210 (4)	1.01 (0.89 to 1.15) 0.0 207 (4)	1.01 (0.90 to 1.13) 0.0 201 (4)	1.04 (0.93 to 1.16) 0.0 196 (4)
			Weighted Mean Difference (95% CI) **I^2 %** **Sample Size, n (Studies)**		
ODI (0-50)‖	-2.33 (-6.59 to 1.93) 36.6 444 (4)	**-5.15 (-10.30, -0.01)** **49.5** 461 (5)	-3.62 (-8.02 to 0.78) 30.4 456 (5)	-3.24 (-8.30 to 1.81) 38.3 441 (5)	-6.94 (-13.90 to 0.02) 61.1 423 (5)
Back pain (0-10)‖	0.22 (-0.38 to 0.82) 22.3 443 (4)	**-0.57 (-1.06 to -0.09)** **0.0** 446 (4)	-0.31 (-0.82 to 0.20) 0.0 442 (4)	-0.51 (-1.19 to 0.16) 21.8 426 (4)	**-0.62 (-1.23 to -0.02**) 0.0 409 (4)
Leg pain (0-10)‖	**-0.57 (-1.12 to -0.02)** **0.0** 443 (4)	-0.28 (-0.80 to 0.25) 0.0 446 (4)	-0.20 (-0.72 to 0.31) 0.0 442 (4)	-0.51 (-1.13 to 0.12) 8.9 426 (4)	-0.55 (-1.15 to 0.05) 0.0 409 (4)

SF-36 PCS (0-100)¶	0.55 (-1.02 to 2.11) 0.0 356 (3)	**2.54 (0.46 to 4.61)** **5.5** 374 (4)	**2.81 (0.85 to 4.76)** 0.0 449 (5)	**2.95 (0.86 to 5.04)** 0.0 440 (5)	**3.34 (0.92 to 5.75)** **5.2** 421 (5)
SF-36 MCS (0-100)¶	-0.36 (-2.45 to 1.72) 0.0 356 (3)	0.75 (-1.34 to 2.84) 0.0 374 (4)	-0.31 (-2.22 to 1.60) 0.0 449 (5)	-0.56 (-2.60 to 1.47) 0.0 440 (5)	2.86 (-0.20 to 5.92) 35.0 421 (5)
PLF**					
		Relative risk (95% CI) **I^2 %** **Sample Size, n (Studies)**			
Overall success	----	----	1.55 (0.90 to 2.67) 79.6 698 (4)	1.17 (0.84 to 1.63) 60.1 687 (4)	1.04 (0.90 to 1.20) 0.0 648 (4)
Fusion	----	----	1.44 (0.95 to 2.19) 89.2 694 (4)	1.29 (0.94 to 1.78) 86.3 686 (4)	1.16 (0.96 to 1.41) 75.8 637 (4)
Neurological success	1.04 (0.99 to 1.10) 0.0 706 (4)	1.00 (0.94 to 1.06) 0.0 705 (4)	1.02 (0.96 to 1.09) 0.0 693 (4)	1.01 (0.95 to 1.07) 0.0 683 (4)	1.02 (0.96 to 1.09) 0.0 636 (4)
ODI success	1.01 (0.85 to 1.20) 0.0 707 (4)	1.04 (0.92 to 1.17) 0.0 704 (4)	1.07 (0.98 to 1.17) 0.0 693 (4)	1.01 (0.89 to 1.15) 19.0 683 (4)	1.02 (0.93 to 1.12) 0.0 640 (4)
Return to work§	1.28 (0.73 to 2.25) 0.0 233 (3)	1.32 (0.72 to 2.43) 0.0 232 (3)	0.96 (0.84 to 1.08) 0.0 225 (3)	1.07 (0.89 to 1.29) 30.0 227 (3)	1.02 (0.91 to 1.15) 9.7 208 (3)
		Weighted mean difference (95% CI) **I^2 %** **Sample Size, n (Studies)**			
ODI (0-50)‖	0.74 (-1.68 to 3.16) 0.0 718 (4)	-1.96 (-4.35 to 0.43) 0.0 714 (4)	-2.41 (-4.86 to 0.04) 0.0 703 (4)	-2.23 (-4.95, 0.49) 0.0 694 (4)	-1.92 (-5.03 to 1.18) 5.9 650 (4)
Back pain (0-10)‖	0.10 (-0.27 to 0.48) 0.0 716 (4)	-0.26 (-0.62 to 0.11) 0.0 713 (4)	-0.45 (-1.07 to 0.17) 35.9 702 (4)	-0.41 (-1.34 to 0.52) 64.5 693 (4)	-0.31 (-0.76 to 0.15) 0.0 649 (4)
Leg pain (0-10)‖	0.23 (-0.21 to 0.66) 0.0 715 (4)	**-0.43 (-0.85 to -0.02)** **0.0** 712 (4)	-0.27 (-0.71 to 0.17) 0.0 701 (4)	-0.29 (-0.74 to 0.17) 0.0 692 (4)	-0.35 (-0.82 to 0.13) 0.0 648 (4)
SF-36 PCS (0-100)¶	-0.10 (-1.15 to 0.95) 0.0 709 (4)	0.65 (-0.67 to 1.96) 0.0 708 (4)	**1.79 (0.26 to 3.31)** 0.0 696 (4)	**1.89 (0.26 to 3.53)** 0.0 689 (4)	1.10 (-0.66 to 2.86) 0.0 644 (4)

SF-36 MCS (0-100)¶	0.50 (-0.95 to 1.96) 0.0 709 (4)	-0.05 (-1.60 to 1.50) 0.0 708 (4)	0.06 (-1.47 to 1.60) 0.0 696 (4)	-0.48 (-2.21 to 1.25) 5.8 696 (4)	0.54 (-2.74 to 3.83) 60.6 644 (4)

ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft; MCS = Mental Component Summary; ODI = Oswestry Disability Index; PCS = Physical Component Summary; PLF = posterolateral lumbar fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2; SF-36 = Short Form-36.

* For overall success, fusion, neurologic success, ODI success, and return to work, values reported are risk ratios (95% CIs). For ODI score, back pain, leg pain, and SF-36 PCS and MCS scores, values reported are weighted mean differences (95% CIs). Values in bold are significant ($P < 0.05$).

† A total of 465 patients were included in the analysis; 4 who had open surgery in study 1 were excluded.

‡ Combined estimates obtained using a 2-step approach.

§ The data include only patients who worked before surgery. For ALIF, 221 patients worked before surgery; for PLF, 241 worked before surgery.

|| High values represent worse outcomes, and a negative difference favors rhBMP-2.

¶ Low values represent worse outcomes, and a positive difference favors rhBMP-2.

** A total of 722 patients were included in the analysis; 11 who were randomly assigned to rhBMP-2 without instrumentation in study 12 were excluded.

Table H-2. Overall and Specific Adverse Events for ALIF and PLF with rhBMP-2 vs. ICBG Based on Two-step Approach

Event*	≤ 4 Weeks After Surgery		≤ 24 Months After Surgery	
ALIF†				
	Patients with BMP vs. ICBG, %	**Risk Ratio (95% CI) I^2 % Sample Size, *n* (Studies)**	**Patients with BMP vs. ICBG, %**	**Risk Ratio (95% CI) I^2 % Sample Size, *n* (Studies)**
Overall adverse events				
Overall adverse event, rate‡	0.48 vs.0.65‖	0.81 (0.63, 1.04)§ 0.0 465 (5)	1.76 vs. 1.73‖	1.01 (0.77,1.34)§ 42.1 465 (5)
≥ 1 Adverse event, any type	38 vs. 45	0.86 (0.70 to 1.06) 0.0 465 (5)	78 vs. 80	0.98 (0.88 to 1.09) 7.7 465 (5
≥ 1 Serious adverse event	9 vs. 8	1.12 (0.61 to 2.07) 0.0 455 (4)	34 vs. 35	1.04 (0.61 to 1.75) 55.3 465 (5)
≥ 1 device-related adverse event	---	----	7 vs. 4	1.50 (0.71 to 3.17) 4.1 465 (5)
Specific adverse events				
Anatomical/technical difficulty	0.9 vs. 3	0.22 (0.05 to 1.08) 0.0 419 (4)	0.9 vs. 3	0.22 (0.05 to 1.08) 0.0 419 (4)
Back and/or leg pain	4 vs. 3	1.05 (0.41 to 2.73) 0.0 455 (4)	26 vs. 24	1.07 (0.47 to 2.46) 68.7 465 (5)
Cardiovascular	2 vs. 4	0.54 (0.16 to 1.78) 0.0 409 (3)	6 vs. 7	0.85 (0.43 to 1.71) 0.0 455 (4)
Gastrointestinal	13 vs. 15	0.84 (0.53 to 1.33) 0.0 465 (5)	17 vs. 19	0.89 (0.60 to 1.30) 0.0 465 (5)
Implant problems	2 vs. 1	1.12 (0.23 to 5.57) 0.0 380 (4)	3 vs. 0.9	2.42 (0.58 to 10.07) 0.0 465 (5)
Infection (all types)	6 vs. 5	1.10 (0.49 to 2.50) 0.0 410 (3)	10 vs. 10	1.07 (0.62 to 1.83) 0.0 455 (4)
Neurological	3 vs. 4	0.80 (0.28 to 2.30) 0.0 409 (3)	16 vs. 14	1.09 (0.69 to 1.72) 0.0 455 (4)
Possible lumbar radiculitis (primary)¶	3 vs. 3	1.02 (0.34 to 3.10) 0.0 455 (4)	23 vs. 24	0.99 (0.71 to 1.38) 0.0 455 (4)
Possible lumbar radiculitis (Definition 2)¶	2 vs. 3	0.47 (0.13 to 1.72) 0.0 455 (4)	16 vs. 14	1.11 (0.72 to 1.72) 0.0 455 (4)
Possible lumbar radiculitis (Definition 3)¶	3 vs. 3	0.84 (0.28 to 2.49) 0.0 455 (4)	26 vs. 22	1.15 (0.83 to 1.60) 0.0 455 (4)

Possible lumbar radiculitis (Definition 4)¶	0.8 vs. 2	0.33 (0.06 to 1.87) 0.0 455 (4)	11 vs. 9	1.27 (0.72 to 2.23) 0.0 455 (4)
Respiratory	2 vs. 3	0.57 (0.16 to 2.00) 0.0 364 (2)	3 vs. 5	0.47 (0.16 to 1.36) 0.0 364 (2)
Retrograde ejaculation	4 vs. 1	2.62 (0.28 to 24.56) --- 144 (1)	6 vs. 1	4.36 (0.52 to 36.40) --- 146 (1)
Spinal event	0 vs. 2	0/167 vs. 3/158 325 (2)	12 vs. 11	1.13 (0.68 to 1.89) 0.0 455 (4)
Subsidence	2 vs. 1	1.43 (0.24 to 8.41) --- 279 (1)	4 vs. 1	3.20 (0.66 to 15.53) 0.0 364 (2)
Urogenital	7 vs. 4	1.91 (0.84 to 4.37) 0.0 420 (4)	13 vs. 8	1.62 (0.90 to 2.92) 0.0 420 (4)
Vertebral fracture	1 vs. 0	2/168 vs. 0/156 324 (2)	1 vs. 0	2/168 vs. 0/156 324 (2)
Urinary retention¶	----	----	6 vs. 2	2.33 (0.84 to 6.43) 0.0 378 (3)
Wound infection¶	----	----	5 vs. 6	0.73 (0.32 to 1.67) 0.0 410 (3)
Wound dehiscence¶	----	----	1 vs. 0	3/253 vs. 0/139 293 (2)
Relevant additional surgeries	----	----	11 vs. 13	0.79 (0.40 to 1.54) 23.3 455 (4)
PLF**				
Overall adverse events				
Overall adverse event, rate‡	0.84 vs.0.91‖	1.04 (0.86, 1.27)§ 0.0 722 (4)	3.22 vs. 3.06‖	1.06 (0.94,1.20)§ 0.0 722 (4)
≥ 1 Adverse event, any type	51 vs. 49	1.02 (0.83 to 1.27) 32.0 722 (4)	88 vs. 87	1.01 (0.96 to 1.06) 0.0 722 (4)
≥ 1 Serious adverse event	20 vs. 23	0.90 (0.68 to 1.19) 0.0 722 (4)	50 vs. 52	0.97 (0.84 to 1.12) 0.0 722 (4)
≥ 1 device-related adverse event	---	----	6 vs. 5	1.37 (0.73 to 2.54) 41.1 722 (4)
Specific adverse events				
Anatomical/technical difficulty	1 vs. 0	4/337 vs. 0/323 660 (2)	1 vs. 0	4/337 vs. 0/323 660 (2)
Back and/or leg pain	8 vs. 4	**1.84 (1.01 to 3.37)**†† **0.0** 706 (3)	49 vs. 42	**1.18 (1.01 to 1.39)**†† **0.0** 722 (4)
Cardiovascular	14 vs. 14	0.97 (0.68 to 1.39) 0.0	19 vs. 21	0.93 (0.70 to 1.24) 0.0

		706 (3)		722 (4)
Dural injury	6 vs. 7	0.76 (0.43 to 1.32) 0.0 722 (4)	6 vs. 8	0.78 (0.45 to 1.35) 0.0 722 (4)
Gastrointestinal	7 vs. 10	0.72 (0.44 to 1.18) 18.9 722 (4)	16 vs. 18	0.81 (0.51 to 1.29) 31.6 722 (4)
Implant problems	2 vs. 0.6	2.86 (0.57 to 14.34) 0.0 706 (3)	3 vs. 2	1.58 (0.57 to 4.33) 0.0 706 (3)
Infection (all types)	9 vs. 10	1.04 (0.55 to 1.98) 30.9 706 (3)	18 vs. 19	1.00 (0.66 to 1.50) 27.4 706 (3)
Neurological	5 vs. 3	1.53 (0.70 to 3.33) 0.0 722 (4)	26 vs. 23	1.14 (0.88 to 1.47) 0.0 722 (4)
Possible lumbar radiculitis (Primary)¶	3 vs. 2	1.31 (0.51 to 3.36) 0.0 722 (4)	24 vs. 26	0.95 (0.74 to 1.22) 0.0 722 (4)
Possible lumbar radiculitis (Definition 2)¶	3 vs. 2	1.65 (0.61 to 4.47) 0.0 722 (4)	14 vs. 15	0.88 (0.61 to 1.26) 0.0 722 (4)
Possible lumbar radiculitis (Definition 3)¶	3 vs. 3	1.32 (0.56 to 3.08) 0.0 722 (4)	24 vs. 26	0.91 (0.70 to 1.18) 0.0 722 (4)
Possible lumbar radiculitis (Definition 4)¶	2 vs. 1	1.54 (0.45 to 5.29) 0.0 455 (4)	10 vs. 11	0.86 (0.57 to 1.32) 0.0 455 (4)
Respiratory	4 vs. 3	1.37 (0.60 to 3.15) 23.9 706 (3)	7 vs. 5	1.45 (0.80 to 2.61) 0.0 706 (3)
Spinal event	1 vs. 1	1.02 (0.25 to 4.10) 0.0 676(3)	9 vs. 10	0.89 (0.56 to 1.40) 0.0 722 (4)
Urogenital	7 vs. 7	1.05 (0.62 to 1.79) 0.0 722 (4)	13 vs. 12	1.11 (0.76 to 1.62) 0.0 722 (4)
Vertebral fracture	2 vs. 0.9	1.26 (0.29 to 5.55) 0.0 660 (2)	1 vs. 1	0.95 (0.24 to 3.73) 0.0 660 (2)
Relevant additional surgeries	---	----	12 vs. 14	0.81 (0.55 to 1.18) 0.0 722 (4)

ALIF = anterior lumbar interbody fusion; ICBG = iliac crest bone graft; PLF = posterolateral lumbar fusion; rhBMP-2 = recombinant human bone morphogenetic protein-2.
* Categories are based on Medtronic data sets unless otherwise indicated.
†A total of 465 patients were included in the analysis, excluding 4 who had open surgery in study 1.
‡We examined rate of overall adverse events (as opposed to proportion of patents having adverse events).
§Rate ratio
‖Rate (number of adverse events per patient)
¶Based on individual adverse event case histories in the internal reports provided by Medtronic.
**A total of 722 patients were included in the analysis, excluding 11 randomly assigned to rhBMP-2 without instrumentation in study 12.
††Statistically significant ($P < 0.05$).

Appendix I (Part 1). Strength of Evidence – Up to 24 Months

Table I-1. Anterior lumbar interbody fusion (ALIF) - rhBMP-2 vs. bone graft - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
5 RCTs *n*=416 2 Cohorts *n*=60	Moderate	Low	Direct	Moderate	RR 1.05, 0.88 to 1.24 No difference	Moderate
Outcome 2. Overall Success						
5 RCTs *n*=418	Moderate	Moderate	Direct	Low	RR 1.19, 0.99 to 1.42	Moderate
Outcome 3. Neurological Success						
4 RCTs *n*=400	Moderate	Moderate	Direct	Moderate	RR 1.08, 0.98 to 1.19	Moderate
Outcome 4. Oswestry Disability Index						
5 RCTs *n*=423	Moderate	Low	Direct	Low	WMD -6.94, -13.90 to 0.02	Low
Outcome 5. ODI Success						
5 RCTs *n*=417	Moderate	High	Direct	Moderate	RR 1.10, 0.97 to 1.24	Moderate
Outcome 6. Back Pain						
4 RCTs *n*=409	Moderate	High	Direct	Low	WMD -0.74, -1.49 to 0.00	Moderate
Outcome 7. Leg Pain						
5 RCTs *n*=409	Moderate	High	Direct	Low	WMD -0.60, -1.28 to 0.08	Moderate
Outcome 8. SF-36 PCS						
5 RCTs *n*=421	Moderate	Moderate	Direct	Moderate	WMD 3.68, 0.86 to 6.49	Moderate
Outcome 9. SF-36 MCS						
5 RCTs *n*=421	Moderate	Low	Direct	Moderate	WMD 2.90, -0.29 to 6.08	Low
Outcome 10. Return to Work						
4 RCTs *n*=196	Moderate	Moderate	Direct	High	RR 1.06, 0.94 to 1.19	Moderate
Outcome 11. Adverse Events						
5 RCTs *n*=465	Moderate	Moderate	Direct	High	RR 0.96, 0.85 to 1.09	Moderate
Outcome 12. Serious Adverse Events						
5 RCTs *n*=465	Moderate	Moderate	Direct	Low	RR 0.94. 0.67 to 1.33	Moderate

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 13. Retrograde Ejaculation						
1 RCTs *n*=146 1 Cohort *n*=243	High	Moderate	Direct	Low	RR 4.36, 0.52 to 36.40 ---- 7.3% vs. 0.6% (p=0.0025)	Low
Outcome 14. Urinary Retention						
3 RCTs *n*=378	High	Low	Direct	Low	RR 2.55, 0.30 to 21.52	Low
Outcome 15. Wound Infection						
3 RCTs *n*=410	High	Moderate	Direct	Low	RR 0.73, 0.38 to 1.43	Low
Outcome 16. Wound Dehiscence						
2 RCTs *n*=293	High	Moderate	Direct	Low	3/253 vs. 0/139	Insufficient
Outcome 17. Bone Resorption/Subsidence						
2 RCTs *n*=364 1 Cohort *n*=24	Moderate	High	Direct	Low	RR 3.15, 0.66 to 14.99 ---- 70% vs. 6% (p=0.0001)	Moderate
Outcome 18. Relevant Reoperations						
4 RCTs *n*=455 1 Cohort *n*=36	Moderate	Moderate	Direct	Low	RR 0.81, 0.49 to 1.33 ---- 33% vs. 26% (p=0.67)	Moderate

*Sample size reflects the total number of patients included in each analysis

Table I-2. Posterolateral lumbar fusion (PLF) - rhBMP-2 vs. bone graft - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Overall Success						
4 RCTs *n*=648	Moderate	High	Direct	High	RR 1.05, 0.91 to 1.21	Moderate
Outcome 2. Fusion						
4 RCTs *n*=637 5 cohorts *n*=351	Moderate	Moderate	Direct	Moderate	RR 1.16, 0.96 to 1.41 ---- Cohorts: Rates range widely; few significant differences	Moderate
Outcome 3. Neurological success						
4 RCTs *n*=636	Moderate	High	Direct	High	RR 1.01, 0.92 to 1.10	Moderate
Outcome 4. ODI success						
4 RCTs *n*=640	Moderate	High	Direct	High	RR1.01, 0.91 to 1.12	Moderate
Outcome 5. Return to work						
3 RCTs *n*=208	Moderate	High	Direct	High	RR 1.03, 0.94 to 1.14	Moderate
Outcome 6. SF-36: PCS						
4 RCTs *n*=644	Moderate	Moderate	Direct	Moderate	WMD 1.10, -0.65 to 2.86	Moderate
Outcome 7. SF-36: MCS						
4 RCTs *n*=644	Moderate	Low	Direct	Low	WMD 0.54, -3.16 to 4.25	Low
Outcome 8. ODI						
4 RCTs *n*=650	Moderate	Moderate	Direct	Moderate	WMD -1.98, -4.86 to 0.90	Moderate
Outcome 9. Leg pain (0-10)						
4 RCTs *n*=648	Moderate	High	Direct	High	WMD -0.34, -0.82 to 0.13	Moderate
Outcome 10. Back pain (0-10)						
4 RCTs *n*=649	Moderate	Moderate	Direct	Moderate	WMD -0.31, -0.76 to 0.15	Moderate
Outcome 11. Adverse Events						
4 RCTs *n*=722	Moderate	Moderate	Direct	High	RR 1.02, 0.95 to 1.10	Moderate
Outcome12. Serious Adverse Events						
4 RCTs *n*=722	Moderate	Moderate	Direct	High	RR 0.96, 0.83 to 1.11	Moderate

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 13. Relevant Reoperations						
4 RCTs *n*=722	Moderate	Moderate	Direct	Moderate	RR 0.72, 0.38 to 1.34	Moderate
Outcome 14. Neurological Adverse Event						
4 RCTs *n*=722	Moderate	High	Direct	High	RR 0.97, 0.62 to 1.51	Moderate

*Sample size reflects the total number of patients included in each analysis

Table I-3. Posterior lumbar interbody fusion (PLIF) - rhBMP-2 vs. bone graft - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
1 RCT *n*=61	Moderate	NA	Direct	Moderate	RR 1.15, 0.86 to 1.54	Low
Outcome 2. Overall Success						
1 RCT *n*=62	Moderate	NA	Direct	Low	RR 1.50, 0.80 to 2.81	Insufficient
Outcome 3. Neurological Success						
1 RCT *n*=60	Moderate	NA	Direct	Low	RR 0.94, 0.72 to 1.23	Insufficient
Outcome 4. Return to work						
1 RCT *n*=22	Moderate	NA	Direct	Low	RR 1.23, 0.80 to 1.87	Insufficient
Outcome 5. Leg pain (0-10 scale)						
1 RCT *n*=59	Moderate	NA	Direct	Low	WMD -0.02, -1.78 to 1.74	Insufficient
Outcome 6. Back pain (0-10 scale)						
1 RCT *n*=59	Moderate	NA	Direct	Low	WMD -0.96, -2.52 to 0.60	Insufficient
Outcome 7. SF-36 PCS (0-100)						
1 RCT *n*=56	Moderate	NA	Direct	Low	WMD 1.30, -5.21 to 7.82	Insufficient
Outcome 8. SF-36 MCS (0-100)						
1 RCT *n*=56	Moderate	NA	Direct	Low	WMD 2.1, -4.59 to 8.77	Insufficient
Outcome 9. Adverse Events						
1 RCT *n*=67	Moderate	NA	Direct	Low	33/34 vs. 33/33	Low
Outcome 10. Serious adverse events						
1 RCT *n*=67	Moderate	NA	Direct	Low	RR 0.67, 0.37 to 1.22	Low

*Sample size reflects the total number of patients included in each analysis

Table I-4. Circumferential posterior lumbar interbody fusion (PLIF)/transforaminal lumbar interbody fusion (TLIF) - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
2 Cohorts *n*=159	High	High	Direct	High	RR 1.00, 0.93 to 1.07	Low
Outcome 2. Overall adverse events						
1 Cohort *n*=119	High	N/A	Direct	Moderate	RR 0.81, 0.60 to 1.03	Insufficient
Outcome 3. Radiculitis						
2 Cohorts *n*=162	High	High	Direct	Low	RR 3.74, 0.74 to 18.90	Low

*Sample size reflects the total number of patients included in each analysis

Table I-5. Circumferential anterior lumbar interbody fusion (ALIF) - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
3 Cohorts *n*=190	High	Moderate	Direct	Moderate	89-100% (rhBMP-2) vs. 72-89%	Insufficient
Outcome 2. Adverse Events						
3 Cohorts *n*=190	High	Low	Direct	Low	21 AEs/104 pts (rhBMP-2) vs. 18 AEs/86 pts	Insufficient

*Sample size reflects the total number of patients included in each analysis

Table I-6. Circumferential axial lumbar interbody fusion - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
1 Cohort *n*=99	High	NA	Direct	Moderate	96% (rhBMP-2) vs. 93%	Insufficient
Outcome 2. Overall adverse events						
1 Cohort *n*=99	High	NA	Direct	Low	Few reported	Insufficient

*Sample size reflects the total number of patients included in each analysis

Table I-7. Mixed lumbar fusion - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Repeat Fusion Surgery						
2 Cohorts *n*=6142	Moderate	Moderate	Direct	Moderate	Cohort 1 *n*=4744 OR 0.66, 0.47 to 0.94 ——— Cohort 2 *n*=1398 41/947 (rhBMP-2) vs. 40/306 (DBM) and 22/145 (autograft)	Moderate

*Sample size reflects the total number of patients included in each analysis

Table I-8. Anterior cervical spine fusion - rhBMP-2 vs. bone graft - strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
1 RCT *n*=33 3 Cohorts *n*=135	Moderate	Moderate	Direct	Low	11/12 vs. 12/12 ---- RR 1.04, 0.96 to 1.12	Low
Outcome 2. Overall Success						
1 RCT *n*=24 pts	Moderate	NA	Direct	Low	10/14 vs. 10/13	Insufficient
Outcome 3. Neurological Success						
1 RCT *n*=27	Moderate	NA	Direct	Low	14/14 vs. 12/13	Insufficient
Outcome 4. NDI Success						
1 RCT *n*=27	Moderate	NA	Direct	Low	13/14 vs. 12/13	Insufficient
Outcome 5. Return to Work						
1 RCT *n*=16	Moderate	NA	Direct	Low	8/8 in each group returned to work	Insufficient
Outcome 6. Neck Disability Index						
1 RCT *n*=33 2 Cohorts *n*=112	Moderate	Moderate	Direct	Low	WMD -4.7, -16.9 to 7.6 ---- Both cohorts reported no treatment effect	Low
Outcome 7. Neck Pain						
1 RCT *n*=33 2 Cohorts *n*=112	Moderate	Moderate	Direct	Low	WMD -2.9, -6.3 to 0.4 ---- Both cohorts reported no treatment effect	Low

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 8. Arm Pain						
1 RCT *n*=33 2 Cohorts *n*=112	Moderate	Moderate	Direct	Low	WMD 0.8, -3.5 to 5.1 ---- Both cohorts reported no treatment effect	Low
Outcome 9. Adverse Events						
1 RCT *n*=33	Moderate	NA	Direct	Moderate	RR 2.88, 1.30 to 6.41	Low
Outcome 10. Heterotopic Bone Formation						
1 RCT *n*=33	Moderate	NA	Direct	Low	2/18 vs. 1/15	Insufficient
Outcome 11. Bone Resorption						
1 Cohort *n*=23	High	NA	Direct	Low	33% of 18 levels vs 0% of 22 levels	Insufficient
Outcome 12. Relevant Reoperations						
1 RCT *n*=33 4 Cohorts *n*=402	Moderate	Low	Direct	Low	1/18 vs. 0/15 ---- RR 3.84, 0.56 to 26.5	Low

*Sample size reflects the total number of patients included in each analysis

Table I-9. Posterior cervical spine fusion - rhBMP-2 vs. bone graft - Strength of evidence (24 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Fusion						
1 Cohort *n*=204	High	NA	Direct	Moderate	RR 1.13, 1.05 to 1.22	Insufficient
Outcome 2. Nurick and ASIA scales						
1 Cohort *n*=204	High	NA	Direct	Low	no difference between groups	Insufficient
Outcome 3. Neck Pain						
1 Cohort *n*=204	High	NA	Direct	Low	48% vs. 29% p=0.003	Insufficient
Outcome 4. Total Adverse Events						
3 Cohorts *n*=364	Moderate	Moderate	Direct	Low	---- RR 0.80, 0.43 to 1.49	Low
Outcome 5. Wound Complications						
2 Cohorts *n*=281	Moderate	Moderate	Direct	Low	---- p-values > 0.05	Low
Outcome 6. Reoperations						
1 Cohort *n*=204	High	NA	Direct	Low	RR 0.71, 0.34 to 1.51	Insufficient
Outcome 7. Dysphagia/dysphonia						
1 Cohort *n*=204	Moderate	NA	Direct	Low	(p=0.48)	Insufficient

*Sample size reflects the total number of patients included in each analysis

Table I-10. Cancer and death – strength of evidence (24 months and 48 months)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1: Cancer						
24 month: 5 RCTs *n*= 1450	Moderate	High	Direct	Low	RR 3.45, 1.98 to 6.00	Low
48 month: 4 RCTs *n*= 1183 1 Cohort N = 125	Moderate	High	Direct	Low	RR 1.82, 0.84 to 3.95 RR 2.10, 0.69 to 6.41	Low
Outcome 2: Death						
24month: 9 RCTs *n*= 1753	Low	Moderate	Direct	Low	RR 0.67, 0.28 to 1.63	Low
48 month: 4 RCTs *n*= 1183	Moderate	High	Direct	Low	RR 0.65, 0.33 to 1.30	Low

*Sample size reflects the total number of patients included in each analysis

Appendix I (Part 2). Strength of Evidence - Earliest Time Point (4 Weeks for Adverse Events; 6 Weeks for Effectiveness)

Table E-11. Anterior lumbar interbody fusion (ALIF) - rhBMP-2 vs. bone graft - Strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Neurological Success						
4 RCTs *n*=434	Moderate	Moderate	Direct	Moderate	RR 1.02, 0.93 to 1.13	Moderate
Outcome 2. Oswestry Disability Index						
4 RCTs *n*=444	Moderate	Low	Direct	Low	WMD -2.36, -6.91 to 2.19	Low
Outcome 3. ODI Success						
4 RCTs *n*=442	Moderate	Moderate	Direct	Moderate	RR 1.04, 0.83 to 1.29	Moderate
Outcome 4. Back Pain						
4 RCTs *n*=443	Moderate	High	Direct	Low	WMD 0.21, -0.28 to 0.71	Moderate
Outcome 5. Leg Pain						
4 RCTs *n*=443	Moderate	High	Direct	Low	WMD -0.57, -1.12 to -0.02	Moderate
Outcome 6. SF-36 PCS						
3RCTs *n*=356	Moderate	Moderate	Direct	Moderate	WMD 0.55, -1.02 to 2.11	Moderate
Outcome 7. SF-36 MCS						
3 RCTs *n*=421	Moderate	Low	Direct	Moderate	WMD -0.36, -2.45 to 1.73	Low
Outcome 8. Return to Work						
4RCTs *n*=211	Moderate	Moderate	Direct	Low	RR 1.21, 0.71 to 2.05	Low
Outcome 9. Adverse Events						
5 RCTs *n*=465	Moderate	Moderate	Direct	Moderate	RR 0.84, 0.61 to 1.17	Moderate

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 10. Serious Adverse Events						
4RCTs *n*=455	Moderate	Moderate	Direct	Low	RR 1.12, 0.72 to 1.74	Moderate
Outcome 11. Retrograde Ejaculation						
1 RCT *n*=144	Moderate	NA	Direct	Low	RR 2.62, 0.28 to 24.56	Low
Outcome 11. Subsidence						
1 RCT *n*=279	Moderate	NA	Direct	Low	RR 1.43, 0.24 to 8.41	Low

*Sample size reflects the total number of patients included in each analysis

Table I-12. Posterolateral lumbar fusion (PLF) - rhBMP-2 vs. bone graft - strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Neurological success						
4 RCTs *n*=706	Moderate	High	Direct	Moderate	RR 1.03, 0.94 to 1.13	Moderate
Outcome 2. ODI success						
4 RCTs *n*=707	Moderate	High	Direct	High	RR1.00, 0.81 to 1.23	Moderate
Outcome 3. Return to work						
3 RCTs *n*=233	Moderate	High	Direct	Low	RR 1.26, 0.71 to 2.21	Moderate
Outcome 4. SF-36: PCS						
4 RCTs *n*=709	Moderate	Moderate	Direct	Moderate	WMD -0.10, -1.15 to 0.96	Moderate
Outcome 5. SF-36: MCS						
4 RCTs *n*=709	Moderate	Moderate	Direct	Moderate	WMD 0.52, -0.94 to 1.98	Moderate
Outcome 6. ODI						
4 RCTs *n*=718	Moderate	High	Direct	Moderate	WMD 0.74, -1.68 to 3.17	Moderate
Outcome 7. Leg pain (0-10)						
4 RCTs *n*=715	Moderate	High	Direct	High	WMD 0.23, -0.21 to 0.66	Moderate
Outcome 8. Back pain (0-10)						
4 RCTs *n*=649	Moderate	High	Direct	High	WMD 0.10, -0.27 to 0.48	Moderate
Outcome 9. Adverse Events						
4 RCTs *n*=722	Moderate	Moderate	Direct	Low	RR 0.93, 0.66 to 1.31	Moderate
Outcome10. Serious Adverse Events						
4 RCTs *n*=722	Moderate	Moderate	Direct	Moderate	RR 0.89, 0.67 to 1.18	Moderate
Outcome 11. Back and/or leg pain						
3 RCTs *n*=706	Moderate	Moderate	Direct	Moderate	RR 1.83, 1.15 to 2.93	Moderate
Outcome 12. Neurological Adverse Event						
4 RCTs *n*=722	Moderate	High	Direct	Moderate	RR1.53, 0.88 to 2.65	Moderate

*Sample size reflects the total number of patients included in each analysis

Table I-13. Posterior lumbar interbody fusion (PLIF) - rhBMP-2 vs. bone graft - strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Neurological Success						
1 RCT *n*=63	Moderate	NA	Direct	Moderate	RR 0.93, 0.73 to 1.18	Insufficient
Outcome 2. Return to work						
1 RCT *n*=24	Moderate	NA	Direct	Low	RR 2.78, 0.86 to 8.94	Insufficient
Outcome 3. Leg pain (0-10 scale)						
1 RCT *n*=63	Moderate	NA	Direct	Low	WMD -0.48, -2.14 to 1.17	Insufficient
Outcome 4. Back pain (0-10 scale)						
1 RCT *n*=63	Moderate	NA	Direct	Low	WMD 0.05, -1.33 to 1.42	Insufficient
Outcome 5. Adverse Events						
1 RCT *n*=67	Moderate	NA	Direct	Low	RR 0.93, 0.66 to 1.30	Low
Outcome 6. Serious adverse events						
1 RCT *n*=67	Moderate	NA	Direct	Moderate	RR 0.35, 0.12 to 0.998	Low

*Sample size reflects the total number of patients included in each analysis

Table I-14. Mixed lumbar fusion - strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Any Complication						
1 cohort *n*=36,807	Moderate	NA	Direct	High	OR 1.03, 0.95 to 1.12	Low
Outcome 2. Wound Complication						
1 cohort *n*=36,807	Moderate	NA	Direct	High	OR 0.93, 0.80 to 1.08	Low
Outcome 3. Renal Insufficiency						
1 Cohort *n*=149	High	NA	Direct	Low	3/24 (rhBMP-2) vs. 0/125	Insufficient

*Sample size reflects the total number of patients included in each analysis

Table I-15. Anterior cervical spine fusion - rhBMP-2 vs. bone graft - strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Neurological Success						
1 RCT *n*=33	Moderate	NA	Direct	Low	14/18 vs 14/15	Insufficient
Outcome 2. Return to Work						
1 RCT *n*=33	Moderate	NA	Direct	Low	7/12 vs 6/9	Insufficient
Outcome 3. Neck Disability Index						
1 RCT *n*=33	Moderate	NA	Direct	Low	WMD -0.21, -11.47 to 11.06	Insufficient
Outcome 4. Neck Pain						
1 RCT *n*=33	Moderate	NA	Direct	Low	WMD -2.04, -5.56 to 1.47	Insufficient
Outcome 5. Arm Pain						
1 RCT *n*=33	Moderate	NA	Direct	Low	WMD 0.14, -4.23 to 4.52	Insufficient
Outcome 6. Adverse Events						
1 RCT *n*=33 1 Cohort *n*=27,067	Moderate	Moderate	Direct	Moderate	RR 1.83, 0.58 to 5.79 ---- OR 1.43, 1.20 to 1.70	Low
Outcome 7. Dysphagia/Dysphonia						
1 RCT *n*=33 1 Cohort *n*=27,067 4 additional Cohorts *n*=1,113	Moderate	Moderate	Direct	Moderate	1/18 vs. 2/15 ---- OR 1.63, 1.30 to 2.05 ---- OR ranges from 6.2 to 10.1, all significant	Moderate
Outcome 8. Wound Complications						
1 RCT *n*=33 1 Cohort *n*=27,067	Moderate	Moderate	Direct	Moderate	2/18 vs. 0/15 ---- OR 1.67, 1.10 to 2.53	Low

*Sample size reflects the total number of patients included in each analysis

Table I-16. Posterior cervical spine fusion - rhBMP-2 vs. bone graft - strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Total Adverse Events						
1 Cohort *n*=2,869	Moderate	NA	Direct	Low	OR 1.03, 0.73 to 1.44	Low
Outcome 2. Wound Complications						
1 Cohort *n*=2,869	Moderate	NA	Direct	Low	OR 1.11, 0.60 to 2.05	Low
Outcome 3. Dysphagia/Dysphonia						
1 Cohort *n*=2,869	Moderate	NA	Direct	Low	OR 1.28, 0.63 to 2.59	Low

*Sample size reflects the total number of patients included in each analysis

Table E-17. Thoracic – strength of evidence (effectiveness at 6 weeks; adverse events at 4 weeks)

Number of Studies; Number of Patients*	Risk of Bias (Design/ Quality - High, Moderate, Low)	Consistency (High, Moderate, Low)	Directness (Direct, Indirect)	Precision (High, Moderate, Low)	Magnitude of Effect	Strength of Evidence (High, Moderate, Low, Insufficient)
Outcome 1. Any Complication						
1 Cohort *n*=3257	Moderate	NA	Direct	Moderate	OR 1.05, 0.83 to 1.32	Low
Outcome 2. Wound Complication						
1 Cohort *n*=3257	Moderate	NA	Direct	Moderate	OR 0.78, 0.53 to 1.17	Low

*Sample size reflects the total number of patients included in each analysis

Appendix J. Included Studies

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5. Anderson CL, Whitaker MC. Heterotopic ossification associated with recombinant human bone morphogenetic protein-2 (infuse) in posterolateral lumbar spine fusion: a case report. *Spine.* 2012;37(8):E502-506. [PMID: 22020605]
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10. Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine.* 2003;28(12):1219-1224; discussion 1225. [PMID: 12811263]
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122. Stachniak JB, Diebner JD, Brunk ES, Speed SM. Analysis of prevertebral soft-tissue swelling and dysphagia in multilevel anterior cervical discectomy and fusion with recombinant human bone morphogenetic protein-2 in patients at risk for pseudarthrosis. *J Neurosurg Spine.* 2011;14(2):244-249. [PMID: 21184639]

123. Stambough JL, Clouse EK, Stambough JB. Instrumented one and two level posterolateral fusions with recombinant human bone morphogenetic protein-2 and allograft: a computed tomography study. *Spine.* 2010;35(1):124-129. [PMID: 20042965]

124. Subach BR, Copay AG, Martin MM, Schuler TC. Anterior lumbar interbody implants: importance of the interdevice distance. *Adv Orthop.* 2011;2011:176497. [PMID: 21994890]

125. Taghavi CE, Lee K-B, Keorochana G, Tzeng S-T, Yoo JH, Wang JC. Bone morphogenetic protein-2 and bone marrow aspirate with allograft as alternatives to autograft in instrumented revision posterolateral lumbar spinal fusion: a minimum two-year follow-up study. *Spine.* 2010;35(11):1144-1150. [PMID: 20139805]

126. Tumialan LM, Pan J, Rodts GE, Mummaneni PV. The safety and efficacy of anterior cervical discectomy and fusion with polyetheretherketone spacer and recombinant human bone morphogenetic protein-2: a review of 200 patients. *J Neurosurg Spine.* 2008;8(6):529-535. [PMID: 18518673]

127. Tumialan LM, Ponton RP, Riccio AI, Gluf WM. Rate of return to military active duty after single level lumbar interbody fusion: a 5-year retrospective review. *Neurosurgery.* 2012;71(2):317-324. [PMID: 22811082]

128. Vaidya R, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J.* 2007;16(8):1257-1265. [PMID: 17387522]

129. Vaidya R, Sethi A, Bartol S, Jacobson M, Coe C, Craig JG. Complications in the use of rhBMP-2 in PEEK cages for interbody spinal fusions. *J Spinal Disord Tech.* 2008;21(8):557-562. [PMID: 19057248]

130. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. *J Bone Joint SurgBr.* 2007;89(3):342-

345. [PMID: 17356146]

131. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine.* 2005;3(6):436-443. [PMID: 16381205]

132. Wang JC, Haid Jr RW, Miller JS, Robinson JC. Comparison of CD HORIZON SPIRE spinous process plate stabilization and pedicle screw fixation after anterior lumbar interbody fusion: Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2005. *J Neurosurg Spine.* 2006;4(2):132-136. [PMID: 16506480]

133. Whang PG, O'Hara BJ, Ratliff J, Sharan A, Brown Z, Vaccaro AR. Pseudarthrosis following lumbar interbody fusion using bone morphogenetic protein-2: intraoperative and histopathologic findings. *Orthopedics.* 2008;31(10). [PMID: 19226004]

134. Wong DA, Kumar A, Jatana S, Ghiselli G, Wong K. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). *Spine J.* 2008;8(6):1011-1018. [PMID: 18037352]

135. Xu R, Bydon M, Sciubba DM, Witham TF, Wolinsky JP, Gokaslan ZL, et al. Safety and efficacy of rhBMP2 in posterior cervical spinal fusion for subaxial degenerative spine disease: Analysis of outcomes in 204 patients. *Surg Neurol Int.* 2011;2:109. [PMID: 21886882]

136. Yaremchuk KL, Toma MS, Somers ML, Peterson E. Acute airway obstruction in cervical spinal procedures with bone morphogenetic proteins. *Laryngoscope.* 2010;120(10):1954-1957. [PMID: 20824786]

Appendix K. Excluded Studies

The following full-text publications were considered for inclusion but did not meet the selection criteria for this report. Reasons for exclusion are coded as:
1 = non-English language
2 = ineligible outcome
3 = ineligible intervention
4= ineligible population
5 = general ineligible publication type
5b = randomized trial available only in abstract form
6 = ineligible study design
7 = ineligible body area
Pending = final results not available at the time of the report

1. Abdullah KG, Steinmetz MP, Benzel EC, Mroz TE. The state of lumbar fusion extenders. *Spine.* 2011;36(20):E1328-1334. [PMID: 21358468] Exclusion code: 5
2. Abraham E, Alexander D, Bailey S, Hurlbert J, McBroom R, Mahood J, et al. A long-term radiographic and clinical evaluation of a new rhBMP-2 formulation in a prospective randomized lumbar posterolateral spine fusion study. *Canadian Journal of Surgery.* 2008;51(3 Suppl):S6-S7. Exclusion code: 5b
3. Abraham EP, Hurlbert J, Alexander D, Bailey S, Fisher C. Evaluation of an rhBMP-2 formulation in 2-level posterolateral lumbar spine arthrodesis. *Spine Journal.* 2010;10(9):105S. Exclusion code: 5b
4. Adetchessi T, Armaganian G, Pech Gourg G, Fuentes S, Dufour H. Anterior spinal fusion and posterior percutaneous osteosynthesis in low-grade lumbar spondylolisthesis due to isthmic lysis in adults. *European Spine Journal.* 2011;20(7):1212-1213. Exclusion code: 5
5. Adogwa O, Parker SL, Shau D, Mendelhall SK, Cheng J, Aaronson O et al. Long-term outcomes of revision fusion for lumbar pseudarthrosis: Clinical article. *Journal of Neurosurgery: Spine.* 2011;15(4):393-398. [PMID: 21699473]. Exclusion code: 3
6. Adogwa O, Parker SL, Shau DN, Mendenhall SK, Aaronson O, Cheng JS, et al. Cost per quality-adjusted life year gained of revision neural decompression and instrumented fusion for same-level recurrent lumbar stenosis: Defining the value of surgical intervention. Clinical article. *Journal of Neurosurgery: Spine.* 2012;16(2):135-140. [PMID: 22054639] . Exclusion code: 3Aebi M, Grob D. SSE Spine Tango: a European Spine Registry promoted by the Spine Society of Europe (SSE). *European Spine Journal.* 2004;13(8):661-662. [PMID: 15614517] Exclusion code: 5
7. Agarwal R, Williams K, Umscheid CA, Welch WC. Osteoinductive bone graft substitutes for lumbar fusion: a systematic review. *Journal of Neurosurgery Spine.* 2009;11(6):729-740. [PMID: 19951027] Exclusion code: 5
8. Alexander D, Oxner W, Soroceanu A, Kelly A, Shakespeare D. A prospective randomized clinical trial of posterolateral lumbosacral spinal fusion with BMP-2 and titanium pedicle screw instrumentation versus BMP-2 alone: preliminary 6-month results. *Canadian Journal of Surgery.* 2009;52(3 Suppl):S21. CN-00726900] Exclusion code: 5b
9. Allareddy V, Turkistani K, Nanda V, Gajendrareddy P, Venugopalan SR. Factors Associated With Hospitalization Charges for Cleft Palate Repairs and Revisions. *Journal of Oral and Maxillofacial Surgery.* 2011. Exclusion code: 2
10. Allen RT, Lee Y-P, Stimson E, Garfin SR. Bone morphogenetic protein-2 (BMP-2) in the treatment of pyogenic vertebral osteomyelitis. *Spine.* 2007;32(26):2996-3006. [PMID: 18091493] Exclusion code: 6
11. Alonso N, Tanikawa DYS, Freitas RdS, Canan L, Jr., Ozawa TO, Rocha DL. Evaluation of maxillary alveolar reconstruction using a resorbable collagen sponge with recombinant human bone morphogenetic protein-2 in cleft lip

and palate patients. *Tissue Engineering - Part C: Methods.* 2010;16(5):1183-1189. [PMID: 20163243] Exclusion code: 7

12. Alt V, Chhabra A, Franke J, Cuche M, Schnettler R, Le Huec J-C. An economic analysis of using rhBMP-2 for lumbar fusion in Germany, France and UK from a societal perspective. *European Spine Journal.* 2009;18(6):800-806. [PMID: 19301041] Exclusion code: 2
13. 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;40(12):1269-1275. [PMID: 19539926] Exclusion code: 7
14. Alt V, Donell ST, Chhabra A, Eicher A, Schnettler R. BMP-2 is a cost-effective therapy in grade III open tibia fractures - a health-economic assessment of the use BMP-2 in open tibia fractures for European health care systems. *Journal of Bone and Joint Surgery - British Volume.* 2009;91-B(SUPP_I):155-115b. CN-00689375] Exclusion code: 5
15. Alt V, Meyer C, Litzlbauer HD, Schnettler R. Treatment of a double nonunion of the femur by rhBMP-2. *Journal of Orthopaedic Trauma.* 2007;21(10):734-737. [PMID: 17986892] Exclusion code: 7
16. An HS, Thonar EJMA, Masuda K. Biological repair of intervertebral disc. *Spine.* 2003;28(15 Suppl):S86-92. [PMID: 12897480] Exclusion code: 3
17. Anderson FA, Jr. Overview of the GLOBAL Orthopaedic Registry (GLORY). *American Journal of Orthopedics (Chatham, Nj).* 2010;39(9 Suppl):2-4. [PMID: 21290025] Exclusion code: 5
18. Ando W, Hashimoto J, Yoshikawa H. [Osteosclerosis related with bone morphogenetic protein (BMP)]. *Nippon Rinsho - Japanese Journal of Clinical Medicine.* 2005;63 Suppl 10:444-449. [PMID: 16279680] Exclusion code: 1
19. Antoni M, Charles YP, Walter A, Bogorin I, Steib JP. Consolidation of anterior grafts in thoracolumbar fractures. *European Spine Journal.* 2011;20(7):1198. Exclusion code: 5
20. Apatech Inc. Actifuse ABX Versus INFUSE in Posterolateral Instrumented Lumbar Fusion. 2012. NCT01018771. Exclusion code: 5
21. Apatech Inc. Actifuse ABX Versus INFUSE in Posterolateral Instrumented Lumbar Fusion (PLIF) With Interbody Fusion. 2012. NCT01013389. Exclusion code: Pending
22. Argintar E, Edwards S, Delahay J. Bone morphogenetic proteins in orthopaedic trauma surgery. *Injury.* 2011;42(8):730-734. [PMID: 21145058] Exclusion code: 5
23. Arnold PM, Klemp JA. Assessment of malunion in spinal fusion. *Neurosurgery Quarterly.* 2005;15(4):239-247. Exclusion code: 5
24. Aro HT, Govender S, Patel AD, Hernigou P, Perera de Gregorio A, Popescu GI, et al. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. *Journal of Bone & Joint Surgery - American Volume.* 2011;93(9):801-808. [PMID: 21454742] Exclusion code: 7
25. Aryan HE, Newman CB, Gold JJ, Acosta FL, Jr., Coover C, Ames CP. Percutaneous axial lumbar interbody fusion (AxiaLIF) of the L5-S1 segment: initial clinical and radiographic experience. *Minimally Invasive Neurosurgery.* 2008;51(4):225-230. [PMID: 18683115] Exclusion code: 3
26. Aspenberg P. Drugs and fracture repair. *Acta Orthopaedica.* 2005;76(6):741-748. [PMID: 16470424] Exclusion code: 5
27. Aspenberg P. Under-reported complications related to BMP use in spine surgery. *Acta Orthopaedica.* 2011;82(5):511-512. [PMID: 21992083] Exclusion code: 5
28. Assael LA. Mandibular reconstruction: expert opinion and outcome studies remain a fragile guide to treatment. *Journal of Oral & Maxillofacial Surgery.* 2009;67(12):2557-2558. [PMID: 19925971] Exclusion code: 5
29. Assiri I, du Plessis S, Hurlbert J, Hu R, Salo P, Whittaker T. A prospective randomized clinical study comparing instrumented lumbar fusion rates of Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2) with autogenous iliac crest bone graft in patients with symptomatic degenerative disc disease. *Canadian Journal of Surgery.* 2004;47(Suppl 4):7-8. CN-00524395] Exclusion code: 5b
30. Axelrad TW, Einhorn TA. Bone morphogenetic proteins in orthopaedic surgery. *Cytokine & Growth Factor Reviews.* 2009;20(5-6):481-488. [PMID: 19892584] Exclusion code: 5
31. Axelrad TW, Steen B, Lowenberg DW, Creevy

WR, Einhorn TA. Heterotopic ossification after the use of commercially available recombinant human bone morphogenetic proteins in four patients. *Journal of Bone & Joint Surgery - British Volume.* 2008;90(12):1617-1622. [PMID: 19043134] Exclusion code: 7

32. Bachy M, Lenoir T, Dauzac C, Guigui P. Radiological analysis of bone consolidation following addition of BMP-2 and autograft in circumferential lumbar fusion. *European Spine Journal.* 2011;20(7):1211. Exclusion code: 5

33. Balaji SM. Use of rhBMP2 with bone grafts in pediatric jaw resection cases. *International Journal of Oral and Maxillofacial Surgery.* 2011;40(10):1096. Exclusion code: 5

34. Baltzer AWA, Ostapczuk MS, Stosch D, Granrath M. The use of recombinant human bone morphogenetic protein-2 for the treatment of a delayed union following femoral neck open-wedge osteotomy. *Orthopedic Reviews.* 2012;4(1):e4. [PMID: 22577505] Exclusion code: 7

35. Barboza EP, Caula AL, Caula Fde O, de Souza RO, Geolás Neto L, Sorensen RG, et al. Effect of recombinant human bone morphogenetic protein-2 in an absorbable collagen sponge with space-providing biomaterials on the augmentation of chronic alveolar ridge defects. *Journal of Periodontology.* 2004;75(5):702-708. [PMID: 15212353] Exclusion code: 4

36. Barrios JMR, Collado FA, Contreras DS, Tudela LL. Economic evaluation of the rhBMP-2 (Inductos) in the treatment of vertebral fusion for chronic lowback pain in Spain. *Pharmacoeconomics - Spanish Research Articles.* 2008;5(4):109-118. Exclusion code: 1

37. Bauer AS, Zampini JM, McGuire KJ. Journal Scan: Spine. *Clinical Orthopaedics and Related Research.* 2009;467(12):3358-3364. Exclusion code: 5

38. Baumgarten KM. Commentary on an article by Jacob S. Vandermeer et al.: "Local administration of ibandronate and bone morphogenetic protein-2 after ischemic osteonecrosis of the immature femoral head. A combined therapy that stimulates bone formation and decreases femoral head deformity". *Journal of Bone & Joint Surgery - American Volume.* 2011;93(10):e57. [PMID: 21593363] Exclusion code: 5

39. Bekelis K, Gottfried ON, Wolinsky JP, Gokaslan ZL, Omeis I. Severe dysphagia secondary to posterior C1-C3 instrumentation in a patient with atlantoaxial traumatic injury: A case report and review of the literature. *Dysphagia.* 2010;25(2):156-160. Exclusion code: 3

40. Bell RB, Gregoire C. Reconstruction of mandibular continuity defects using recombinant human bone morphogenetic protein 2: a note of caution in an atmosphere of exuberance. *Journal of Oral & Maxillofacial Surgery.* 2009;67(12):2673-2678. [PMID: 19925990] Exclusion code: 5

41. 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):ONS423-431; discussion ONS431. [PMID: 18596525] Exclusion code: 5

42. Bennett M, Reynolds AS, Dickerman RD. Recent article by Shields et al titled "adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion". *Spine.* 2006;31(17):2029-2030. [PMID: 16924224] Exclusion code: 3

43. Betz RR, Lavelle WF, Samdani AF. Bone grafting options in children. *Spine.* 2010;35(17):1648-1654. Exclusion code: 5

44. Bhattacharyya T. Commentary on an article by Hannu T. Aro, MD, PhD, et al.: "Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation".[Erratum appears in J Bone Joint Surg Am. 2011 May 4;93(9):e50]. *Journal of Bone & Joint Surgery - American Volume.* 2011;93(9):e50. [PMID: 21454741] Exclusion code: 5

45. Bianchi J, Fiorellini JP, Howell TH, Sekler J, Curtin H, Nevins ML, et al. Measuring the efficacy of rhBMP-2 to regenerate bone: a radiographic study using a commercially available software program. *International Journal of Periodontics & Restorative Dentistry.* 2004;24(6):579-587. [PMID: 15626320] Exclusion code: 5

46. Bibbo C. Practical use of adjuvant rhBMP-2 to augment bone healing in foot and ankle surgery. *Techniques in Orthopaedics.* 2011;26(1):28-31. Exclusion code: 5

47. Bibbo C, Haskell MD. Recombinant bone morphogenetic protein-2 (rhBMP-2) in high-risk foot and ankle surgery: Surgical techniques and preliminary results of a prospective, intention-to-

treat study. *Techniques in Foot and Ankle Surgery.* 2007;6(2):71-79. Exclusion code: 7

48. Bibbo C, Patel DV, Haskell MD. Recombinant bone morphogenetic protein-2 (rhBMP-2) in high-risk ankle and hindfoot fusions. *Foot & Ankle International.* 2009;30(7):597-603. [PMID: 19589304] Exclusion code: 7

49. Billon-Grand R, Petit A, Launay O, Czorny A. [Thoracic spine pseudarthrosis treated by transpleural corporectomy and bone morphogenic protein]. *Neuro-Chirurgie.* 2011;57(1):28-30. [PMID: 21247607] Exclusion code: 1

50. Birke O, Schindeler A, Ramachandran M, et al. Treatment of congenital pseudarthrosis of the tibia using recombinant bone morphogenetic protein and bisphosphonates. *Bone.* 2010;46:S20-S21. Exclusion code: 5

51. Bishop GB, Einhorn TA. Current and future clinical applications of bone morphogenetic proteins in orthopaedic trauma surgery. *International Orthopaedics.* 2007;31(6):721-727. [PMID: 17668207] Exclusion code: 5

52. Block MS, Achong R. Bone morphogenetic protein for sinus augmentation. *Atlas of the Oral & Maxillofacial Surgery Clinics of North America.* 2006;14(1):99-105. [PMID: 16522512] Exclusion code: 5

53. Blokhuis TJ, Lindner T. Allograft and bone morphogenetic proteins: an overview. *Injury.* 2008;39 (Suppl 2):S33-36. [PMID: 18804571] Exclusion code: 5

54. Blumenthal S, McAfee PC, Guyer RD, Hochschuler SH, Geisler FH, Holt RT, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes.[Erratum appears in Spine. 2005 Oct 15;30(20):2356]. *Spine.* 2005;30(14):1565-1575; discussion E1387-1591. [PMID: 16025024] Exclusion code: 3

55. Boachie-Adjei O, Cho W, King AB. Axial lumbar interbody fusion (AxiaLIF) approach for adult scoliosis. *European Spine Journal.* 2012:1-7. Exclusion code: 3

56. Boden SD. Evaluation of carriers of bone morphogenetic protein for spinal fusion. *Spine.* 2001;26(8):850. [PMID: 11317102] Exclusion code: 5

57. Boden SD. Clinical application of the BMPs. *Journal of Bone & Joint Surgery - American Volume.* 2001;83-A Suppl 1(Pt 2):S161. [PMID: 11314796] Exclusion code: 4

58. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine.* 2002;27(16 Suppl 1):S26-31. [PMID: 12205416] Exclusion code: 2

59. Boden SD. Efficacy of autologous growth factors in lumbar intertranverse fusions: Point of view. *Spine.* 2003;28(17):1971. Exclusion code: 5

60. Boden SD. The ABCs of BMPs. *Orthopaedic Nursing.* 2005;24(1):49-52; quiz 53-44. [PMID: 15722975] Exclusion code: 5

61. Boden SD. Spinescope. *Seminars in Spine Surgery.* 2011;23(1):76-81. Exclusion code: 5

62. Boden SD. Spinescope. *Seminars in Spine Surgery.* 2012;24(1):81-86. Exclusion code: 5

63. Boden SD, Andersson GBJ, Anderson DG, **Damien C, Ebara S, Helm G**, et al. Summary statement: Overview of bone morphogenetic proteins for spine fusion. *Spine.* 2002;27(16 SUPPL.):S1. Exclusion code: 5

64. Boden SD, Lane JM, Finnegan M. Breakout session 2: Bone. *Clinical Orthopaedics and Related Research.* 1999(367 SUPPL.):S130-S132. Exclusion code: 5

65. Boraiah S, Paul O, Hawkes D, Wickham M, Lorich DG. Complications of recombinant human BMP-2 for treating complex tibial plateau fractures: a preliminary report. *Clinical Orthopaedics & Related Research.* 2009;467(12):3257-3262. [PMID: 19693635] Exclusion code: 7

66. Boyne PJ. Maxillofacial surgical application of bone inductor materials. *Implant Dentistry.* 2001;10(1):2-4. [PMID: 11307643] Exclusion code: 5

67. Boyne PJ. Application of bone morphogenetic proteins in the treatment of clinical oral and maxillofacial osseous defects. *Journal of Bone and Joint Surgery - Series A.* 2001;83(SUPPL. 1 II):S1146-S1150. Exclusion code: 4

68. Boyne PJ, Lilly LC, Marx RE, Moy PK, Nevins M, Spagnoli DB, et al. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. *Journal of Oral & Maxillofacial Surgery.* 2005;63(12):1693-1707. [PMID:

16297689] Exclusion code: 7

69. Boyne PJ, Marx RE, Nevins M, Triplett G, Lazaro E, Lilly LC, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. *International Journal of Periodontics & Restorative Dentistry.* 1997;17(1):11-25. [PMID: 10332250] Exclusion code: 7

70. Boyne PJ, Nakamura A, Shabahang S. Evaluation of the long-term effect of function on rhBMP-2 regenerated hemimandibulectomy defects. *British Journal of Oral & Maxillofacial Surgery.* 1999;37(5):344-352. [PMID: 10577748] Exclusion code: 4

71. Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A. Bone morphogenetic proteins: a critical review. *Cellular Signalling.* 2011;23(4):609-620. [PMID: 20959140] Exclusion code: 5

72. Branch CL, Jr. Physican-directed (off-label) use of recombinant bone morphogenic protein-2: let us do it well! *Spine Journal: Official Journal of the North American Spine Society.* 2011;11(6):469-470. [PMID: 21729795] Exclusion code: 5

73. Buchowski JM, Riew KD, Nussenbaum B. In reference to acute airway obstruction in cervical spinal procedures with bone morphogenetic proteins. *Laryngoscope.* 2011;121(11):2501. Exclusion code: 5

74. Burkhart KJ, Rommens PM. Intramedullary application of bone morphogenetic protein in the management of a major bone defect after an Ilizarov procedure. *Journal of Bone & Joint Surgery - British Volume.* 2008;90(6):806-809. [PMID: 18539677] Exclusion code: 3

75. Burks MV, Nair L. Long-term effects of bone morphogenetic protein- based treatments in humans. *Journal of Long-Term Effects of Medical Implants.* 2010;20(4):277-293. [PMID: 21488821] Exclusion code: 5

76. 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. *Journal of Neurosurgery Spine.* 2004;1(3):254-260. [PMID: 15478362] Exclusion code: 6

77. Burkus JK. Surgical treatment of the painful motion segment: Matching technology with indications. *Spine.* 2005;30(16 SUPPL.):S7-S15. Exclusion code: 5

78. 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. *Journal of Bone & Joint Surgery - American Volume.* 2009;91(5):1181-1189. [PMID: 19411467] Exclusion code: 6

79. 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: Reply. *Journal of Bone and Joint Surgery - Series A.* 2010;92(15):2615-2616. Exclusion code: 5

80. Burnei G, Vlad C, Gavriliu S, Georgescu I, Hodorogea D, Pârvan A, et al. Upper and lower limb length equalization: diagnosis, limb lengthening and curtailment, epiphysiodesis. *Rom. J. Intern. Med.* 2012;50(1):43-59. [PMID: 22788093] Exclusion code: 3

81. Cahill KS, Claus EB. Complications associated with use of bone-morphogenetic proteins in spinal fusion procedures: Reply. *JAMA - Journal of the American Medical Association.* 2009;302(19):2091. Exclusion code: 5

82. 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.[Erratum appears in Injury. 2007 Oct;38(10):1224]. *Injury.* 2006;37 Suppl 3:S43-50. [PMID: 16963360] Exclusion code: 3

83. Calori GM, Mazza E, Colombo M, Ripamonti C, Tagliabue L. Treatment of long bone non-unions with polytherapy: indications and clinical results. *Injury.* 2011;42(6):587-590. [PMID: 21524745] Exclusion code: 2

84. Cannada LK, Anglen JO, Archdeacon MT, Herscovici Jr D, Ostrum RF. Avoiding complications in the care of fractures of the tibia. *Journal of Bone and Joint Surgery - Series A.* 2008;90(8):1760-1768. Exclusion code: 5

85. Canter HI, Vargel I, Mavili ME. Reconstruction of mandibular defects using autografts combined with demineralized bone matrix and cancellous allograft. *Journal of Craniofacial Surgery.* 2007;18(1):95-100; discussion 101-103. [PMID: 17251844] Exclusion code: 5

86. Capital District Health Authority Canada. Spine Fusion Instrumented With BMP-2 vs Uninstrumented With Infuse BMP-2 Alone. 2010. NCT00405600. Exclusion code: Pending

87. Capital District Health Authority Canada, Canadian Orthopaedic Trauma Society. A Randomized Controlled Cost Study of Infuse BMP 2 vs Iliac Crest Autograft for Non Union of Long Bone Fractures. 2010. NCT00856479. Exclusion code: 7

88. Capo JT, Marcus MS, Shamian B. Treatment of a segmental defect in open radial and ulnar shaft fractures using rhBMP-2 and iliac crest bone graft: A case report. *Hand.* 2011;6(4):424-428. Exclusion code: 2

89. Cardoso MJ, Sciubba DM. Is use of bone-morphogenetic proteins for spine fusion surgery cost-effective? *Archives of Surgery.* 2009;144(11):996-997. Exclusion code: 5

90. Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. *Spine Journal: Official Journal of the North American Spine Society.* 2005;5(6 Suppl):240S-249S. [PMID: 16291119] Exclusion code: 5

91. Carragee E, Mitsunaga K, Abrams J, Scuderi G. Local bone graft harvesting with careful facet arthodesis in posterolateral lumbar fusion: Outcomes and morbidity compared with amplify trial data. *Spine Journal.* 2011;11(10):60S-61S. Exclusion code: 3

92. Carragee E, Weiner B, Hurwitz E. Comparison of adverse events and disclosures in the original rhBMP-2 trials with fda data and subsequent publications. *Spine Journal.* 2011;11(10):21S-22S. Exclusion code: 5

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Appendix L. Individual Patient Data (IPD) Summary Data

Table L-1. IPD Summary Data for Oswestry Score Outcomes, Medtronic RCT Studies

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		N	Mean	SD	N	Mean	SD		Lower	Upper	
Infuse-LT-Cage Pilot, 1997 ALIF Study 1	pre-operative	7	41.1	8.9	3	34.7	13.3				
	3 months	7	38.0	19.2	3	42.7	14.5	-11.9	-37.8	14.0	0.3
	6 months	7	30.9	19.2	3	28.0	26.2	-5.6	-35.8	24.6	0.7
	12 months	7	23.1	17.7	3	27.3	27.0	-13.7	-39.2	11.7	0.2
	24 months	7	17.0	18.8	3	20.0	22.3	-14.4	-29.7	1.0	0.1
Infuse-LT-Cage Pivotal, 1998 ALIF Study 2	pre-operative	143	53.7	12.7	136	55.1	11.8				
	6 weeks	140	42.1	17.4	131	41.4	18.4	1.4	-2.7	5.5	0.5
	3 months	141	33.4	17.7	134	34.2	18.5	0.1	-4.0	4.1	1.0
	6 months	136	29.3	18.8	131	29.4	18.2	0.5	-3.7	4.7	0.8
	12 months	130	25.5	18.2	125	25.6	19.1	0.5	-3.9	4.9	0.8
	24 months	124	23.9	18.7	111	23.7	20.8	0.4	-4.6	5.4	0.9
Infuse-Bone Dowel Pilot, 1998 ALIF Study 4	pre-operative	24	52.4	13.1	22	55.3	13.5				
	6 weeks	24	39.9	16.8	21	47.2	18.8	-5.3	-14.2	3.7	0.2
	3 months	24	29.0	14.7	21	42.0	19.0	-10.1	-18.4	-1.7	0.0
	6 months	24	21.4	16.1	20	34.4	21.8	-10.7	-20.3	-1.0	0.0
	12 months	24	20.8	14.9	20	32.0	22.5	-8.5	-18.3	1.4	0.1
	24 months	24	18.9	14.5	20	38.3	25.2	-16.7	-27.9	-5.6	0.0
Infuse-Bone Dowel Pivotal, 2000 ALIF Study 5	pre-operative	55	54.2	9.6	30	57.5	9.4				
	6 weeks	54	39.1	16.8	29	47.9	15.3	-6.6	-13.7	0.5	0.1
	3 months	55	28.2	16.3	29	36.0	15.6	-6.7	-14.0	0.7	0.1
	6 months	54	21.5	15.7	30	28.4	17.4	-5.8	-13.2	1.5	0.1
	12 months	51	21.0	17.9	24	28.8	20.2	-6.1	-15.0	2.8	0.2

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		N	Mean	SD	N	Mean	SD		Lower	Upper	
	24 months	48	21.1	20.6	22	26.0	23.2	-3.8	-14.8	7.3	0.5
Infuse-Interfix PLIF, 1999 PLIF Study 6	pre-operative	34	54.6	11.4	33	52.7	12.0				
	6 weeks	33	45.5	14.4	31	39.4	17.6	5.8	-2.3	13.9	0.2
	3 months	33	32.8	15.5	32	33.6	17.4	-1.2	-9.4	6.9	0.8
	6 months	32	30.2	16.6	31	31.8	19.3	-1.8	-10.9	7.3	0.7
	12 months	32	27.9	17.6	28	32.2	16.5	-4.6	-13.5	4.3	0.3
	24 months	29	29.5	19.7	30	27.9	17.7	1.3	-8.6	11.2	0.8
Infuse-Cornerstone ACDF, 1999 CERVICAL Study 7	pre-operative	18	61.3	11.9	15	55.4	13.9				
	6 weeks	18	23.9	17.3	15	22.8	12.6	-0.2	-11.5	11.1	1.0
	3 months	17	21.3	20.0	15	21.9	16.4	-3.4	-16.2	9.3	0.6
	6 months	17	12.9	13.3	13	13.4	10.9	-1.6	-11.7	8.4	0.7
	12 months	15	16.3	17.7	14	12.3	12.7	3.2	-9.7	16.2	0.6
	24 months	14	10.1	14.9	13	13.4	12.4	-4.7	-16.9	7.6	0.4
Infuse-Mastergraft Pilot, 2003 PLF Study 8	pre-operative	25	52.1	13.3	21	49.7	12.8				
	6 weeks	25	39.2	17.6	21	37.1	17.0	0.9	-8.8	10.6	0.8
	3 months	25	29.4	17.5	21	30.1	18.4	-1.7	-12.0	8.6	0.7
	6 months	25	27.6	18.0	21	30.2	18.6	-3.7	-14.2	6.9	0.5
	12 months	23	21.1	16.7	21	27.9	19.9	-7.4	-18.4	3.5	0.2
	24 months	23	19.7	15.7	20	25.8	19.0	-6.9	-17.5	3.7	0.2
Infuse-Interfix Pilot, 1999 ALIF Study 9	pre-operative	25	54.3	13.5	19	52.2	12.4				
	6 weeks	25	40.2	14.6	17	41.8	15.0	-2.4	-11.8	7.0	0.6
	3 months	24	30.2	17.1	16	32.8	16.6	-3.7	-14.8	7.3	0.5
	6 months	24	23.7	17.8	16	24.9	14.6	-3.0	-13.7	7.7	0.6
	12 months	23	25.7	20.7	16	21.5	12.3	2.6	-8.7	13.8	0.6
	24 months	21	19.0	18.0	15	25.1	21.1	-7.3	-19.9	5.3	0.2

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		N	Mean	SD	N	Mean	SD		Lower	Upper	
Maverick Disc Pivotal, 2003 ALIF Study 10	pre-operative	172	54.5	12.6	405	53.3	13.0				
	6 weeks	166	41.4	17.1	395	31.2	19.5	9.6	6.4	12.9	0.0
	3 months	159	32.1	16.8	386	23.4	18.8	8.2	4.9	11.4	0.0
	6 months	158	26.7	17.4	385	20.0	18.1	6.4	3.2	9.5	0.0
	12 months	154	24.9	19.8	389	19.0	17.8	5.5	2.1	8.8	0.0
	24 months	137	24.0	19.5	366	19.0	19.9	4.6	0.8	8.3	0.0
BCP US, 1999 PLF Study 12	pre-operative	11	47.9	13.0	5	54.4	15.3				
	6 weeks	11	44.8	15.0	5	43.0	22.3	5.7	-13.3	24.7	0.5
	3 months	11	30.9	10.7	5	39.6	20.2	-6.4	-22.9	10.0	0.4
	6 months	10	28.7	16.2	5	37.1	19.3	2.4	-13.0	17.9	0.7
	12 months	10	33.7	23.5	5	38.9	19.0	1.7	-17.1	20.6	0.8
	24 months	10	36.8	20.0	4	27.0	28.2	12.7	-12.7	38.1	0.3
BCP Canada, 1999 PLF Study 13	pre-operative	98	51.6	11.9	99	51.7	11.6				
	6 weeks	98	43.6	15.0	98	42.1	17.6	1.4	-2.9	5.7	0.5
	3 months	97	31.6	14.8	98	33.4	19.0	-1.9	-6.3	2.5	0.4
	6 months	97	27.1	16.1	98	28.8	19.1	-1.9	-6.5	2.7	0.4
	12 months	97	28.8	19.3	97	27.6	19.9	1.1	-4.3	6.4	0.7
	24 months	97	28.1	19.4	95	27.9	22.2	0.1	-5.4	5.6	1.0
Amplify Pivotal, 2002 PLF Study 14	pre-operative	239	49.9	13.1	224	51.6	13.3				
	6 weeks	234	37.3	18.6	215	37.7	16.9	0.2	-3.0	3.4	0.9
	3 months	232	27.9	17.0	215	30.3	17.3	-1.8	-4.9	1.2	0.2
	6 months	229	23.8	18.0	208	27.4	17.9	-2.8	-5.9	0.3	0.1
	12 months	226	22.6	19.2	204	26.5	18.5	-3.2	-6.6	0.2	0.1
	24 months	210	22.0	18.3	181	26.0	20.8	-2.6	-6.3	1.0	0.2

Table L-2. IPD Summary Data for SF-36 Physical Component Summary (PCS) Outcomes, Medtronic RCT Studies

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
Infuse-LT-Cage Pilot, 1997 ALIF Study 1	pre-operative	7	31.6	3.9	3	26.5	5.6				
	3 months	7	35.9	8.0	3	29.0	8.7	6.9	-9.7	23.5	0.4
	6 months	7	41.6	11.3	3	38.8	15.2	8.7	-14.2	31.6	0.4
	12 months	7	39.6	6.8	3	40.6	10.6	1.7	-13.7	17.0	0.8
	24 months	7	47.3	3.6	3	37.9	10.6	10.5	-1.9	22.9	0.1
Infuse-LT-Cage Pivotal, 1998 ALIF Study 2	pre-operative	142	27.7	5.7	136	29.4	6.2				
	6 weeks	139	32.4	8.0	130	32.7	7.9	0.7	-1.1	2.5	0.5
	3 months	141	36.5	9.8	133	35.9	9.4	1.6	-0.6	3.7	0.2
	6 months	140	39.2	11.2	132	38.6	10.8	1.9	-0.6	4.4	0.1
	12 months	135	41.2	11.1	130	40.4	12.1	2.1	-0.5	4.8	0.1
	24 months	131	41.8	11.9	121	41.4	12.9	1.6	-1.3	4.6	0.3
Infuse-Bone Dowel Pilot, 1998 ALIF Study 4	pre-operative	24	29.6	6.6	22	29.4	9.2				
	6 weeks	23	32.3	8.0	21	31.9	6.7	0.4	-3.9	4.7	0.9
	3 months	24	37.5	9.4	21	31.1	8.4	6.0	0.7	11.2	0.0
	6 months	23	43.0	9.1	20	37.1	11.2	5.8	-0.2	11.8	0.1
	12 months	24	45.6	10.3	20	39.0	11.0	6.5	0.2	12.9	0.0
	24 months	24	45.1	9.8	20	37.8	11.9	7.1	0.4	13.7	0.0
Infuse-Bone Dowel Pivotal, 2000 ALIF Study 5	pre-operative	54	29.0	5.6	30	26.4	5.1				
	6 months	51	43.5	10.8	29	36.8	9.1	5.4	0.6	10.3	0.0
	12 months	52	44.9	11.2	27	37.8	11.3	4.8	-0.4	10.1	0.1
	24 months	49	44.5	11.7	25	38.7	14.2	4.6	-2.0	11.1	0.2
Infuse-Interfix PLIF, 1999	pre-operative	34	26.5	5.9	32	26.6	5.6				
	6 weeks	32	31.2	7.3	31	28.3	6.5	3.2	-0.2	6.7	0.1

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
PLIF Study 6	3 months	33	36.0	9.0	32	33.6	9.8	2.4	-2.2	7.1	0.3
	6 months	32	37.1	10.3	30	34.2	10.2	3.0	-2.2	8.2	0.3
	12 months	31	38.3	11.6	28	34.3	11.7	3.9	-2.3	10.1	0.2
	24 months	28	38.2	12.8	29	36.9	11.4	1.3	-5.2	7.8	0.7
Infuse-Cornerstone ACDF, 1999 CERVICAL Study 7	pre-operative	17	31.2	6.5	15	32.6	6.2				
	6 weeks	18	40.4	8.9	15	39.6	10.1	0.9	-6.2	8.0	0.8
	3 months	16	44.4	9.4	15	44.6	9.7	1.0	-6.2	8.2	0.8
	6 months	15	45.6	11.7	12	46.5	11.4	1.5	-7.5	10.4	0.7
	12 months	15	45.7	11.3	14	48.7	8.0	-1.8	-9.6	5.9	0.6
	24 months	14	48.6	12.3	13	48.2	9.6	2.5	-6.6	11.6	0.6
Infuse-Mastergraft Pilot, 2003 PLF Study 8	pre-operative	25	25.8	7.2	21	26.5	6.9				
	6 weeks	25	31.7	6.5	21	31.2	7.0	0.8	-2.8	4.4	0.6
	3 months	25	35.1	8.7	21	34.9	8.8	0.4	-4.7	5.5	0.9
	6 months	25	37.7	11.7	21	36.7	9.6	1.5	-4.4	7.4	0.6
	12 months	23	39.4	10.8	21	36.5	11.5	3.7	-2.8	10.1	0.3
	24 months	23	40.0	12.2	20	37.1	10.9	3.6	-3.4	10.5	0.3
Infuse-Interfix Pilot, 1999 ALIF Study 9	pre-operative	25	28.3	6.2	19	29.3	7.4				
	6 weeks	25	31.9	7.6	17	32.6	7.8	-0.2	-5.1	4.7	0.9
	3 months	24	38.5	10.5	16	37.0	8.1	2.5	-3.6	8.5	0.4
	6 months	24	39.2	13.0	16	41.0	9.2	-0.8	-8.4	6.7	0.8
	12 months	22	41.4	14.1	16	42.0	9.6	1.0	-6.8	8.9	0.8
	24 months	21	44.3	11.1	15	42.7	11.9	2.5	-5.2	10.1	0.5
Maverick Disc Pivotal, 2003 ALIF	pre-operative	172	27.3	5.6	404	27.9	6.1				
	6 weeks	166	31.6	7.2	391	36.6	9.7	-4.7	-6.2	-3.1	0.0
	3 months	159	36.9	9.0	385	41.4	11.0	-4.3	-6.2	-2.4	0.0

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		*P*-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
Study 10	6 months	158	39.6	10.6	385	43.7	11.3	-3.7	-5.7	-1.7	0.0
	12 months	154	42.0	11.6	389	44.7	11.6	-2.4	-4.5	-0.2	0.0
	24 months	135	42.6	11.9	366	45.3	12.1	-2.5	-4.9	-0.2	0.0
BCP US, 1999 PLF Study 12	pre-operative	11	29.1	8.1	5	25.5	9.6				
	6 weeks	11	31.1	6.9	5	26.4	8.9	3.5	-5.1	12.0	0.4
	3 months	11	29.2	6.3	5	29.3	9.2	-1.2	-9.5	7.2	0.8
	6 months	10	35.6	12.1	5	28.0	15.1	2.6	-6.8	12.0	0.6
	12 months	10	34.6	14.2	5	27.9	6.2	3.7	-8.4	15.8	0.5
	24 months	9	33.4	15.2	4	32.9	13.9	-0.8	-16.4	14.8	0.9
BCP Canada, 1999 PLF Study 13	pre-operative	98	26.6	6.0	99	27.3	6.9				
	6 weeks	98	30.7	6.9	97	30.8	7.4	0.1	-1.9	2.1	0.9
	3 months	97	34.9	8.2	98	34.8	8.4	0.3	-2.0	2.6	0.8
	6 months	97	37.5	9.8	98	37.2	10.8	0.7	-2.2	3.5	0.6
	12 months	97	37.7	10.1	97	38.1	11.2	-0.1	-3.0	2.9	1.0
	24 months	97	38.5	10.5	94	38.7	12.3	0.3	-2.9	3.4	0.9
Amplify Pivotal, 2002 PLF Study 14	pre-operative	236	27.8	6.3	224	27.4	6.7				
	6 weeks	231	31.6	7.5	213	31.8	7.7	-0.4	-1.8	0.9	0.5
	3 months	231	37.3	9.8	212	36.1	9.6	1.0	-0.8	2.7	0.3
	6 months	227	40.8	11.0	207	38.2	10.4	2.3	0.4	4.3	0.0
	12 months	226	41.6	12.0	202	38.8	11.0	2.6	0.5	4.8	0.0
	24 months	209	41.1	11.6	181	39.8	11.8	1.3	-1.0	3.6	0.3

Table L-3. IPD Summary Data for the SF-36 Health Survey, Mental Component Summary (MCS) Outcomes, Medtronic RCT Studies

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		N	Mean	SD	n	Mean	SD		Lower	Upper	
Infuse-LT-Cage Pilot, 1997 ALIF Study 1	Pre-operative	7	39.5	13.3	3	40.5	18.0				
	3 months	7	49.3	13.9	3	50.0	10.4	0.0	-12.9	13.0	1.0
	6 months	7	41.9	13.3	3	49.3	10.1	-6.8	-23.4	9.8	0.4
	12 months	7	41.1	14.0	3	44.7	5.1	-3.3	-22.3	15.8	0.7
	24 months	7	52.9	8.6	3	50.9	10.2	1.9	-13.6	17.5	0.8
Infuse-LT-Cage Pivotal, 1998 ALIF Study 2	Pre-operative	142	44.1	13.2	136	41.1	11.7				
	6 weeks	139	47.4	11.8	130	47.1	12.8	-1.2	-3.8	1.3	0.3
	3 months	141	50.9	11.8	133	48.5	12.5	0.9	-1.6	3.4	0.5
	6 months	140	49.2	11.6	132	48.9	11.6	-1.1	-3.6	1.3	0.4
	12 months	135	49.5	11.7	130	49.5	11.7	-1.2	-3.9	1.5	0.4
	24 months	131	50.4	10.6	121	48.8	12.5	0.7	-2.0	3.5	0.6
Infuse-Bone Dowel Pilot, 1998 ALIF Study 4	Pre-operative	24	42.8	10.0	22	43.1	12.3				
	6 weeks	23	46.7	12.2	21	45.1	10.6	1.6	-3.9	7.0	0.6
	3 months	24	48.2	12.0	21	49.2	13.6	0.1	-5.4	5.5	1.0
	6 months	23	48.5	13.9	20	49.4	10.6	-0.6	-7.0	5.8	0.8
	12 months	24	46.9	11.5	20	47.1	12.5	0.6	-5.3	6.5	0.8
	24 months	24	51.1	9.6	20	43.7	12.4	8.6	2.7	14.4	0.0
Infuse-Bone Dowel Pivotal, 2000 ALIF Study 5	Pre-operative	54	48.2	12.4	30	41.6	10.9				
	6 months	51	52.7	9.4	29	50.2	11.2	1.0	-3.7	5.6	0.7
	12 months	52	52.9	11.2	27	48.5	12.1	2.4	-2.9	7.7	0.4
	24 months	49	51.2	12.3	25	48.1	14.3	0.9	-5.2	7.1	0.8
Infuse-Interfix	Pre-operative	34	44.6	14.9	32	43.6	9.3				

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		N	Mean	SD	n	Mean	SD		Lower	Upper	
PLIF, 1999 PLIF Study 6	6 weeks	32	47.9	10.2	31	45.9	11.8	1.8	-3.0	6.7	0.5
	3 months	33	49.4	12.4	32	48.6	11.1	0.7	-4.5	6.0	0.8
	6 months	32	47.7	11.8	30	47.0	12.6	0.5	-5.8	6.8	0.9
	12 months	31	46.5	13.7	28	45.5	12.5	0.9	-5.7	7.5	0.8
	24 months	28	49.5	13.8	29	46.3	12.7	2.1	-4.6	8.8	0.5
Infuse-Cornerstone ACDF, 1999 CERVICAL Study 7	Pre-operative	17	33.4	9.5	15	42.9	10.9				
	6 weeks	18	51.2	9.7	15	52.7	10.4	1.7	-6.2	9.6	0.7
	3 months	16	48.2	11.3	15	47.8	16.5	7.8	-1.4	16.9	0.1
	6 months	15	55.0	6.7	12	54.6	11.4	3.9	-3.6	11.5	0.3
	12 months	15	54.1	6.6	14	50.7	10.6	6.2	-1.2	13.6	0.1
	24 months	14	54.9	7.4	13	50.0	12.4	5.1	-4.1	14.4	0.3
Infuse-Mastergraft Pilot, 2003 PLF Study 8	Pre-operative	25	43.8	12.4	21	46.5	9.5				
	6 weeks	25	45.8	9.9	21	46.6	11.3	0.2	-5.6	6.1	0.9
	3 months	25	47.6	12.9	21	48.6	10.3	-0.1	-6.8	6.6	1.0
	6 months	25	48.9	10.2	21	44.9	14.4	5.3	-1.4	12.0	0.1
	12 months	23	49.7	10.2	21	49.4	11.5	1.3	-4.8	7.4	0.7
	24 months	23	51.0	8.6	20	46.2	12.1	5.8	-0.3	11.9	0.1
Infuse-Interfix Pilot, 1999 ALIF Study 9	Pre-operative	25	42.1	10.2	19	44.2	12.4				
	6 weeks	25	47.9	10.6	17	47.9	10.6	1.4	-3.9	6.7	0.6
	3 months	24	51.4	11.0	16	51.5	11.7	1.5	-5.6	8.5	0.7
	6 months	24	52.8	10.0	16	50.3	11.7	4.1	-2.2	10.5	0.2
	12 months	22	48.8	10.1	16	52.7	11.1	-3.0	-9.3	3.4	0.3
	24 months	21	51.8	9.0	15	49.5	12.0	3.3	-3.4	10.0	0.3
Maverick Disc_Pivotal,	Pre-operative	172	41.7	11.9	404	43.2	12.4				
	6 weeks	166	46.4	11.7	391	48.9	11.2	-1.9	-3.8	-0.1	0.0

Study and Approach	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		N	Mean	SD	n	Mean	SD		Lower	Upper	
2003 ALIF Study 10	3 months	159	48.6	12.1	385	51.2	11.3	-2.1	-4.0	-0.1	0.0
	6 months	158	50.0	12.1	385	51.6	10.7	-1.1	-3.0	0.8	0.3
	12 months	154	49.4	11.8	389	51.3	10.9	-1.3	-3.3	0.6	0.2
	24 months	135	50.4	10.9	366	51.4	11.0	-0.4	-2.4	1.7	0.7
BCP US, 1999 PLF Study 12	Pre-operative	11	38.7	13.6	5	49.9	9.6				
	6 weeks	11	42.0	8.6	5	52.0	13.2	-9.8	-23.2	3.6	0.1
	3 months	11	50.5	10.7	5	49.1	12.3	3.2	-11.3	17.8	0.6
	6 months	10	48.3	15.4	5	49.1	13.1	4.1	-13.8	22.0	0.6
	12 months	10	49.8	10.4	5	48.0	14.5	4.8	-10.4	19.9	0.5
	24 months	9	50.4	10.6	4	53.8	10.5	-2.9	-18.6	12.8	0.7
BCP Canada, 1999 PLF Study 13	Pre-operative	98	45.2	12.7	99	45.0	12.0				
	6 weeks	98	48.5	11.6	97	47.7	11.1	0.7	-2.1	3.6	0.6
	3 months	97	50.3	11.9	98	50.3	10.2	-0.1	-3.0	2.8	0.9
	6 months	97	50.5	10.7	98	50.3	10.6	0.0	-2.6	2.6	1.0
	12 months	97	48.6	12.2	97	50.9	10.7	-2.4	-5.3	0.4	0.1
	24 months	97	47.8	12.0	94	50.1	10.0	-2.4	-5.3	0.5	0.1
Amplify Pivotal, 2002 PLF Study 14	Pre-operative	236	43.9	13.1	224	42.9	12.3				
	6 weeks	231	48.4	11.8	213	47.3	11.5	0.7	-1.1	2.5	0.5
	3 months	231	49.7	12.4	212	49.3	12.2	-0.1	-2.0	1.8	0.9
	6 months	227	49.6	12.7	207	49.8	12.1	-0.5	-2.5	1.6	0.7
	12 months	226	49.5	12.9	202	49.0	11.4	0.3	-1.8	2.4	0.8
	24 months	209	51.0	11.6	181	49.3	12.0	1.1	-0.9	3.2	0.3

Table L-4. IPD Summary Data for Back Pain Outcomes, Medtronic RCT Studies

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	n	Mean	SD		Lower	Upper	
Infuse-LT-Cage Pivotal, 1998 ALIF Study 1	Pre-operative	143	7.4	1.9	136	7.7	1.7				
	6 weeks	140	4.3	2.6	132	4.1	2.8	0.2	-0.4	0.9	0.5
	3 months	141	4.0	2.5	134	4.4	2.8	-0.3	-1.0	0.3	0.3
	6 months	140	4.1	2.8	132	4.1	2.7	0.0	-0.7	0.6	0.9
	12 months	133	3.7	2.9	130	4.0	3.0	-0.3	-1.0	0.4	0.5
	24 months	132	3.5	2.9	121	3.9	3.2	-0.3	-1.0	0.5	0.5
Infuse-Bone Dowel Pilot, 1998 ALIF Study 4	Pre-operative	24	7.7	2.0	22	7.5	1.7				
	6 weeks	24	4.3	2.5	21	4.8	2.3	-0.6	-2.0	0.9	0.4
	3 months	24	3.5	2.2	21	4.5	2.3	-1.0	-2.4	0.3	0.1
	6 months	24	3.2	2.1	20	4.3	2.5	-1.2	-2.5	0.1	0.1
	12 months	24	3.6	2.9	20	4.2	3.0	-0.7	-2.4	1.0	0.4
	24 months	24	3.9	3.3	20	5.4	3.2	-1.6	-3.6	0.3	0.1
Infuse-Bone Dowel Pivotal, 2000 ALIF Study 5	Pre-operative	55	7.0	2.3	30	8.0	1.5				
	6 weeks	54	3.8	2.9	29	4.3	2.5	0.0	-1.2	1.2	1.0
	3 months	55	3.6	2.5	29	4.7	2.9	-0.6	-1.8	0.5	0.3
	6 months	54	3.2	2.9	30	3.9	3.0	-0.4	-1.8	0.9	0.5
	12 months	52	2.8	2.8	27	4.8	3.2	-1.6	-2.9	-0.2	0.0
	24 months	49	3.4	3.3	25	4.6	3.9	-0.9	-2.6	0.9	0.3
Infuse-Interfix PLIF, 1999 PLIF Study 6	Pre-operative	34	8.1	1.4	33	7.1	2.4				
	6 weeks	33	4.8	2.6	30	4.8	2.7	0.0	-1.3	1.4	0.9
	3 months	33	3.7	2.6	31	3.8	2.6	-0.3	-1.7	1.0	0.6
	6 months	32	4.1	2.6	31	3.8	2.4	0.1	-1.2	1.4	0.9
	12 months	32	4.3	2.9	28	4.6	2.7	-0.5	-2.0	1.0	0.5
	24 months	29	3.9	2.7	30	4.4	3.2	-1.0	-2.5	0.6	0.2
Infuse-Cornerstone ACDF, 1999	Pre-operative	18	7.4	2.7	15	6.5	2.2				
	6 weeks	18	2.4	2.6	15	2.7	1.8	-0.4	-2.0	1.3	0.7
	3 months	17	2.8	2.7	15	3.2	2.5	-0.6	-2.6	1.4	0.5

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	n	Mean	SD		Lower	Upper	
CERVICAL Study 7*	6 months	17	2.2	2.3	13	1.8	1.9	0.2	-1.4	1.9	0.8
	12 months	15	1.3	1.3	14	2.0	2.6	-0.9	-2.4	0.7	0.3
	24 months	14	1.2	1.6	13	2.2	2.8	-1.3	-3.0	0.4	0.1
Infuse-Mastergraft Pilot, 2003 PLF Study 8	Pre-operative	25	7.5	2.3	21	7.5	1.8				
	6 weeks	25	3.6	2.4	21	4.0	2.8	-0.4	-2.0	1.1	0.6
	3 months	25	3.2	2.7	21	3.3	3.0	-0.1	-1.8	1.5	0.9
	6 months	25	3.0	2.4	21	4.2	2.9	-1.2	-2.8	0.3	0.1
	12 months	23	2.9	2.5	21	3.9	3.2	-1.0	-2.8	0.7	0.2
	24 months	23	2.7	2.7	20	3.7	3.4	-1.1	-2.9	0.8	0.2
Infuse-Interfix Pilot, 1999 ALIF Study 9	Pre-operative	25	8.0	1.4	19	7.3	2.2				
	6 weeks	25	5.2	2.4	16	3.6	1.9	1.3	-0.1	2.7	0.1
	3 months	24	3.3	3.0	16	4.4	2.4	-1.5	-3.4	0.3	0.1
	6 months	24	3.5	2.8	16	3.4	2.7	-0.4	-2.2	1.3	0.6
	12 months	23	3.6	2.8	16	2.9	2.2	0.3	-1.4	1.9	0.8
	24 months	21	2.9	3.0	15	3.8	3.3	-1.5	-3.4	0.4	0.1
Maverick Disc Pivotal, 2003 ALIF Study 10	Pre-operative	172	8.1	1.6	405	8.0	1.5				
	6 weeks	166	4.9	2.7	394	3.4	2.6	1.5	1.0	2.0	0.0
	3 months	159	4.3	2.6	386	3.1	2.6	1.2	0.8	1.7	0.0
	6 months	158	3.8	2.7	386	3.0	2.7	0.8	0.3	1.3	0.0
	12 months	154	3.6	2.8	388	2.8	2.8	0.8	0.3	1.3	0.0
	24 months	137	3.4	2.8	366	2.6	2.8	0.8	0.2	1.3	0.0
BCP US, 1999 PLF Study 12	Pre-operative	11	7.1	2.5	5	7.6	2.7				
	6 weeks	11	4.2	2.2	5	4.4	2.8	-0.1	-2.9	2.7	0.9
	3 months	11	3.4	1.9	5	4.8	1.9	-1.3	-3.3	0.8	0.2
	6 months	10	4.5	3.0	5	5.2	3.0	-0.5	-4.2	3.2	0.8
	12 months	10	4.4	3.1	5	5.8	2.2	-1.3	-4.8	2.2	0.4
	24 months	10	5.3	3.3	4	4.3	2.2	1.1	-2.6	4.7	0.5
BCP Canada,	Pre-operative	98	7.1	2.4	99	7.0	2.4				

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	n	Mean	SD		Lower	Upper	
1999 PLF Study 13	6 weeks	98	3.6	2.4	98	3.4	2.4	0.1	-0.6	0.8	0.8
	3 months	97	3.3	2.4	98	3.3	2.4	0.0	-0.7	0.6	1.0
	6 months	97	3.5	2.8	98	3.2	2.8	0.2	-0.6	0.9	0.6
	12 months	97	4.0	3.0	97	3.4	2.9	0.6	-0.2	1.4	0.2
	24 months	97	3.6	3.0	95	3.7	3.0	-0.1	-0.9	0.7	0.8
Amplify Pivotal, 2002 PLF Study 14	Pre-operative	238	7.4	1.9	224	7.6	2.0				
	6 weeks	234	3.9	2.7	214	3.7	2.6	0.2	-0.3	0.7	0.5
	3 months	232	3.3	2.6	215	3.7	2.7	-0.3	-0.8	0.2	0.2
	6 months	229	3.1	2.7	208	3.8	2.9	-0.7	-1.2	-0.2	0.0
	12 months	226	3.0	2.8	204	3.9	3.0	-0.8	-1.3	-0.2	0.0
	24 months	210	3.2	2.9	181	3.6	3.1	-0.4	-1.0	0.2	0.2

* Infuse-Cornerstone ACDF, 1999 shows results for neck pain.

Table L-5. IPD Summary Data for Leg Pain Outcomes, Medtronic RCT Studies

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
Infuse-LT-Cage Pivotal, 1998 ALIF Study 2	pre-operative	143.0	6.1	2.8	136.0	6.2	2.5				
	6 weeks	140.0	3.6	3.0	132.0	4.1	3.5	-0.6	-1.4	0.1	0.1
	3 months	141.0	3.3	3.0	134.0	3.3	3.0	0.1	-0.6	0.8	0.8
	6 months	140.0	3.0	3.2	132.0	3.1	3.1	-0.1	-0.8	0.6	0.8
	12 months	133.0	3.0	3.2	130.0	3.4	3.3	-0.4	-1.1	0.4	0.3
	24 months	132.0	3.1	3.1	121.0	3.4	3.4	-0.2	-1.0	0.5	0.5
Infuse-Bone Dowel Pilot, 1998 ALIF Study 4	pre-operative	24.0	6.3	2.9	22.0	6.9	2.4				
	6 weeks	24.0	3.5	3.0	21.0	4.0	3.0	-0.4	-2.2	1.4	0.7
	3 months	24.0	2.7	2.0	21.0	3.8	2.7	-1.0	-2.4	0.4	0.2
	6 months	24.0	2.3	2.3	20.0	2.5	1.8	0.1	-1.2	1.3	0.9
	12 months	24.0	2.7	2.6	20.0	4.4	3.2	-1.6	-3.4	0.2	0.1
	24 months	24.0	3.1	3.0	20.0	5.0	3.1	-1.7	-3.4	0.0	0.1
Infuse-Bone Dowel Pivotal, 2000 ALIF Study 5	pre-operative	55.0	6.1	2.7	30.0	6.7	2.9				
	6 weeks	54.0	2.7	2.8	29.0	3.8	2.8	-0.8	-2.0	0.4	0.2
	3 months	55.0	3.2	2.8	29.0	4.1	3.4	-0.7	-2.0	0.7	0.3
	6 months	54.0	2.6	2.9	30.0	3.8	3.5	-0.9	-2.2	0.4	0.2
	12 months	52.0	2.6	3.1	27.0	3.9	3.4	-0.9	-2.3	0.5	0.2
	24 months	49.0	2.8	3.2	25.0	4.0	3.8	-1.0	-2.6	0.6	0.2
Infuse-Interfix PLIF, 1999 PLIF Study 6	pre-operative	34.0	7.2	2.2	33.0	6.9	2.2				
	6 weeks	33.0	3.8	3.1	30.0	4.3	3.6	-0.5	-2.1	1.2	0.6
	3 months	33.0	3.1	2.8	31.0	3.6	3.4	-0.5	-2.1	1.1	0.5
	6 months	32.0	3.2	3.2	31.0	3.8	3.3	-0.6	-2.2	1.0	0.4
	12 months	32.0	3.8	3.3	28.0	5.0	3.4	-1.2	-2.9	0.5	0.2
	24 months	29.0	3.8	3.5	30.0	3.8	3.6	0.0	-1.8	1.7	1.0

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
Infuse-Cornerstone ACDF, 1999 CERVICAL Study 7*	pre-operative	18.0	8.3	2.1	15.0	5.6	3.2				
	6 weeks	18.0	1.6	2.8	15.0	1.2	2.1	0.1	-1.9	2.2	0.9
	3 months	17.0	1.6	2.6	15.0	1.3	2.8	0.0	-2.4	2.4	1.0
	6 months	17.0	1.2	2.1	13.0	0.3	0.8	0.7	-0.8	2.2	0.3
	12 months	15.0	1.5	2.6	14.0	0.7	2.4	1.0	-1.3	3.2	0.4
	24 months	14.0	1.6	2.4	13.0	0.8	2.2	0.3	-1.9	2.4	0.8
Infuse-Mastergraft Pilot, 2003 PLF Study 8	pre-operative	25.0	7.7	1.6	21.0	7.0	2.2				
	6 weeks	25.0	2.7	2.9	21.0	3.0	3.3	-0.4	-2.3	1.4	0.6
	3 months	25.0	2.7	2.7	21.0	2.6	3.0	-0.2	-1.9	1.4	0.8
	6 months	25.0	2.6	2.7	21.0	3.0	3.1	-0.8	-2.5	0.9	0.4
	12 months	23.0	2.6	3.1	21.0	2.9	3.2	-0.8	-2.6	1.0	0.4
	24 months	23.0	2.2	2.5	20.0	3.1	3.4	-1.0	-2.9	0.9	0.3
Infuse-Interfix Pilot, 1999 ALIF Study 9	pre-operative	25.0	6.4	3.1	19.0	5.6	3.8				
	6 weeks	25.0	3.8	3.4	16.0	3.5	2.7	-0.1	-1.8	1.6	0.9
	3 months	24.0	2.5	2.8	16.0	3.1	3.1	-0.8	-2.6	1.0	0.4
	6 months	24.0	2.8	3.2	16.0	2.8	2.6	-0.3	-2.0	1.5	0.7
	12 months	23.0	3.5	3.0	16.0	2.7	2.9	0.4	-1.2	2.1	0.6
	24 months	21.0	2.5	3.5	15.0	2.7	2.9	-0.4	-2.5	1.6	0.7
Maverick Disc Pivotal, 2003 ALIF Study 10	pre-operative	172.0	5.9	2.8	405.0	5.7	3.0				
	6 weeks	166.0	3.9	3.0	394.0	3.4	3.2	0.4	-0.2	0.9	0.2
	3 months	159.0	3.0	2.7	386.0	2.8	3.0	0.1	-0.4	0.6	0.7
	6 months	158.0	2.8	2.8	386.0	2.4	2.9	0.3	-0.2	0.8	0.2
	12 months	154.0	3.0	3.0	388.0	2.4	2.9	0.6	0.1	1.1	0.0
	24 months	137.0	2.9	3.1	366.0	2.4	2.9	0.4	-0.1	1.0	0.1
BCP US, 1999 PLF Study 12	pre-operative	11.0	6.3	3.6	5.0	4.8	3.0				
	6 weeks	11.0	3.4	3.4	5.0	2.2	2.0	0.9	-2.8	4.6	0.6
	3 months	11.0	3.6	3.2	5.0	4.8	3.7	-1.7	-5.5	2.2	0.4
	6 months	10.0	5.1	4.3	5.0	4.6	2.4	0.0	-4.4	4.4	1.0

Study	Period	rhBMP-2			ICBG			Adjusted Mean Difference	95% CI		P-Value
		n	Mean	SD	N	Mean	SD		Lower	Upper	
	12 months	10.0	3.8	3.3	5.0	5.0	3.0	-1.6	-5.4	2.1	0.4
	24 months	10.0	3.4	2.7	4.0	3.3	1.3	0.0	-2.7	2.7	1.0
BCP Canada, 1999 PLF Study 13	pre-operative	98.0	6.8	2.7	99.0	7.0	2.6				
	6 weeks	98.0	3.2	2.8	98.0	2.8	2.9	0.4	-0.4	1.2	0.3
	3 months	97.0	2.4	2.4	98.0	3.2	2.9	-0.8	-1.5	0.0	0.0
	6 months	97.0	2.8	2.8	98.0	3.1	3.0	-0.3	-1.1	0.5	0.4
	12 months	97.0	2.9	2.9	97.0	3.3	3.1	-0.3	-1.2	0.5	0.4
	24 months	97.0	3.4	3.2	95.0	3.5	3.3	-0.1	-1.0	0.9	0.9
Amplify Pivotal, 2002 PLF Study 14	pre-operative	238.0	6.9	2.5	223.0	6.9	2.7				
	6 weeks	234.0	2.9	3.1	214.0	2.7	2.9	0.2	-0.4	0.7	0.5
	3 months	232.0	2.7	2.9	215.0	2.9	3.1	-0.2	-0.8	0.3	0.4
	6 months	229.0	2.8	3.0	208.0	3.0	3.1	-0.2	-0.8	0.4	0.5
	12 months	226.0	2.9	3.1	204.0	3.1	3.2	-0.2	-0.7	0.4	0.6
	24 months	210.0	2.9	3.1	181.0	3.4	3.3	-0.4	-1.0	0.2	0.2

* Infuse-Cornerstone_ACDF, 1999 shows results for arm pain.

Table L-6. IPD Data for Adverse Events* at 4 Weeks, Medtronic RCT studies

	Infuse-LT-Cage Pilot ALIF		Infuse LT Cage Pivotal, ALIF		Infuse-Bone Dowel Pilot, ALIF		Infuse-Bone Dowel Pivotal, ALIF		Infuse-Interfix PLIF, PLIF		Infuse-Cornerstone ACDF,		Infuse-Mastergraft Pilot, PLF		Infuse-Interfix Pilot, ALIF		Maverick Disc Pivotal, ALIF		BCP US, PLF		BCP Canada, PLF		Amplify Pivotal, PLF	
	Study 1		Study 2		Study 4		Study 5		Study 6		Study 7		Study 8		Study 9		Study 10		Study 12		Study 13		Study 14	
CATEGORY	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG†**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**
Anatomical/ Technical Difficulty	0	1	0	2			1	2	0	0					1	1	1	9			3	0	1	0
Back and/or Leg Pain			6	4	2	0	2	2	8	8	1	0	2	2	0	1	18	44			9	6	18	8
Cancer													1	0										
Cardiovascular			2	5			3	1	7	10	1	0	0	1	0	1	2	3			11	9	45	43
Death															0	1	0	1			0	1		
Dural Injury									3	2			1	1					1	0	5	7	14	18
Dysphagia/Dysphonia											1	2												
Gastrointestinal	1	1	21	21	1	3	8	6	10	8	1	0	1	4	2	1	14	45	0	1	8	15	19	16
Graft Site Related			0	8			0	1	0	2			0	1							0	2	0	4
Headache											0	1									1	0		
Implant Displacement/ Loosening/ Malposition	0	1	1	0	1	0							1	0	1	2					1	1	4	1
Infection			11	9	0	1	4	2	6	6	2	0	1	1			3	7			15	8	20	27
Neck and/or Arm Pain											0	0					0	1			1	2		
Neurological			5	5			3	1	9	9	1	0	2	2	0	1	12	53	2	0	5	3	9	6
Other	2	1	12	16	1	0	2	8	19	16	2	1	3	5			19	65	1	0	29	33	52	39
Other Pain			2	1	1	0	0	1	8	7	0	0	1	0			1	8			3	0	2	3
Respiratory			2	2			2	3	0	2	1	0	0	1			2	4			5	1	8	7
Retrograde Ejaculation			3	1													1	3						
Spinal Event			0	2	0	1			2	2	0	0					2	11	2	0	0	1	3	3
Subsidence			3	2													3	2						
Trauma	1	0	1	5			2	0	4	3	1	0					7	10					2	2
Urogenital	0	1	13	4	1	0	4	2	1	4	0	1	1	0			6	13	0	1	14	17	10	6
Vascular Intra-Op			6	5	2	3	1	0									8	14			3	1		
Vertebral Fracture			1	0											1	0	0	2			1	0	3	3

CG =comparator group (ICBG or artificial disc); IG = investigational group (rhBMP-2)

*The number of adverse events represents the number of events and one patient may have more than one of the same event.

† The comparator group is artificial disc**.**

Table L-7. IPD Data for Adverse Events* at 24 Months, Medtronic RCT Studies

	Infuse-LT-Cage Pilot ALIF		Infuse LT Cage Pivotal, ALIF		Infuse-Bone Dowel Pilot, ALIF		Infuse-Bone Dowel Pivotal, ALIF		Infuse-Interfix PLIF, PLIF		Infuse-Cornerstone ACDF,		Infuse-Mastergraft Pilot, PLF		Infuse-Interfix Pilot, ALIF		Maverick Disc Pivotal, ALIF		BCP US, PLF		BCP Canada, PLF		Amplify Pivotal, PLF	
	Study 1		Study 2		Study 4		Study 5		Study 6		Study 7		Study 8		Study 10		Study 10		Study 12		Study 13		Study 14	
CATEGORY	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG†**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**
Allergic Reaction													1	0			4	12						
Anatomical/ Technical Difficulty	0	1	0	2			1	2	0	0					1	1	1	9			3	0	1	0
Back and/or Leg Pain	3	0	45	37	9	1	10	15	13	11	4	1	15	7	5	5	96	203	6	0	92	81	136	105
Cancer			2	1	1	0	1	0					1	0			3	3			1	2	11	2
Cardiovascular			9	14	1	0	3	2	9	11	2	1	2	5	2	1	8	14	1	0	19	18	70	68
Death			0	1	0	1			1	1			1	0	0	1	1	3			1	2	3	4
Dural Injury			0	1					3	2			2	2					2	0	5	7	14	18
Dysphagia/Dysphonia											2	2							1	0				
Gastrointestinal	2	1	38	31	1	3	8	8	11	11	5	0	4	10	3	2	20	99	2	1	18	27	46	43
Graft Site Related			0	8	0	1	0	1	0	2			0	4	0	1					0	11	0	17
Headache											0	2									4	0		
Implant Displacement/ Loosening/ Malposition	1	1	3	0	1	0	1	0					2	0	1	2	1	1			2	2	6	4
Infection			22	17	0	1	5	4	8	6	4	0	4	5	1	0	15	29			31	21	52	51
Neck and/or Arm Pain											1	0	2	1	1	0	5	12			10	12		
Neurological			24	24	2	1	16	4	16	18	7	2	5	4	2	2	74	185	3	0	19	14	93	77
Other	6	3	35	40	3	3	7	14	21	23	6	1	18	14	2	6	57	195	4	2	69	68	129	111
Other Pain			23	16	7	2	16	5	14	11	2	1	4	0			24	79	1	1	15	7	30	31
Respiratory			3	4			2	4	0	2	1	0	2	2			4	9			8	3	18	13
Retrograde Ejactulation			5	1													2	4						
Spinal Event			26	18	6	3	4	1	5	5	3	1	4	3	1	2	29	64	5	0	3	4	29	31
Subsidence			6	2			1	0									14	14						

	Infuse-LT-Cage Pilot ALIF Study 1		Infuse LT Cage Pivotal, ALIF Study 2		Infuse-Bone Dowel Pilot, ALIF Study 4		Infuse-Bone Dowel Pivotal, ALIF Study 5		Infuse-Interfix PLIF, PLIF Study 6		Infuse-Cornerstone ACDF, Study 7		Infuse-Mastergraft Pilot, PLF Study 8		Infuse-Interfix Pilot, ALIF Study 10		Maverick Disc Pivotal, ALIF Study 10		BCP US, PLF Study 12		BCP Canada, PLF Study 13		Amplify Pivotal, PLF Study 14	
CATEGORY	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG†**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**
Trauma	4	0	43	39	5	5	12	14	8	9	3	1	1	0	8	2	66	145	2	0	19	29	89	69
Urogenital	0	1	24	13	2	0	7	2	1	5	2	1	2	2			17	41	0	1	22	21	28	25
Vascular Intra-Op			6	5	2	3	1	0									8	15			3	1		
Vertebral Fracture			1	0											1	0	0	3			1	0	3	4

CG =comparator group (ICBG or artificial disc); IG = investigational group (rhBMP-2)

*The number of adverse events represents the number of events and one patient may have more than one of the same event.

† The comparator group is artificial disc**.**

Table M-8. IPD Data for Adverse Events* at 4 Weeks, Medtronic Intervention Series

	INFUSE/ LT-CAGE lap pivotal Study 3	**INFUSE/TELAMON PEEK PLIF pilot** Study 11	**rhBMP-2/CRM 2-level pilot** Study 15	**rhBMP-2/BCP Mexico pilot** Study 16
CATEGORY	**Frequency**	**Frequency**	**Frequency**	**Frequency**
Anatomical/ Technical Difficulty	9			
Back and/or Leg Pain	11	3		
Cancer	1			
Cardiovascular	6	2		
Dural Injury		1	1	
Gastrointestinal	22	2	2	1
Hematological		1	1	
Implant Displacement/ Loosening/ Malposition	5			1
Incision Related			5	
Infection	8	2		
Neurological	8			
Other	21	3	3	
Other Pain	10			
Respiratory	2		1	
Retrograde Ejactulation	2			
Spinal Event	4			
Trauma	13			
Upper Extremity Pain			1	
Urogenital	14	1	1	
Vascular Intra-Op	8			
Vertebral Fracture				1

*The number of adverse events represents the number of events and one patient may have more than one of the same event..

Table M-9. IPD Data for Adverse Events* at 24 Months, Medtronic Intervention Series

	INFUSE/ LT-CAGE lap pivotal Study 3	**INFUSE/TELAMON PEEK PLIF pilot** Study 11	**rhBMP-2/CRM 2-level pilot** Study 15	**rhBMP-2/BCP Mexico pilot** Study 16
CATEGORY	**Frequency**	**Frequency**	**Frequency**	**Frequency**
Accidental Injury/Muscle Strain		8	7	
Anatomical/ Technical Difficulty	9			
Back and/or Leg Pain	41	20	12	3
Cancer	2			
Cardiovascular	13	2	1	
Dural Injury		1	1	
Gastrointestinal	37	5	6	1
Hemotological		1	1	
Implant Displacement/ Loosening	2			1
Incision Related		1	5	
Infection	18	3	1	
Lower Extremity Pain, Not of Back Etiology		8	6	
Malpositioned Implant	4			
Neurological	29	6	6	
Other	50	11	7	1
Other Pain	24	1	2	
Respiratory	3	2	1	
Retrograde Ejactulation	6			
Spinal Event (all levels)	14	6	7	
Trauma	48	3	2	
Upper Extremity Pain		2	5	
Urogenital	25	1	4	
Vascular Intra-Op	9			
Vertebral Fracture				1

*The number of adverse events represents the number of events and one patient may have more than one of the same event.

Appendix M. Evidence Tables

For Medtronic-sponsored randomized controlled trials (RCTs), we abstracted data from internal documents Medtronic had provided to the U.S. Food and Drug Administration (FDA data summary) in order to compare the data with published results. For unpublished RCTs, we did not abstract information on results but relied on individual patient data (IPD) provided by Medtronic.

The information provided in the evidence tables for the rhBMP-2 (BMP) and control groups include percentages, followed by the total sample size (N) from which that percentage is derived.

NR = not reported
NA = not applicable

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions	BMP 1 level	BMP 2 level	BMP Comb	Control 1 level	Control 2 level
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	ACDF (Randomized pilot trial) 24 months	Inclusion Criteria: -Cervical disk disease -Preoperative Neck Disability score ≥ 30 -C2-C3 to C7-T1 disc level involvement -1 or 2 treatment levels -At least 18 years of age -No response to 6 weeks of nonsurgical treatment or presence of progressive symptoms Exclusion Criteria: -Cervical spinal condition requiring surgical treatment other than symptomatic cervical disc disease at the involved level(s) -Has received drugs which may interfere with metabolism within 2 weeks prior to surgery (e.g. steroids, methotrexate) -Has osteopenia, osteoporosis, or osteomalacia to a degree that anterior plating would be contraindicated -Substance abuser -Previous exposure to BMP	A. Cervical discectomy and anterior implantation of BMP-2 applied to ACS placed inside the Cornerstone-SR fibular allograft with ATLANTIS Anterior Cervical Plate System B. Cervical discectomy and anterior implantation of autogenous iliac crest bone graft placed inside the Cornerstone-SR fibular allograft with ATLANTIS Anterior Cervical Plate System	Randomized=33; BMP=18; ICBG=15 Withdrawn=0 Lost to Followup: BMP=3; Control=1 but absent for most 24 month outcomes: BMP=4; Control=3 Fewer patients included in fusion outcome	Soft collar Hard collar Other None	90.0 0 0 10.0	37.5 62.5 0 0	66.7 27.8 0 5.6	75.0 25.0 0 0	28.6 57.1 0 14.3

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Control Comb
Baskin, 2003* USA	53.3
Conerstone ACDF-Pilot study	40.0 0
Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	6.7

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary							Medical history Baseline characteristics from FDA data summary						
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**
	N=	10	8	18	8	7	15							
	Age:	46.3	57.5	51.3	43.7	51.1	47.1	Prior Tobacco:	40.0	12.5	27.8	50.0	42.9	46.7
	Height:	67.9	66.8	67.4	67.9	68.1	68.0	Alcohol use:	50.0	25.0	38.9	37.5	28.6	33.3
	Weight:	165.3	175.0	169.6	176.3	170.7	173.7	Prior Back Surgery:	10.0	0	5.6	0	0	0
	% Male:	60.0	25.0	44.4	50.0	42.9	46.7	Diabetic:	0	0	0	0	0	0
	% White:	80.0	100.0	88.9	100.0	100.0	100.0	% not taking Non Narcotic:	NR	NR	NR	NR	NR	NR
	% Married:	70.0	50.0	61.1	87.5	85.7	86.7	% not taking Weak Narcotic:	NR	NR	NR	NR	NR	NR
	% ED>HS:	50.0	62.5	55.6	50.0	28.6	40.0	% not taking Strong Narcotic:	NR	NR	NR	NR	NR	NR
	% Working:	80.0	50.0	66.7	100.0	14.3	60.0	% not taking Muscle Relaxer:	NR	NR	NR	NR	NR	NR
	% Worker's Comp:	0	0	0	0	0	0							
	% Spinal Litigation:	0	12.5	5.6	0	0	0	Characteristics of Degenerative Disc Disease:						
								%Instability:	NR	NR	NR	NR	NR	NR
								%Osteophytes:	NR	NR	NR	NR	NR	NR
								%↓Disc Height:	NR	NR	NR	NR	NR	NR
								%Thick Ligaments:	NR	NR	NR	NR	NR	NR
								%Disc Herniation:	NR	NR	NR	NR	NR	NR
								%Facet Joint Degeneration:	NR	NR	NR	NR	NR	NR
								% ≥ 3 of above:	NR	NR	NR	NR	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary	ODI results from published study
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary							SF-36 results from published study		
		BMP 1 level	BMP 2 level	BMP Comb	Control 1 level	Control 2 level	Control Comb		BMP	Control
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	SF-36 MCS:							SF-36 MCS:		
	Preop	37.3 (10)	27.7 (7)	33.3 (17)	46.4 (8)	37.9 (7)	42.5 (15)	Preop	32.4 (16)	42.5 (15)
	6 weeks	49.9 (10)	53.1 (8)	51.4 (18)	53.1 (8)	52.0 (7)	52.6 (15)	6 weeks	51.4 (18)	52.6 (15)
	3 months	50.7 (10)	44.6 (6)	48.4 (16)	51.3 (8)	43.3 (7)	47.6 (15)	3 months	48.4 (16)	47.6 (15)
	6 months	57.1 (8)	52.5 (7)	54.9 (15)	56.7 (7)	51.1 (5)	54.4 (12)	6 months	54.9 (15)	54.4 (12)
	12 months	56.4 (7)	52.1 (8)	54.1 (15)	53.3 (8)	46.6 (6)	50.4 (14)	12 months	54.1 (15)	50.4 (14)
	24 months	57.3 (6)	52.5 (8)	54.6 (14)	47.8 (7)	50.8 (5)	49.0 (12)	24 months	54.6 (14)	49.0 (12)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	NR
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	NR
	SF-36 PCS:							SF-36 PCS:		
	Preop	30.4 (10)	32.3 (7)	31.2 (17)	32.3 (8)	33.1 (7)	32.6 (15)	Preop	31.7 (16)	32.6 (15)
	6 weeks	41.5 (10)	38.9 (8)	40.4 (18)	40.8 (8)	38.2 (7)	39.6 (15)	6 weeks	40.4 (18)	39.6 (15)
	3 months	46.0 (10)	41.9 (6)	44.4 (16)	48.4 (8)	40.2 (7)	44.6 (15)	3 months	44.4 (16)	44.6 (15)
	6 months	48.6 (8)	42.3 (7)	45.6 (15)	50.9 (7)	40.2 (5)	46.5 (12)	6 months	45.6 (15)	46.5 (12)
	12 months	48.0 (7)	43.7 (8)	45.7 (15)	50.9 (8)	45.8 (6)	48.7 (14)	12 months	45.7 (15)	48.7 (14)
	24 months	49.0 (6)	48.3 (8)	48.6 (14)	51.5 (7)	44.9 (5)	48.7 (12)	24 months	48.6 (14)	48.7 (12)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	NR
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary							Neck disability index from published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP**	**Control**
	NDI Scores (n):							NDI Scores (n):		
	Preop	57.0 (10)	66.8 (8)	61.3 (18)	49.1 (8)	62.6 (7)	55.4 (15)	Preop	61.3 (18)	55.4 (15)
	6 weeks	23.8 (10)	24.0 (8)	23.9 (18)	21.5 (8)	24.3 (7)	22.8 (15)	6 weeks	23.9 (17)	22.8 (15)
	3 months	23.2 (10)	18.6 (7)	21.3 (17)	16.0 (8)	28.6 (7)	21.9 (15)	3 months	21.3 (17)	21.9 (15)
	6 months	11.1 (9)	15.0 (8)	12.9 (17)	11.7 (7)	15.3 (6)	13.4 (13)	6 months	12.9 (17)	13.4 (13)
	12 months	10.3 (7)	21.5 (8)	16.3 (15)	9.5 (8)	16.0 (6)	12.3 (14)	12 months	16.3 (15)	12.3 (14)
	24 months	12.3 (6)	8.5 (8)	10.1 (14)	11.1 (7)	16.0 (6)	13.4 (13)	24 months	10.1 (14)	14.5 (12)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	NR
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary						
Baskin, 2003* USA		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**
Conerstone ACDF-Pilot study	Neck Pain Scores (n):						
	Preop	16.3 (10)	15.9 (8)	16.1 (18)	15.0 (8)	13.4 (7)	14.3 (15)
	6 weeks	6.7 (10)	3.3 (8)	5.2 (18)	7.4 (8)	6.3 (7)	6.9 (15)
Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	3 months	6.4 (10)	6.0 (7)	6.2 (17)	6.6 (8)	6.7 (7)	6.7 (15)
	6 months	3.9 (9)	5.4 (8)	4.6 (17)	4.3 (7)	3.8 (6)	4.1 (13)
	12 months	3.0 (7)	3.9 (8)	3.5 (15)	3.6 (8)	7.8 (6)	5.4 (14)
	24 months	3.0 (6)	2.6 (8)	2.8 (14)	4.1 (7)	5.8 (6)	4.9 (13)
	48 months	NR	NR	NR	NR	NR	NR
	72 months	NR	NR	NR	NR	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary							Arm pain scores from published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP**	**Control**
	Arm Pain Scores (n):							Arm Pain Scores (n):		
	Preop	17.0 (10)	17.8 (8)	17.3 (18)	12.6 (8)	10.1 (7)	11.5 (15)	Preop	17.3 (18)	11.5 (15)
	6 weeks	4.0 (10)	2.6 (8)	3.4 (18)	2.3 (8)	3.0 (7)	2.6 (15)	6 weeks	3.4 (18)	2.6 (15)
	3 months	3.8 (10)	3.3 (7)	3.6 (17)	0.9 (8)	5.3 (7)	2.9 (15)	3 months	3.6 (17)	2.9 (15)
	6 months	1.9 (9)	3.4 (8)	2.6 (17)	0.0 (7)	1.7 (6)	0.8 (13)	6 months	2.6 (17)	0.8 (13)
	12 months	2.1 (7)	3.6 (8)	2.9 (15)	0.4 (8)	3.0 (6)	1.5 (14)	12 months	2.9 (15)	1.5 (14)
	24 months	3.0 (6)	3.5 (8)	3.3 (14)	0.6 (7)	2.7 (6)	1.5 (13)	24 months	3.3 (14)	1.7 (12)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	NR
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary							Neurological results from published summary		
Baskin, 2003* USA		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP**	**Control**
Conerstone ACDF-Pilot study	% Overall Neuro Success (n):							% Overall Neuro Success (n):		
	6 weeks	100.0 (10)	87.5 (8)	94.4 (18)	100.0 (8)	100.0 (7)	100.0 (15)	6 weeks	94 (18)	100 (15)
	3 months	100.0 (10)	100.0 (8)	100.0 (18)	100.0 (8)	100.0 (7)	100.0 (15)	3 months	100 (18)	100 (15)
Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)	6 months	77.8 (9)	100.0 (8)	88.2 (17)	100.0 (7)	100.0 (6)	100.0 (13)	6 months	88 (17)	100 (13)
	12 months	100.0 (7)	100.0 (8)	100.0 (15)	87.5 (8)	100.0 (6)	92.9 (14)	12 months	100 (15)	93 (14)
	24 months	100.0 (6)	100.0 (8)	100.0 (14)	100.0 (7)	100.0 (6)	100.0 (13)	24 months	100 (14)	100 (12)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	NR
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary							Radiologic fusion results from published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP N=18**	**Control N=15**
	% Radiographic Fusion (n):							% Radiographic Fusion (n):		
	6 months	100.0 (9)	100.0 (6)	100.0 (15)	100.0 (7)	100.0 (6)	100.0 (13)	6 months	100 (15)	100 (13)
	12 months	100.0 (6)	100.0 (8)	100.0 (14)	100.0 (7)	100.0 (6)	100.0 (13)	12 months	100 (14)	100 (12)
	24 months	100.0 (4)	100.0 (7)	100.0 (11)	100.0 (6)	100.0 (5)	100.0 (11)	24 months	100 (10)	100 (10)
	48 months	NR	NR	NR	NR	NR	NR	48 months	NR	
	72 months	NR	NR	NR	NR	NR	NR	72 months	NR	
								No significant differences between groups.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data							Overall success in published study
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**	
	% Overall Success (n):							Not Reported
	6 months	77.8 (9)	83.3 (6)	80.0 (15)	85.7 (7)	100.0 (6)	92.3 (13)	
	12 months	100.0 (6)	87.5 (8)	92.9 (14)	71.4 (7)	100.0 (6)	84.6 (13)	
	24 months	NR	NR	NR	NR	NR	NR	
	48 months	NR	NR	NR	NR	NR	NR	
	72 months	NR	NR	NR	NR	NR	NR	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP**	**Control**		**BMP**	**Control**
	Number of patients with surgeries:			Number of patients with surgeries:		
	Revisions	0	0	Revisions	0	0
	Removals	1	0	Removals	1	0
	Supplemental Fixations	0	0	Supplemental Fixations	0	0
	Reoperations	1	0	Reoperations	0	0
				One patient in the BMP groups required surgical intervention at a segment adjacent to the original 2-level fusion, unrelated to the original procedure, requiring removal of the cervical plate.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP**	**Control**	
	% Working (n)			Not reported
	Preop	66.7 (18)	60.0 (15)	
	6 weeks	38.9 (18)	40.0 (15)	
	3 months	55.6 (18)	60.0 (15)	
	6 months	64.7 (18)	69.2 (13)	
	12 months	66.7 (17)	71.4 (14)	
	24 months	57.1 (14)	69.2 (13)	
	48 months	NR	NR	
	72 months	NR	NR	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days							Hospitalization days from published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP 1 level**	**BMP 2 level**	**BMP Comb**	**Control 1 level**	**Control 2 level**	**Control Comb**		**BMP**	**Control**
	Hospitalization days	1.2 (10)	1.8 (8)	1.4 (18)	1.0 (8)	1.1 (7)	1.1 (15)	Hospitalization days	1.4	1.1
	Not a significant difference. One patient in control group stayed 56 days. Maximum stay in BMP group was 7 days.									

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Baskin, 2003* USA Conerstone ACDF-Pilot study Cornerstone Allograft Ring and the ATLANTIS Anterior Cervical Plate (Study 7)		**BMP**	**Control**		**BMP**	**Control**		**BMP**	**Control**
	Adverse Events* (n):			Patients Reporting Event (n):			There were no device-related adverse events.	NR	NR
	Anatomic Difficulty	NR	NR	Wound Infection					
	Back and/or Leg Pain	4	2	Wound Dehiscence	2	0			
	Cancer	NR	NR	Urinary Retention	0	0			
	Cardiovascular	3	1	Cancer	0	1			
	Death	1	0	Dysphagia	0	0			
	Dural Injury	NR	NR		1	0			
	Gastrointestinal	5	0						
	Implant Displaced	NR	NR						
	Infection	4	0						
	Malpositioned Implant	NR	NR						
	Neurological	8	2						
	Non-Union	NR	NR						
	Other	7	1						
	Other Pain	2	1						
	Respiratory	1	0						
	Retrograde Ejaculation	NR	NR						
	Spinal Event	3	1						
	Subsidence	NR	NR						
	Trauma	3	1						
	Urogenital	2	1						
	Vascular Intra-Op	NR	NR						
	Vertebral Fracture	NR	NR						
	Dysphagia/dysphonia	2	2						
	Headache	0	2						
	Neck/Arm Pain	1	1						
	Total Events	46	15						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	**Control**
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	ALIF (Randomized pilot trial) 24 months	Inclusion Criteria: -Discogenic back pain -≤ Grade 1 spondylolisthesis -Single-level DDD from L2-S1 -18-65 years old -No response to 6 months of conservative treatment Exclusion Criteria: -Other spine disease or surgery at level of surgery -Requires steroids or NSAIDs ->40% over ideal weight -On worker's comp or has unresolved spinal litigation -Has psychogenic magnification of pain -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. BMP-2/ACS/TIF (1.5mg/ml of BMP-2) in an open ALIF surgical approach (However, 4 patients had laparoscopic surgery) B. TIF device filled with autogenous bone taken from the patient's iliac crest, which will also be implanted using an open ALIF surgical approach	14 patients randomized 3:1, 11 in BMP group (of which 7 had an open procedure and 4 had a laparoscopic procedure) and 3 in the control group (all had open procedure) 14 patients analyzed (11 in the BMP group and 3 in the control group) Withdrawn: NR Lost to follow-up:0	% Brace: % Corset: % Other:	72.7 27.3 0	66.7 0 33.3

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Boden, 2000 USA		**BMP**	**Control**		**BMP**	**Control**
1-Infuse-LT-Cage_Pilot	Age:	42.5	40.2	Prior Tobacco:	9.1	33.3
	Height:	68.5	71.3	Alcohol use:	36.4	33.3
	Weight:	166.4	211.3	Pain Meds:	63.6	100
(Study 1)	% Male:	45.5	66.7	Prior Back Surgery:	45.5	0
	% White:	100	66.7	Diabetic:	0	0
	% Married:	54.6	66.7	% not taking Non Narcotic:	81.8	66.7
	% Ed > HS:	54.5	66.7	% not taking Weak Narcotic:	63.6	66.7
	% Working:	54.5	66.7	% not taking Strong Narcotic:	90.9	100
				% not taking Muscle Relaxer:	72.7	33.3

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary				ODI results from published study		
Boden, 2000 USA		**BMP open**	**BMP lap**	**Control**		**BMP**	**Control**
1-Infuse-LT-Cage_Pilot	ODI Scores (n):				ODI Scores:		
	Preop:	41.1 (7)	34.9 (4)	34.7 (3)	Pre-operation	38.9	34.7
	6 weeks:	53.0 (2)	---	72.0 (1)	3 months	29.8	42.7
(Study 1)	3 months:	38.0 (7)	15.4 (4)	42.7 (3)	6 months	26.9	28.0
	6 months:	30.9 (7)	19.9 (4)	28.0 (3)	12 months	17.7	27.3
	12 months:	23.1 (7)	8.1 (4)	27.3 (3)	24 months	13.5	20.0
	24 months:	17.0 (7)	7.2 (4)	8.0 (2)			
					ODI scores for the BMP group included those who underwent both an open and a laparoscopic procedure.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary				SF-36 results from published study		
Boden, 2000 USA		BMP - open	BMP - lap	Control		BMP	Control
1-Infuse-LT-Cage_Pilot	SF-36 Physical Function:				SF-36 Physical Function:		
(Study 1)	Preop	46.4 (7)	51.3 (4)	30.0 (3)	Preop	48.2	30.0
	6 weeks	47.5 (2)	---	0.0 (1)	3 months	57.7	43.3
	3 months	52.9 (7)	66.3 (4)	43.3 (3)	6 months	65.5	56.7
	6 months	59.3 (7)	76.3 (4)	56.7 (3)	12 months	75.0	66.7
	12 months	68.6 (7)	86.6 (4)	66.7 (3)	24 months	85.9	66.7
	24 months	80.2 (7)	95.8 (4)	91.7 (2)			
					SF-36 Pain Index:		
	SF-36 Pain Index:				Preop	25.9	17.7
	Preop	25.7 (7)	26.3 (4)	17.7 (3)	3 months	47.5	37.7
	6 weeks	16.5 (2)	---	0.0 (1)	6 months	53.0	57.3
	3 months	43.6 (7)	54.3 (4)	37.7 (3)	12 months	51.6	45.7
	6 months	54.4 (7)	50.5 (4)	57.3 (3)	24 months	69.4	44.7
	12 months	41.6 (7)	69.3 (4)	45.7 (3)			
	24 months	69.6 (7)	69.0 (4)	51.2 (2)	SF-36 Mental Health:		
					Preop	61.1	58.7
	SF-36 Mental Health:				3 months	74.5	70.7
	Preop	55.4 (7)	71.0 (4)	58.7 (3)	6 months	64.2	72.0
	6 weeks	86.0 (2)	---	88.0 (1)	12 months	68.8	65.3
	3 months	69.7 (7)	83.0 (4)	70.7 (3)	24 months	76.7	72.0
	6 months	57.4 (7)	76.0 (4)	72.0 (3)			
	12 months	57.9 (7)	88.0 (4)	65.3 (3)	SF-36 scores for the BMP group included those who underwent an open and a laparoscopic procedure.		
	24 months	74.3 (7)	81.0 (4)	78.0 (2)			
	Data at 6 weeks was not required. MCS and PCS results were given but not reported here.						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	Not reported	Not reported

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	Not reported	Not reported

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary				Neurological results from published summary
Boden, 2000 USA		**BMP open**	**BMP lap**	**Control**	
1-Infuse-LT-Cage_Pilot	Sensory Function:				Mean scores for all neurologic parameters were ≥ preop values at 3, 6, 12, and 24 months with the exception of one patient who was normal to slightly hyporeflexic at 24 months.
(Study 1)	Preop	98.8 (7)	93.8 (4)	97.2 (3)	
	6 weeks	100.0 (4)	NR	91.7 (2)	
	3 months	100.0 (7)	100.0 (4)	100.0 (3)	
	6 months	100.0 (7)	100.0 (4)	100.0 (3)	
	12 months	100.0 (7)	100.0 (4)	100.0 (3)	
	24 months	100.0 (7)	100.0 (4)	100.0 (2)	
	Straight Leg Raise:				
	Preop	92.9 (7)	100.0 (4)	75.0 (3)	
	6 weeks	100.0 (4)	NR	100.0 (2)	
	3 months	96.4 (7)	100.0 (4)	100.0 (3)	
	6 months	96.4 (7)	100.0 (4)	83.3 (3)	
	12 months	100.0 (7)	100.0 (4)	100.0 (3)	
	24 months	71.9 (7)	100.0 (4)	66.7 (3)	
	Reflexes:				
	Preop	85.7 (7)	93.8 (4)	66.7 (3)	
	6 weeks	81.3 (4)	NR	100.0 (2)	
	3 months	85.7 (7)	100.0 (4)	91.7 (3)	
	6 months	85.7 (7)	100.0 (4)	66.7 (3)	
	12 months	92.9 (7)	100.0 (4)	66.7 (3)	
	24 months	71.4 (7)	100.0 (4)	100.0 (2)	
	Neurological Status: Motor Function mean score was 100.0 for all groups at all time periods.				

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary				Radiologic fusion results from published study
Boden, 2000 USA		**BMP open**	**BMP lap**	**Control**	
1-Infuse-LT-Cage_Pilot	Radiographic Fusion:				3 months post-operation: 10 of 11 (90.9%) patients in the BMP group had solid fusions compared with 2 of 3 (66.7%) of control group. 11 of 11 in the BMP groups were fused by 6 months and thereafter; at 6, 12, and 24 months 2 of 3 control patients were fused.
	Angulation Stability <5degrees:				
	3 months	1/1	4/4	1/1	
	6 months	7/7	4/4	2/3	
(Study 1)	12 months	7/7	4/4	3/3	
	24 months	7/7	4/4	3/3	
	Number of lines covering 50% of implant 1:				
	3 months	4/4	1/1	1/1	
	6 months	7/7	4/4	2/3	
	12 months	7/7	4/4	3/3	
	24 months	7/7	4/4	3/3	
	Number of lines covering 50% of implant 2:				
	3 months	4/4	1/1	1/1	
	6 months	7/7	4/4	2/3	
	12 months	7/7	4/4	2/3	
	24 months	7/7	4/4	3/3	
	Fused:				
	3 month radiograph	0/0	1/1	1/1	
	6 month radiograph	7/7	4/4	2/3	
	12 month radiograph	7/7	4/4	3/3	
	24 month radiograph	7/7	4/4	2/3	
	6 month CT, (number of 3 radiologists out of 3)	11/11 (3)		2/3 (2), 3/3 (1)	
	12 month CT	11/11 (3)		2/3 (1), 3/3 (2)	
	24 month CT	11/11 (3)		2/3 (3)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data	Overall success in published study
Boden, 2000 USA 1-Infuse-LT-Cage_Pilot (Study 1)	3 months post-operation: 10 of 11 (90.9%) patients in the BMP group had solid fusions compared with 2 of 3 (66.7%) of control group. 11 of 11 in the BMP groups were fused by 6 months and thereafter; at 6, 12, and 24 months 2 of 3 control patients were fused.	Not Reported

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study
Boden, 2000 USA		**BMP**	**Control**	
1-Infuse-LT-Cage_Pilot (Study 1)	Number of patients with surgeries:			Not reported
	Revisions	0	0	
	Removals	0	0	
	Supplemental Fixations	0	1	
	Reoperations	0	0	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary				Employed postoperatively from published study		
Boden, 2000 USA		BMP - open	BMP - lap	Control		BMP	Control
1-Infuse-LT-Cage_Pilot	%Working Preop	71.4	25.0	66.7	% Working preop	54.5	66.7
	%Working 6 weeks	14.3	25.0	0	% Working 3 months	54.5	0
(Study 1)	%Working 3 months	57.1	50.0	0	% Working 6 months	72.7	66.7
	%Working 6 months	71.4	75.0	66.7	% Working 12 months	81.8	66.7
	%Working 12 months	57.1	100.0	66.7	% Working at 24 months	81.8	66.7
	%Working 24 months	71.4	100.0	66.7			
	"At 24 months following surgery, 9 of 11 (81.8%) investigational patients had returned to work. Of the two investigational patients not working at 24 months, one was not working prior to surgery. The other patient had been working preoperatively and had returned to work at both the 3and 6 month visits. However, at the 12 and 24 month visits, the patient was incarcerated and was, therefore, unable to work."				Those working in the BMP group included those who underwent an open and a laparoscopic procedure.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
Boden, 2000 USA		**BMP**	**Control**		**BMP**	**Control**
1-Infuse-LT-Cage_Pilot (Study 1)	Hospitalization Days	1.4	1.1	Hospitalization Days	2	3.3

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Boden, 2000 USA		**BMP**	**Control**		**BMP**	**Control**		**BMP**	**Control**
1-Infuse-LT-Cage_Pilot	Event:			Patients Reporting Event (n):			Event:		
	Ileus	1	1	Wound Infection	0	0	Ileus	1	1
(Study 1)	Wound dehiscence	1	0	Wound Dehiscence	1	0	Wound dehiscence	1	0
	Back Pain	2	0	Urinary Retention	0	1	Low Back Pain	1	0
	Postop Trauma	4	0	Retrograde Ejaculation	0	0	Urinary Retention	0	1
	Back Strain	1	0	Cancer	0	0	Postop Trauma	3	0
	Endcap Event	3	2				Back and leg pain	1	0
	Urinary Retention	0	1						
	Fracture	2	0						
	Pseudoarthrosis	1	1						
	Shortness of Breath	1	0						
	Numbness/SLE	1	0						
	Drug Use	1	0						
	Facet Joint Pain	1	0						
	Rectal Bleeding/ Hemorrhoids	1	1						
	Removals	0	0						
	Revisions	0	0						
	Reoperations	0	0						
	Supplemental Fixation	0	1						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions	BMP Only	BMP/ TSRH	Control
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	PLF (Prospective randomized trial) 24 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 30 -≤ Grade 1 spondylolisthesis -Single-level DDD from L1-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Previous fusion surgery at same level -Requires medications that might interfere with fusion or bone metabolism -Has osteopenia, osteoporosis, or osteomalacia -Weight > 40% over ideal for age/height -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. Bilateral posterolateral implantation of the rhBMP-2/BCP device B. Bilateral posterolateral implantation of the rhBMP-2/BCP/TSRH Spinal System C. Bilateral posterolateral implantation of autogenous bone harvested from the iliac crest with the TSRH Spinal System	Number Randomized: 27 (BMP=22, Control=5) Number Analyzed: BMP=18 to 22, Control=4 to 5 Number Withdrawn: 2 were excluded from analysis Number Lost to follow-up: None	% Low Profile Brace: % High Profile Brace: % Corset: % Other:	27.3 0.0 45.5 27.3	36.4 0.0 36.4 27.3	40.0 0.0 20.0 40.0

Evidence Table 1. Medtronic randomized controlled trials

Author **Year** **Country** **Trial # or Name**
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary				Medical history Baseline characteristics from FDA data summary			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA	Age	50.1	57.6	52.9	Prior Tobacco:	18.2	0.0	20.0
	Height	67.7	66.0	66.8	Alcohol use:	27.3	54.5	40.0
rhBMP-2/BCP US Pilot RCT	Weight	185.2	173.6	162.2	Prior Back Surgery:	18.2	27.3	0.0
	% Male	54.5	27.3	40.0	Diabetic:	9.1	0.0	40.0
(Study 12)	% White	90.9	90.9	100.0	% not taking Non Narcotic:	54.5	27.3	60.0
	% Married	81.8	90.9	60.0	% not taking Weak Narcotic:	72.7	72.7	60.0
	% ED>HS*	80.0	100.0	40.0	% not taking Strong Narcotic:	100.0	72.7	100.0
	% Working				% not taking Muscle Relaxer:	90.9	90.9	80.0
	% Worker's Comp	18.2	9.1	20.0				
	% Spinal Litigation	0.0	9.1	0.0	Characteristics of Degenerative Disc Disease:			
	*p=0.021				%Instability:	NR	NR	NR
					%Osteophytes:	NR	NR	NR
					%↓Disc Height:	NR	NR	NR
					%Thick Ligaments:	NR	NR	NR
					%Disc Herniation:	NR	NR	NR
					%Facet Joint Degeneration:	NR	NR	NR
					% ≥ 3 of above:	NR	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary				ODI results from published study			
Boden, 2002 USA		**BMP Only**	**BMP/TSRH**	**Control**		**BMP Only**	**BMP/TSRH**	**Control**
rhBMP-2/BCP US Pilot RCT	ODI Scores (n):				ODI Scores (n):			
	Preop	39.8 (11)	47.9 (11)	54.5 (5)	Preop			
	6 weeks	21.6 (11)	44.8 (11)	43.0 (5)	6 weeks	-17.6		
(Study 12)	3 months	18.7 (10)	30.9 (11)	39.6 (5)	3 months		-17.0	
	6 months	18.1 (10)	28.7 (10)	37.1 (5)	6 months			-17.3
	12 months	15.6 (10)	33.7 (10)	38.9 (5)	12 months			
	24 months	13.1 (8)	36.8 (10)	27.0 (4)	24 months			
					Only improvements from baseline given; no difference between groups			
					Values provided here represent significant improvement from baseline			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary				SF-36 results from published study			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	SF-36 MCS:				SF-36 MCS:			
	Preop	43.7 (11)	38.7 (11)	49.9 (5)	Preop			
	6 weeks	53.4 (11)	42.0 (11)	52.0 (5)	6 weeks			
	3 months	54.9 (10)	50.5 (11)	49.1 (5)	3 months			
	6 months	55.8 (9)	55.8 (9)	49.1 (5)	6 months			
	12 months	51.3 (10)	49.8 (10)	48.0 (5)	12 months			
	24 months	53.6 (8)	50.4 (9)	53.8 (4)	24 months			
	SF-36 PCS:				SF-36 PCS:			
	Preop	32.9 (11)	29.1 (11)	25.5 (5)	Preop			
	6 weeks	34.4 (11)	31.1 (11)	26.4 (5)	6 weeks			
	3 months	41.7 (10)	29.2 (11)	29.3 (5)	3 months	9.1		
	6 months	44.4 (9)	35.6 (10)	28.0 (5)	6 months		6.2	
	12 months	46.1 (10)	34.6 (10)	27.9 (5)	12 months			
	24 months	48.9 (8)	33.4 (9)	32.9 (4)	24 months			
					Scores represent significant improvements from baseline; no differences in improvement from baseline between groups.			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary				Back pain results from published study			
Boden, 2002 USA		**BMP Only**	**BMP/TSRH**	**Control**		**BMP Only**	**BMP/TSRH**	**Control**
rhBMP-2/BCP US Pilot RCT	Back Pain Scores (n)				Decrease in back pain at the most recent followup assessment, as compared with preoperative values was significant for each group and the lowest mean back pain score was in the BMP only group, mean=2.9. The differences among the groups was statistically significant (p=0.025) (but not sure if this refers to the mean being different or the degree of improvement from baseline being different)	(-10.4)	(-5.1)	(-6.2)
(Study 12)	Preop	13.2 (11)	15.8 (11)	16.8 (5)				
	6 weeks	4.8 (11)	10.5 (11)	9.4 (5)				
	3 months	4.1 (10)	7.9 (11)	10.6 (5)				
	6 months	5.0 (10)	9.2 (10)	11.6 (5)				
	12 months	4.3 (10)	9.2 (10)	13.6 (5)				
	24 months	4.9 (8)	12.2 (10)	9.3 (4)				
	No differences in improvement from baseline between groups.							

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary				Leg pain results from published study			
Boden, 2002 USA		**BMP Only**	**BMP/TSRH**	**Control**	**BMP Only**	**BMP/TSRH**	**Control**
rhBMP-2/BCP US Pilot RCT	Leg Pain Scores (n)				Decrease at most recent follow-up; between-group differences, p=0.042	NR	NR
	Preop	13.4 (11)	12.2 (11)	11.8 (5)	(-9.9)		
	6 weeks	4.5 (11)	8.4 (11)	4.6 (5)			
(Study 12)	3 months	4.2 (10)	8.0 (11)	9.2 (5)			
	6 months	7.5 (10)	10.7 (10)	9.0 (5)			
	12 months	4.5 (10)	8.0 (10)	9.8 (5)			
	24 months	6.6 (8)	8.0 (10)	7.0 (4)			
	No differences in improvement in leg pain between groups.						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary				Neurological results from published summary			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA	%Overall Neuro Success (n):				%Overall Neuro Success (n):			
rhBMP-2/BCP US Pilot RCT	6 weeks	100 (11)	100 (11)	100 (5)	6 weeks			
	3 months	90.9 (11)	100 (11)	100 (5)	3 months	NR	NR	NR
(Study 12)	6 months	100 (11)	100 (10)	100 (5)	6 months			
	12 months	100 (10)	90.0 (10)	100 (5)	12 months			
	24 months	87.5 (8)	100 (10)	100 (4)	24 months			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary				Radiologic fusion results from published study			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	% Radiographic Fusion (n): 6 months 12 months 24 months	 88.9 (9) 80.0 (10) 70.0 (10)	 100 (9) 100 (10) 90.9 (11)	 40.0 (5) 40.0 (5) 100 (3)	% Radiographic Fusion (n): 6 months 12 months 24 months	 100 (9)	 100 (11)	 40 (5)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data				Overall success in published study
Boden, 2002 USA		BMP Only	BMP/ TSRH	Control	
rhBMP-2/BCP US Pilot RCT (Study 12)	% Overall Success (based on success from ODI, Neurological status, Fusion, Second Surgery Failure, Serious Associated Adverse Events) (n)				Not Reported
	6 months	70.0 (10)	55.6 (9)	20.0 (5)	
	12 months	70.0 (10)	40.0 (10)	20.0 (5)	
	24 months	60.0 (10)	45.5 (11)	66.7 (3)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data				Additional surgeries in published study			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA	Number of patients with surgeries:				Number of patients with surgeries:			
rhBMP-2/BCP US Pilot RCT	Revisions	2	0	0	Revisions	2	1	0
	Removals	0	1	0	Removals	0	1	0
(Study 12)	Supplemental Fixations	0	0	0	Supplemental Fixations	0	0	0
	Reoperations	0	0	0	Reoperations	1	1	0
					One patient in the BMP/TSRH group had a revision decompression involving removal of the internal fixation and is counted as 1 revision and 1 removal. Two patients, one in the BMP Only group and one in the BMP/TSRH group had evacuation of hematomas in the immediate post operative period, which are counted as reoperations.			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary				Employed postoperatively from published study		
Boden, 2002 USA		BMP Only	BMP/TSRH	Control			
rhBMP-2/BCP US Pilot RCT	% Working (n)				% Working (n)	NR	NR
	Preop	54.5 (11)	54.5 (11)	0 (5)	Preop		
	6 weeks	9.1 (11)	0 (11)	0 (5)	6 weeks		
(Study 12)	3 months	9.1 (11)	18.2 (11)	0 (5)	3 months		
	6 months	40.0 (10)	30.0 (10)	20.0 (5)	6 months		
	12 months	40.0 (10)	30.0 (10)	20.0 (5)	12 months		
	24 months	50.0 (8)	40.0 (10)	25.0 (4)	24 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days				Hospitalization days from published study			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT (Study 12)	Hospitalization Days	4	3.3	4.4	Hospitalization Days	4	3.3	4.4

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events				Selected adverse events from case histories				Adverse events from published study			
		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control		BMP Only	BMP/ TSRH	Control
Boden, 2002 USA	Patients Reporting Event (n):				Patients Reporting Event (n):				Patients Reporting Event (n):			
rhBMP-2/BCP US Pilot RCT	Anatomic Difficulty	0	0	0	Wound Infection	1	0	0	Anatomic Difficulty			
	Back and/or Leg Pain	3	5	0	Wound Dehiscence	0	0	0	Back and/or Leg Pain	1	1	
(Study 12)	Cancer	0	0	0	Urinary Retention	0	0	1	Cancer			
	Cardiovascular	0	1	0	Retrograde Ejaculation	0	0	0	Cardiovascular			
	Death	0	0	0	Cancer	0	0	0	Death			
	Dural Injury	0	2	0					Dural Injury			
	Dysphagia/Dysphonia	0	1	0					Dysphagia/Dysphonia			
	Gastrointestinal	1	2	1					Gastrointestinal			
	Graft Site Related	0	0	0					Graft Site Related			
	Implant Displaced/ Loosened	0	0	0					Implant Displaced/Loosened			
	Infection	2	0	0					Infection			
	Malpositioned Implant	0	0	0					Malpositioned Implant			
	Neurological	2	0	0					Neurological		1	
	Non-Union	1	0	1					Non-Union			
	Other	2	4	2					Other	1	1	
	Other Pain	2	1	0					Other Pain			
	Respiratory	1	0	0					Respiratory			
	Retrograde Ejaculation	0	0	0					Retrograde Ejaculation			
	Spinal Event	0	2	0					Spinal Event			
	Subsidence	0	0	0					Subsidence			
	Trauma	1	1	0					Trauma			
	Urogenital	0	0	1					Urogenital			
	Vascular Intra-Op	0	0	0					Vascular Intra-Op			
	Vertebral Fracture	0	0	0					Vertebral Fracture			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)	ALIF (multicenter, prospective, randomized, nonblinded, trial) 24 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 35 -≤ Grade 1 spondylolisthesis -Single-level DDD from L4-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion ->40% over ideal weight -Has osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. Open anterior interbody implantation of the rhBMP-2/ACS/LT device B. Open anterior interbody implantation of the LT-CAGE device filled with autogenous bone	Randomized: Total N = 279, BMP=143, Control=136 Analyzed: BMP 125 to 143, Control 111 to 136 Failures: BMP 9 (3 additional failures after 24 months), Control 12 (2 additional failures after 24 months) Not analyzed at 24 months: BMP 6.3%, Control 8.8%		**BMP**	**Control**
					% Low Profile Brace:	51.4	51.9
					% High Profile Brace:	7.1	3.8
					% Corset:	34.3	35.3
					% Other	7.1	9.0

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)		**BMP**	**Control**		**BMP**	**Control**
	Age	43.3	42.3	Prior Tobacco:	32.9	36.0
	Height	68.1	68.1	Alcohol use:	27.3	31.6
	Weight	179.1	181.1	Prior Back Surgery:	37.8	40.4
	% Male	54.5	50.0	Diabetic:	4.2	0.7
	% White	88.8	81.6	% not taking Non Narcotic:	44.1	44.9
	% Married	66.4	66.9	% not taking Weak Narcotic:	46.2	50.7
	% ED>HS	59.4	58.5	% not taking Strong Narcotic:	78.3	75.7
	% Working	46.9	36.8	% not taking Muscle Relaxer:	68.5	72.8
	% Worker's Comp	32.9	34.6			
	% Spinal Litigation	11.9	16.2	Characteristics of Degenerative Disc Disease:		
				%Instability:	7.7	7.4
				%Osteophytes:	28.7	21.3
				%↓Disc Height:	88.8	94.1
				%Thick Ligaments:	21.0	17.6
				%Disc Herniation:	55.9	47.8
				%Facet Joint Degeneration:	25.2	20.6
				% ≥ 3 of above:	31.1	32.4

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	ODI Scores (n):			ODI Scores:		
	Preop	53.7 (143)	55.1 (136)	Preop	53.7 (143)	55.1 (136)
	6 weeks	42.1 (140)	41.4 (131)	6 weeks	42.1 (140)	41.4 (131)
	3 months	33.4 (141)	34.2 (134)	3 months	33.5 (141)	34.2 (134)
	6 months	29.3 (136)	29.4 (131)	6 months	29.3 (136)	29.4 (131)
(Study 2)	12 months	25.5 (130)	25.6 (125)	12 months	25.5 (130)	25.6 (125)
	24 months	23.9 (124)	23.7 (111)	24 months	23.9 (122)	23.8 (108)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)		**BMP**	**Control**	None Reported
	SF-36 MCS:			
	Preop	44.1 (142)	41.1 (136)	
	6 weeks	47.6 (138)	47.1 (130)	
	3 months	50.9 (140)	48.5 (133)	
	6 months	49.6 (136)	49.0 (131)	
	12 months	49.8 (131)	49.7 (125)	
	24 months	50.6 (123)	49.8 (111)	
	SF-36 PCS:			
	Preop	27.2 (142)	29.4 (136)	
	6 weeks	32.5 (138)	32.7 (130)	
	3 months	36.6 (140)	35.9 (133)	
	6 months	39.4 (136)	38.6 (131)	
	12 months	41.3 (131)	40.8 (125)	
	24 months	42.4 (123)	42.2 (111)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	Back Pain Scores (n)			Back Pain Scores (n)		
	Preop	15.8 (143)	16.1 (136)	Preop	15.8 (143)	16.1 (136)
	6 weeks	9.3 (139)	8.8 (132)	6 weeks	9.3 (139)	8.8 (132)
	3 months	8.7 (140)	9.0 (134)	3 months	8.7 (140)	9.0 (134)
(Study 2)	6 months	8.6 (136)	8.9 (131)	6 months	8.6 (136)	8.9 (131)
	12 months	8.0 (129)	8.4 (125)	12 months	8.0 (129)	8.4 (125)
	24 months	7.4 (124)	7.9 (111)	24 months	7.3 (122)	7.9 (108)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	Leg Pain Scores (n)			Leg Pain Scores (n)		
	Preop	12.5 (143)	12.4 (136)	Preop	12.5 (143)	12.5 (136)
	6 weeks	7.5 (139)	8.4 (132)	6 weeks	7.5 (139)	8.4 (132)
	3 months	6.8 (140)	6.8 (134)	3 months	6.8 (140)	6.8 (134)
(Study 2)	6 months	6.3 (136)	6.3 (131)	6 months	6.3 (136)	6.3 (131)
	12 months	6.3 (129)	6.6 (125)	12 months	6.3 (129)	6.6 (125)
	24 months	6.3 (124)	6.2 (111)	24 months	6.3 (122)	6.3 (108)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)		**BMP**	**Control**		**BMP**	**Control**
	% Overall Neuro Success (n):			% Overall Neuro Success (n):		
	6 weeks	80.3 (137)	83.7 (129)			
	3 months	84.4 (141)	77.4 (133)	6 weeks	80.3 (137)	83.7 (129)
	6 months	77.9 (136)	80.9 (131)			
	12 months	81.8 (132)	84.7 (124)	3 months	84.4 (141)	77.4 (133)
	24 months	82.3 (124)	83.8 (111)			
					77.9 (136)	80.9 (131)
				6 months		
					81.8 (132)	84.7 (124)
				12 months	82.8 (122)	83.8 (108)
				24 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)		**BMP**	**Control**		**BMP**	**Control**
	%Radiographic Fusion (n): 6 months 12 months 24 months	97.0 (132) 96.9 (131) 94.6 (130)	95.8 (120) 92.6 (121) 89.1 (119)	% (n) Radiographic Fusion: 6 months 12 months 24 months	97.0 (128/132) 96.9 (127/131) 94.5 (120/127)	95.8 (115/120) 92.6 (112/121) 88.7 (102/115)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study
Burkus, 2002 USA		**BMP**	**Control**	
2-Infuse-LT-Cage_ Open_Pivotal	% Overall Success (n)			Not reported
(Study 2)	6 months	51.9 (135)	53.7 (121)	
	12 months	59.7 (134)	60.8 (125)	
	24 months	58.6 (133)	56.6 (122)	
	Intent to treat analysis with all missing data considered as failure and serious AEs and second surgery failures not taken into account:			
	6 months	NR	NR	
	12 months	55.9 (143)	55.9 (136)	
	24 months	54.5 (143)	50.7 (136)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	Number of patients with surgeries:			Number of patients with surgeries:		
	Revisions	0	0	Revisions	0	0
	Removals	2	0	Removals	2	0
	Supplemental Fixations	10	15	Supplemental Fixations	9	15
(Study 2)	Reoperations	6	4	Reoperations	NR	NR
	1 BMP patient had both a removal and a supplemental fixation during the second surgery.			In 90% of these patients (7/7 in the BMP group and 11/13 in the Control group) the fusion was radiographically solid at the visit before the supplemental fixation, but posterior instrumentation was inserted by the treating physician based on clinical symptoms of persistent pain. In 53.3% of these patients, pain improved after the second posterior surgical procedure.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	% Working (n)			% Working (n)		
	Preop	46.9 (67)	36.8 (50)	Preop	47.6 (68)	36.8 (50)
	6 weeks	15.6 (22)	12.0 (16)	6 weeks	NR	NR
	3 months	39.0 (55)	28.4 (38)	3 months	38.8 (54)	28.4 (38)
(Study 2)	6 months	50.7 (69)	45.5 (60)	6 months	50.7 (69)	45.5 (60)
	12 months	55.0 (72)	51.2 (64)	12 months	55.0 (72)	50.4 (63)
	24 months	66.1 (82)	56.8 (63)	24 months	66.1 (80)	56.1 (60)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days	Hospitalization days from published study
Burkus, 2002 USA 2-Infuse-LT-Cage_ Open_Pivotal (Study 2)	Not reported	Not reported

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**		**BMP**	**Control**
2-Infuse-LT-Cage_ Open_Pivotal	Patients Reporting Event (n):			Patients Reporting Event (n):			Event:		
	Anatomic Difficulty			Wound Infection			Vascular event	6	5
	Back and/or Leg Pain	0	2	Wound Dehiscence	8	10			
	Cancer	41	34	Urinary Retention	2	0	Retrograde Ejaculation- 6 total, treatment groups not specified	NR	NR
(Study 2)	Cardiovascular	3	1	Retrograde Ejaculation	11	2			
	Death	8	12	Cancer	5	1			
	Dural Injury	1	2	Leg Swelling/Edema	3	1			
	Gastrointestinal	0	1	Osteopenia/Osteoporosis	6	6	Iliac Crest Graft events	NA	8
	Graft Site Related	31	26		2	5			
	Implant Displaced/	0	8						
	Loosened	2	0						
	Infection								
	Malpositioned Implant	18	16						
	Neurological	1	0						
	Non-Union	19	24						
	Other	1	3						
	Other Pain	26	36						
	Respiratory	18	14						
	Retrograde Ejaculation	3	4						
	Spinal Event	5	1						
	Subsidence	23	20						
	Trauma	6	2						
	Urogenital	34	35						
	Vascular Intra-Op	20	12						
	Vertebral Fracture	6	5						
		1	0						
	Total Patients with ≥ 1 Event								
		122	114						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	**Control**
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)	ALIF (Prospective, nonblinded, multicenter trial) 24 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 35* -≤ Grade 1 spondylolisthesis -Single-level DDD from L4-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion ->40% over ideal weight -Has osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. Open anterior interbody implantation of the rhBMP-2/ACS /allograph bone dowels B. Open anterior interbody implantation of allograph bone dowels in which the intramedullary cavity is filled with autogenous bone	Randomized 47 Analyzed in BMP group = 17-24 Analyzed in control group = 15-22 analyzed 1 patient in control group did not receive implant due to sizing issues. 0 patients lost to follow-up in BMP group 1 patient lost to follow-up in control group where LTF is defined as not being seen for two or more consecutive time periods 1 control patient died in house fire 6 months after surgery.	% Low Profile Brace: % High Profile Brace: % Corset: % Other:	NR NR NR NR	NR NR NR NR

Evidence Table 1. Medtronic randomized controlled trials

Author **Year** **Country** **Trial # or Name**
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Burkus, 2002 USA		**BMP n=24**	**Control n=22**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	Age	41.5	45.6			
	Height	67.2	67.0	Prior Tobacco:	33.3	27.3
	Weight	172.7	175.9	Alcohol use:	25.0	27.3
	% Male	33.3	45.5	Prior Back Surgery:	45.8	31.8
	% White	83.3	81.8	Diabetic:	8.3	4.5
	% Married	58.3	63.6	% not taking Non Narcotic:	54.2	31.8
	% ED>HS	50.0	50.0	% not taking Weak Narcotic:	50.0	50.0
	% Working	NR	NR	% not taking Strong Narcotic:	83.3	90.9
	% Worker's Comp	20.8	31.8	% not taking Muscle Relaxer:	70.8	63.6
	% Spinal Litigation	16.7	18.2			
				Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	ODI Scores (n):			ODI Scores:		
	Preop	52.4 (24)	55.3 (22)	Preop	52.4	55.3
	6 weeks	39.9 (24)	47.2 (21)	6 weeks	39.9	47.2
	3 months	29.0 (24)	42.0 (21)	3 months	29.0	42.0
	6 months	21.4 (24)	34.4 (20)	6 months	21.4	34.4
	12 months	20.8 (24)	30.0 (19)	12 months	20.8	30.0
	24 months	18.9 (24)	32.8 (17)	24 months	18.9	32.8
	48 months	30.3 (18)	36.4 (18)	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	SF-36 MCS:			SF-36 MCS:	shown in figure form	shown in figure form
	Preop	42.8 (24)	43.1 (22)	Preop		
	6 weeks	46.7 (23)	45.1 (21)	6 weeks		
	3 months	48.2 (24)	49.2 (21)	3 months		
	6 months	48.5 (23)	49.4 (20)	6 months		
	12 months	46.9 (24)	47.1 (19)	12 months		
	24 months	51.1 (24)	44.8 (17)	24 months		
	48 months	46.2 (18)	44.3 (18)	48 months		
	72 months	NR	NR	72 months		
	SF-36 PCS:			SF-36 PCS:	shown in figure form	shown in figure form
	Preop	29.6 (24)	29.4 (22)	Preop		
	6 weeks	32.3 (23)	31.9 (21)	6 weeks		
	3 months	37.5 (24)	31.1 (21)	3 months		
	6 months	43.0 (23)	37.1 (20)	6 months		
	12 months	45.6 (24)	40.0 (19)	12 months		
	24 months	45.1 (24)	39.8 (17)	24 months		
	48 months	39.9 (18)	33.8 (18)	48 months		
	72 months	NR	NR	72 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	Back Pain Scores (n)			Back Pain Scores		
	Preop	16.3 (24)	16.3 (22)	Preop	16.3	16.3
	6 weeks	8.9 (24)	10.4 (21)	6 weeks	8.9	10.4
	3 months	7.9 (24)	10.9 (21)	3 months	7.9	10.9
	6 months	6.8 (24)	9.9 (20)	6 months	6.8	9.9
	12 months	7.4 (24)	9.2 (19)	12 months	7.4	9.2
	24 months	7.4 (24)	10.9 (17)	24 months	7.4	10.9
	48 months	10.3 (18)	11.2 (18)	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Burkus, 2002 USA						
Infuse Bone Dowel Pilot RCT (Study 4)		**BMP**	**Control**		**BMP**	**Control**
	Leg Pain Scores (n)			Back Pain Scores		
	Preop	12.8 (24)	14.6 (22)	Preop	12.8	14.6
	6 weeks	7.0 (24)	8.8 (21)	6 weeks	7.0	8.8
	3 months	6.2 (24)	8.3 (21)	3 months	6.2	8.3
	6 months	5.0 (24)	6.1 (20)	6 months	5.0	6.1
	12 months	5.5 (24)	8.1 (19)	12 months	5.5	8.1
	24 months	6.3 (24)	11.5 (17)	24 months	6.3	11.5
	48 months	9.8 (18)	10.4 (18)	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	%Overall Neuro Success (n):			%Overall Neuro Success:		
	6 weeks	87.5 (24)	90.0 (20)	6 weeks	87.5 (24)	90.0 (20)
	3 months	87.5 (24)	95.2 (21)	3 months	87.5 (24)	95.2 (21)
	6 months	87.5 (24)	89.5 (19)	6 months	87.5 (24)	89.5 (19)
	12 months	95.8 (24)	84.2 (19)	12 months	95.8 (24)	84.2 (19)
	24 months	91.3 (23)	73.3 (15)	24 months	87.5 (24)	73.3 (15)
	48 months	84.2 (19)	77.8 (18)	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	%Radiographic Fusion (n):			%Radiographic Fusion:		
	6 months	90.5 (21)	65.0 (20)	6 months	90.5	65.0
	12 months	100.0 (24)	89.5 (19)	12 months	100.0	89.5
	24 months	100.0 (24)	68.4 (19)	24 months	100.0	68.4
	48 months	94.1 (17)	70.6 (17)	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	%Overall Success (n):			Not Reported	NR	NR
	6 months	63.6 (22)	40.0 (20)			
	12 months	79.2 (24)	45.0 (20)			
	24 months	70.8 (24)	31.6 (19)			
	48 months	42.1 (19)	26.3 (19)			
	72 months	NR	NR			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
Burkus, 2002 USA		**BMP**	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	Number of patients with surgeries:			Number of patients with surgeries:		
	Revisions	0	0	Revisions	0	0
	Removals	0	0	Removals	0	0
	Supplemental Fixations	1	4	Supplemental Fixations	1	3
	Reoperations	0	1	Reoperations	0	1
	"One investigational patient had a supplemental fixation with the 24 month time period, but is not classified as a second surgery failure until the 48 month time period because the second surgery occurred after the 24 month evaluation."					

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	Working (n)			% Working (n)		
	Preop	11	9	Preop	45.8	40.9
	6 weeks	3	2	6 weeks	12.5	9.5
	3 months	10	4	3 months	41.7	18.2
	6 months	14	6	6 months	58.3	30.0
	12 months	15	7	12 months	62.5	36.8
	24 months	16	7	24 months	66.7	35.0
	48 months	14	7	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
Burkus, 2002 USA						
		BMP	**Control**		**BMP**	**Control**
Infuse Bone Dowel Pilot RCT (Study 4)	Hospitalization days	3.4	3.7	Hospitalization days	3.4	3.7

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Burkus, 2002 USA Infuse Bone Dowel Pilot RCT (Study 4)		**BMP**	**Control**		**BMP**	**Control**		**BMP**	**Control**
	Adverse Events* (n):			Patients Reporting Event (n):			"No unanticipated adverse events that were related to the use of InFUSE Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study." No adverse events were reported.	NR	NR
	Anatomic Difficulty	0	0	Wound Infection	0	1			
	Back and/or Leg Pain	9	3	Wound Dehiscence	0	0			
	Cancer	1	0	Urinary Retention	0	0			
	Cardiovascular	1	0	Retrograde Ejaculation	0	0			
	Death	0	1	Cancer*	2	0			
	Dural Injury	0	0	Leg Swelling/Edema	0	2			
	Gastrointestinal	2	3	Osteopenia/Osteoporosis	0	1			
	Implant Displaced	1	0						
	Infection	0	1	Medtronic reports not learning of a breast cancer patient until approximately 4 years following the original surgery. One patient developed thyroid cancer which was reported by Medtronic.					
	Malpositioned Implant	0	0						
	Neurological	4	1						
	Non-Union	1	6						
	Other	3	6						
	Other Pain	7	3						
	Respiratory	0	0						
	Retrograde Ejaculation	0	0						
	Spinal Event	5	4						
	Subsidence	0	0						
	Trauma	5	8						
	Urogenital	3	1						
	Vascular Intra-Op	2	3						
	Vertebral Fracture	0	0						
	Total Events	44	40						
	*Number of events instead of number of patients with events is reported here as data reported to FDA does not allow calculation of cumulative patients.								

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions	BMP	Control
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)	PLF (Prospective, randomized, multicenter, pilot trial) 2-year	Inclusion Criteria: -Discogenic back pain -preoperative Oswestry score ≥ 30 -≤ Grade 1 spondylolisthesis -Single-level DDD from L1-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion -Has osteopenia, osteoporosis, or osteomalacia -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. INFUSE bone graft/ACS/MasterGraft granules as a bulking agent to provide compression resistance in posterolateral fusion with titanium CD Horizon Spinal System B. Autogenous iliac crest bone graft in conjunction with titanium CD Horizon Spinal System	Randomized: Total N=50; BMP=27; Control = 23 Analyzed: BMP=22; Control=18 Withdrawn: BMP=2 (did not have surgery); Control=2 (had different procedure) Failures: BMP=2: Control=2 Death: BMP=1 Lost to follow-up: BMP=0; Control=1 patient without 24 month evaluation	% Low Profile Brace: % High Profile Brace: % Corset: % Other % None	28.0 20.0 36.0 12.0 4.0	23.8 42.9 23.8 9.5 0.0

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	Age	55.9	56.9			
	Height	65.6	66.8	Prior Tobacco:	24.0	23.8
	Weight	176.0	184.9	Alcohol use:	20.0	28.6
	% Male	40.0	42.9	Prior Back Surgery:	24.0	28.6
	% White	92.0	90.5	Diabetic:	0	14.3
	% Married	80.0	66.7	% not taking Non Narcotic:	48.0	52.4
	% ED>HS	52.0	52.4	% not taking Weak Narcotic:	40.0	38.1
	% Working	28.0	42.9	% not taking Strong Narcotic:	80.0	90.5
	% Worker's Comp*	0	19.0	% not taking Muscle Relaxer:	64.0	76.2
	% Spinal Litigation	12.0	0			
				Characteristics of Degenerative Disc Disease:		
	* p=0.037			%Instability:	24.0	9.5
				%Osteophytes:	36.0	38.1
				%↓Disc Height:	76.0	81.0
				%Thick Ligaments:	48.0	38.1
				%Disc Herniation:	92.0	100
				%Facet Joint Degeneration:	40.0	38.1
				% ≥ 3 of above:	64.0	52.4

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
Dawson, 2009 USA		**BMP**	**Control**		**BMP**	**Control**
Mastergraft Pilot	ODI Scores (n):			ODI Scores (n):		
	Preop	52.1 (25)	49.7 (21)	Preop	NR	NR
CD HORIZON	6 weeks	39.0 (24)	37.1 (21)	6 weeks	12	13
	3 months	30.0 (24)	30.1 (21)	3 months	21	20
(Study 8)	6 months	28.7 (24)	30.2 (21)	6 months	22	20
	12 months	24.1 (23)	27.9 (21)	12 months	27	22
	24 months	22.8 (23)	26.1 (20)	24 months	28	23
	36 months	29.7	15.3 (21)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				Mean improvements from baseline		
				p=0.953	Improved 28.3 points over preop at 24 months	Improved 23 points over preop at 24 months

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	SF-36 MCS:			SF-36 MCS:		
	Preop	43.8 (25)	46.5 (21)	Preop	NR	NR
	6 weeks	45.5 (24)	46.6 (21)	6 weeks	NR	NR
	3 months	47.1 (24)	48.6 (21)	3 months	NR	NR
	6 months	48.5 (24)	44.9 (21)	6 months	NR	NR
	12 months	48.2 (23)	49.4 (21)	12 months	NR	NR
	24 months	49.6 (23)	45.5 (20)	24 months	NR	NR
	36 months	46.8 (5)	54.1 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
	SF-36 PCS:			SF-36 PCS:		
	Preop	25.8 (25)	26.5 (21)	Preop	NR	NR
	6 weeks	31.8 (24)	31.2 (21)	6 weeks	NR	NR
	3 months	34.5 (24)	34.9 (21)	3 months	NR	NR
	6 months	37.0 (24)	36.7 (21)	6 months	NR	NR
	12 months	37.9 (23)	36.5 (21)	12 months	NR	NR
	24 months	38.4 (23)	36.6 (20)	24 months	NR	NR
	36 months	33.0 (5)	39.1 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				mean improvement in PCS is reported at 24 mo only BMP=13.9, Control=9.9, p=0.927)		
				mean improvement in physical functioning subscale at 24 mo BMP=36.3, Control=18.5, p=0.200)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	Back Pain Scores (n)			Back Pain Scores (n)		
	Preop	66.1 (25)	62.2 (21)	Preop	NR	NR
	6 weeks	19.0 (24)	22.2 (21)	6 weeks	NR	NR
	3 months	21.8 (24)	22.0 (21)	3 months	NR	NR
	6 months	16.7 (24)	24.0 (21)	6 months	NR	NR
	12 months	21.2 (23)	22.9 (21)	12 months	NR	NR
	24 months	17.3 (23)	25.7 (20)	24 months	NR	NR
	36 months	30.4 (5)	20.0 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
					mean improvement in back pain scores at 24 mo, BMP=9.6	mean improvement in back pain scores at 24 mo, Control=7.2 (p=0.664)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	Leg Pain Scores (n)			Leg Pain Scores (n)		
	Preop	57.2 (25)	52.8 (21)	Preop	NR	NR
	6 weeks	13.0 (24)	19.9 (21)	6 weeks	NR	NR
	3 months	14.5 (24)	17.1 (21)	3 months	NR	NR
	6 months	15.6 (24)	20.7 (21)	6 months	NR	NR
	12 months	20.2 (23)	20.0 (21)	12 months	NR	NR
	24 months	15.1 (23)	22.0 (20)	24 months	NR	NR
	36 months	42.8 (5)	7.0 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
					mean improvement in leg pain scores at 24 mo, BMP=9.3	mean improvement in leg pain scores at 24 mo, Control=7.2 (p=0.892)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	%Overall Neuro Success (n):			%Overall Neuro Success (n):		
	6 weeks	91.7 (24)	95.2 (21)	6 weeks	NR	NR
	3 months	87.5 (24)	90.5 (21)	3 months	NR	NR
	6 months	100 (24)	85.7 (21)	6 months	NR	NR
	12 months	91.3 (23)	85.7 (21)	12 months	NR	NR
	24 months	95.7 (23)	90.0 (20)	24 months	NR	NR
	36 months	80.0 (5)	100 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	%Radiographic Fusion (n):			%Radiographic Fusion (n):		
	6 months	81.8 (22)	60.0 (20)	6 months	18/22 (81.8)	12/20 (60.0)
	12 months	81.0 (21)	65.0 (20)	12 months	17/21 (81.0)	13/20 (65.0)
	24 months	94.7 (19)	70.0 (20)	24 months	18/19 (94.7)	14/20 (70.0)
	36 months	100 (3)	0 (0)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				p values were 0.160 at 6 months, 0.359 at 12 months, and 0.174 at 24 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	%Overall Success (n)			%Overall Success (n)		
	6 months	62.5 (24)	45.0 (20)	6 months	NR	NR
	12 months	60.9 (23)	52.4 (21)	12 months	NR	NR
	24 months	81.0 (21)	55.0 (20)	24 months	81 (21)	55 (20)
	36 months	NR	NR	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				p=0.345 at 24 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
Dawson, 2009 USA		**BMP**	**Control**		**BMP**	**Control**
Mastergraft Pilot	Number of patients with surgeries:			Number of patients with surgeries:		
	Revisions	2	2	Revisions	1	2
CD HORIZON	Removals	1	0	Removals	1	0
	Supplemental Fixations	0	0	Supplemental Fixations	0	0
(Study 8)	Reoperations	0	1	Reoperations	0	0

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Dawson, 2009 USA		**BMP**	**Control**		**BMP**	**Control**
Mastergraft Pilot	Working (n)			Working (n)		
	Preop	28.0 (25)	42.9 (21)	Preop	NR	NR
CD HORIZON	6 weeks	0 (24)	9.5 (21)	6 weeks	NR	NR
	3 months	12.5 (24)	14.3 (21)	3 months	NR	NR
(Study 8)	6 months	16.7 (24)	28.6 (21)	6 months	NR	NR
	12 months	26.1 (23)	23.8 (21)	12 months	NR	NR
	24 months	34.8 (23)	30.0 (21)	24 months	35% (23)	30% (20)
	36 months	60.0 (5)	33.3 (3)	36 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**
	Hospitalization days	4.0 (25)	4.1 (21)	Hospitalization days p=0.844	4.0 (25)	4.1 (21)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study
Dawson, 2009 USA Mastergraft Pilot CD HORIZON (Study 8)		**BMP**	**Control**		**BMP**	**Control**	
	Adverse Events* (n):			Patients Reporting Event (n):			None reported
	Accidental Injury/Muscle Strain	12	4	Wound Infection	1	2	
				Wound Dehiscence	1	1	There was one reported
	Allergic Reaction	1	0	Urinary Retention	2	0	death in the BMP group but
	Back and/or Leg Pain	16	7	Retrograde Ejaculation	0	0	the reason for the death not
	Cancer	1	0	Cancer	1	0	given.
	Cardiovascular	2	5				
	Dural Injury	2	2				
	Electrolyte Imbalance	0	1				
	Endocrine	0	1				
	Gastrointestinal	4	11				
	Incision Related	1	1				
	Implant Displaced	1	0				
	Infection	5	6				
	Malpositioned Implant	1	0				
	Neck/Arm Pain	3	3				
	Neurological	5	4				
	Non-Union	0	2				
	Other	4	6				
	Other Pain	5	0				
	Respiratory	2	2				
	Skin Disorder	0	2				
	Spinal Event other levels	3	4				
	Spinal Event Target levels	2	0				
	Trauma	1	0				
	Urogenital	2	2				
	Total Events	73	63				
	*Number of events instead of number of patients						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	PLF (Multicenter, prospective, randomized, controlled trial) 60 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 30 -≤ Grade 1 spondylolisthesis -Single-level DDD from L1-S1 -≥ 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Previous fusion surgery at same level -Requires steroids or other medications that might interfere with fusion or bone metabolism -Previous diagnosis of osteopenia or osteomalacia -DEXA scan-confirmed osteoporosis -Has Waddel signs ≥ 3 -History of endocrine or metabolic disorder known to affect osteogenesis -Currently undergoing substance abuse treatment -Previous exposure to BMP	A. Open bilateral posterolateral implantation of the rhBMP-2 2.0 mg/mL (Amplify)/CRM/CD HORIZON® Spinal System B. Bilateral posterolateral implantation of the autogenous bone harvested from the iliac crest with the CD HORIZON® Spinal System			BMP	Control
				Total (BMP/Control): 518 (262/256) randomized 463 patients had surgery: Analyzed: BMP=239; Control=224 Deaths=7	% Low Profile Brace: % High Profile Brace: % Corset: % Other *Note: Protocol recommends use of external orthosis approximately 6 weeks following surgery (pg 34).*	32.6 14.6 32.6 15.1	32.1 11.2 31.3 19.6

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**		**BMP**	**Control**
	Age	53.2	52.3	Prior Tobacco:	26.4	26.3
	Height	67.1	66.8	Alcohol use:	37.7	34.8
	Weight	187.2	188.5	Prior Back Surgery:	30.5	27.7
	% Male	45.2	42.4	Diabetic:	7.1	12.1
	% White	91.2	90.6	% not taking Non Narcotic:	35.3	37.5
	% Married	73.9	69.2	% not taking Weak Narcotic:	51.5	48.2
	% ED>HS	63.2	54.1	% not taking Strong Narcotic:	84.0	81.6
	% Working	34.7	41.1	% not taking Muscle Relaxer:	76.9	75.3
	% Worker's Comp	11.3	12.5			
	% Unresolved spinal Litigation	2.5	6.7	Characteristics of Degenerative Disc Disease:		
				%Instability:	12.6	10.7
				%Osteophytes:	23.0	26.8
				%↓Disc Height:	59.8	60.7
				%Thick Ligaments:	20.1	21.9
				%Disc Herniation:	86.2	89.7
				%Facet Joint Degeneration:	41.0	47.3
				% ≥ 3 of above:	39.3	42.8

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**		**BMP**	**Control**
	ODI Scores (n):			Improvement in mean ODI Scores plotted on a graph for 5 time points between 2 months and 24 months. Scores were similar in both groups over all time intervals.		
	Preop	49.9 (239)	51.6 (224)			
	6 weeks	37.1 (231)	37.5 (214)			
	3 months	27.8 (229)	30.2 (213)			
	6 months	24.2 (226)	27.0 (206)			
	12 months	23.2 (223)	26.0 (203)			
	24 months	22.9 (208)	26.4 (183)			
	36 months	24.8 (172)	27.0 (164)			
	48 months	28.4 (104)	29.1 (95)			
	60 months	24.5 (169)	27.0 (149)			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**	
	SF-36 PCS:			Only reported mean PCS Scores plotted on a graph. Scores were similar in both groups over all time intervals between 0 and 25 months.
	Preop	27.8 (236)	27.4 (224)	
	6 weeks	31.6 (228)	31.9 (212)	
	3 months	37.4 (239)	36.1 (210)	
	6 months	40.7 (224)	38.4 (206)	
	12 months	41.5 (223)	39.1 (201)	
	24 months	40.9 (207)	39.7 (183)	
	36 months	39.6 (171)	37.8 (162)	
	48 months	37.9 (103)	36.8 (94)	
	60 months	40.4 (168)	37.8 (148)	
	SF-36 MCS:			
	Preop	43.9 (236)	42.9 (224)	
	6 weeks	48.4 (228)	47.4 (212)	
	3 months	49.6 (228)	49.4 (210)	
	6 months	49.4 (224)	49.8 (206)	
	12 months	49.4 (223)	49.0 (201)	
	24 months	50.7 (207)	49.2 (183)	
	36 months	50.3 (171)	49.6 (162)	
	48 months	48.8 (103)	48.7 (94)	
	60 months	49.9 (168)	50.1 (148)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Dimar, 2009 (2-year results) USA		**BMP**	**Control**		**BMP**	**Control**
Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Preop	15.6 (238)	15.8 (224)	Preop	15.6	15.8
	6 weeks	8.7 (231)	8.1 (213)	6 weeks	NR	NR
	3 months	7.0 (228)	7.8 (213)	3 months	NR	NR
	6 months	6.8 (226)	7.9 (206)	6 months	NR	NR
	12 months	6.6 (223)	8.1 (203)	12 months	NR	NR
	24 months	7.1 (208)	7.8 (183)	24 months	7.1	7.8
	36 months	7.8 (171)	8.8 (164)	36 months	NR	NR
	48 months	8.7 (104)	9.6 (94)	48 months	NR	NR
	60 months	8.0 (169)	9.0 (149)	60 months	NR	NR
				Both groups showed similar improvements over all time intervals (Figure 3)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Dimar, 2009 (2-year results) USA		**BMP**	**Control**		**BMP**	**Control**
Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Preop	14.0 (238)	14.0 (238)	Preop	14.0	14.0
	6 weeks	6.1 (231)	5.6 (213)	6 weeks	NR	NR
	3 months	5.6 (229)	5.8 (213)	3 months	NR	NR
	6 months	5.8 (226)	5.9 (206)	6 months	NR	NR
	12 months	6.1 (223)	6.3 (203)	12 months	NR	NR
	24 months	6.2 (208)	6.7 (183)	24 months	6.2	6.7
	36 months	7.1 (171)	7.1 (164)	36 months	NR	NR
	48 months	7.9 (104)	7.2 (94)	48 months	NR	NR
	60 months	6.9 (169)	7.2 (149)	60 months	NR	NR
				Both groups showed similar improvements over all time intervals (Figure 4)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**			
	% Overall Neuro Success (n):			Not reported	NR	NR
	6 weeks	NR	NR			
	3 months	NR	NR			
	6 months	87.3 (200)	87.9 (182)			
	12 months	87.6 (197)	88.7 (180)			
	24 months	87.0 (180)	84.2 (154)			
	36 months	87.8 (151)	82.2 (134)			
	48 months	87.6 (92)	80.2 (77)			
	60 months	87.6 (148)	83.2 (124)			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
		BMP	**Control**		**BMP**	**Control**
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	% Radiographic Fusion (n):			% Radiographic Fusion (n):		
	6 weeks	NR	NR	6 weeks	NR	NR
	3 months	NR	NR	3 months	NR	NR
	6 months	79.1 (196)	65.3 (176)	6 months	79 (196)	65 (176)
	12 months	87.5 (208)	82.5 (183)	12 months	88 (208)	83 (183)
	24 months	95.9 (194)	89.3 (169)	24 months	96 (194)	89 (169)
	36 months	97.0 (135)	92.6 (122)	36 months	NR	NR
	48 months	95.7 (94)	87.5 (72)	48 months	NR	NR
	60 months	97.1 (138)	92.0 (113)	60 months	NR	NR
				p=0.002 at 6 months p=0.107 at 12 months p=0.014 at 24 months		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**			
	% Overall Success (n):			Not Reported	NR	NR
	6 weeks					
	3 months	NR	NR			
	6 months	NR	NR			
	12 months	50.0 (204)	40.2 (189)			
	24 months	54.7 (214)	53.8 (197)			
	36 months	60.0 (200)	55.5 (182)			
	48 months	50.0 (152)	44.8 (143)			
	60 months	48.5 (103)	32.5 (83)			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
		BMP	**Control**		**BMP**	**Control**
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Number of patients with surgeries (total through 60 months):			Number of patients with surgeries through 24 months:		
	Revisions	6	6	Revisions	4	4
	Removals	26	37	Removals (nonelective)	10	23
	Supplemental Fixations	6	11	Supplemental Fixations	6	9
	Reoperations	14	15	Reoperations	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**		**BMP**	**Control**
	Working (n)					
	Preop	83	92	% Return to work at 24 months (N)	42 (207)	48 (184)
	6 weeks	22	17			
	3 months	53	57			
	6 months	77	86			
	12 months	93	95			
	24 months	89	89			
	36 months	73	78			
	48 months	47	45			
	60 months	75	72			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
		BMP	Control		BMP	Control
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Hospital stay (days)	4.1	4	Hospital stay (days)	4.1	4

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Dimar, 2009 (2-year results) USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)		**BMP**	**Control**		**BMP**	**Control**		**BMP**	**Control**
	Adverse Events* (n):			Patients Reporting Event (n):			Any Adverse Events ≤ 24		
	Anatomic Difficulty	1	0	Wound Infection			Months (n):		
	Back and/or Leg Pain	216	183	Wound Dehiscence	2	24	Anatomic Difficulty	1	0
	Cancer	15	5	Urinary Retention	0	2	Back and/or Leg Pain	104	90
	Cardiovascular	108	88	Retrograde Ejaculation	1	4	Cancer	8	2
	Death	7	8	Cancer	0	0	Cardiovascular	52	54
	Dural Injury	15	20		4	5	Death	3	4
	Gastrointestinal	86	74				Dural Injury	14	18
	Implant Displaced	1	2				Gastrointestinal	37	33
	Infection	64	67				Implant Displaced and/or loosening	1	3
	Malpositioned Implant	5	2				Infection	39	45
	Neurological	120	97				Malpositioned Implant	5	2
	Non-Union	6	19				Neurological	70	60
	Other	193	157				Non-Union	6	18
	Other Pain	58	59				Other	70	62
	Respiratory	21	20				Other Pain	29	28
	Retrograde Ejaculation	NR	NR				Respiratory	15	12
	Spinal Event	50	45				Retrograde Ejaculation	NR	NR
	Subsidence	NR	NR				Spinal Event	17	18
	Trauma	145	108				Subsidence	NR	NR
	Urogenital	42	35				Trauma	67	59
	Vascular Intra-Op	NR	NR				Urogenital	26	21
	Vertebral Fracture	3	4				Vascular Intra-Op	NR	NR
	Total Events	1215	1067				Vertebral Fracture	3	5
	*Number of events instead of number of patients with events is reported here as data reported to FDA does not allow calculation of cumulative patients.								

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	Control Maverick
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	ALIF (Randomized, controlled, multicenter trial) ≥ 24 months	Inclusion Criteria: -Discogenic back pain -Has modic changes, high intensity zones in the annulus, loss of disc height, decreased hydration of the disc -Intact facet joints of involved vertebrae -Preoperative Back and Leg Pain Questionnaire score ≥ 20 -Preoperative Oswestry score ≥ 30 -Single-level DDD from L4-S1 -18 to 70 years -No response to 6 months of conservative treatment Exclusion Criteria: -Any previous anterior lumbar spinal surgery at involved level (including fusion) -Requires steroids or other medications that might interfere with fusion -At involved level: severe pathology of facet joints or rotatory scoliosis -Any posterior element insufficiency -Has osteoporosis -Has spondylolisthesis or spinal canal stenosis -History of endocrine or metabolic disorder known to affect osteogenesis -Has Waddel signs ≥ 3 -Substance abuser -Previous exposure to BMP	A. Open anterior interbody implantation of the INFUSE bone Graft 4.2-12.0 mg/ml/LT-CAGE Lumbar Tapered Fusion Device A. Open anterior interbody implantation of the MAVERICK Total Disc Replacement	577 randomized (172/405) BMP/Maverick: Number analyzed: 38-172/80-405 Number death: 2/6 Number lost to follow-up: NR	% Low Profile Brace: % High Profile Brace: % Corset: % Other	47.1 4.1 31.2 0.6	NR NR NR NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)	Age	40.2	39.9	Prior Tobacco:	32.6	28.9
	Height	67.9	68.0	Alcohol use:	41.9	47.7
	Weight	176.2	177.1	Prior Back Surgery:	27.9	28.4
	% Male	50.0	50.6	Diabetic:	NR	NR
	% White	90.1	89.9	% not taking Non Narcotic:	39.0	28.2
	% Married	73.3	70.6	% not taking Weak Narcotic:	48.0	55.4
	% ED>HS	62.2	63.5	% not taking Strong Narcotic:	69.2	71.0
	% Working	55.8	61.2	% not taking Muscle Relaxer:	57.6	66.0
	% Worker's Comp	17.4	17.8	:		
	% Spinal Litigation	18.0	15.6			
				Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
		BMP	Control Maverick		BMP	Control Maverick
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	ODI Scores (n):			ODI Scores (n):		
	Preop	54.5 (172)	53.3 (405)	Preop	54.5 (172)	53.3 (405)
	6 weeks	41.4 (166)	31.2 (395)	6 weeks	41.4 (NR)	31.2 (NR)
	3 months	32.0 (159)	23.4 (386)	3 months	32.0 (NR)	23.4 (NR)
	6 months	26.8 (158)	20.1 (385)	6 months	26.8 (NR)	20.1 (NR)
	12 months	25.3 (156)	19.2 (389)	12 months	25.3 (NR)	19.2 (NR)
	24 months	24.8 (138)	19.4 (370)	24 months	24.8 (NR)	19.4 (NR)
	36 months	22.2 (108)	18.4 (283)	36 months	NR	NR
	48 months	26.3 (47)	20.4 (94)	48 months	NR	NR
	60 months	22.6 (118)	17.9 (302)	60 months	NR	NR
	84 months	26.6 (37)	19.6 (79)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study		
		BMP	Control Maverick		BMP	Control Maverick
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	SF-36 PCS:			SF-36 PCS:		
	Preop	27.3 (172)	27.9 (404)	Preop	27.3 (NR)	27.9 (NR)
	6 weeks	31.6 (166)	36.6 (391)	6 weeks	31.6 (NR)	36.6 (NR)
	3 months	36.9 (159)	41.4 (385)	3 months	36.9 (NR)	41.4 (NR)
	6 months	39.6 (158)	43.7 (385)	6 months	39.6 (NR)	43.7 (NR)
	12 months	41.6 (156)	44.7 (389)	12 months	41.6 (NR)	44.7 (NR)
	24 months	42.1 (136)	45.1 (370)	24 months	42.1 (NR)	45.1 (NR)
	36 months	42.7 (108)	44.6 (285)	36 months	NR	NR
	48 months	40.6 (47)	44.7 (93)	48 months	NR	NR
	60 months	42.2 (117)	45.4 (301)	60 months	NR	NR
	84 months	39.0 (37)	45.2 (79)	84 months	NR	NR
	SF-36 MCS:			SF-36 MCS:		
	Preop	41.7 (172)	43.2 (404)	Preop	41.7 (NR)	43.2 (NR)
	6 weeks	46.4 (166)	48.9 (391)	6 weeks	46.4 (NR)	48.9 (NR)
	3 months	48.5 (159)	51.3 (385)	3 months	48.5 (NR)	51.3 (NR)
	6 months	49.9 (158)	51.5 (385)	6 months	49.9 (NR)	51.5 (NR)
	12 months	49.3 (156)	51.3 (389)	12 months	49.3 (NR)	51.3 (NR)
	24 months	50.0 (136)	51.4 (370)	24 months	50.0 (NR)	51.4 (NR)
	36 months	51.4 (108)	52.5 (285)	36 months	NR	NR
	48 months	48.8 (47)	52.8 (93)	48 months	NR	NR
	60 months	51.9 (117)	52.7 (301)	60 months	NR	NR
	84 months	48.5 (37)	51.2 (79)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)	Preop	73.3 (172)	71.7 (405)	Preop	73.3 (NR)	71.7 (NR)
	6 weeks	35.1 (165)	21.0 (394)	6 weeks	35.1 (NR)	21.0 (NR)
	3 months	27.0 (159)	17.8 (386)	3 months	27.0 (NR)	17.8 (NR)
	6 months	24.1 (158)	18.1 (386)	6 months	24.1 (NR)	18.1 (NR)
	12 months	24.7 (156)	17.6 (388)	12 months	24.7 (NR)	17.6 (NR)
	24 months	23.6 (138)	18.0 (370)	24 months	23.6 (NR)	18.0 (NR)
	36 months	21.0 (108)	20.0 (284)	36 months	NR	NR
	48 months	30.1 (47)	22.4 (93)	48 months	NR	NR
	60 months	22.7 (118)	18.9 (301)	60 months	NR	NR
	84 months	31.7 (37)	18.7 (78)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)				Leg Pain Scores (n)		
	Preop	42.4 (172)	42.7 (405)	Preop	42.4 (NR)	42.7 (NR)
	6 weeks	24.5 (166)	21.9 (394)	6 weeks	24.5 (NR)	21.9 (NR)
	3 months	17.4 (159)	18.0 (386)	3 months	17.4 (NR)	18.0 (NR)
	6 months	16.8 (158)	15.0 (386)	6 months	16.8 (NR)	15.0 (NR)
	12 months	19.8 (156)	14.7 (388)	12 months	19.8 (NR)	14.7 (NR)
	24 months	19.5 (138)	15.9 (370)	24 months	19.5 (NR)	15.9 (NR)
	36 months	15.3 (108)	16.7 (285)	36 months	NR	NR
	48 months	19.2 (47)	20.3 (93)	48 months	NR	NR
	60 months	16.6 (118)	15.7 (302)	60 months	NR	NR
	84 months	18.4 (37)	18.5 (77)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
		BMP	Control Maverick		BMP	Control Maverick
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	% Overall Neuro Success (n)			% Overall Neuro Success (n)		
	6 weeks	87.0 (169)	88.3 (400)	6 weeks	87.0 (169)	88.3 (400)
	3 months	89.2 (166)	89.8 (391)	3 months	89.2 (166)	89.8 (391)
	6 months	90.7 (161)	92.0 (387)	6 months	90.7 (161)	92.0 (387)
	12 months	91.7 (157)	90.5 (391)	12 months	91.7 (157)	90.5 (391)
	24 months	89.2 (139)	90.8 (370)	24 months	89.2 (139)	90.8 (370)
	36 months	87.2 (109)	90.7 (291)	36 months	NR	NR
	48 months	91.3 (46)	91.6 (95)	48 months	NR	NR
	60 months	87.3 (118)	91.1 (302)	60 months	NR	NR
	84 months	37 (86.5)	96.2 (79)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
Gornet, 2011 USA		**BMP**	**Control Maverick**		**BMP**	**Control Maverick**
MAVERICK™ Disc Pivotal RCT (Study 10)	% Radiographic Fusion (n)		NA	% Radiographic Fusion (n)		**NA**
	6 weeks	NR		6 weeks	NR	
	3 months	NR		3 months	NR	
	6 months	100 (78)		6 months	NR	
	12 months	100 (123)		12 months	100%	
	24 months	100 (103)		24 months	100%	
	36 months	100 (78)		36 months	NR	
	48 months	96.6 (29)		48 months	NR	
	60 months	98.6 (73)		60 months	NR	
	84 months	100 (22)		84 months	NR	

Maverick not fused

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)	% Overall Success (n):			% Overall Success (n):		
	3 months	59.3 (135)	69.9 (332)	3 months	59.3 (135)	69.3 (332)
	6 months	65.6 (128)	76.7 (322)	6 months	65.1 (129)	76.4 (322)
	12 months	63.9 (119)	74.5 (330)	12 months	63.3 (120)	74.2 (330)
	24 months	55.9 (102)	73.7 (312)	24 months	55.3 (103)	73.5 (313)
	36 months	56.8 (74)	70.1 (241)	36 months	NR	NR
	48 months	28.6 (35)	68.7 (83)	48 months	NR	NR
	60 months	62.5 (80)	68.3 (249)	60 months	NR	NR
	84 months	25.0 (16)	64.1 (64)	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study		
		BMP	Control Maverick		BMP	Control Maverick
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Number of patients with surgeries:			Number of patients with surgeries:		
	Revisions	0	0	Revisions	0	0
	Removals	0	2	Removals	0	2
	Supplemental Fixations	15	16	Supplemental Fixations	12	15
	Reoperations	5	25	Reoperations	3	23

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)	Working (n)			Working (% patients, number NR)		
	Preop	96	248	Preop	55.8	61.2
	6 weeks	44	126	6 weeks	26.0	31.5
	3 months	69	213	3 months	41.6	54.3
	6 months	102	268	6 months	63.4	68.7
	12 months	105	282	12 months	66.9	72.1
	24 months	102	274	24 months	73.4	74.1
	36 months	83	224	36 months	NR	NR
	48 months	31	71	48 months	NR	NR
	60 months	86	229	60 months	NR	NR
	84 months	26	51	84 months	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
Gornet, 2011 USA		BMP	Control Maverick		BMP	Control Maverick
MAVERICK™ Disc Pivotal RCT (Study 10)	Hospital stay (days)	2.3	2.2	Hospital stay (days)	2.3	2.2

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)		BMP	Control Maverick		BMP	Control Maverick		BMP	Control Maverick
	Number of patients with Adverse Events up to 24 months/total			Patients Reporting Event (n):			Any Adverse Events ≤ 24 months (n):		
	Anatomic Difficulty	1/1	9/10	Wound Infection			Anatomic Difficulty	1	9
	Back and/or Leg Pain	14/25	34/48	Wound Dehiscence	6	19	Back and/or Leg Pain	14	34
	Cancer	3/3	3/7	Urinary Retention	1	5	Cancer	2	3
	Cardiovascular	8/12	14/27	Retrograde Ejaculation	4	9	Cardiovascular	7	14
	Death	1/2	3/7	Cancer	2	4	Death	1	3
	Dural Injury	NR	NR		3	7	Dural Injury	NR	NR
	Gastrointestinal (ileus+other)	19/27	80/137				Gastrointestinal (ileus+other)	19	80
	Implant Displacement/ loosening/malposition	1/1	1/1				Implant Displacement/ loosening/malposition	1	1
	Infection	12/17	24/37				Infection	12	24
	Malpositioned Implant	NR	NR				Malpositioned Implant	NR	NR
	Neurological	59/76	138/153				Neurological	59	138
	Non-Union	7/8	0/0				Non-Union	7	0
	Other	24/60	75/119				Other	25	75
	Other Pain	11/19	60/80				Other Pain	11	60
	Respiratory	3/7	8/14				Respiratory	3	8
	Retrograde Ejaculation	2/2	4/4				Retrograde Ejaculation	2	4
	Spinal Event	2/3	14/15				Spinal Event	1	14
	Subsidence	14/17	14/21				Subsidence	14	13
	Trauma	53/69	110/143				Trauma	53	109
	Urogenital	16/29	39/54				Urogenital	16	38
	Vascular Intra-Op	8/8	15/15				Vascular Intra-Op	8	15
	Vertebral Fracture	0/9	3/3				Vertebral Fracture	0	3
	Any Events	153/165	345/370				Any Events	153	345

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	**Control**
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)	PLIF (Prospective, randomized, nonblinded, pilot trial) 24 months	<u>Inclusion Criteria:</u> -Discogenic back pain -Preoperative Oswestry score ≥ 35* -≤ Grade 1 spondylolisthesis -Single-level DDD from L2-S1 -At least 18 years of age -No response to 6 months of conservative treatment <u>Exclusion Criteria:</u> -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion ->40% over ideal weight -Has osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. Open posterior interbody implantation of the rhBMP-2/ACS/ NOVUS LC (INTERFIX) B. Open posterior interbody implantation of INOVUS LC (NTERFIX) filled with autogenous bone	16 patients withdrawn after randomization with no data on group assigned (4 patient caged mind, 5 insurance denials, 2 obesity, 2 surgery cancelled due to hold on study, 1 allergic reaction to Ancef, 1 cortico-steroids within one week of surgery, 1 Oswestry score too low). 1 BMP patient did not receive device at surgery; 3 control patients did not received device at surgery.	% Low Profile Brace: % High Profile Brace: % Corset: % Other:	32.4 14.7 32.4 20.6	18.2 21.2 45.5 15.2

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	Age	46.3	46.1			
	Height	67.7	67.0	Prior Tobacco:	52.9	45.5
	Weight	180.5	172.8	Alcohol use:	44.1	27.3
	% Male	50.0	45.5	Prior Back Surgery:	35.3	39.4
	% White	79.4	93.9	Diabetic:	2.9	3.0
	% Married	61.8	72.7	% not taking Non Narcotic:	47.1	48.5
	% ED>HS	41.2	51.6	% not taking Weak Narcotic:	47.1	30.3
	% Working	26.5	45.5	% not taking Strong Narcotic:	82.4	78.8
	% Worker's Comp	23.5	27.3	% not taking Muscle Relaxer:	58.8	51.5
	% Spinal Litigation	8.8	3.0			
				Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary			ODI results from published study		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	ODI Scores (n):			ODI Scores (n):		
	Preop	54.6 (34)	52.7 (33)	Preop	NR	NR
	6 weeks	45.5 (33)	39.4 (31)	6 weeks	less improved	more improved
	3 months	32.8 (33)	33.6 (32)	3 months	more improved	less improved
	6 months	30.2 (32)	31.8 (31)	6 months	more improved	less improved
	12 months	25.9 (29)	31.7 (27)	12 months	more improved	less improved
	24 months	26.4 (25)	27.5 (28)	24 months	improved 29.6	improved 24.9
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				more/less improved is relative to the contrasting group; Differences not significant.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary			SF-36 results from published study		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	SF-36 MCS:			SF-36 MCS:		
	Preop	44.6 (34)	43.6 (32)	Preop	NR	NR
	6 weeks	47.9 (32)	45.9 (31)	6 weeks	NR	NR
	3 months	49.4 (33)	48.6 (32)	3 months	NR	NR
	6 months	47.7 (32)	47.0 (30)	6 months	NR	NR
	12 months	47.4 (28)	45.8 (27)	12 months	NR	NR
	24 months	50.9 (24)	46.1 (27)	24 months	NR	NR
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
	SF-36 PCS:			SF-36 PCS:		
	Preop	26.5 (34)	26.6 (32)	Preop	more improved	less improved
	6 weeks	31.2 (32)	28.3 (31)	6 weeks	more improved	less improved
	3 months	36.0 (33)	33.6 (32)	3 months	more improved	less improved
	6 months	37.1 (32)	34.2 (30)	6 months	more improved	less improved
	12 months	39.6 (28)	34.2 (27)	12 months	more improved	less improved
	24 months	39.8 (24)	37.3 (27)	24 months	more improved	less improved
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
				More/less improved is relative to the contrasting group.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary			Back pain results from published study		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	Back Pain Scores (n)			Back Pain Scores (n)		
	Preop	16.8 (34)	14.8 (33)	Preop	NR	NR
	6 weeks	10.0 (33)	10.0 (30)	6 weeks	more improved	less improved
	3 months	7.8 (33)	8.5 (31)	3 months	more improved	less improved
	6 months	9.1 (32)	8.1 (31)	6 months	more improved	less improved
	12 months	8.7 (29)	9.6 (27)	12 months	more improved	less improved
	24 months	7.9 (25)	10.0 (28)	24 months	improved 9.0	improved 4.5
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
	BMP group had greater pain reduction at 3 and 24 months from preoperative scores (p=0.048 and 0.009, respectively)			Significant difference in improvement at 24 months (p<0.05)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary			Leg pain results from published study		
Haid, 2004 USA		**BMP**	**Control**		**BMP**	**Control**
Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease	Leg Pain Scores (n)			Leg Pain Scores (n)		
	Preop	15.5 (34)	14.3 (33)	Preop	NR	NR
	6 weeks	7.2 (33)	8.6 (30)	6 weeks	more improved	less improved
	3 months	6.2 (33)	7.5 (31)	3 months	more improved	less improved
	6 months	7.1 (32)	7.7 (31)	6 months	more improved	less improved
	12 months	7.7 (29)	10.1 (27)	12 months	more improved	less improved
	24 months	7.5 (25)	7.8 (28)	24 months	improved 7.7	improved 6.5
	48 months	NR	NR	48 months	NR	NR
(Study 6)	72 months	NR	NR	72 months	NR	NR
	No significant differences between groups			No significant differences between groups		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary			Neurological results from published summary		
Haid, 2004 USA		**BMP**	**Control**		**BMP**	**Control**
Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease	%Overall Neuro Success (n):			%Overall Neuro Success (n):		
	6 weeks	93.8 (32)	100.0 (31)	6 weeks	ND	ND
	3 months	93.8 (32)	96.9 (32)	3 months	ND	ND
	6 months	96.8 (31)	96.9 (32)	6 months	ND	ND
	12 months	92.9 (28)	92.9 (28)	12 months	ND	ND
	24 months	100.0 (26)	100.0 (28)	24 months	100%	100%
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
(Study 6)	No significant differences between groups. Note: Hyporeflexia counted as "normal".			ND = there was no difference between groups		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary			Radiologic fusion results from published study		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	%Radiographic Fusion (n):			%Radiographic Fusion (n):		
	6 months	93.1 (29)	93.1 (29)	6 months	93.1	93.1
	12 months	85.2 (27)	92.0 (25)	12 months	85.2	92.0
	24 months	92.3 (26)	77.8 (27)	24 months	92.3	77.8
	48 months	NR	NR	48 months	NR	NR
	72 months	NR	NR	72 months	NR	NR
	No significant differences between groups.			No significant differences between groups. "This decrease in fusion rate in the investigational group at 12 months appears to be artificially low because seven patients who were evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views of poor-quality films."		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data			Overall success in published study
Haid, 2004 USA		**BMP**	**Control**	
Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease	%Overall Success (n):			Not Reported
	6 months	60.0 (30)	50.0 (30)	
	12 months	55.2 (29)	50.0 (26)	
	24 months	60.7 (28)	42.9 (28)	
	48 months	NR	NR	
	72 months	NR	NR	
(Study 6)	(Overall success means that a patient had successes in fusion, (No Suggestions) pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgery associated, adverse event.")			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data			Additional surgeries in published study
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**	
	Number of patients with surgeries:			Not Reported
	Revisions	1	0	
	Removals	0	0	
	Supplemental Fixations	2	3	
	Reoperations	2	1	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary			Employed postoperatively from published study		
Haid, 2004 USA		**BMP**	**Control**		**BMP**	**Control**
Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease	Working (n)			Working %		
	Preop	9	15	Preop	26.5%	45.5%
	6 weeks	5	3	6 weeks	NR	NR
	3 months	6	7	3 months	NR	NR
	6 months	12	13	6 months	NR	NR
	12 months	14	15	12 months	NR	NR
	24 months	12	14	24 months	35.3% = 12 pts	42.4% = 14 pts
	48 months	NR	NR	48 months	NR	NR
(Study 6)	72 months	NR	NR	72 months	NR	NR
				No significant differences between groups.		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days			Hospitalization days from published study		
Haid, 2004 USA Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease (Study 6)		**BMP**	**Control**		**BMP**	**Control**
	Hospitalization days Not a significant difference. One patient in control group stayed 56 days. Maximum stay in BMP group was 7 days.	3.4 (34)	5.2 (33)	Hospitalization days	3.4	5.2

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories			Adverse events from published study		
Haid, 2004 USA		BMP	Control		BMP	Control		BMP	Control
Interfix Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease	Adverse Events* (n):			Patients Reporting Event (n):			Patients Reporting Event (n):		
	Anatomic Difficulty	1	3	Wound Infection	3	1	Deep Vein Thrombosis	0	1
	Back and/or Leg Pain	13	11	Wound Dehiscence	1	1	Dural Tears	3	2
	Cancer	NR	NR	Urinary Retention	0	4	Neurological complications	16	18
	Cardiovascular	9	11	Retrograde Ejaculation	0	0		24	4
	Death	1	1	Cancer	0	0			
	Dural Injury	3	2	Leg Swelling/Edema	1	0	New bone formation extending outside the disc space and into the spinal canal or neuroforaminal (p<0.0001).		
	Gastrointestinal	11	11	Osteopenia/Osteoporosis	0	0			
(Study 6)	Implant Displaced	NR	NR						
	Infection	8	6						
	Malpositioned Implant	NR	NR						
	Neurological	16	18						
	Non-Union	2	3				"Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence of increase in leg pain from the preoperative state."		
	Other	21	23						
	Other Pain	14	11						
	Respiratory	0	2						
	Retrograde Ejaculation	NR	NR						
	Spinal Event	5	5						
	Subsidence	NR	NR						
	Trauma	8	9						
	Urogenital	1	5				"In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal...No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal."		
	Vascular Intra-Op	NR	NR						
	Vertebral Fracture	NR	NR						
	Total Events	113	121						
	*Number of events instead of number of patients with events is reported here as data reported to FDA does not allow calculation of cumulative patients.								

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
Unpublished study** Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)	ALIF 48 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 35* -≤ Grade 1 spondylolisthesis -Single-level DDD from L4-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion ->40% over ideal weight -Has osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. Open anterior interbody implantation of the rhBMP-2/ACS /allograph bone dowels B. Open anterior interbody implantation of allograph bone dowels in which the intramedullary cavity is filled with autogenous bone	95 patients randomized BMP patients analyzed = 44-55 Control patients analyzed = 22-30 9 patients in BMP group withdrew prior to surgery 1 patient in control group withdrew prior to surgery 3 patients lost to followup in BMP group where LTF is defined as not being seen for two or more consecutive time periods 1 patient lost to followup in control group		**BMP** 45.8 20.8 25.0 8.3	**Control** 45.5 13.6 40.9 0

Evidence Table 1. Medtronic randomized controlled trials

Author **Year** **Country** **Trial # or Name**	
Unpublished study**	
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Unpublished study**		**BMP**	**Control**		**BMP**	**Control**
	Age	39.7	42.1			
Infuse Bone Dowel Pivotal Study	Height	67.0	66.2	Prior Tobacco:	32.7	36.7
	Weight	172.1	171.3	Alcohol use:	18.2	20.0
	% Male	43.6	30.0	Prior Back Surgery:	32.7	33.3
	% White	96.4	86.7	Diabetic:	0	3.3
(enrolled 85 patients prior to termination)	% Married	70.9	70.0	% not taking Non Narcotic:	47.3	53.3
	% ED>HS	49.1	36.7	% not taking Weak Narcotic:	34.5	26.7
	% Working	65.5	53.3	% not taking Strong Narcotic:	92.7	76.7
(Study 5)	% Worker's Comp	32.7	33.3	% not taking Muscle Relaxer:	81.8	60.0
	% Spinal Litigation	5.5	6.7			
				Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary	ODI results from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary	SF-36 results from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Unpublished study**	Not Relevant	Not Relevant
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Unpublished study**	
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Unpublished study**		
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)	Not Relevant	Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary	Neurological results from published summary
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary	Radiologic fusion results from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data	Overall success in published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data	Additional surgeries in published study
Unpublished study** Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		Not applicable

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary	Employed postoperatively from published study
Unpublished study**		Not applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days	Hospitalization days from published study
Unpublished study**		Not Applicable
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events			Selected adverse events from case histories	Adverse events from published study
Unpublished study**		**BMP**	**Control**		
Infuse Bone Dowel Pivotal Study (enrolled 85 patients prior to termination) (Study 5)	Adverse Events* (n):				Not applicable
	Anatomic Difficulty	1	2		
	Back and/or Leg Pain	9	12		
	Cancer	1	0		
	Cardiovascular	3	2		
	Death	NR	NR		
	Dural Injury	NR	NR		
	Gastrointestinal	8	8		
	Graft site related	0	1		
	Implant Displaced	1	0		
	Infection	5	3		
	Malpositioned Implant	NR	NR		
	Neurological	15	4		
	Non-Union	1	3		
	Other	7	11		
	Other Pain	12	4		
	Respiratory	2	4		
	Retrograde Ejaculation	NR	NR		
	Spinal Event	3	1		
	Subsidence	1	0		
	Trauma	10	9		
	Urogenital	7	2		
	Vascular Intra-Op	1	0		
	Vertebral Fracture	NR	NR		
	Total Events	NR	NR		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	**Control**
Unpublished study** Infuse/Inter Fix ALIF Pilot RCT (Study 9)	ALIF ≥ 24 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score ≥ 35 -≤ Grade 1 spondylolisthesis -Single-level DDD from L2-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Other fusion surgery at same level -Requires steroids or other medications that might interfere with fusion ->40% over ideal weight -Has osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated -History of endocrine or metabolic disorder known to affect osteogenesis -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. BMP-2/ACS/LC: Open implantation of 8.4-16.8 mg/ml of BMP-2 B. LC/Bone: Open implantation of NOVUS™ LC device packed with autogenous bone taken from the iliac crest	45 randomized (25/20) BMP/control: Number Analyzed: 23-25/15-20 Number Death: 0/1 Number Failure: 0/2: Number lost to follow-up: 0/2	% Low Profile Brace: % High Profile Brace: % Corset: % Other	64.0 0.0 28.0 8.0	52.6 0.0 42.1 5.3

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Unpublished study**
Infuse/Inter Fix ALIF Pilot RCT (Study 9)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Unpublished study**		**BMP**	**Control**		**BMP**	**Control**
Infuse/Inter Fix ALIF Pilot RCT	Age	45.9	44.9	Prior Tobacco:	40.0	30.0
	Height	66.7	69.2	Alcohol use:	24.0	20.0
	Weight	178.1	189.4	Prior Back Surgery:	44.0	35.0
(Study 9)	% Male	44.0	45.0	Diabetic:	0.0	5.0
	% White	100.0	90.0	% not taking Non Narcotic:	48.0	36.8
	% Married	84.0	80.0	% not taking Weak Narcotic:	56.0	63.2
	% ED>HS	25.0	45.0	% not taking Strong Narcotic:	88.0	100.0
	% Working	NR	NR	% not taking Muscle Relaxer:	72.0	84.2
	% Worker's Comp	24.0	25.0	:		
	% Spinal Litigation	8.0	5.0			
				Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary	ODI results from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		Not Applicable

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary	SF-36 results from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		Not Applicable

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Unpublished study**	
Infuse/Inter Fix ALIF Pilot RCT (Study 9)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary	Neurological results from published summary
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary	Radiologic fusion results from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data	Overall success in published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data	Additional surgeries in published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary	Employed postoperatively from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days	Hospitalization days from published study
Unpublished study**		
Infuse/Inter Fix ALIF Pilot RCT (Study 9)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events	Selected adverse events from case histories	Adverse events from published study
Unpublished study**			
Infuse/Inter Fix ALIF Pilot RCT (Study 9)			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
Unpublished Study** rhBMP-2/BCP Canada Pivotal RCT (Study 13)	PL 72 months	Inclusion Criteria: -Discogenic back pain -Preoperative Oswestry score > 30 -≤ Grade 1 spondylolisthesis -Single-level DDD from L1-S1 -At least 18 years of age -No response to 6 months of conservative treatment Exclusion Criteria: -Previous fusion surgery at same level -Requires medications that might interfere with fusion or bone metabolism -Has osteopenia, osteoporosis, or osteomalacia -Weight > 40% over ideal for age/height -Has Waddel signs ≥ 3 -Tobacco user at time of surgery -Substance abuser -Previous exposure to BMP	A. 2.l mg/ml rhBMP-2BCP posterolateral implantation bilaterally on each side of the spine with either TSRH Spinal System or the CD HORIZON Spinal System B. Posterolateral implantation bilaterally on each side of the spine with autogenous bone from the patient's iliac crest with either TSRH Spinal System or the CD HORIZON Spinal System	Number Randomized: 197 (BMP=98, Control=99) Number Analyzed: BMP=2 to 98, Control=1 to 98 Number Withdrawn: NR Number Lost to follow-up: BMP=1, Control=3		**BMP**	**Control**
					% Low Profile Brace:	9.1	11.5
					% High Profile Brace:	0.0	0.0
					% Corset:	68.8	66.7
					% Other	22.1	21.8

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Unpublished Study**
rhBMP-2/BCP Canada Pivotal RCT (Study 13)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Unpublished Study**		**BMP**	**Control**		**BMP**	**Control**
rhBMP-2/BCP Canada Pivotal RCT (Study 13)	Age	53.0	53.0	Prior Tobacco:	29.6	26.3
	Height	65.9	66.5	Alcohol use:	37.8	44.4
	Weight	177.6	172.1	Prior Back Surgery:	19.4	20.2
	% Male	35.7	48.5	Diabetic:	2.0	6.1
	% White	98.9	95.7	% not taking Non Narcotic:	53.1	52.0
	% Married	72.5	70.5	% not taking Weak Narcotic:	57.1	65.3
	% ED>HS	48.2	37.9	% not taking Strong Narcotic:	64.3	63.6
	% Working	20.4	24.2	% not taking Muscle Relaxer:	74.5	77.6
	% Worker's Comp	11.2	14.1			
	% Spinal Litigation	5.1	3.0	Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary	ODI results from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary	SF-36 results from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Unpublished Study**	
rhBMP-2/BCP Canada Pivotal RCT (Study 13)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary	Neurological results from published summary
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary	Radiologic fusion results from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data	Overall success in published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data	Additional surgeries in published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary	Employed postoperatively from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days	Hospitalization days from published study
Unpublished Study**		
rhBMP-2/BCP Canada Pivotal RCT (Study 13)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events	Selected adverse events from case histories	Adverse events from published study
Unpublished Study**			
rhBMP-2/BCP Canada Pivotal RCT (Study 13)			

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Number randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group	Co-Interventions		
						BMP	**Control**
Unpublished Study** INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)	ACDF 24 months	Inclusion Criteria: -Cervical disk disease -Preoperative Neck Disability score > 30 -Single level requiring fusion from C2-C7 -No previous surgical intervention at involved level -At least 18 years of age -No response to 6 weeks of nonsurgical treatment or presence of progressive symptoms Exclusion Criteria: -Cervical spinal condition requiring surgical treatment other than symptomatic cervical disc disease at the involved level(s) -Requires post-operative medications that interfere with fusion (e.g. steroids, prolonged NSAIDs) -Has received drugs that may interfere with bone metabolism within 2 weeks of surgery (e.g., steroids, methotrexate) -Previous diagnosis of osteopenia, osteomalacia, or osteoporosis -Substance abuser -Previous exposure to BMP	A. Anterior cervical implantation of the InFUSE Bone Graft/CORNERSTONE-SR Allograft Ring/ATLANTIS Anterior Cervical Plate System B. Anterior cervical implantation of CORNERSTONE-SR Allograft Ring/ATLANTIS Anterior Cervical Plate System filled with autogenous bone	Randomized=3 (BMP N=2, Control N=1) No patients withdrawn or lost to follow-up No analysis due to early stopping of trial	Soft collar Hard collar Other None	NR NR NR NR	NR NR NR NR

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name
Unpublished Study**
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical History Baseline Characteristics from FDA data summary			Medical history Baseline characteristics from FDA data summary		
Unpublished Study**		**BMP**	**Control**		**BMP**	**Control**
INFUSE®/CORNERSTONE® ACDF Pivotal RCT	Age	NR	NR	Prior Tobacco:	NR	NR
	Height	NR	NR	Alcohol use:	NR	NR
	Weight	NR	NR	Prior Back Surgery:	NR	NR
	% Male	NR	NR	Diabetic:	NR	NR
	% White	NR	NR	% not taking Non Narcotic:	NR	NR
	% Married	NR	NR	% not taking Weak Narcotic:	NR	NR
	% ED>HS	NR	NR	% not taking Strong Narcotic:	NR	NR
	% Working	NR	NR	% not taking Muscle Relaxer:	NR	NR
	% Worker's Comp	NR	NR			
	% Spinal Litigation	NR	NR	Characteristics of Degenerative Disc Disease:		
				%Instability:	NR	NR
				%Osteophytes:	NR	NR
				%↓Disc Height:	NR	NR
				%Thick Ligaments:	NR	NR
				%Disc Herniation:	NR	NR
				%Facet Joint Degeneration:	NR	NR
				% ≥ 3 of above:	NR	NR
(Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)						

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	ODI Results from FDA data summary	ODI results from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	SF-36 results from FDA data summary	SF-36 results from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from FDA data summary	Back pain results from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Leg pain results from FDA data summary	Leg pain results from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck disability index from FDA summary	Neck disability index from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neck pain score from FDA summary
Unpublished Study**	
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)	

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Arm pain scores from FDA summary	Arm pain scores from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		Not Relevant

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Neurological Status Results from FDA data summary	Neurological results from published summary
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Radiologic fusion results from FDA data summary	Radiologic fusion results from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success FDA summary data	Overall success in published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Additional surgeries from FDA summary data	Additional surgeries in published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Employed postoperatively FDA data summary	Employed postoperatively from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	Hospitalization days	Hospitalization days from published study
Unpublished Study**		
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)		

Evidence Table 1. Medtronic randomized controlled trials

Author Year Country Trial # or Name	FDA adverse events	Selected adverse events from case histories	Adverse events from published study
Unpublished Study**			
INFUSE®/CORNERSTONE® ACDF Pivotal RCT (Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.) (Study 17)			

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the method of randomization adequate?	PUBLICATION Was the method of randomization adequate?	PROTOCOL Was the treatment allocation concealed?	PUBLICATION Was the treatment allocation concealed?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in SAS	Unclear	Probably: "Both the investigator and the patient will be blinded to the randomization until the Informed Consent Form is signed. After the patient signs the informed consent form, the investigator or designee will open the envelope that corresponds to the patient's assigned clinical trial number..."	Unclear
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	Yes; "Patients will be randomized to a randomization schedule generated using the Plan Procedure in Statistical Analysis System (SAS)"	Unclear; "The patients were randomized in a 3:1 investigational: control block fashion to receive anterior lumbar arthrodesis ...Randomization within each site was achieved by the marginal balancing method."	"Following affirmation of eligibility, the investigator or designee will open the envelope that corresponds to the patient's assigned study number to determine if the patient will be randomized into the control or investigational group. **Randomization will be revealed to the patient prior to the patient providing informed consent to enter the study.**"	Unclear
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	Yes; Generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher	NA-unpublished	Yes; Investigator or designee opens envelope corresponding to assigned sequential number	NA-unpublished

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the patient blinded to the intervention?	PUBLICATION Was the patient blinded to the intervention?	PROTOCOL Was the care provider blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	No	No - non-blinded	Surgeon not blinded	Surgeon not blinded
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	No	No - non-blinded	No	No
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	No	NA-unpublished	No	NA-unpublished

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the outcome assessor blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	FDA SUMMARY Was the drop-out rate described and acceptable?	PUBLICATION Was the drop-out rate described and acceptable?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	For fusion: "Independent radiologists who evaluate the radiographs will be blinded to treatment" Other outcomes unclear	For fusion: "Two independent radiologists, blinded to treatment groups, reviewed all the radiographs and CT scans. A third independent, blinded radiologist was used to resolve conflicting fusion findings."	Treatment group: 4/18 (22%) not analyzed at 24 months; Control group: 3/15 (20%) not analyzed at 24 months However, 39% fusion data missing for treatment group vs 27% missing for control group	"Three investigational patients and one control patient were lost to follow-up at 24 months." No explanation for missing data for one investigational patient and two control patients. However, fusion data missing for 44% for treatment group and 33% for control group
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	"Fusion will be determined by an independent evaluator and reported on the Radiographic CT Review form in the Case Report Forms."	"Plain radiographs were evaluated by three blinded radiologists for evidence of fusion, which was defined as …Computed tomography scans were evaluated by three blinded neuroradiologist and two blinded surgeons for evidence of fusion…"	BMP group: 0/11=0% Control group: 1/3=33% (1 patient was considered a failure)	BMP group: 0/11=0% Control group: 1/3=33% (1 patient was considered a failure)
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	Yes; independent radiologists who evaluate the radiographs and CT scans will be blinded to treatment.	NA-unpublished	Unclear; not described	NA-unpublished

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were all randomized participants analyzed in the group to which they were allocated?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?	FDA SUMMARY Are reports of the study free from suggestion of bias?	PUBLICATION Are reports of the study free from suggestion of bias?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	No; missing data is not included and the patient is removed from the numerator and denominator in calculation of percentages. For some outcomes, this greatly overestimates success.	No; missing data is not included and the patient is removed from the numerator and denominator in calculation of percentages. For some outcomes, this greatly overestimates success.	Yes	Did not report percentages of tobacco use by group when other variables reported by percentages as well.
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	Only attrition was 1 fusion failure in control group.	Only attrition was 1 fusion failure in control group.	Yes	Yes
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	No; 89% evaluated for fusion at 24 months; variable for other outcomes	NA-unpublished	Yes	Yes

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	FDA SUMMARY Were co-interventions avoided or similar?	PUBLICATION Were co-interventions avoided or similar?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	Yes, except for Tobacco use: 28% in BMP group vs 47% in control group	Unclear; as no information on those with missing information	Investigational group: **67% soft collar, 28% hard collar**, 6% none Control group: **53% soft collar, 40% hard collar**, 7% none	"Postoperative bracing requirements were left to the discretion of the individual surgeons."
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	No; BMP group weighed 166 lbs on average vs 211 lbs in control group; BMP group 46% male vs 67% in control group; 55% of BMP group employed vs 67% in control group; 9% of BMP group use tobacco vs 33% in control group; 46% of BMP group has history of back surgery vs 0% in control group	Only patient weight listed as statistically significant	BMP Group: Brace 73%, Corset 27%, Other 0% Control group: Brace 67%, Corset 33%; Other 33%	Unclear; NR
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	No; BMP group had significantly more patients with > HS education (82% vs 40%; p=0.021) and fewer with diabetes (4.5% vs 40%; p=0.079)	NA-unpublished	Yes, similar	NA-unpublished

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Was the compliance acceptable in all groups?	PUBLICATION Was the compliance acceptable in all groups?	FDA SUMMARY Was the timing of the outcome assessment similar in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	Unclear; NR	Unclear; NR	Yes	Yes
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	Unclear; NR	Unclear; NR	Yes	Yes
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	Yes; > 80% brace still used at 6 weeks	NA-unpublished	Yes	NA-unpublished

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	RISK OF BIAS Based on all Data	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Baskin, 2003 USA Anterior Cervical Spine N=33 (Study 7)	Moderate (Fair quality) for outcomes other than fusion High (Poor quality) for fusion outcomes due to large amount of missing data and no ITT	High (Poor quality)	Is not a Low ROB (Good quality) due to missing data, lack of intention to treat analysis, and uncertain blinding of outcome assessors other than radiologists
Boden, 2000 USA The use of BMP-2 in interbody fusion cages ALIF N=14 (Study 1)	High (Poor quality) for all outcomes	High (Poor quality) for all outcomes	Randomization revealed to patient before Informed consent given; control group too small; significant baseline differences
Boden, 2002 USA rhBMP-2/BCP US Pilot RCT PLF (Study 12)	Poor	NA-unpublished.	

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the method of randomization adequate?	PUBLICATION Was the method of randomization adequate?	PROTOCOL Was the treatment allocation concealed?	PUBLICATION Was the treatment allocation concealed?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in SAS	Unclear	Probably: "Both the investigator and the patient will be blinded to the randomization until the Informed Consent Form is signed. After the patient signs the informed consent form, the investigator or designee will open the envelope that corresponds to the patient's assigned clinical trial number..."	Unclear
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in SAS	Unclear	Probably: "Both the investigator and the patient will be blinded to the randomization until the Informed Consent Form is signed. After the patient signs the informed consent form, the investigator or designee will open the envelope that corresponds to the patient's assigned clinical trial number..."	Unclear

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the patient blinded to the intervention?	PUBLICATION Was the patient blinded to the intervention?	PROTOCOL Was the care provider blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	No	Unclear	Surgeon not blinded	Unclear
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	No	Unclear	Surgeon not blinded	Unclear

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the outcome assessor blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	FDA SUMMARY Was the drop-out rate described and acceptable?	PUBLICATION Was the drop-out rate described and acceptable?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	For fusion: "The radiographic review will be completed by two independent, blinded radiologists and reported on the Radiographic Review case report form. If there is a disagreement regarding the ultimate fusion status of the patient between the two radiologists, a third independent, blinded radiologist will be used to break the tie." Other outcomes unclear	For fusion: "Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings."	BMP group: 18/143 = 13% (not included are 0 deaths and 9 failures) Control group: 25/136=18% (not included are 1 death and 12 failures)	BMP group: 20/143 = 14% Control group: 27/136=20%
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	For fusion: "The radiographic review will be completed by an independent, blinded radiologist and reported on the Radiographic Review case report form." Other outcomes unclear	For fusion: "Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings." Other outcomes unclear	BMP group: 0/24 =0% Control group: 5/22=23% (not included in the 17 are 1 death and 3 failures)	BMP group: 0% Control group: 23%

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were all randomized participants analyzed in the group to which they were allocated?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?	FDA SUMMARY Are reports of the study free from suggestion of bias?	PUBLICATION Are reports of the study free from suggestion of bias?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	No; missing data is not included.	No; missing data is not included.	Yes	Yes
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	No; missing data is not included.	No; missing data is not included.	Yes	Yes

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	FDA SUMMARY Were co-interventions avoided or similar?	PUBLICATION Were co-interventions avoided or similar?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	Yes; no characteristic > 10% difference between group	Unclear; as no information on those with missing information	BMP group: Low profile brace 51%; High profile brace: 7%; Corset 34%; Other 7% Control group: Low profile brace 52%; High profile brace: 4%; Corset 35%; Other: 9%	"Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and an exercise program were started at 6 weeks after surgery."
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	No; Although no p-values were significant, 33% male in the BMP group vs 46% male in the control group; 21 % receiving worker's compensation in the BMP group vs 32% in the control group; 46% had previous back surgery in the BMP group vs 32% in the control group	Table 1 includes data on gender, worker's comp, and previous surgeries but no p-values were given	BMP group: Low profile brace 46%; High profile brace: 21%; Corset **25%;** Other 8% Control group: Low profile brace 46%; High profile brace: 14%; Corset **41%;** Other: 0% Differences in Corset use	"All patients were instructed to wear an external orthosis for 6 to 12 weeks after surgery. Patients were encouraged to ambulate immediately after surgery. Physical activities were advanced at the discretion of the attending surgeon."

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Was the compliance acceptable in all groups?	PUBLICATION Was the compliance acceptable in all groups?	FDA SUMMARY Was the timing of the outcome assessment similar in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	Unclear, NR	Unclear; NR	Yes	Yes
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	Unclear, NR	Unclear; NR	Yes	Yes

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	RISK OF BIAS Based on all Data	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Burkus, 2002 USA Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages ALIF N=279 (Study 2)	Moderate (Fair quality) for all outcomes	Moderate (Fair quality) for all outcomes	Is not a Low ROB (Good quality) due to lack of intention to treat analysis and uncertain blinding of outcome assessors other than radiologists
Burkus, 2002 USA Clinical and radiographic outcomes of anterior lumbar interbody fusion using BMP-2 ALIF N=46 (Study 4)	Moderate (Fair quality) for all outcomes	Moderate (Fair quality) for all outcomes	Is not a Low ROB (Good quality) due to lack of intention to treat analysis and uncertain blinding of outcome assessors other than radiologists and groups not similar at baseline

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the method of randomization adequate?	PUBLICATION Was the method of randomization adequate?	PROTOCOL Was the treatment allocation concealed?	PUBLICATION Was the treatment allocation concealed?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in Statistical analysis System	Unclear	No; Patients were not blinded	Unclear
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Yes; Generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher	Unclear; Centrally generated	Yes; Investigator or designee opens envelope corresponding to assigned sequential number	Yes; Sealed envelopes with sequential numbers
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Yes; Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher	Unclear; schedule centrally generated, but method NR	Yes; sequentially numbered, sealed envelopes	Yes; sequentially numbered, sealed envelopes provided by sponsor, but controlled on-site by investigator

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the patient blinded to the intervention?	PUBLICATION Was the patient blinded to the intervention?	PROTOCOL Was the care provider blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	No	Unclear	No; Surgeons not blinded	Unclear
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	No	No - non-blinded	No	No
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	No	No - non-blinded	No	No - non-blinded

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the outcome assessor blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	FDA SUMMARY Was the drop-out rate described and acceptable?	PUBLICATION Was the drop-out rate described and acceptable?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	Yes; The independent radiographic reviewers who evaluate the radiographs and CT scans will not be informed of the treatment.	Yes	Yes; 0% in the BMP group and 5.3% in the Control group	Yes;
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Yes; independent radiologists who evaluate the radiographs and CT scans will not be informed of the treatment	Yes; radiographs and CT scans evaluated by 2 independent radiologists, blinded to which patient group they were evaluating and a third adjudication reviewer was used as needed	Yes; Amplify=89.4% and control=84.5% at 24 months	Yes; 89% available for assessment at 2 years (Amplify=90%, control=87%)
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	No, but radiographic outcome measurements were made by two independent reviewers, with a third independent radiologist reviewer used adjudicate conflicting findings	No, but radiographic outcome measurements were made by two independent reviewers, with a third independent radiologist reviewer used adjudicate conflicting findings	Yes; 24 months not evaluated: overall=12% (67/577), INFUSE=19% (33/172) vs MAVERICK=9% (34/405)	Yes: Overall at 24 months=8.6% (INFUSE=15%/MAVERICK=6%)

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were all randomized participants analyzed in the group to which they were allocated?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?	FDA SUMMARY Are reports of the study free from suggestion of bias?	PUBLICATION Are reports of the study free from suggestion of bias?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	Unclear; Do not see anything about missing data	Yes		
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	No	No; The protocol predefined the as-treated analysis as the primary analysis for the study, on the basis of the statistical consideration that intent-to-treat analysis may not be conservative for assessing a noninferiority hypothesis	Yes	Yes
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	No; severity bias depends on outcome. For example, 24-month fusion status only evaluated for 60% of patients in BMP group (103/172) and data NR for Maverick group. And, for fusion status, there is a note that "if discrepancies between the first two reviewers could not be resolved by the third reviewer, the fusion success status is considered	Unclear for continuous outcomes (i.e., mean scores). No for many dichotomous outcomes (success/failure). For example, primary outcome analysis of overall success at 24 months only included 72% of patients.		No. Variation in sample sizes analyzed for each outcome are not reported.

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	FDA SUMMARY Were co-interventions avoided or similar?	PUBLICATION Were co-interventions avoided or similar?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	No; Worker's comp indicator was significantly different with more cases in the control group (19% vs 0%). However more unresolved spinal litigations in the BMP group (12% vs 0%)	Unclear; More previous surgeries in the control group (29% vs 25%) but not statistically significant.	No; More high profile brace used in the control group (42.9% vs 20%). More corsets used in the BMP group (36% vs 23%).	Unclear; NR
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Yes; no characteristic > 10% difference between group	Unclear; control group had significantly higher involvement in litigation (6.7% vs 2.5%, p=0.042), but unclear of clinical importance.	Yes	Unclear; NR
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	No; INFUSE group had lower preoperative non-narcotic medication use (61% vs 72%; *P*= 0.014)	No; INFUSE group had lower preoperative non-narcotic medication use (61% vs 72%; *P*= 0.014)	No; rigid external orthosis required in INFUSE group and prohibited in MAVERICK group	NR

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Was the compliance acceptable in all groups?	PUBLICATION Was the compliance acceptable in all groups?	FDA SUMMARY Was the timing of the outcome assessment similar in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	Unclear; NR	Unclear; NR	Yes	Yes
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Unclear; Amplify=94.9% and control=94.2% external orthosis use at discharge, but compliance at 6 weeks NR.	Unclear; NR	Yes	Yes
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Unclear; 83% of INFUSE group used external orthosis at discharge, but compliance at 6 weeks NR	NR	Yes	Yes

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	RISK OF BIAS Based on all Data	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Dawson, 2009 USA Mastergraft Pilot CD HORIZON IDE G020056 (Study 8)	Fair	Fair	
Dimar, 2009 USA Amplify (rhBMP-2/CRM) Pivotal RCT (Study 14)	Fair	Fair	
Gornet, 2011 USA MAVERICK™ Disc Pivotal RCT (Study 10)	Poor for those outcomes with extremely high levels of missing data excluded from analysis (i.e., fusion), fair for other outcomes.	Fair	

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the method of randomization adequate?	PUBLICATION Was the method of randomization adequate?	PROTOCOL Was the treatment allocation concealed?	PUBLICATION Was the treatment allocation concealed?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in SAS	Unclear	Probably: "Both the investigator and the patient will be blinded to the randomization until the Informed Consent Form is signed. After the patient signs the informed consent form, the investigator or designee will open the envelope that corresponds to the patient's assigned clinical trial number..."	Unclear
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	Yes; Patients will be randomized according to a randomization schedule generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher. Treatment randomization will be 2: 1 (investigational: control) on a site basis.	NA	No	NA
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	Yes; Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher	NA	Yes; serially numbered envelopes	NA

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the patient blinded to the intervention?	PUBLICATION Was the patient blinded to the intervention?	PROTOCOL Was the care provider blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	No	Unclear	Surgeon not blinded	Unclear
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	No	NA	No	NA
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	No	NA	No	NA

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the outcome assessor blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	FDA SUMMARY Was the drop-out rate described and acceptable?	PUBLICATION Was the drop-out rate described and acceptable?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	For fusion: "The radiographic review will be completed by two independent, masked radiologist and reported on the Radiographic Review case report form, If there is a disagreement regarding the ultimate fusion status of the patient between the two radiologists, a third independent, masked radiologist will be used to break the tie." Other outcomes unclear	For fusion: "Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings." Other outcomes unclear	BMP group: 8/34=24% (not included are 1 death and 4 failures) Control group: 5/33=15% (not included are 1 death and 3 failures)	For many outcomes only percents are given, so unclear how many patients are actually included
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	Yes; Independent radiologists who evaluate the radiographs and CT Scans will be blinded to treatment	NA	Yes; No	NA
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	Yes; independent radiologist who evaluates the radiographs and CT scans will be blinded to treatment.	NA	Yes; Yes	NA

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were all randomized participants analyzed in the group to which they were allocated?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?	FDA SUMMARY Are reports of the study free from suggestion of bias?	PUBLICATION Are reports of the study free from suggestion of bias?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	No; missing data is not included.	For many outcomes only percents are given, so unclear how many patients are actually included	Yes	Yes
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	Yes	NA		
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	No	NA		

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	FDA SUMMARY Were co-interventions avoided or similar?	PUBLICATION Were co-interventions avoided or similar?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	No; In the BMP group 79% Caucasian vs 94% in the control group; 27% working before surgery in BMP group vs 46% in control group	Although no p-values significant, work status provided in Table 1 but race not provided	BMP group: Low profile brace **32%**; High profile brace: 15%; Corset **32%;** Other 21% Control group: Low profile brace **18%**; High profile brace: 21%; Corset **46%;** Other: 15% Differences in Low Profile Brace and Corset use	"Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were stated at 6 weeks after surgery."
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	Unclear; Previous surgery slightly higher in the BMP group (45.8% vs 31.8%). Although none were statistically significant	NA	Unclear; fewer BMP patients using corset (25% vs 40.9%). Higher number of BMP patients wearing high profile brace (20.8% vs 13.6%)	NA
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	Unclear, some differences: BMP group had lower rate of > high school education (25% vs 45%), higher tobacco use (40% vs 30%)	NA	Unclear; fewer BMP patients using corset at discharge (28% vs 42%)	NA

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Was the compliance acceptable in all groups?	PUBLICATION Was the compliance acceptable in all groups?	FDA SUMMARY Was the timing of the outcome assessment similar in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	Yes except that at 24 months 13% of BMP group still using brace vs 0% in control group	Unclear; NR	Yes	Yes
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	NR	NA	Yes	NA
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	NR	NA	Yes	NA

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	RISK OF BIAS Based on all Data	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Haid, 2004 USA Posterior lumbar interbody fusion using BMP-2 with cylindrical interbody cages PLIF N=67 (Study 6)	Moderate (Fair quality) for all outcomes	Moderate (Fair quality) for all outcomes	Is not a Low ROB (Good quality) due to lack of intention to treat analysis and uncertain blinding of outcome assessors other than radiologists and groups not similar at baseline
Unpublished study? Infuse Bone Dowel Pivotal Study (Study 5-enrolled 85 patients prior to termination)	Fair	NA	
Unpublished study Infuse/Inter Fix= ALIF Pilot RCT (Study 9)	Fair	NA	

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the method of randomization adequate?	PUBLICATION Was the method of randomization adequate?	PROTOCOL Was the treatment allocation concealed?	PUBLICATION Was the treatment allocation concealed?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	Yes; Generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher	NA-unpublished	Yes; Investigator or designee opens envelope corresponding to assigned sequential number	NA-unpublished
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the patient blinded to the intervention?	PUBLICATION Was the patient blinded to the intervention?	PROTOCOL Was the care provider blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	No	NA-unpublished	No	NA-unpublished
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PROTOCOL Was the outcome assessor blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	FDA SUMMARY Was the drop-out rate described and acceptable?	PUBLICATION Was the drop-out rate described and acceptable?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	Yes. Radiologists will be blinded to the treatment group in which the patient is randomized	NA-unpublished	Unclear; not described	NA-unpublished
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were all randomized participants analyzed in the group to which they were allocated?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?	FDA SUMMARY Are reports of the study free from suggestion of bias?	PUBLICATION Are reports of the study free from suggestion of bias?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	No; number Analyzed: BMP=2 to 98, Control=1 to 98	NA-unpublished	Yes	Yes
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	FDA SUMMARY Were co-interventions avoided or similar?	PUBLICATION Were co-interventions avoided or similar?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	No; BMP group had fewer males (35.7% vs 48.5%) and more with education above HS (48.2% vs 37.9%)	NA-unpublished	Yes, similar	NA-unpublished
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	FDA SUMMARY Was the compliance acceptable in all groups?	PUBLICATION Was the compliance acceptable in all groups?	FDA SUMMARY Was the timing of the outcome assessment similar in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	No; BMP=67.5% and control=69.8% at 6 weeks, 35.4% vs 44.8% at 3 months, 19.8% vs 19.5% at 6 months	NA-unpublished	Yes	NA-unpublished
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.				

Evidence Table 2. Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	RISK OF BIAS Based on all Data	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Unpublished study rhBMP-2/BCP Canada Pivotal RCT (Study 13)	Fair to poor; variable by outcome, depending on number of patients analyzed.	NA-unpublished.	
Unpublished study INFUSE®/CORNER STONE® ACDF Pivotal RCT (Study 17) Enrollment stopped after 3 patients, not based on any safety concerns, but because of pursing different strategic initiatives.			

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Type of trial Length of trial Intervention Series	Protocol inclusion criteria/ Protocol exclusion criteria	Intervention	Co-Interventions
INFUSE/LT-CAGE Lap Pivotal Single-Arm Study (Study 3)	ALIF 72 months	Inclusion: Degenerative disc disease; Preoperative Oswestry score ≥ 35; no greater than Grade 1 spondylolisthesis; Single level disease from L4-S1; at least 18 years of age Exclusion: Previous anterior spinal fusion at the involved level; has posterior spinal instrumentation; requires postoperative medications that interfere with fusion; is >40% over ideal weight for age; is a tobacco user at the time of surgery; is an alcohol or drug abuser	rhBMP-2/ACS/LT-Cage using laparoscopic implantation	Wear external orthosis (corset or brace) for ambulation approximately 6 weeks following surgery; begin abdominal strengthening program after 30 days following surgery.

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Number analyzed Number withdrawn Number lost to follow-up	Nonmedical history Baseline characteristics from FDA data summary		Medical history Baseline characteristics from FDA data summary	
			BMP		**BMP**
INFUSE/LT-CAGE Lap	136 went to surgery; 134 actually	Age	42.4		
Pivotal Single-Arm Study	received the investigational device;	Height	67.5	Prior Tobacco:	29.9
	9 failures; 9 lost to follow-up; 13	Weight	169.8	Alcohol use:	49.3
(Study 3)	not analyzed but not considered	% Male	42.5	Prior Back Surgery:	24.6
	lost to follow-up	% White	93.3	Diabetic:	2.2
		% Married	67.9	% not taking Non Narcotic:	27.6
		% ED>HS	65.7	% not taking Weak Narcotic:	54.5
		% Working	52.2	% not taking Strong Narcotic:	87.3
		% Worker's Comp	21.3	% not taking Muscle Relaxer:	63.4
		% Spinal Litigation	8.2		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Radiographic fusion		FDA adverse events	BMP	Second surgeries	BMP
INFUSE/LT-CAGE Lap	Percent Radiographic Fusion (n):		Patients Reporting Event (n):		Second Surgeries (n)	
Pivotal Single-Arm Study	6 months	94.7 (94)	Anatomic Difficulty	12	Revisions	1
	12 months	94.1 (101)	Back and/or Leg Pain	31	Removals	2
(Study 3)	24 months	92.9 (99)	Cancer	0	Supplemental Fixations	7
	36 months	NR	Cardiovascular	10	Reoperations	3
	48 months	NR	Death	0		
	72 months	NR	Dural Injury	0		
			Gastrointestinal	24		
			Graft Site Related	0		
			Implant Displaced/Loosened	2		
			Infection	17		
			Malpositioned Implant	4		
			Neurological	18		
			Non-Union	4		
			Other	30		
			Other Pain	10		
			Respiratory	1		
			Retrograde Ejaculation	6		
			Spinal Event	6		
			Subsidence	1		
			Trauma	28		
			Urogenital	16		
			Vascular Intra-Op	8		
			Vertebral Fracture	NR		
			Total Patients with ≥ 1 Event	102		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Type of trial Length of trial Intervention Series	Protocol inclusion criteria/ Protocol exclusion criteria	Intervention	Co-Interventions
INFUSE/TELAMON PEEK Instrumented PLIF Pilot, Single-Arm Study (Study 11) 36 months	Circumferential PLIF 24 months	Inclusion: Degenerative disc disease; Preoperative Oswestry score ≥ 30; preoperative back pain score ≥ 25; no greater than Grade 1 spondylolisthesis; Single level disease from L1-S1; at least 18 years of age Exclusion: Previous anterior spinal fusion at the involved level; requires fusion at more than one lumbar level; has a diagnosis of osteopenia or osteomalacia; if a post-menopausal non-black female over 60 or a postmenopausal female with a non-traumatic hip, spine, or wrist fracture or is a male over 70 or a male over 60 with a nontraumatic hip or spine fracture, a DEXA scan will be require; requires post-operative medications that interfere with fusion; is an alcohol or drug abuser	TELAMON Impacted Implant, INFUSE, and the CD Horizon Spinal System in PLIF	Wear external orthosis (corset or brace) for ambulation approximately 6 weeks following surgery; begin abdominal strengthening program after 30 days following surgery.

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Number analyzed Number withdrawn Number lost to follow-up	Nonmedical history Baseline characteristics from FDA data summary		Medical history Baseline characteristics from FDA data summary	
			BMP		**BMP**
INFUSE/TELAMON	35 enrolled	Age	51.0		
PEEK Instrumented PLIF	5 patients did not receive study	Height	66.5	Prior Tobacco:	26.7
Pilot, Single-Arm Study	treatment: one insurance denial,	Weight	184.9	Alcohol use:	40.0
	one had previous fusion at same	% Male	40.0	Prior Back Surgery:	46.7
(Study 11)	level, one had ODI score too low,	% White	66.7	Diabetic:	NR
	one had history of breast cancer,	% Married	63.3	% not taking Non Narcotic:	46.7
36 months	one was discovered	% ED>HS	65.5	% not taking Weak Narcotic:	70.0
	intraoperatively to need surgery at	% Working	30.0	% not taking Strong Narcotic:	83.3
	two levels	% Worker's Comp	13.3	% not taking Muscle Relaxer:	56.7
		% Spinal Litigation	3.3		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Radiographic fusion		FDA adverse events		Second surgeries	
				BMP		**BMP**
INFUSE/TELAMON	Percent Radiographic Fusion (n):		Adverse Events (n):		Second Surgeries (n)	
PEEK Instrumented PLIF	6 months	100 (26)	Anatomic Difficulty	NR	Revisions	0
Pilot, Single-Arm Study	12 months	100 (27)	Back and/or Leg Pain	34	Removals	1
	24 months	100 (24)	Cancer	NR	Supplemental Fixations	0
(Study 11)	36 months	100 (11)	Cardiovascular	2	Reoperations	0
			Death	NR		
36 months			Dural Injury	1		
			Gastrointestinal	5		
			Graft Site Related	NR		
			Implant Displaced/Loosened	NR		
			Infection	4		
			Malpositioned Implant	NR		
			Neurological	8		
			Non-Union	NR		
			Other	17		
			Other Pain	1		
			Respiratory	3		
			Retrograde Ejaculation	NR		
			Spinal Event	6		
			Subsidence	NR		
			Trauma	4		
			Urogenital	1		
			Vascular Intra-Op	NR		
			Vertebral Fracture	NR		
			Total Patients with ≥ 1 Event	29		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Type of trial Length of trial Intervention Series	Protocol inclusion criteria/ Protocol exclusion criteria	Intervention	Co-Interventions
rhBMP-2/BCP Mexico Pilot (Study 16)	PLF 12 months	Inclusion: Spinal degeneration with instability of ≥ 4mm translation or ≥ 5 degrees of angulation with intractable back pain; one level involvement L3-S1; 18 years or older Exclusion: Spinal stenosis or a condition requiring a full laminectomy; had a previous fusion, discectomy or laminectomy at any level L3-S1; requires medication which may interfere with bone metabolism; unwilling to return for required follow-up; has severe osteopenia or osteoporosis	Cohort 1: rhBMP-2/BCP device implanted unilaterally; autograph was implanted on the other side Cohort 2: rhBMP-2/BMP device implanted bilaterally with GDLH Spinal System	The type and duration of bracing is to be left to the discretion of the investigator; treatment with electrical bone growth stimulation at any time during 12 month follow-up is not permitted

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Number analyzed Number withdrawn Number lost to follow-up	Nonmedical history Baseline characteristics from FDA data summary		Medical history Baseline characteristics from FDA data summary	
			BMP		**BMP**
rhBMP-2/BCP Mexico	7 patient cohort 1; 8 patients	Cohort1:		Cohort 1:	
Pilot	cohort 2	Age	53.9	Prior Tobacco:	0
		Height	58.3	Alcohol use:	14.3
(Study 16)	4 patients in cohort 2 did not	Weight	131.7	Prior Back Surgery:	0
	receive instrumentation	% Male	14.3	Diabetic:	0
		% White	NR	% not taking Non Narcotic:	0
		% Married	57.1	% not taking Weak Narcotic:	100
		% ED>HS	42.9	% not taking Strong Narcotic:	100
		% Working	28.6	% not taking Muscle Relaxer:	100
		% Worker's Comp	0		
		% Spinal Litigation	0		
		Cohort 2:		Cohort 2:	
		Age	41.7	Prior Tobacco:	0
		Height	65.1	Alcohol use:	0
		Weight	154.1	Prior Back Surgery:	0
		% Male	50	Diabetic:	0
		% White	NR	% not taking Non Narcotic:	25
		% Married	62.5	% not taking Weak Narcotic:	87.5
		% ED>HS	37.5	% not taking Strong Narcotic:	100
		% Working	37.5	% not taking Muscle Relaxer:	100
		% Worker's Comp	0		
		% Spinal Litigation	0		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Radiographic fusion		FDA adverse events	BMP	Second surgeries	BMP
rhBMP-2/BCP Mexico Pilot (Study 16)	Cohort 1, Reader 1 6 months: BMP=80% (5); autograft=33.3% (6) 12 months: BMP=83.3% (6); autograft=50% (6) Cohort 2, Reader 1 6 months: Side A: 87.5% (8); Side B: 100% (8) 12 months: Side A: 100% (8) Side B: 100% (8) Note: Cohort 1 is BMP on one side and autograft on the other; Cohort 2 is BMP on both sides	Cohort 1, Reader 2 6 months: BMP=71.4% (7); autograft=28.6% (7) 12 months: BMP=100% (7); autograft=71.4% (7) Cohort 2, Reader 2 6 months: Side A: 87.5% (8); Side B: 100% (8) 12 months: Side A: 87.5% (8) Side B: 100% (8) Note: Cohort 1 is BMP on one side and autograft on the other; Cohort 2 is BMP on both sides	Number of Events (n) Loose Screw-Cohort 1 Gastric Ulcer-Cohort 1 Sacroiliitis-Cohort 1 Stenosis-Cohort 1 Bone Fracture-Cohort 1 Bone Fracture-Cohort 1	 2 1 3 1 1 1	Second Surgeries (n) Revisions Removals Supplemental Fixations Reoperations	 0 0 NR 1 (Cohort 1)

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Type of trial Length of trial Intervention Series	Protocol inclusion criteria/ Protocol exclusion criteria	Intervention	Co-Interventions
rhBMP-2/CRM 2-level Pilot, Single-Arm Study (Study 15)	PLF 36 months	Inclusion: Degenerative disc disease at two adjacent levels; Preoperative Oswestry score ≥ 30; No greater than Grade 1 spondylolisthesis; Two level disease from L1-S1; at least 18 years of age Exclusion: Previous anterior spinal fusion at the involved level; requires postoperative medications that interfere with fusion; is an alcohol or drug abuser; if a post-menopausal non-black female over 60 and weight less than 140 lbs or a postmenopausal female with a non-traumatic hip, spine, or wrist fracture or is a male over 70 or a male over 60 with a nontraumatic hip or spine fracture, a DEXA scan will be require; diagnosed with osteopenia, osteomalacia, or osteoporosis	2-level application of rhBMP-2/CRM/CD Horizon Spinal System	An external orthosis (i.e., corset or brace) should be worn for ambulation until approximately 6 weeks following surgery; an abdominal strengthening program should be started approximately 30 days after surgery

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Number analyzed Number withdrawn Number lost to follow-up	Nonmedical history Baseline characteristics from FDA data summary		Medical history Baseline characteristics from FDA data summary	
			BMP		**BMP**
rhBMP-2/CRM 2-level	30 patients were consented, and	Age	53.9		
Pilot, Single-Arm Study	29 received the investigational	Height	67.8	Prior Tobacco:	41.4
	device (the patient who did not go	Weight	196.5	Alcohol use:	41.4
(Study 15)	through the surgery had insurance	% Male	51.7	Prior Back Surgery:	24.1
	reimbursement issues)	% White	93.1	Diabetic:	10.3
		% Married	79.3	% not taking Non Narcotic:	41.4
		% ED>HS	65.5	% not taking Weak Narcotic:	51.7
		% Working	44.8	% not taking Strong Narcotic:	89.7
		% Worker's Comp	0	% not taking Muscle Relaxer:	79.3
		% Spinal Litigation	0		

Evidence Table 3. Medtronic intervention series

Author Year Country Trial # or Name	Radiographic fusion		FDA adverse events	Second surgeries	
				BMP	BMP
rhBMP-2/CRM 2-level	Percent Radiographic Fusion (n):		Adverse Events (n):		
Pilot, Single-Arm Study	6 months		Anatomic Difficulty	NR	
	12 months	47.6 (21)	Back and/or Leg Pain	18	
(Study 15)	24 months	56.5 (23)	Cancer	NR	
	36 months	85.0 (20)	Cardiovascular	2	
		93.3 (15)	Death	NR	
			Dural Injury	1	
			Gastrointestinal	7	
			Graft Site Related	NR	
			Implant Displaced/Loosened	NR	
			Infection	1	
			Malpositioned Implant	NR	
			Neurological	11	
			Non-Union	1	
			Other	7	
			Other Pain	NR	
			Respiratory	1	
			Retrograde Ejaculation	NR	
			Spinal Event	16	
			Subsidence	NR	
			Trauma	2	
			Urogenital	4	
			Vascular Intra-Op	NR	
			Vertebral Fracture	NR	
			Total Patients with ≥ 1 Event	26	

Evidence Table 4. Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
INFUSE/LT-CAGE Lap Pivotal Single-Arm Study Study 3	Unclear; 136 patients from 14 sites.	Yes	Yes; two independent blinded radiologists	Yes; 9 lost to follow-up at 24 months
INFUSE/TELAMON PEEK Instrumented PLIF Pilot, Single-Arm Study Study 11	Unclear; 30 patients from 5 sites.	Yes	No; two independent radiologists	No
rhBMP-2/BCP Mexico Pilot Study 16	Unclear; 12 evaluable patients	Yes	Unclear; Do not mention anything	No
rhBMP-2/CRM 2-level Pilot, Single-Arm Study Study 15	Unclear; 30 patients at no more than 5 investigational sites	Yes	No; the independent radiologists who evaluate the radiographs and CT scans will not be specifically in formed of the treatment although they may have access to the study protocol.	Yes; 15% loss to follow-up at 36 months

Evidence Table 4. Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes prespecified and defined, and ascertained using accurate methods? Was the method to determine fusion described?	Quality Rating	Comments
INFUSE/LT-CAGE Lap Pivotal Single-Arm Study Study 3	Unclear	No	Yes	Poor	
INFUSE/TELAMON PEEK Instrumented PLIF Pilot, Single-Arm Study Study 11	No	Unclear	Yes	Poor	
rhBMP-2/BCP Mexico Pilot Study 16	Yes	Unclear	Yes	Fair	
rhBMP-2/CRM 2-level Pilot, Single-Arm Study Study 15	Yes	No; 15%	Yes	Poor	

Evidence Table 5. Non-Medtronic randomized controlled trials

Author Year Country Trial # or Name	Type of trial Length of trial	Protocol inclusion criteria/ Protocol exclusion criteria	Interventions	Co-Interventions	Number Randomized Number analyzed by group Number withdrawn by group Number lost to follow-up by group
Glassman 2008 USA	RCT 2 years	NR	rhBMP-2/ACS vs. ICBG	NR	Randomized=106; BMP=50; ICBG=52 Withdrawn=0 Lost to Follow-up: BMP=5 Control=1

Evidence Table 5. Non-Medtronic randomized controlled trials

Author Year Country Trial # or Name	Nonmedical history Baseline characteristics			ODI results from published study			SF-36 results from published study		
Glassman 2008 USA		**BMP**	**ICBG**		**BMP**	**ICBG**		**BMP**	**ICBG**
	N	50	52	Average ODI Scores	49.9+-12.9	47.0+-16.8	Physical Component	27.7+-5.9	28.4+-7.3
	M:F	15:35	17:35						
	Age	96.2+-5.5	69.9+-5.8						
	Smokers	11	9						
	BMI	29.4+-5.7	28.1+-6.1						

Evidence Table 5. Non-Medtronic randomized controlled trials

Author Year Country Trial # or Name	Back pain results from published study			Leg pain results from published study			Radiologic fusion results from published study			
Glassman 2008 USA		**BMP**	**ICBG**		**BMP**	**ICBG**		**BMP**	**ICBG**	**p-value**
	Preoperative NRS Back Pain	16.4+-2.8	15.2+-5.3	Total NRS leg Pain	14.4+-3.8	15.4+-5.1	2-year composite CT grade Fusion rate (%)	4.3+-1.3 86.3	3.8+-0.9 70.8	0.03

Evidence Table 5. Non-Medtronic randomized controlled trials

Author Year Country Trial # or Name	Overall success in published study	Additional surgeries in published study			Adverse events from published study			Funding	Comments
			BMP	ICBG		BMP	ICBG		
Glassman 2008 USA	NR	N	4	11	Cardiac	1	7	Norton	
		At 3 months			Wound Infection	1	4	Healthcare	
		Wound Infection	1	1	Back or Leg Pain	0	3		
		Pedicle Screw Adjustment	0	2	Gastrointestinal	2	3		
		Proximal Extension for Compression Fracture	1	0	UTI	1	1		
					Neurologic Deficit	0	1		
		1-2 Years			Line related Sepsis	1	0		
		Non-Union	1	5	Broken Toe	1	0		
		Late Screw Removal	0	1	Shingles	1	0		
		Pain Pump Insertion	0	1					
		Revision for Adjascent-level degeneration	1	1					

Evidence Table 6. Non-Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PUBLICATION Was the method of randomization adequate?	PUBLICATION Was the treatment allocation concealed?	PUBLICATION Was the patient blinded to the intervention?	PUBLICATION Was the care provider blinded to the intervention?	PUBLICATION Was the outcome assessor blinded to the intervention?	PUBLICATION Was the drop-out rate described and acceptable?	PUBLICATION Were all randomized participants analyzed in the group to which they were allocated?
Glassman 2008 USA	Unclear; Do not mention it in the published data	Yes	Unclear	Yes; 3 spine surgeons were blinded	Yes; surgeons evaluted the CT grade	Yes	Yes

Evidence Table 6. Non-Medtronic randomized controlled trials: Risk of bias

Author Year Country Trial # or Name	PUBLICATION Are reports of the study free from suggestion of bias?	PUBLICATION Were the groups similar at baseline regarding the most important prognostic indicators?	PUBLICATION Were co-interventions avoided or similar?	PUBLICATION Was the compliance acceptable in all groups?	PUBLICATION Was the timing of the outcome assessment similar in all groups?	RISK OF BIAS Based on Publication (and Protocol if Publically Available)	Comments
Glassman 2008 USA	Unclear; The study does not mention any confounding factors	Unclear; some information is provided but not enough	Unclear	Unclear; NR	Yes	Moderate (Fair Quality)	

Evidence Table 7. Non-Medtronic Cohort studies

Author, year Type of Study Approach	*n* (BMP vs. Control)	Interventions	Baseline Characteristics rhBMP-2 vs. control (unless otherwise noted)	Results	Funder	Quality
Butterman, 2008 **Prospective** **ACDF**	66 (30 vs. 36)	rhBMP-2 vs. ICBG 0.9mg BMP per level	**Age (yr):** 49 vs. 48 **Female (%):** 50 vs. 67 **Smoker (%):** 37 vs. 53 **Diagnosis (%):** DDD: 40 vs. 38 HNP: 10 vs. 17 Stenosis: 50 vs. 46	**Fusion:** NR **Patient rating of success (1-2 yrs) (%):** 90 vs. 94 **Neck pain**: NS (difference between groups at all time periods) **Arm pain:** NS (difference between groups at all time periods)	NR	Poor
Cahill, 2009 **Retrospective** **Anterior/ Posterior Cervical, Lumbar, Thoracic** **Nationwide Inpatient Sample database**	70649 (17623 vs. 53026)	rhBMP-2 vs. No rhBMP-2 Dosage: NR	**Age (yr):** 53.79 vs. 53.26 **Male (%):** 43.74 vs. 46.65 **Diagnosis:** DDD (%): 70.72 vs. 75.65 **Segment of fusion (%):** Cervical: 16.4 vs. 52.0 Thoracic: 4.2 vs. 4.7 Lumbosacral: 79.3 vs. 43.1	**Fusion:** NR **Complications (BMP-2 vs. Control)** **Any Complications (%):** Anterior Cervical: 7.09 vs. 4.68 Posterior Cervical: 10.04 vs. 9.95 Thoracic: 16.47 vs. 17.44 Lumbar: 6.97 vs. 7.18 **Dysphagia or Hoarseness (%):** Anterior Cervical: 4.35 vs. 2.45 Posterior Cervical: 2.09 vs. 1.63 Thoracic: 0.80 vs. 1.31 Lumbar: 0.25 vs. 0.21 **Wound Complication (%):** Anterior Cervical: 1.22 vs. 0.65 Posterior Cervical: 2.93 vs. 2.51 Thoracic: 4.69 vs. 5.81 Lumbar: 2.01 vs. 2.15	Brain Science Foundation	Fair

Cahill, 2011 **Retrospective** **Lumbar** **MarketScan claims data set**	15862 (2373 vs. 13489)	rhBMP-2 vs. No rhBMP-2 Dosage: NR	**Age (yr):** 48 vs. 48 **Male (%):** 51 vs. 49 **Osteoporosis (%):** 1 vs. 1 **Tobacco User (%):** 27 vs. 26 **Diabetes (%):** 11 vs. 10 **Diagnosis (%):** LDH: 47 vs. 44 DDD: 64 vs. 63 Spondylolisthesis: 34 vs. 36	**Fusion:** NR **Additional Surgeries (Adjusted OR):** With BMP: 0.66 (0.47, 0.94) DDD: 1.98 (1.28, 3.07) Spondylolisthesis: 0.85 (0.56, 1.29)	Federal and Institutional funds received in support of this work. Benefits received for professional or personal use from a commercial party.	Fair
Carragee, 2011 **Retrospective** **ALIF**	243 (69 vs. 174)	rhBMP-2 vs. local osteophytes or ICBG Small INFUSE kit	**Age (yr):** 42.4 vs. 40.9 **Smoker (%):** 28 vs. 24 **Diagnosis (%):** Degenerative spondylolisthesis: 48 vs. 46 DDD: 19 vs. 23 Isthmic spondylolisthesis: 33 vs. 31	**Fusion:** NR **Retrograde ejaculation (%, 90% CI):** 7.3 (2.11 to 12.39) vs. 0.6 (-0.37 to 1.51)	No funds received from Medtronic	Poor
Crawford, 2009 **Retrospective** **Posterior Cervical**	77 (41 vs. 36)	rhBMP-2/ACS vs. ICBG 19: large INFUSE kit, 22 small INFUSE kit	**Age (yr):** 56.2 vs. 54.3 **Males (%):** 32 vs. 42 **Smokers (%):** 24 vs. 36	**Fusion:** NR **Adverse Events (%):** Wound Complications: 15 vs. 3 Wound complications by INFUSE kit size (%): Large kit: 11 Small kit: 18 Prolonged Drainage: 2 vs. 1 Deep Infection: 4 vs. 0 Iliac Crest site Deep Infection: 0 vs. 1	No funds received in support of this work. Benefits received for professional or personal use from a commercial party.	Poor

Crawford, 2010 **Prospective** **ALIF Circ.**	60 (36 vs. 24)	rhBMP-2 vs. autogenous group Mean dose 11.4 mg rhBMP-2/ level anterior, 17.3 mg/ level posterior	**Age (yr):** 49.7 vs. 43.5 **Male (%):** 8.3 vs. 4.2	**Fusion (%):** 88.9 vs. 79.2, p =NS **ODI score:** NS (difference between groups at all time periods) **Revision for pseudoarthrosis (%):** 5.6 vs. 12.5 **Adverse Events (%):** Total Complications: 50 vs. 71 Deep Wound Infection: 3 vs. 4	No funds received in support of this work. Benefits received for professional or personal use from a commercial party.	Poor
Gerszten, 2011 **Retrospective** **AxiaLIF Circ.**	99 (45 vs. 54)	rhBMP-2/ACS vs. bone marrow aspirate + Actifuse medium INFUSE kit	**Age (yr):** 42.6 vs. 42.9 **Male (%):** 44 vs. 44	**Fusion (%):** 96 vs. 93 (NS) **Back pain:** VAS scores (range 0-100) Pre-op: 72.9 vs. 81.3, p = .007 24 months: 30.1 vs. 22.6, p = .111 **Additional Surgery (%):** 16 vs. 4	Multiple author disclosures, funder NR.	Poor
Glassman, 2007 **Retrospective** **PLF**	148 76 vs. 72	rhBMP-2 + ICBG vs. ICBG 10mL HA/TCP and collagen compression matrix + 20 mg rhBMP-2 per side	**Smokers (%):** 27.6 vs. 29.2 **Male (%):** 47 vs. 49 Smokers (n = 42): **Age (yr):** 50.8 vs. 48.1 **Male (%):** 52 vs. 69 Non-Smokers: **Age (yr):** 51.8 vs. 51.7 **Male (%):** 45 vs. 43	**Fusion in smokers (%):** 95.2 vs. 76.2 **Fusion in non-smokers (%):** 100 vs. 94, p = NS (difference between) **ODI score mean improvement 24 months:** Non-smokers: 26.4 vs. 24.6, p = NS Smokers: 22.1 vs. 21.0, p = NS **Back pain mean improvement 24 months**: VAS score (range NR) Non-smokers: 7.4 vs. 7.5, p = NS Smokers: 7.9 vs. 6.1, p = NS	Institutional funds received in support of this work. No benefits from a commercial party received.	Poor

Hiremath, 2009 **Retrospective** **Posterior Cervical**	83 (16 vs. 67)	rhBMP-2 vs. ICBG or local autograft or other synthetic agent Average dose rhBMP-2 = 1.3 mL per level	**Age (yr):** 59 vs. 58 **Male (%):** 23 vs. 75 **Diagnosis (%):** Pseudoarthrosis following ACDF: 38 vs. 19 Trauma or nonhealed fracture: 38 vs. 19 Cervical spondylotic myelopathy: 13 vs. 48	**Short-Term Complications (%):** Medical Complications: 13 vs. 7 New Neurological Deficits: 6 vs. 4 Wound Infection: 0 vs. 12 **Symptoms attributable to BMP (%):** 6 **Long-Term Complications (%):** Persistent pain: 1.5 vs. 7 Instrument failure: 3 vs. 1.5 Unimproved neurological deficit: 1.5 vs. 4	No funds received in support of this work.	Poor
Hoffman, 2012 **Retrospective** **Posterior lumbar fusion to include PLIF and TLIF with and without instrumentation**	1398 (947 vs. 306 vs. 145)	rhBMP-2 + BCS vs. DBM vs. autograft mean rhBMP-2 dosage (range) = 12.7 mg per pt (4.2 – 48.0 mg)	**Age:** 59 vs. 63 vs. 58 **Male (%):** 40.8 vs. 37.3 vs. 51.7 **Diabetes:** 14.5 vs. 7.2 vs. 7.6 **Smoking:** 11.1 vs. 5.9 vs. 11.8 Authors note significant differences in all categories listed here.	**Adverse Events (%):** Non-unions: 4.3 vs. 13.1 vs. 15.2, $p < 0.001$ for both comparisons Infection: 2.3 vs. 1.6 vs. NR, NS Seroma formation: 3.2 vs. 2.0 vs. 1.4, p = NS	The authors did not receive grants or outside funding in support of their research or preparation of the manuscript.	Poor
Joseph, 2007 **Prospective** **PLIF Circ./ TLIF Circ.**	33 (23 vs. 10)	rhBMP-2/ACS vs. local autologous bone small INFUSE kit + nonthreaded cages	Overall **Age (yr):** 49.7 **Male (%):** 61 **Diagnosis (%):** Spondylolisthesis: 85 DDD: 15 **Surgical Approach (%):** PLIF Circ.: 30 TLIF Circ.: 70	**Fusion (%):** 6 months: 91 vs. 50, p = 0.016 12 months: 100 vs. 90 **Adverse Events:** Heterotopic bone formation (% of levels): 21 vs. 8, p = NS Additional surgery %: Total = 9 (rhBMP-2 vs. control not reported)	No funds received in support of this work. Benefits received for professional or personal use from a commercial party.	Poor
Katayama, 2009 **Prospective** **PLF**	11	rhBMP-2/ PLGA on right side vs. ICBG on left side	Overall **Age (yr):** 56 **Male (%):** 36.4	**Fusion at 24 months (%):** 82 vs. 91, p = NS	NR	Fair

Latzman, 2010 **Retrospective** **Lumbar**	125 (20 vs. 101 + 4 with one surgery of each)	rhBMP-2 vs. No rhBMP-2 Dosage: NR	**Age (yr):** 50.1 vs. 55.8 **Male (%):** 78 vs. 90 **Diabetics (%):** 7 vs. 37 **Smokers (%):** 44 vs. 40	**Fusion (%):** NR **Adverse Events (%):** Cancer: 17 vs. 8, p = NS Increases in BUN (to > 30 mg/dL) and creatinine (to >1.5 mg/dL): 13 vs. 0, p = 0.006	No funds received in support of this work.	Poor
Lee, 2010 **Retrospective** **PLF** **Companion to Lee, 2012**	127 (34 vs. 52 vs. 41)	Group A: Age ≥ 65 + rhBMP-2 + allograft Group B: Age < 65 + rhBMP-2 + allograft Group C: Age ≥ 65+ autograft	Group A vs. B vs. C Age (yr): 74.1 vs. 49.9 vs. 72.4 Male (%): 53 vs. 39 vs. 42 Smokers: 15 vs. 27 vs. 17 Osteoporosis: 41 vs. 12 vs. 44	Fusion, groups A and B (%): 82 vs. 94, NS Fusion, groups A and C (%): 82 vs. 78, NS	NR	Fair
Lee, 2012 **Retrospective** **PLF**	195 (86 vs. 109)	Group A: rhBMP-2 + allograft + Risk Factors Group B: rhBMP-2 + Allograft - Risk Factors Group C: ICBG + Risk Factors Group D: ICBG - Risk Factors	**Age (yr):** 74.1 vs. 72.4 **Male (%):** 44 vs. 43 **Smoker (%):** 22 vs. 19 **Diabetics (%):** 20 vs. 20	**Fusion (%):** p = NS (difference between groups A and C given all risk factors)	Royalties received by at least one author from Medtronic and other commercial parties.	Fair
Lindley, 2012 **Retrospective** **ALIF** **Circumferential**	95 (54 vs. 41)	rhBMP-2 vs. artificial disk replacement	**Age (yr):** 49 vs. 35 **Diagnosis (%):** DDD: 72 vs. 40 Spondylolisthesis: 9 vs. 2 Degenerative Scoliosis: 4	**Retrograde Ejaculation (%):** 7.4 vs. 9.8, p = 0.7226 **Sexual Dysfunction, other than RE (%):** 2 vs. NR	No funds received in support of this work. One or more author(s)	Poor

			vs. 0 Pseudoarthrosis: 15 vs. 0, p < 0.05		will receive benefits from a commercial party related to the subject of this manuscript.	
Maeda, 2009 **Prospective** **ALIF Circ.**	55 (23 vs. 32) correct	rhBMP-2/ ACS or local bone + allograft vs. ICBG mean concentration 2.1 mg/mL rhBMP-2	**Age (yr):** 55.6 vs. 52.6 **Smokers (%):** 13.0 vs. 12.5	**Fusion (%):** 95.7 vs. 71.9 **Perioperative complication (%):** 4 vs 0	No funds received in support of this work. Benefits received for professional or personal use from a commercial party.	Poor
Mindea, 2009 **Retrospective** **TLIF Circ.**	43 (35 vs. 8)	rhBMP-2/ BCS vs. No rhBMP-2 4.2 mg rh-BMP-2/level	Overall **Age (yr):** 50.8 **Male (%):** 42 rhBMP-2 vs. control: **Spondylolisthesis (%):** 46 vs. 63	**Fusion (%):** NR **Radiculitis (%):** 11 vs. 0	No funds received in support of this work.	Poor
Mines, 2011 **Retrospective** **Lumbar** **U.S. Medicare claims data**	93,654 (15,460 vs. 78,194)	BMP vs. no BMP Unclear if BMP-2 or BMP-7	**Age (yr):** 74.2 vs. 74.6 **Male (%):** 33.0 vs. 34.6 **Diabetes (%):** 36.4 vs. 35.5	**Pancreatic Cancer, *n*:** 8 vs. 83, p = NS	Wyeth pharmaceuticals	Fair
Mummaneni, 2004 **Retrospective** **TLIF Circ.**	40 (21 vs. 19)	9 rhBMP-2 only + 12 ICBG also vs. ICBG only	Overall **Age (yr):** 53 **Male (%):** 57.5 **Smokers (%):** 10	**Fusion at 6 months (%):** 95 vs. 95	NR	Poor

		medium INFUSE kit	**Diagnosis (%):** DDD: 30 Spondylolisthesis: 70			
Pradhan, 2006 **Prospective** **ALIF**	36 (27 vs. 9)	rhBMP-2/ACS vs. ICBG/FRA Dosage unclear	**Age (yr):** 51.2 vs. 53.4 **Male (%):** 33.3 vs. 18.5	**Fusion at 24 months (%):** 44 vs. 63, p = NS **Additional Surgeries (%):** 26.0 vs. 33.3	No funds received in support of this work.	Poor
Rihn, 2009 **Retrospective** **TLIF Circ.**	119 (86 vs. 33)	rhBMP-2 vs. autograft Dosage: NR	Overall **Age (yr):** 47.4 **Male (%):** 53 **Diagnosis (%):** DDD: 11 DDD/HNP: 13 RHNP: 28 IS: 33 DS: 15	**Fusion (%):** 97 vs. 97, p = NS **Reoperations (%):** 9 vs. 12 **Adverse Events (%):** Lumbar Infection: 4 vs. 6 Radiculitis: 14 vs. 3 Patients with complications: 29 vs.46 Total complications: 43 vs. 54	Multiple author disclosures, funder NR.	Poor
Rogozinski, 2009 **Prospective** **PLF**	31 (15 vs. 16)	rhBMP-2 + ICBG vs. ICBG + bone stimulation large INFUSE kit	Age (yr): 46.5 vs. 44.3	Fusion at 24 months (%): 100 vs. 100 Back Pain: Significance NR at all time points	NR	Poor
Rowan, 2012 **Retrospective** **PLF/ PLIF Circ.**	104 (64 vs. 40)	rhBMP-2 vs. no rhBMP-2 (12 mg InductOs + collagen matrix (+BCS and bone marrow aspirate in 3 cases)	rhBMP-2 vs. control **Age (yr):** 54.8 vs. 56.5 **Male (%):** 48 vs. 30 **Diagnosis:** Degenerative spondylolisthesis: 50 vs. 55 DDD: 50 vs. 40 Central stenosis: 42 vs. 35 **Surgical Approach (%):** PLF: 70 vs. 75 PLIF: 30 vs. 25	**Fusion (%):** NR **Leg Pain**: Postop: 25 vs. 12, p = NS 3 months: 12 vs. 8, p = NS **Subsequent Intervention (%):** Overall: 8 vs. 10 Revision surgery: 2 vs. 0 Selective nerve root block: 5 vs. 5	No conflict of interest reported.	Poor
Singh, 2006	52	rhBMP-2/ACS	**Age (yr):** 65 vs. 54	**Fusion at 24 months (%):** 97 vs. 77	NR	Poor

Prospective PLF	(41 vs. 11)	+ ICBG vs. ICBG only large INFUSE kit	**Male (%):** 44 vs. 46			
Slosar, 2007 Prospective ALIF Circ.	75 (45 vs. 30)	rhBMP-2/AVS vs. allograft chips 3mg rhBMP-2/level	**Age (yr):** 45.1 vs. 43.6 **Male (%):** 51.1 vs. 60 **Tobacco use (%):** 18 vs. 8	**Patients with united grafts (%):** 100 vs. 83, p < 0.011 **Adverse Events (%):** Wound Dehiscence: 0 vs. 2.2 Wound Infection: 3.3 vs. 0 Revision Surgeries: 0 vs. 13	Research supported by a grant from Medtronic	Poor
Smucker, 2006 Retrospective Anterior Cervical	234 (69 vs. 165)	rhBMP-2 vs. Autograft 1.5 mg/Ml per level rhBMP-2	**Age (yr):** 52 vs. 50 **Male (%):** 49 vs. 49 **Smoker (%):** 29 vs. 15, p = 0.02	**Adverse Events (%):** Dysphagia: 7.2 vs. 1.2 Neck swelling: 27.5 vs. 3.6, p < 0.001	No funds received in support of this work.	Fair
Taghavi, 2010 Retrospective PLF	62 (24 vs. 18 vs. 20)	rhBMP-2/ACS vs. BMAA vs. Autograft Large INFUSE kit	**Age (yr):** 57.3 vs. 59.7 vs. 55.8 **Male (%):** 45.8 vs. 55.6 vs. 55.0 **Smokers (%):** 8.3 vs. 11.1 vs. 15.0 **Diabetes (%):** 8.3 vs. 5.5 vs. 10	**Fusion (%):** 100 vs. 77.8 vs. 100, (p = 0.005 when comparing groups 1 and 2 **Back pain, 24 months VAS scores:** NS between groups at all time points **Adverse Events (%):** Dural Tear: 4 vs. 0 vs. 5 Additional surgery: 8 vs. 22 vs. 10	No funds received in support of this work.	Poor
Vaidya, 2007 (C) Retrospective ACDF	46 (22 vs. 24)	rhBMP-2 vs. Allograft 1 mg/mL rhBMP-2/level + PEEK cage	**Age (yr):** 50 vs. 48 **Male (%):** 31.8 vs. 41.7	**Probable Fusion (%):** 100 vs. 96 **ODI:** p = NS (difference between groups at all time periods) **Arm Pain:** p = NS (difference between groups at all time periods) **Neck Pain:** p = NS (difference between groups at all time periods) **Adverse Events (%):** Dysphagia: 85 vs. 56 Reoperations: 9 vs. 4	NR	Poor

Vaidya, 2007 (I) **Prospective** **ALIF Circ./ TLIF Circ./ Anterior Cervical**	77 (36 vs. 41)	rhBMP-2/ACS vs. demineralized bone matrix lumbar = 2 mg BMP2/ level, cervical = 1 mg/level	**Age (yr):** 48 vs. 45 **Male (%):** 44 vs. 44 **Surgical Approach (%):** ALIF Circ.: 36 vs. 27 TLIF Circ: 33 vs. 44 ACDF: 31 vs. 29	**Fusion (%):** ALIF Circ: 100 vs. 100 TLILF Circ.: 100 vs. 100 ACDF: 100 vs. 92 **ODI improvement final follow-up:** 89 vs. 88 (surgical approach NR) **Adverse Events (%):** Dysphagia with ACDF: 55 vs. 0 Additional Surgery: 11 vs. 12	No benefits received from a commercial party related to this article.	Poor
Xu, 2011 **Retrospective** **Posterior Cervical**	204 48 vs. 156	rhBMP-2 vs. No rhBMP-2 Dosage: NR	**Age (%):** 60.3 vs. 60.8 **Male (%):** 47.9 vs. 64.1 **Diabetes (%):** 15.1 vs. 25.0 **Smoking history (%):** 30.2 vs. 22.4	**Fusion (%):** 100 vs. 87.6, p = 0.01 **Neck Pain at last follow-up:** 47.5 vs. 23.3, p = 0.003 **Adverse Events (%):** Infection: 10.9 vs. 10.9, NS Dysphagia: 6.3 vs. 3.8, NS Wound dehiscence: 2.2 vs. 5.1, NS Reoperation: 15.2 vs. 20.5, NS	NR	Poor
Yaremchuck, 2010 **Retrospective** **Anterior Cervical**	775 260 vs. 515	rhBMP-2 vs. No rhBMP-2 Dosage: NR	NR	**Adverse Events (%):** Percutaneous endoscopic gastrostomy: 2.3 vs. 0.8, p = 0.089 Tracheotomies: 3.1 vs. 0.6, p = 0.024 Readmissions: 8.8 vs. 5.0, p = 0.040 Dysphasia: 0.4 vs. 0.6, p = 0.888 Dysphagia: 6.9 vs. 3.3, p = 0.001 Dyspnea: 20.4 vs. 8.0, p = 0.001 Hoarseness: 2.3 vs. 1.2, p = 0.427 Respiratory failure: 13.1 vs. 4.7, p = 0.001	NR	

ACDF = anterior cervical discectomy and fusion, ACS = absorbable collagen sponge, ALIF = anterior lumbar interbody fusion, BCS = bovine collagen sponge, BMAA = bone marrow aspirate with allograft, Circ. = circumferential, DBM = Demineralized Bone MatrixDDD = degenerative disc disease, DS = degenerative spondylolisthesis, FRA = femoral ring allograft, HNP = herniated nucleus pulposus, IS = isthmic spondylolisthesis, LDH = lumbar disc herniation, PLF = posterior lumbar fusion, PLIF = posterior lumbar interbody fusion, rhBMP-2 = recombinant human bone morphogenetic protein-2, RHNP = recurrent herniated nucleus pulposus, TLIF = transforaminal lumbar interbody fusion

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Butterman 2008 USA ACDF	Yes	No; differences between groups on: gender distribution, smoking status, and levels fused	Baseline differences were maintained
Cahill 2009 USA Anterior/Posterior Cervical, Lumbar, Thoracic	Yes; Total = 328,468	No; several statistically significant differences	No
Cahill 2011 USA Lumbar	Yes; NIS database for 2006	No; differences in age and a number of other characteristics (table 1)	NA
Carragee 2011 USA ALIF	Yes; Consecutive patients meeting inclusion criteria. "Consecutive" in abstract	Yes; Matched Table but no information on diabetes	Yes; No withdrawals reported.
Crawford 2009 USA Posterior Cervical	Yes	Unclear; BMP group had 10% lower rate of males and 12% lower rate of smokers; differences not significant likely due to small sample size	Yes

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Butterman 2008 USA ACDF	Prospective study; pre and postoperative surveys given	Unclear	1 patient lost to follow-up between 2-3 years	Subgroup analysis of patients with 2 levels fused; some analysis of confounders such as effect of smoking on outcomes. However, within subgroup of patients with 2 levels, there was significantly more males in the BMP group (62% vs 21%, p=0.021), which wasn't controlled for.
Cahill 2009 USA Anterior/Posterior Cervical, Lumbar, Thoracic	Yes; retrospective review of NIS database using ICD-9 codes	Unclear	Unclear; missing data not described	Yes; Multivariate Analysis
Cahill 2011 USA Lumbar	Yes; retrospective review of NIS database using ICD-9 codes	Unclear	Unclear; missing data not described	Yes; multivariate logistic regression
Carragee 2011 USA ALIF	Unclear; Retrospective database study. Details of ascertainment not specified.	Yes; Post-operative complications were recorded by independent research assistants in a deidentified database.	No	No
Crawford 2009 USA Posterior Cervical	Unclear; details of retrospective chart review not clearly specified.	Possibly-"Hospital and clinic charts were reviewed by an individual not involved in the care of the patients."	No attrition reported	No, significant difference in follow-up time (30 months vs. 23 months)

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Butterman 2008 USA ACDF	No	Unclear; Specific postoperative complications were not prespecified	Poor	Information on age, gender, and levels provided along with subgroup analysis and analysis of effect of smoking, number of levels fused, and workers comp
Cahill 2009 USA Anterior/Posterior Cervical, Lumbar, Thoracic	Unclear	Yes	Good	
Cahill 2011 USA Lumbar	Unclear	Yes	Good	Although it does not differentiate between BMP-7 and BMP-2, we believe there is a very low likelihood of any use of BMP-7 because of its indication, humanitarian device restrictions and because we could find no trials of its use in the US in the cervical spine or any trials on clinicaltrials.gov.
Carragee 2011 USA ALIF	No	No; Retrograde ejaculation was not defined	Poor	
Crawford 2009 USA Posterior Cervical	Unclear; attrition NR	Yes	Poor	No adjustment for length of followup

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Crawford 2010 USA ALIF Circ.	Yes; Consecutive patients	No; some differences including BMP group was younger (43.5 vs 49.8 years, p=0.04) and had more anterior levels fused (3.3 vs 1.9, P=0.01)	No
Gerzten 2011 USA AxiaLIF Circ.	Unclear; 99 patients	Unclear; Only age and female comparison	Unclear
Glassman 2007 USA PLF	Unclear; Randomized but not sure if all the patients were included	Yes; table 1 shows certain risk factors similar. The age in the smokers group is slightly lower but acceptable.	Unclear
Hiremath 2009 USA Posterior Cervical	Yes	Yes; No-large difference in gender distribution 75% vs. 23% Male	N/A
Hoffman 2012 USA PLF/PLIF Circ.A16	Yes. Consecutive patients meeting inclusion criteria. Exclusions reported.	No. rhBMP-2 group had higher rates of diabetes (14.5% vs 7.2% vs 7.6%), cardiovascular disease (45.4% vs 23.9% vs 25.5%), steroid medication (21.4% vs 8.2% vs 9.0%) and NSAID medication (33.1% vs 11.4% vs 15.9%)	N/A
Joseph 2007 USA PLIF Circ./ TLIF Circ.	Unclear	Unclear; No comparison Table	Unclear
Katayama 2008 USA PLF	Unclear; Do not mention All/Consecutive	Yes; Patients served as own controls.	Yes; Paired

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Crawford 2010 USA ALIF Circ.	Unclear; retrospective review of various data sources, but criteria and process not explicitly described	Unclear; Fusion evaluated by two independent surgeons	Yes	No; No Adjusted Results
Gerzten 2011 USA AxiaLIF Circ.	Unclear	No; Don't mention	Yes	No; No adjusted Results
Glassman 2007 USA PLF	Unclear; smoking status was based on patient's preoperative response and extent of cigarette use was not determined.	Yes - Independent, Blinded Radiologist	No	No; No adjusted Results
Hiremath 2009 USA Posterior Cervical	Unclear; details of retrospective chart review not clearly specified.	Unclear	No attrition reported	No
Hoffman 2012 USA PLF/PLIF Circ.A16	Yes for exposures (CPT codes). Unclear for potential confounders; details of retrospective chart review not explicitly described.	No.	No information about missing data.	No
Joseph 2007 USA PLIF Circ./ TLIF Circ.	Unclear; criteria not described for how patients were retrospectively identified from hospital and clinical chart review	Unclear; outcome data underwent independent review	Yes; 1 Loss to follow-up	No
Katayama 2008 USA PLF	Unclear; insufficient description of diagnostic criteria	No; Independent surgeons	Yes; 1 died, 1 moved	No

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Crawford 2010 USA ALIF Circ.	No	Yes	Poor	
Gerzten 2011 USA AxiaLIF Circ.	No	No. Complications not prespecified.	Poor	
Glassman 2007 USA PLF	Unclear; attrition NR	Yes	Poor	
Hiremath 2009 USA Posterior Cervical	No	Unclear; Specific postoperative complications were not prespecified	Poor	
Hoffman 2012 USA PLF/PLIF Circ.A16	Unclear	No. Complications and ascertainment methods not explicitly defined.	Poor	
Joseph 2007 USA PLIF Circ./ TLIF Circ.	No	Unclear; ambiguous criteria for repeat CT scan (when fusion was "in doubt")	Poor	
Katayama 2008 USA PLF	No; less than 20% over 6 years.	Yes	Fair	

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Latzman 2010 USA Lumbar	Yes; all patients in an 8-year period	No; more females (22% vs 10%) and fewer diabetics (7% vs 37%) in BMP group	No
Lee 2010 USA PLF	No; required > 2-year follow-up	No; differences in sex, comorbidity, osteoporosis, smoking, fusion level and revision.	NA; not comparable at baseline
Lee 2011 USA PLF	No; required > 2-year follow-up	Yes; p values insignificant	Yes
Lindley 2012 USA ALIF	Unclear. "All" patients meeting inclusion criteria. But, exclusions not reported.	No. rhBMP-2 group was older (49 vs 35 years; $P<0.001$), more had primary diagnosis of pseudoarthrosis (14.8% vs 0; $P<0.05$), and fewer had single-level L5-S1 (31.5% vs 58.5%, $P<0.05$) and anterior surgery only (50% vs 100%, $P<0.001$)	N/A
Maeda 2009 USA ALIF Circ.	No; Consecutive but min. 2 year follow-up	Yes; Nothing was significant except follow-up time.	Yes; But the time frames were different between groups: 1997-2002 for ICBG and after 2002 for BMP.
Mindea 2008 USA TLIF Circ.	Yes; All consecutive patients	Unclear; Have a table but cannot differentiate between groups	Unclear

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Latzman 2010 USA Lumbar	Unclear; criteria not described for retrospective review of computerized VA hospital records	Unclear; Not Reported	Yes	No
Lee 2010 USA PLF	Unclear; retrospective review of medical record database, process not specified.	Unclear; No mention of blinding	NA, only included patients with > 2 years of follow-up	Yes; Multivariate Analysis
Lee 2011 USA PLF	Unclear; retrospective review of medical record database, process not specified.	Unclear; No mention of blinding	NA, only included patients with > 2 years of follow-up	Yes
Lindley 2012 USA ALIF	Unclear; process for retrospective chart review not explicitly described	Unclear; No mention of blinding	No	No.
Maeda 2009 USA ALIF Circ.	Yes; Prospective study. Unclear; criteria for determining spinal deformity NR	Unclear; Blinding not specified.	No; Missing data not specified	No
Mindea 2008 USA TLIF Circ.	Unclear; process for retrospective chart review not explicitly described	Unclear	No	No

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Latzman 2010 USA Lumbar	No	Yes	Poor	
Lee 2010 USA PLF	NA, only included patients with > 2 years of follow-up	Yes	Fair	
Lee 2011 USA PLF	N/A, only included patients with > 2 years of follow-up	Yes	Fair	
Lindley 2012 USA ALIF	Unclear	Unclear; chart notes verified by phone calls, but retrograde ejaculation was not explicitly defined.	Poor	
Maeda 2009 USA ALIF Circ.	Yes; No Lost to follow-up	Yes	Poor	
Mindea 2008 USA TLIF Circ.	No	Unclear; radiculitis criteria not explicitly defined	Poor	

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Mines 2011 USA Lumbar	Yes; inclusion criteria described and reported numbers and reasons for exclusions	Unclear; BMP administration was statistically significantly more common in younger patients, women, blacks, and those with diabetes or prior cholecystectomy, but differences were very small and likely not clinically important and all baseline differences were controlled for in the multivariate analysis	N/A, but the length of followup is different between two groups
Mummaneni 2004 USA TLIF Circ.	Yes; 40 out of 44	Yes; Table for all patients	Yes
Pradhan 2005 USA ALIF	Yes; Consecutive	No; Table 2 shows significant differences in baseline characteristics	No; They were not similar to start with
Rihn 2009 USA TLIF Circ.	Yes; 119 out of 130	Unclear; stated no significantly differences, but data NR	Unclear
Rogozinski 2012 USA PLF	Yes	No; more patients in BMP group had previously undergone a laminotomy or laminectomy (31% vs 7%) and I don't see gender mentioned at all.	No; Groups not comparable at baseline and different timeframes

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Mines 2011 USA Lumbar	Unclear for exposure: Because rhBMP-2 could not be specifically ascertained from Medicare claims, the ICD-9 code for BMP had to be used as a surrogate. Although this code also covers use of rhBMP-7, authors suspected that utilization of rhBMP-7 was low. Unclear for potential confounders: retrospective review of ICD-9 codes	Unclear	No	Yes
Mummaneni 2004 USA TLIF Circ.	Unclear; process for retrospective chart review not explicitly described	Unclear	Yes; 40 were followed through	No
Pradhan 2005 USA ALIF	Yes; prospective study with detailed information provided about diagnostic criteria.	Yes; An independent, blinded radiologist interpreted all radiographs	No	No
Rihn 2009 USA TLIF Circ.	Unclear; process for retrospective chart review not explicitly described	Unclear; Do not mention anything	Yes	No
Rogozinski 2012 USA PLF	Unclear; insufficient description of diagnostic criteria	Yes; Blinded and went through extra care to hide the surgery	No	No

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Mines 2011 USA Lumbar	No information provided about missing data	Yes	Fair	
Mummaneni 2004 USA TLIF Circ.	No; 4 out of 40	Unclear; radiculitis criteria not explicitly defined	Poor	
Pradhan 2005 USA ALIF	Unclear	Yes	Poor	
Rihn 2009 USA TLIF Circ.	No	Yes	Poor	
Rogozinski 2012 USA PLF	Unclear; attrition NR	Yes	Poor	

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Rowan 2012 Ireland PLF/PLIF Circ.	Yes; All patients were reviewed	No; Different time frames (BMP: 2007 - 2009 vs Control: 2005 - 2007) and previous fusion surgery variable is significantly different	N/A; groups not comparable at baseline
Singh 2006 USA PLF	Yes; 39/41	No; Higher age in BMP group (65.3 vs 54.2); number of levels fused NR	No; Groups not comparable at baseline.
Slosar 2007 USA ALIF Circ.	Yes; Consecutive	Unclear. Data on number of levels fused NR. Tobacco use 10% higher in BMP group. Although NSS due to small sample size, 10% difference may be clinically significant.	Yes; Some LTFU (1 in Control and 2 in BMP) but they do not mention if that was significant
Smucker 2006 USA Anterior Cervical	Yes	No; differences between groups on prior anterior cervical fusion, smoking, # levels fused, inclusion of C4-C5, use of a plate, and type of bone graft used	NA
Taghavi 2010 USA PLF	No; Minimum 2-year follow-up	Unclear; no statistically significant differences, but BMP group had more with single level (54.2% vs BMAA=38.9%) and fewer with 2 levels (16.7% vs 33.3% vs 25.0%)	Unclear
Vaidya 2007c ACDF	Yes	Yes on the characteristics listed but no information on smoking status, working status, spinal litigation status, etc	Unclear

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Rowan 2012 Ireland PLF/PLIF Circ.	Unclear	Unclear; Blinding not specified.	Yes, four (out of 64) in the rhBMP- 2 treated group and one (out of 40) in the non-rhBMP-2 treated group.	No
Singh 2006 USA PLF	Yes	Yes; all imaging studies blindly evaluated by 2 orthopedic surgeons and a board-certified radiologist	Yes; 96% available at 2 years (50/52)	No
Slosar 2007 USA ALIF Circ.	Unclear; prospective design, but diagnostic criteria NR	Yes; Three Independent reviewers, blinded to group status	Yes; 1 in Control and 2 in BMP	No
Smucker 2006 USA Anterior Cervical	Unclear; details of retrospective chart review not clearly specified.	Unclear	No; No attrition reported	Yes
Taghavi 2010 USA PLF	Unclear; retrospective review of medical records, but process not described	Yes; Blinded	NA, only included patients with > 2 years of follow-up	No
Vaidya 2007c ACDF	Retrospective study and unclear how information was obtained	Unclear; Radiologist and three observers were "independent"	No; No attrition reported	No

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Rowan 2012 Ireland PLF/PLIF Circ.	No, four (out of 64) in the rhBMP- 2 treated group and one (out of 40) in the non-rhBMP-2 treated group.	Unclear about accuracy of surgeon discretion in determining severity of leg pain based on criteria of of "when symptoms were disproportionately high or new".	Poor	
Singh 2006 USA PLF	Yes, 2 of 52 dropped out	Yes	Poor	
Slosar 2007 USA ALIF Circ.	No; 1 in Control and 2 in BMP	Yes; Molinari-Bridwell grading used to assess fusion. Scales identified that were used to measure clinical outcomes.	Poor	
Smucker 2006 USA Anterior Cervical	No	Yes	Fair	
Taghavi 2010 USA PLF	NA, only included patients with > 2 years of follow-up	Yes	Poor	
Vaidya 2007c ACDF	No	Unclear; Fusion not defined	Poor	No adjustment for confounding

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?
Vaidya 2007 (I) USA ALIF Circ./ TLIF Circ./ Anterior Cervical	Yes; Consecutive	Unclear; Matched for age and gender, but mean # of levels and other prognostic factors NR	Unclear; CT scans only available for 42% patients
Xu, 2011 Posterior Cervical	Yes, consecutive enrollment	No; differences were reported but rhBMP-2 group was 48% male vs 64% male in control group; # levels to be fused not given; 10% lower rate of diabetes in BMP group	NA
Yaremchuck, 2010 Retrospective Anterior Cervical	Yes, BMP-2 pateints enrolled	NR	NR

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?
Vaidya 2007 (I) USA ALIF Circ./ TLIF Circ./ Anterior Cervical	Unclear; prospective study but diagnostic criteria for indications not described	No; Don't mention blinding but independent radiologists	Unclear; attrition NR	No
Xu, 2011 Posterior Cervical	Unclear; details of retrospective chart review not clearly specified.	Unclear	Yes; 35 (17%) excluded due to radiographic follow-up < 6 months	No
Yaremchuck, 2010 Retrospective Anterior Cervical	Unclear; Retrospective study and the data were obtained using hospital claims system.	Unclear	No, Missing data not reported	Unclear, adjusted for diagnoses and time since the initial use of BMP. Patient charactersitics were not adequately adjusted for.

Evidence Table 8. Non-Medtronic cohorts: Risk of bias

Author Year Country Trial # or Name	Is there important differential loss to follow-up or overall high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Vaidya 2007 (I) USA ALIF Circ./ TLIF Circ./ Anterior Cervical	Yes	Yes	Poor	
Xu, 2011 Posterior Cervical	No for overall; yes for differential, control=29%, BMP=0	Fusion not defined	Poor	No adjustment for confounding; No information on levels fused
Yaremchuck, 2010 Retrospective Anterior Cervical	Unclear, NA	Unclear	Poor	

Evidence Table 9. Non-Medtronic Intervention Series

Author, year Approach Mean Follow-up	*n*	Intervention	Baseline Characteristics rhBMP-2 vs. control (unless otherwise noted)	Results	Funder	Quality
Abd-El-Barr, 2011 Cervical, Thoracic, and Lumbar 24.1 Months	17 (15 at final follow up)	rhBMP-2 + ACS with allograft or autograft	**Mean age, years:** 12.3 **Male, %:** 29 **Area fused, n:** Lumbar: 4 Thoracolumbar: 2 Thoracic: 3 Thoracic/cervical: 1 Cervical/occipital: 7	**Fusion rate, %:** 100 **Neurological improvement of 8 patients reporting deficits at presentation, %:** Improvement: 75 Stabilization: 25 **Complications, n:** Kyphosis: 1 Pneumothorax: 1 Screw revision: 2 Plate removal: 1 CSF leak: 1	Not reported.	Fair
Acosta, 2009 ALIF Circ., TLIF Circ., posterior spinal fusion with pedicle screw instrumentation 32 Months	200	rhBMP-2 + PSF/PSI	**Mean age, years:** 59 **Male, %:** 44 **Diagnosis, %:** DDD: 53.0 Degenerative spondylolisthesis: 26.0 Spondylolysis: 12.5 Scoliosis: 8.5 **Surgery type, %:** ALIF Circ: 65 TLIF Circ: 25 PLIF: 10	**Fusion rate, %:** Overall: 97 ALIF Circ: 100 TLIF Circ: 92 PLIF: 90 **Mean levels fused:** 3.2 **Total adverse events, %** : 8.5 **Complications, n:** Infection: 5 CSF Leak: 2 DVT: 3 Pneumonia: 1 Pseudoarthrosis: 6	Not reported.	Poor
Anand, 2006 TLIF Circ. 30 Months	100	rhBMP-2	**Mean Age, years:** 52 **Male, %:** 58 **Smokers, %:** 1 **Levels of Fusion, %:**	**Fusion rate, %:** 99% **ODI score:** Preoperative: 35 Final follow-up: 12	No funds were received in support of this work.	Poor

			Single-level: 76 Two-level: 24	**Radicular pain**, **%**: 3		
Anand, 2008 AxiaLIF Circ., XLIF Circ., DLIF Circ 75.5 Days	12	rhBMP-2 + ACS with local bone and Grafton Putty BDM	**Mean age, years:** 73 **Male, %**: 58 **Mean levels of fusion:** 3.5	**Adverse events, n:** Thigh dysesthesias: 3 Transient quadracep weakness: 1	Not reported.	Poor
Anderson, 2011 ALIF Circumferential Minimum 12 Months	50	rhBMP-2, INFUSE)	**Male, %:** 52 **Mean age:** 48.2 **Diagnosis, n:** Spondylolisthesis: 23 DDD: 24 Recurrent herniated disc disease: 2 Painful spondylolysis: 1 **Levels of fusion, %:** Single-level: 48 Two-level: 52	**Fusion rate, %:** Definitely Fused: 61 Probably Fusion: 31 Probably Not Fused: 8 **Adverse events, n:** Ileus requiring an NG tube for 2 days: 1 Scrotal Edema: 1 Tachycardia, Transient hypotension with trace pericardial effusion: 1 Urinary Retention: 1 Urinary Tract Infection: 1	Conflict of interest: None	Poor
Aryan, 2007 Cervical, Thoracic and Lumbar 20 Months	15	rhBMP-2 (INFUSE) + titanium cages with allograft and/or autograft	**Mean age, years:** 51 **Segment of fusion, n:** Cervical: 6 Thoracic: 5 Lumbar: 4 **Diabetes, n:** 4 **Smokers, n**: 4 **Osteoporosis/Osteopenia, n:** 2 **Vertebral Osteomyelitis, n:** 15	**Fusion, %:** 92.3 **Adverse events, n:** Superficial Wound Infection: 2 Dysphagia/Dysphonia: 4 Intraoperative Venous Injury: 1 Lower-Extremity Edema: 1	No conflict of interest reported.	Poor
Boakye, 2005 Anterior Cervical 13 Months	24 (23 in follow up)	rhBMP-2 (INFUSE) with PEEK cages	**Mean age, years:** 52 **Male, %:** 50 **Presenting diagnosis, %:**	**Fusion rate, %:** 100 **Clinical outcome according to Odom criteria, %:**	Not reported.	

Companion to Tumialan, 2008			Radiculopathy: 63 Myeloradiculopathy: 33 Quadriparesis: 4 **Levels of fusion, %:** Single-level: 50 Two-level: 38 Three-level: 13	Good/excellent: 95 Fair: 5 **Complications, n:** Transient dysphagia: 2 CSF leakage: 1 Transient C-5 paresis: 1 Transient vocal cord paresis: 1 **Heterotopic bone formation, n:** 3		
Carreon, 2008 All Approaches/ Levels Follow up not reported, study period = 4 years.	96	rhBMP-2 (INFUSE)	**Male, n:** 44 **Smokers, n:** 35 **1st Surgery w/ rhBMP-2, n:** Primary fusions: 90 Revisions: 6 Cervical: 28 Thoracic: 3 Lumbar: 65 **2nd Surgery w/ rhBMP-2, n:** Primary fusions: 25 All revisions: 71 Cervical: 24 Thoracic: 5 Lumbar: 67	**Adverse events, n:** First surgery: Complications (overall): 38 Hematoma/wound drainage: 9 Deep wound infection: 2 Second surgery: Complications: 27 Hematoma/wound drainage: 11 Deep wound infection: 5 **Difference in incidence of overall wound complications between first and second exposure to rhBMP-2:** NS, p = 0.839	No funds received in support of this work. One or more authors received benefits from a commercial party related to this manuscript.	Poor
Fahim, 2010 Posterior occipital, cervical, thoracic, lumbar, or lumbosacral 19 Months	19	rhBMP-2 + ACS with bone graft or a compression resistant matrix	**Mean age, years:** 12 **Male, n:** 11	**Fusion, %:** 100 **Adverse events, n:** Superficial wound infection: 2 Deep wound infection: 0 Bony overgrowth: 1	Authors have no financial or institutional interest in the drugs, etc described in this article.	Poor-Fair
Geibel, 2009 PLIF Circumferential 53.8 Months	48	rhBMP-2 (INFUSE) + impacted interbody or Titanium or	**Mean age, years:** Male: 50 Female: 51 **Male, %:** 52 **Smokers, %:** 35	**Fusion, %:** 100 **Subsequent surgeries at adjacent level, n:** 5 **ODI scores:** Preoperative: Not recorded	Supported by The Texas Center for Spinal Research and financed by	Fair

		PEEK cages	**Diabetic, %:** 2 **Diagnosis, %:** DDD: 100 Spondylolisthesis: 25 Radiculopathy: 100 Pseudoarthrosis: 0 HNP: 100	17 months post-surgery: 31.4	Medtronic Sofamor Danek.	
Glassman, 2007 PLF 27 Months	91	rhBMP-2 (INFUSE) with local bone or allograft cancellous chips or DBM or HA/TCP ceramic	**Mean age, years:** 60 **Male, %:** 40 **Smokers, %:** 15 **Diagnosis, n:** Disc pathology: 20 Spondylolisthesis: 17 Degenerative scoliosis: 2	**Nonunion rate, %:** 12 **Union rates for graft extenders:** Differences between graft extenders were not significant, p = .200	Research supported by grants from Norton Healthcare and Medtronic. Authors acknowledge a financial relationship related to this research.	Fair
Glassman, 2011 PLF 3 Months	1037	rhBMP-2 + ACS	**Mean age, years:** 58.4 **Male, %:** 38.6 **Smokers, %:** 29 **Diagnosis, %:** Stenosis: 24.4 Spondylolisthesis: 19.7 Disc pathology: 10.2 Nonunion: 11.1 Adjacent disc degeneration: 17.4 Post-discectomy instability: 12.3	**Mean surgical levels fused (range):** 1.8 (1-5) **Major complications, %:** Overall: 7.8 Deep wound infection: 2.12 Pneumonia: 1.64 Hematoma (−)culture: .96 **Minor complications, %:** Overall: 10.2 Dural tear: 5.59 Mental status change: 3.66 Ileus: 2.60 Urinary tract infection: 1.83 Superficial wound infection: 1.74	No funds were received in support of this work. One or more author will receive benefits from a commercial party related to the subject of this manuscript.	Fair
Hamilton, 2008	55	rhBMP-2	**Mean age, years:** 68	**Significant fusion, %:** 80	Not reported.	Poor

PLF 34 Months	(47 at FU)	(INFUSE)	**Male, %:** 45 **Symptoms, n:** Debilitating back pain: 47 Radicular symptoms: 46 Neurogenic claudication: 34	**Complications requiring additional surgery, n (%):** Total: 5 (9) Epidural hematoma: 2 Thecal sac compression: 1 Wound infection: 1 Radicular nerve impingement: 1 **Stenosis at adjacent level, n:** 10		
Hamilton, 2010 Posterior Cervical 45 Months Companion to Hamilton, 2011	23	rhBMP-2 + ACS	**Mean age, years:** 60.9 **Male, %:** 43 **Patients under age 10, n:** 2 **Surgical indications, n:** Atlantoaxial instability: 16 Basilar invagination: 6 Kyphoscoliosis: 1	**Fusion rate, %:** 100 **Complications, n:** 0	Source of support: nil. Conflict of interest: none declared.	Poor
Hamilton, 2011 Posterior Cervical 40 Months	53	rhBMP-2 + ACS	**Mean age, years:** Male: 55 Female: 56 **Male, %:** 42 **Patients under age 10, n:** 3 **Surgical indications, n:** Kyphosis/kyphoscoliosis: 22 Atlantoaxial instability: 16 Basilar invagination: 6 Fracture: 6 Other: 3	**Fusion rate, %:** 100 Lenke, Grade A: 94 Lenke, Grade B: 6 **Adverse events, n (%):** Total complications: 2 (4) Superficial wound infection: 1 Adjacent-level degeneration requiring revision surgery: 1	The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.	Poor
Helgeson, 2011 TLIF Circumferential 1 -2 Years	23	rhBMP-2 (INFUSE)	**Mean age, years:** 38.2 **Male, %:** 78 **Levels of fusion, n:** Single-level: 12 Two-level: 6 Three-level: 5	**Fusion rate, %:** 83 **Osteolysis, %**: At 3 to 6 months: 54 At 1 to 2 years: 41	Funding from Medtronic and Defense Advanced Research Projects Agency. Author relationships	Poor

					with Medtronic and U.S. Government.	
Hodges, 2012 Posterior Cervical Minimum 12 Months	29	rhBMP-2 + ACS with autograft or allograft bone	**Mean age, years:** 50 **Male, %:** 45 **Mean BMI:** 29 **Tobacco use, %:** 21 **Diabetes, %:** 14 **Previous anterior cervical Pseudoarthrosis, %:** 28 **Operative levels, n:** 69	**Pseudoarthrosis, %:** Patients: 10.3 Levels: 5.8 Patients with previous pseudoarthrosis: 12.5 (1 of 8) Patients with a previous anterior fusion at an adjacent level: 20 (2 of 10)	No relevant financial information to disclose.	Poor
Jagannathan, 2009 TLIF Circ. 34 Months	87 (80 at FU)	rhBMP-2 (INFUSE) with allograft spacer	**Mean age, years:** 63.2 **Male, %:** 27.5 **Previous surgery, %:** 57 **Preoperative findings, %:** Recurrent disc herniation: 44 Spondylolisthesis: 81 Preoperative deformity: 75 Scoliosis: 25 Sagittal imbalance: 50	**Adverse events, %:** Reoperation: 4 Pseudoarthrosis: 3	Royalties received from Medtronic for spinal instrumentation devices. Authors have no other disclosures.	Poor
Kleeman, 2001 ALIF Maximum 24 months Companion	22 (21 at FU)	rhBMP-2 + BCS with NOVUS LT cages	**Mean age, years:** 38 **Male, %:** 36 **Smokers, %**: 9	**Fusion rate, %:** 100 **ODI score:** Preoperative: 47 6 months: 16 12 months: 11 **SF-36:** Improvement in all categories	Conflict of interest category: 16	
Klimo, 2009 Anterior Cervical 14.5 Months	22	rhBMP-2 with Cornerstone PEEK implants	**Mean age, years:** 53 **Male, %:** 64 **Mean BMI:** 27.1 **Smokers, %:** 27 **Previous posterior cervical Foraminotomies, n:** 2 **Levels fused, n:** 38	**Fusion rate, %:** 89 **Adverse events, %:** Recurrent laryngeal nerve palsy: 1 Neck swelling: 1 Pseudoarthrosis: 4 **Levels experiencing, %:** Excessive bone growth: 68	Author disclosure: none.	Fair

				Moderate of severe end-plate resorption: 57		
Knox, 2011 TLIF Circ. 4.3 Months	58	rhBMP-2 (5 mg per level) + ACS with PEEK Capstone or Perimeter cage and local autograft	**Mean age, years:** 36.8 **Male, %:** 72 **Levels fused, n:** 77 **Levels of fusion, n:** Single- level: 39 Two-level: 19	**Osteolysis, %:** Patients with: 28 Levels with: 26 **Incidence of graft subsidence**, **%:** 10 **Incidence of cage migration, %:** 9	No funds or benefits received in support of this work.	Poor
Kuklo, 2004 TLIF Circ. 12.4 Months	22	rhBMP-2 (INFUSE) + ACS with HYDROSORB	**Mean age, years:** 41.6 **Male, %:** 77 **Diagnosis, %:** DDD: 27 Ishemic spondylolisthesis: 23 Degenerative scoliosis: 18 Degenerative spondylolisthesis: 18 Failed-back syndrome: 9 Congenital scoliosis: 5 **Levels fused, n:** 39	**Fusion rate of levels fused, %:** Levels with radiographic fusion: 87 Levels with fusion according to CT scan: 97 **Adverse events, n:** Instrumentation failure: 1	Not reported.	Poor
Lanman, 2004 (L) TLIF Circ. 9.8 Months	43 (42 at 6 month FU, 11 at 12 month FU)	rhBMP-2 + ACS with HYDROSORB implant	**Mean age, years:** 48.6 **Male, %:** 56 **Diagnosis, %:** Discogenic pain: 79 Spondylolisthesis: 12 Nonunion from previous surgery: 9 **Levels fused, n:** 56 **Levels of fusion, %:** Single- level: 70 Two-level: 30	**Fusion rate, %:** At 3 months: 45 (19 of 42 patients) At 6 months: 98 (40 of 41 patients) At 12 months: 100 (11 of 11 patients)	Primary author is a paid consultant for Medtronic.	Poor
Lanman, 2004 (E)	20	rhBMP-2	**Mean age, years:** 46.2	**Fusion rate, %:**	Primary author	Fair

Anterior Cervical March 31, 2003 – July 3, 2003		(INFUSE) + ACS with Cornerstone) HSR spacer	**Male, %:** 70 **Presenting diagnosis, n:** Disc herniation: 8 DDD: 5 Discogenic pain: 2 Nonunion: 4 Spondylosis: 3 **Levels of fusion, %:** Single-level: 70 Two-level: 20 Three-level: 10	At 3 months: 100 (20 of 20 patients) At 6 months: 100 (17 of 17 patients) **Adverse events, n:** Severe dysphagia: 1 Additional surgery for nonunion: 1	is a paid consultant for Medtronic.	
Luhmann, 2005 ALIF, PLF, circumferential 17.9 Months	70	rhBMP-2 with titanium mesh cages	**Mean age, years:** 49.3 **Male, %:** 20 **Surgical approach, n:** ALIF: 46 PLF: 41 Compassionate use (CU): 8 Circumferential: 25 **Diagnosis, n:** Degenerative scoliosis: 11 Transition syndrome: 10 Pseudoarthrosis: 8 Spondylolisthesis: 6 AIS/congenital scoliosis: 4 Other: 7 **Levels fused, n:** 263 **Previous surgery, %:** 61	**Fusion rate, %:** ALIF: 96, 90 of 93 levels PLF: 93, 110 of 118 levels CU: 100, 52 of 52 levels **Complications:** Superficial wound dehiscence: 1 Deep wound infection: 1 Wound hematoma: 1	No funds or benefits received in support of this work.	Poor
Mannion, 2011 PLIF Circ., TLIF Circ. 7.1 Months	30	rhBMP-2	**Mean age, years:** 51 **Male, %:** 47 **Levels fused, n:** Total: 36 PLIF, n: 4 TLIF, n: 32	**Fusion rate, %:** 7.1 Months: 92 12 Months: 97 **Adverse events, n:** Heterotopic ossification: 2 Perineural cyst formation: 2 Non-union: 1	Multiple author disclosures regarding Medtronic: consulting, speaking arrangements,	Poor

				Revision surgery: 1	fellowship support, advisory board	
McClellan, 2006 TLIF Circ. 4.4 Months	26	rhBMP-2 (INFUSE) + ACS with various interbody implants	**Mean age, years:** 46 **Male, %:** 54 **Total levels fused, n:** 32	**Fusion rate, % of levels:** 59 **Bone resorption rate, % of levels without fusion:** 92, 12 of 13 levels **Osteolytic defects, n:** Mild: 11 Moderate: 4 Severe (Graft Subsidence/ Loss of End plate integrity): 7	Not reported.	Poor
Meisel, 2008 PLIF Circ. 24 Months	17	rhBMP-2 + BCS with Telamon PEEK cages	**Mean age, years:** 67 **Male, %:** 47 **DDD, %:** 100	**Fusion rate, %:** 3 months: 100% of patients with evidence of vertebral endplate osteoclastic activity 6 months: 100% of patients with radiographic evidence of fusion **Intracanalar bone formation, n**: 1	Not reported.	Poor
Mulconrey, 2008 Thoracic and Lumbar: ALIF, PLF 2.6 Years	98	rhBMP-2 + ACS with titanium mesh cage (ALIF) vs. rhBMP-2 + ACS with local bone graft and TCP-HA vs. rhBMP-2 (PLF) + collagen resistant matrix with TCP-HA	**Mean age, years:** 51.4 **Male, %:** 14 **Patients per group, n:** Group 1: 47 Group 2: 43 Group 3: 8 **Total levels fused:** 308 **Mean levels with BMP use:** 3.15 **Preoperative factors, %:** Medical comorbidities: 26 Tobacco use: 17 Revision surgery: 34 Previous laminectomy: 51 Pseudarthrosis: 27	**Fusion rate, %:** Overall: 95 Group 1: 91 Group 2: 97 Group 3: 100 **Fusion ratings by group (1-5, 1 = fused):** Group 1: 1.39 Group 2: NR Group 3: 1.03 **Fusion rate, % levels:** Group 1: 91 Group 2: 97 Group 3: 100 **Additional surgery, n:** 1 **Pseudoarthrosis, %:** 5	No funds received in support of this work and no benefits from a commercial party received from a party related to the subject of this manuscript.	Poor

Oetgen, 2010 Lumbar, Thoracic, Cervical Spine, also Femur, Tibia, and Ribs 22 Months	81	rhBMP-2 with a variety of approaches	**Mean age, years:** 11.3 **Male, %:** 46 **Skeletally immature, %:** 65 **Surgical procedures, n:** 91 **Region of surgery, n:** Thoracic/lumbar spine: 47 Cervical spine: 5 Femur: 7 Tibia: 21 Ribs: 1	**Overall complication rate, %:** 17.5 (16 problems in 91 procedures) **Complication rate in patients with multiple exposures to BMP, %:** 27 (3 of 9 patients) **Complications, n:** Wound drainage: 5 Wound swelling: 2 Wound dehiscence: 2 Enlargement of optic glioma: 1 Deep infection: 3 (2 of 3 spine) Compartment syndrome: 1 (tibia) Progressive myelopathy: 1 (cervical) Dural fibrosis: 1 (spinal)	Not reported.	Poor
O'Shaughnessy, 2008 ALIF, TLIF, and circumferential 40 Months	20	rhBMP-2 with Titanium mesh (90%), PEEK (5%) or femoral allograft (5%)	**Mean age, years:** 55 **Male, %:** 60 Vertebral Osteomyelitis:20 **Region of surgery, %:** Thoracic: 5 Thoracolumbar: 25 Lumbar: 55 Lumbosacral: 15 **Surgical approach, n:** Anterior/posterior: 40 Anterior: 20 Posterior/posterolateral: 25 Direct posterior: 15	**Fusion rate, %:** 100 **Intraoperative complications, n:** Pseudoarthrosis: 1 Durotomy: 1 Major vessel injuries: 2 Deep venous thrombosis: 2 Superficial wound dehiscence: 1 *C. difficile* colitis: 1 **Neurological status Frankel grade, n:** Improved: 6 Stable: 14	Corporate/ industry and foundation funds received in support of this work. One or more authors received benefits from a commercial party related to the subject of this manuscript.	Poor
O'Shaughnessy, 2012 Upper and Lower Thoracic 2.8 Years (UT)	58	rhBMP-2	**Mean age, years:** 55.7 **Region of surgery, n:** Upper thoracic (UT): 20 Lower thoracic (LT): 38 **Smokers, %:**	**ODI score, preop vs. final:** UT: 37.1 vs. 21.9, $p = 0.001$ LT: 35.8 vs. 16.8, $p < 0.001$ **Complication rate, UT vs. LT, %:** Overall: 50 vs. 37	Institutional funds received in support of this work. One or more authors	Poor

3.1 Years (LT)			UT: 5 LT: 5 **Comorbidities, %:** UT: 50 LT: 45 **Mean fused segments:** UT: 15.8 LT: 8.6	Perioperative: 30 vs. 16 Pseudoarthrosis: 20 vs. 5 Proximal junctional kyphosis: 10 vs. 18 Revision surgery: 20 vs. 11	received benefits from a commercial party related to the subject of this manuscript.	
Owens, 2011 TLIF Circ. 29.8 Months	204	rhBMP-2 + ACS with local autograft, iliac crest bone graft and/or other graft extender and PEEK cage	**Mean age, years:** 49.3 **Male, %:** 44.6 **Smokers, %:** 40.7 **Diagnosis, %:** Spondylolisthesis: 27 Instability: 5.4 Stenosis: 10.8 Scoliosis: 2.9 Disc pathology: 26 Nonunion: 1.5 Adjacent level degeneration: 8.3 Post discectomy instability: 18.1 **Levels fused, %:** One level: 69.9 Two level: 20.1	**Complications, %:** Overall: 21.6 Pneumonia: 0.5 Vascular Injury: 0.5 Neurologic: 3.4 Wound infection: 1.5 Wound hematoma/seroma: 1 Radiculopathy: 2.9 Superficial wound dehiscence: 1.0 Ileus: 2.9 Urinary tract infection: 1.0 Other: 8.8	Conflict of interest statement: none.	Fair
Rinh, 2009 TLIF Circ. 27.4 Months	53 (48 at final follow up)	rhBMP-2 (InFUSE) + ACS	**Mean age, years:** 48.3 **Male, %**: **52** **Smoker, %:** 35 **Diagnosis, %:** DDD: 13 DDD/HNP: 6 RHNP: 29 IS: 35 DS: 15	**Fusion Rate, %:** 96 **Adverse events, n:** Lumbar infection: 1 Lumbar hematoma: 1 Lumbar seroma: 1 Radiculitis: 8 Ectopic bone formation: 1 Vertebral osteolysis: 3 Dural tear: 1	No sources of funding were used to perform this study.	Fair

			Failed lami fusion: 2 **Previous surgery, %:** 44	Nonunion: 2 Malpositioned instrumentation: 1		
Scheufler, 2010 TLIF Circ. 19.6 Months	30	rhBMP-2	**Mean age, years:** 73.2 **Male, %:** 40 **Presenting Diagnosis, %:** Disabling back pain: 90 Radiculopathy: 77 Neurogenic Claudication: 47 **Medical comorbidities, %:** Arterial hypertension: 43 Osteoporosis: 33 Diabetes: 30 Full metabolic syndrome: 20 Cardiac arrhythmias: 23 Congestive heart disease: 27 Morbid obesity: 17 Rheumatoid arthritis: 77 **Fused segments, n:** 179	**Fusion according to rigid CT-based criteria, %:** Segmental fusion: 90 Intersomatic fusion: 92 **Fusion according to standard radiographic assessment, %:** Segmental fusion: 98 Patient fusion: 90 **Adverse events, n:** Lumbosacral pseudoarthrosis: 3 Revision surgery: 10	The primary author is a consultant for Medtronic. Authors have no additional personal interest in any materials discussed in this article.	Fair
Sethi, 2011 Anterior Cervical, ALIF, TLIF, PLIF Maximum: 24 Months	95	rhBMP-2 with PEEK cage or allograft bone	**Mean age, %:** 51 **Male, %:** 55 **Surgical approach, n:** ALIF: 23 TLIF: 36 PLIF: 2 ACDF: 34 **Interbody spacer type, %:** PEEK: 62 Allograft bone: 38 **Levels fused by area, n:** Lumbar: 87 Cervical: 50	**Fusion rate with PEEK, %:** Cervical spine, 6 months: 91 Cervical spine, 9 months: 100 Lumbar spine, 6 months: 56 Lumbar spine, 9 months: 83 Lumbar spine, 12 months: 100 **Fusion rate with allograft spacer, %:** Cervical spine, 6 months: 82 Lumbar spine, 6 months: 88 Lumbar spine, 12 months: 100 **Adverse events, n:** Cage migration: 11 (10/11 with TLIF) Mean prevertebral swelling (ACDF): 1 week: 15.7 mm 2 weeks: 11.8 mm	Not reported.	Fair

				3 weeks: 8.0 mm Other adverse events discussed, but no numbers provided: heterotopic bone formation		
Shen, 2010 ACDF 2.9 Years	127	rhBMP-2 with structural allograft or PEEK cage	**Male, %:** 43 **Mean age, years:** 54 **Prior surgery, %:** Prior ACDF: 44 Postlaminectomy kyphosis: 5 **Number of levels fused, %:** 3 levels: 59 4 levels: 27 5 levels: 14 **Fusion segments, n:** 451	**Pseudoarthrosis rate, %:** By patient: 10 By fusion segments: 3 In 3-level fusion: 4 In 4-level fusion: 17, p = 0.0251 when compared with 3-level rate In 5-level fusion: 22, p = 0.0245 when compared with 3-level rate **Swelling/ difficulty swallowing:** n not provided but noted in most patients initially following surgery.	No funds were received in support of this work. One or more authors received benefits from a commercial party related to the subject of this manuscript.	Fair
Shields, 2006 ACDF and anterior cervical vertebrectomy and fusion Follow up not reported, study period = July 2003 to March 2004.	151	rhBMP-2 with Hydrosorb (n = 135) or cornerstone (n = 3) or pyramesh (n = 13)	**Mean age, year:** 49.9 **Male, %:** 41 **Diagnosis, %:** Spondylosis: 74 Disc herniation: 26 **Symptoms, %:** Neck pain: 98 Arm pain: 90 Arm numbness: 70 Arm weakness: 56 **Previous cervical surgical procedures, %:** 20 **Smoker, %:** 39 **Hypertension, %:** 35 **Diabetes, %:** 10	**Adverse events, %:** Hematoma: 10 Requiring surgical evacuation, n: 8 Readmission (for dysphagia/ respiratory difficulty/ incisional swallowing): 8 Syndrome of inappropriate secretion of antidiuretic hormone: 1 Partial lung collapse: 1 Horner Syndrome: 2 Vocal cord palsy: 2 Superficial stitch abscess: 1 Implant dislodgement: 2 Graft resorption: 1	No funds were received in support of this work. One or more authors received benefits from a commercial party related to the subject of this manuscript.	Poor
Stachniak, 2011 Anterior Cervical Maximum 9 Months	30 (21 at 6 months)	rhBMP-2 + ACS with PEEK spacer	**Mean age, years:** 52.5 **Male, %:** 20 **Mean BMI:** 28.8 **Risk factors, %:**	**Fusion rate, %:** 6 months: 95 9 months: 100 **Dysphagia according to SWAL-QOL**	Financial support from Medtronic. Primary author	Poor

			Smoking: 33 Diabetes: 13 Obesity: 43 **Previous ACDF, n:** 1	**Questionnaire at 2 weeks, %:** Frequent choking on food: 19 Frequent choking when drinking: 5 Frequent food sticking in throat: 48 **Peak cervical soft tissue swelling, mean:** 21.8 mm at 2 weeks **Mean scores at baseline (postop Day 1), 2 weeks, 6 weeks, 10 weeks, 6 months (n):** Neck disability index: 23.9 (29), 21.8 (28), 15.2 (24), 12.7 (22), 11.2 (21) Neck pain: 15.3 (28), 9.6 (28), 8.0 (28), 7.8 (25), 5.8 (20) Arm pain: 12.8 (28), 8.8 (28), 6.3 (28), 5.6 (25), 4.7 (20)	was a former consultant for Medtronic.	
Stambough, 2009 PLF 28.6 Months	36	rhBMP-2 (Infuse) + ACS with autogenous bone and allograft	**Mean age, years:** 66.3 **Male, %:** 22 **Smokers, %:** 14 **Levels of fusion, n:** Single-level: 20 Two-level: 16	**Fusion rate, %:** Lenke grading system: 88 CT scan: 97 **Mean peri- and postoperative verbal rating scale scores (times not given):** Back pain: 7.7 to 3.9 Leg pain: 6.02 to 2.02, $p < 0.05$ **Mean pre- and post-operative ODI scores (times not given):** 54 to 14, $p < 0.05$ **Improvement in select SF-26 areas (bodily pain, vitality, mental health, social functioning):** score not provided, $p < 0.05$	Research supported by an unrestricted research grant from Medtronic.	Fair
Subach, 2010 ALIF 12 Months	47	rhBMP-2 with LT-cage lumbar tapered fusion device	**Mean age, years:** 44 **Male, %:** 49 **Mean BMI:** 26.8 **Smoker, %:** 32 **Cage placement, n:**	**Mean wide cage vs. narrow cage subsidence, mm:** Anterior region: 2.16 vs. 3.50 Posterior region: 1.25 vs. 3.33 Significance: subsidence significantly	Not reported.	Poor

			Narrow: 12 Wide: 35	greater in narrow cage group **Subsidence in narrow cages vs. wide cage, %:** 83 vs 43, $p < 0.05$		
Tumialan, 2008 Anterior Cervical 16.7 Months	200 (193 for long term follow up)	rhBMP-2 (Infuse) with PEEK cage	**Mean age, years:** 53.9 **Male, %:** 48.5 **Active smokers, %:** 18.5 **Previous anterior cervical surgery, %:** 15.5 **Levels of fusion, n:** Single-level: 96 Two-level: 62 Three-level: 36 Four-level: 6 **rhBMP-2 dosage, n:** Group A, 2.1 mg: 24 Group B, 1.05 mg: 93 Group C, 0.7 mg: 83	**Odom outcome, % (n = 193):** Good: 85 Fair: 12.4 Poor: 2 **Overall adverse events, %:** 7 **Overall reoperation, %**: **2** For postoperative hematoma, n: 2 For postoperative seroma, n: 2 **Dysphagia, n (%):** 14 (7) Mild dysphagia: 6 (3), 0 patients symptomatic at 6 weeks Moderate dysphagia: 3 (1.5), 2 patients symptomatic at 6 months Severe dysphagia: 5 (2.5), 4 required PEG tube, 1 permanently **Excess interbody bone formation**: noted in first 24 patients, dosage decreased thereafter.	No financial support received for the generation of this study. Authors disclosed consultancy relationships with Sofamor Danek, Medtronic, and DuPuy Spine.	Poor
Tumialan, 2012 ALIF, PLIF and TLIF 24.6 Months	102	rhBMP-2 with stand-alone tapered cages or femoral ring allograft or stand-alone PEEK spacer	**Mean age, years:** 34 **Male, %:** 89 **Surgical indication, %:** Discogenic back pain: 59 Spondylolisthesis: 39 Spinal stenosis: 2 **Surgical approach, %:** ALIF: 38 Posterior (PLIF or TLIF): 62 **Tobacco use, %:** 20	**Radiographic evidence of fusion, n:** Evidence of bridging bone: 84 Evidence of pseudoarthrosis: 8 Indeterminate evidence of fusion: 10 **Return to active duty**, **%:** 55 **Revision surgery, n:** 3 **Complications, n:** Dural tear: 2 Iliac vein injury: 1 Wound infections: 4 Nerve root compression: 1 Deep venous thrombosis: 1 Hardware complications: 3	Primary author is a consultant for Medtronic. Authors have no additional personal interest in any materials discussed in this article.	Fair

Vaidya, 2008 Anterior Cervical, ALIF, TLIF circ, PLIF circ 26 Months Companion to Sethi, 2011	59	rhBMP-2 with PEEK cages	**Mean age, year:** 52 **Male, %:** 41 **Surgical approach, n:** ACDF: 23 ALIF: 10 TLIF: 24 PLIF: 2 **Levels fused, n:** 82 ACDF: 32 Lumbar: 50	**Fusion rate, %:** ACDF at 6 months: 91 ACDF at 9 months: 100 All lumbar categories at: 6 months: 72 9 months: 83 12 months: 100 **Adverse events, n:** Cage migration: 11 Requiring revision surgery: 8 **Mean clinical outcome scores:** Improvement noted in all categories	Not reported.	
Villavicencio, 2005 TLIF Circ. 20.6 Months	74 (71 completed follow up of at least 12 months)	rhBMP-2 (Infuse)+ ACS with structural bone allografts and locally harvested autograft	**Mean age, years:** 56.9 **Male, %:** 38 **Previous lumbar surgery, %:** 34 **Approach, %:** Minimally invasive: 58 Open approach: 42 **Levels of fusion, %:** Single-level: 60 Two- level: 36 Three-level: 4	**Fusion rate, %:** At 12 months: 100 At 24 months: 100 **Surgical complications, n:** Total: 29 CSF leak: 3 Screw malposition: 12 Graft malposition: 1 Hematoma: 2 Infection: 2 Neural injury: 9	Not reported.	Poor
Wang, 2006 ALIF Circ. 4.9 to 7.2 Months (depends on group)	32	rhBMP-2 with SPIRE (n = 21) or Open BPS fixation (n = 3) or MAST BPS fixation (n = 8)	**Mean age, years:** SPIRE: 46.2 Open PS: 49.5 MAST PS: 48.8 **Males, %:** 63	**Fusion rate, %:** NR **Pseudoarthrosis, %**: 0 **Hardware failure, %:** 0 **Intraoperative complications, %:** 0	One author is the inventor of SPIRE devices and receives royalties from Medtronic.	Fair

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
Abd-El-Bar 2011	Unclear; inclusion criteria described, but required ≥ 3 months' follow-up	Unclear; retrospective collection of data, methods not explicitly described	No; But independent	Yes; 12% excluded due to insufficient radiographic follow-up
Acosta 2009 USA ALIF Circumferential	Yes; consecutive patients presenting with symptomatic degenerative disease of the lumbar spine.	Yes	Unclear; Assessors not specified.	No
Anand 2006 USA TLIF	Yes; Consecutive patients	Yes; Smoker/Compensation	Unclear	No
Anand 2008 USA Circumferential	Yes; 12 Consecutive patients	No; Do not mention any confounders	Unclear; Do not mention anything about blinding	No
Anderson 2011 USA ALIF Circumferential	No; Focused only on the 60% (50/83) with ≥ 12 months follow-up.	Yes	Yes; 3 observers blinded to each other, patient identity, clinical status.	Yes
Aryan 2007 Cervical, thoracic, and lumbar	Unclear; Does not say all or consecutive	Yes	No; But independent	Yes
Carreon 2008 All approaches/ Levels	Yes; 96 Consecutive patients	Yes; Smoker, gender but do not mention age	Unclear; Do not mention	No

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Abd-El-Bar 2011	Yes; Detailed description of patient demographics and potential confounders. Smoking status, presence of diabetes, and prior surgery at the same level were not reported, but unclear of relevance in pediatric population.	No	No	Fair	
Acosta 2009 USA ALIF Circumferential	Unclear; Heterogeneity not specified and no analyses performed.	Unclear; Attrition NR.	Yes	Poor	
Anand 2006 USA TLIF	No	Unclear	Yes	Poor	
Anand 2008 USA Circumferential	No	Unclear	Yes	Poor	
Anderson 2011 USA ALIF Circumferential	Unclear; Heterogeneity not specified and no analyses performed.	Radiographs: No, available for 90% (45/50). Clinical outcome data: Yes, only available for 44% (22/50)	Yes	Poor	
Aryan 2007 Cervical, thoracic, and lumbar	No	Yes	Yes	Poor	
Carreon 2008 All approaches/ Levels	No	Unclear	Yes	Poor	

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
Fahim 2010 Posterior occipital, cervical, thoracic, lumbar, or lumbosacral	Yes; 19 consecutive patients	No; Just mention age and gender but lists out all the patient characteristics individually?	No; But independent	No
Geibel 2009 USA PLIF	Yes; 48 consecutive patients	Yes; Known source as well as various confounders	No; Independent Radiologist	Yes; 45 out of 48 patients available for follow-up
Glassman 2007 USA PLF	Unclear; Selection criteria and timeframe not described	Unclear; retrospective review of medical records, methods not explicitly described	No; 2 independent orthopedic spine surgeons	No
Glassman 2011 USA PLF	Yes; Consecutive series of 1037 patients	Unclear; retrospective review of medical records, methods not explicitly described	Unclear	Unclear; Completeness of data not described
Hamilton 2008 USA PLF	Yes; 47 out of 55	Yes	No; Independent	Yes; 14% excluded (8/55)
Hamilton 2011 Cervical	No; Only patients with 2 years of followup included	Unclear; Retrospective chart review; specifics not given	No; Independent Radiologist	Yes; 12% were excluded due to not having 2 years of follow-up
Helgeson 2011 USA TLIF	Yes; 23 out of 88	Unclear; Mentioned nothing	Unclear; No mention of any blinding	No
Hodges, 2012	No; Inclusion/exclusion criteria explicitly described, but required ≥ 12 months' follow-up.	Unclear; methods not described	No; single reviewer	Yes; 22% refused to participate

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Fahim 2010 Posterior occipital, cervical, thoracic, lumbar, or lumbosacral	No	Unclear	Yes	Poor - Fair	
Geibel 2009 USA PLIF	No; Oswestry Scores were the outcome used t-test so no	No; 3 out of 48	Yes	Fair	
Glassman 2007 USA PLF	Yes; Detailed description of patient demographics and potential confounders	Unclear	Yes	Fair	
Glassman 2011 USA PLF	Yes; Detailed description of patient demographics and potential confounders	Unclear	Yes	Fair	
Hamilton 2008 USA PLF	No	No	Yes	Poor	
Hamilton 2011 Cervical	No; No statistical analysis but stratification by diagnosis	No	Yes	Poor	No information on smoking, diabetes, or prior surgery.
Helgeson 2011 USA TLIF	No	Yes; 65 out of 88…used only 23	Yes	Poor	
Hodges, 2012	Yes; sufficient information on all required variables.	Yes.	Yes for pseudoarthrosis; no for others	Poor	

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
Jagannathan 2009 USA TLIF	No; Minimum 2-year follow-up included	Unclear	Unclear	Yes; 7 out of 87
Klimo, 2009 Cervical	Yes	Unclear	No; "Analysis of the CT scans was done by both treating surgeons independently; discrepancies were evaluated jointly."	No attrition reported
Knox 2011 USA TLIF	Yes; Consecutive patients	Unclear	Unclear	No
Kuklo 2004 USA TLIF	Yes; 22 out of 35 total	Yes; Table	No; Don't mention blinding	No
Lanman 2004 (L) USA TLIF	No; Does not mention out of how many or consecutive	Yes	Unclear; Do not mention	Yes
Lanman, 2004 (E) Cervical	Yes	Yes	Unclear	No
Luhmann 2005 USA	No; Focused only on the 29% (70/241) with ≥ 12 months follow-up.	Yes	Yes; Surgeons not involved in operative procedure assessed radiographs and CT scans	No
Mannion 2011 USA PLIF	No; 30 Patients	No; The source is vague and have not mentioned many confounding factors	Yes; Blinded Radiologist	No; No attrition reported

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Jagannathan 2009 USA TLIF	No	No	Yes	Poor	
Klimo, 2009 Cervical	NA	No	Yes	Fair	
Knox 2011 USA TLIF	Unclear	Unclear	Yes	Poor	
Kuklo 2004 USA TLIF	No	No	Yes	Poor	
Lanman 2004 (L) USA TLIF	No	Yes; 11 by the 12-mo follow up time	Yes	Poor	
Lanman, 2004 (E) Cervical	NA	No	Yes	Fair	Information on revision surgery given by patient
Luhmann 2005 USA	Unclear; Only mentioned finding no association between fusion and gender, age, amount of rhBMP-2 used and presence of pseudoarthrosis.	Unclear; Attrition NR.	Yes	Poor	
Mannion 2011 USA PLIF	No	Unclear	Yes	Poor	

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
McClellan 2006 USA TLIF	Yes	Unclear	Yes	No
Meisel 2008 Germany PLIF	Unclear; Mention 17 but do not say out of or that was it	No; Know the source but no confounding factors were identified	No; Independent Radiologist	Yes; No attrition reported
Mulconrey 2007 USA PLF	Unclear; Inclusion criteria not explicitly described	Unclear; prospective study, case definition not explicitly described	Yes	No
Oetgen 2010 USA	Yes; All pediatric patients	Unclear; retrospective review but confounders not listed	Unclear	No
O'Shaughnessy 2008 Upper and lower thoracic	Yes; Consecutive in the Conclusion	Yes; Mention Age and Gender	Unclear; Do not mention	Yes; No patients lost to follow-up
O'Shaughnessy 2012	No; Inclusion/exclusion criteria explicitly described, but required ≥ 12 months' follow-up.	Yes for etiology of scoliosis, unclear for other variables. Retrospective review methods not clearly described.	No	No
Owens 2010 USA TLIF	Yes; Consecutive patients	Yes; Table	NA; Not detecting Fusion	NA; Retrospective
Rihn 2009 USA TLIF	Yes; 48 out of 53 total	Yes; Table 1	No; Don't mention blinding	Yes

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
McClellan 2006 USA TLIF	No	Unclear	Yes	Poor	
Meisel 2008 Germany PLIF	No	No	Yes	Poor	
Mulconrey 2007 USA PLF	Yes; Detailed description of patient demographics and potential confounders	Unclear	Yes	Poor	
Oetgen 2010 USA	No	Unclear	Yes	Poor	
O'Shaughnessy 2008 Upper and lower thoracic	No	No	Yes	Poor	
O'Shaughnessy 2012	No; no data on gender	Unclear	No; Not all variables were adequately defined. Yes for PJK and severity classification of complications. No for pseudoarthrosis and the complications themselves.	Poor	
Owens 2010 USA TLIF	No	No	Yes	Fair	
Rihn 2009 USA TLIF	No	No	Yes	Fair	

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
Scheufler 2009 Germany TLIF	Unclear	Yes; Comorbidities	No; Do not mention anything about blinding	Yes; 4 lost to follow-up
Sethi 2011 USA ALIF	Unclear	Yes, prospective study	No; Independent Radiologist	No
Sethi, 2011 USA Cervical	Unclear	Yes	Probably-"Radiographic measurements were made by three independent observers"	No
Shen, 2010 Cervical	No; A consecutive series of those with two year followup	Unclear; patients were "analyzed by experienced, independent spine surgeons"	No; Independent Radiologist	No
Shields, 2006 Cervical	Unclear	Unclear; Retrospective chart review; specifics not given	Unclear	No
Stachniak, 2011 Cervical	Unclear	Unclear	No; Independent Radiologist	No Not Reported
Stambough 2009 USA PLF	Yes; consecutive	Unclear; selection criteria somewhat vague	Yes	Yes

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Scheufler 2009 Germany TLIF	No	No	Yes	Fair; Because they report for all 30 patients in a table.	
Sethi 2011 USA ALIF	No	No	Yes; defined criteria for rating new bone formation and endplate resorption.	Fair	
Sethi, 2011 USA Cervical	No; Study does not report gender, age, levels fused by type of surgery (cervical fusion vs. lumbar fusion)	No	Yes	Poor	No baseline characteristics by type of surgery
Shen, 2010 Cervical	Unclear; Some statistical analysis showing relationship between potential confounders given; details of those with pseudoarthrosis given	No	Yes; Pseudoarthrosis defined	Fair	Would like information on number who had less than 2 years of followup and what their last recorded outcomes were
Shields, 2006 Cervical	Unclear; Does not adjust statistically, but does give additional confounder information on some patients who had complications	No	Unclear; Fusion outcomes not provided	Poor	Unclear if this represents a consecutive series or if any persons were omitted from this analysis; unclear how information obtained
Stachniak, 2011 Cervical	Yes; ANCOVA was conducted to assess the significance of the relationship between cervical swelling and the amount of dysphagia.	No	No; Fusion not defined.	Poor	Unclear if this represents a consecutive series or if any persons were omitted from this analysis
Stambough 2009 USA PLF	Yes; Age, gender, number levels fused and smoking status reported	No	Yes	Fair	

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?
Subach 2010 USA ALIF	Unclear, only enrolled those with adequate postoperative and follow-up x-rays in the database.	Unclear; Retrospective study. Exposure ascertained based on search of electronic database. But no information about search details or about ascertainment of potential confounders.	Unclear	NA - Retrospective study that only enrolled patients with available x-ray data
Tumialan, 2008 Cervical	Unclear	Unclear; Retrospective chart review; specifics not given	Unclear	No; No attrition reported
Tumialan, 2012	Yes; 102 of 116 patients who met explicit inclusion criteria.	Unclear; Retrospective chart review; specifics not given	No	Yes; No attrition
Villavicencio 2005 USA TLIF	Yes; According to Criteria	Unclear; Do not mention any	No; Independent	Yes
Wang 2006 USA ALIF Circumferential	Yes; 32 out of 62	No; Only Age and Gender information	Unclear	NA; Retrospective so does not matter

Evidence Table 10. Non-Medtronic intervention series: Risk of bias

Author Year Country Trial # or Name	Did the study perform appropriate statistical analyses on potential confounders?	Is there high loss to follow-up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality Rating	Comments
Subach 2010 USA ALIF	No	NA; Retrospective study that only enrolled patients with available x-ray data	Yes	Poor	
Tumialan, 2008 Cervical	Unclear; Does not adjust statistically, but does give additional confounder information on some patients who had complications	No; 4% lost to followup	No; Fusion not defined.	Poor	
Tumialan, 2012	Yes; sufficient information on all required variables.	No; all patients included in analysis	Yes	Fair	
Villavicencio 2005 USA TLIF	No	No; 3 out of 74	Yes	Poor	
Wang 2006 USA ALIF Circumferential	No	NA	Yes	Fair	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Anderson 2011 USA	Case Report	**Case 1** Age Diagnosis Fusion Site **Case2** Age Previous Surgeries Diagnosis Fusion Site	68 Spondylosis at multiple levels without kyphosis, severe stenois C3-C7 44 Two-level ACDF Psuedoarthrosis and central stenosis with artifact present C5-C7	**Case 1** rhBMP-2 (12mg) + posterior instrumental arthrodesis using Magerl tequniqe and laminectomy **Case 2** rhBMP-2 (4.2mg) + posterior instrumentation, arthrodesis, and laminectomy	**Case 1** Evacuation of fluid collection and patrial laminectmy at C6-C7, drain removed post-op Day 2 **Case 2** Evacuation of fluid colelction, removal of fibrinous material on the spinal cord, drain removed post-op Day 2
Anderson CL 2012 USA	Case Report	Age Diagnosis Fusion Site	**73** **low back, right buttock and right lower extremity pain** **Previous L3-S1 laminectomy, TLIF at L3-L4, PLF from L2 to S1**	In previous surgery: undergone L3–S1 laminectomy, TLIF with interbody cage at L3–L4, and instrumented posterolateral fusion from L2 to S1. The PLF was augmented with emineralized bone matrix, local autograft, crushed allograft cancellous bone, and a large kit of rhBMP-2 placed in the posterolateral gutter after thorough irrigation.	**No additional surgeries**
Balseiro 2010 USA	Case Report	**Case 1** Age Diagnosis Fusion Site **Case 2** Age Diagnosis Fusion Site	54 Recurrent disc herniation and mechanical back pain L3-L5 73 Post laminectomy instability L4-L5	**Case 1** rhBMP-2 (INFUSE) + TLIF with collagen sponge morcellized allograft bone, demineralized bone matrix putty **Case 2** rhBMP-2 (Medium INFUSE kit) + same as patient 1	**Case 1** @ 3 mos: removal of interbody cage at L4-L5 level, revision of fusion with iliac crest autograph **Case 2** **D**eclined further surgery

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Anderson 2011 USA	**Case 1** Days 9 to 12: Decline in neuroloigcal status. Inability to: raise arms, open or close both hands, stand or walk withoutassistance. Loss of sensation in bilateral hands. 2 weeks: Computed tomographic myelogram revealed postoperative fluid collection posterior to the thecal sac causing moderate-to-severe central spinal stenosis between C3 and C6. **Case 2** Day 5: Acute onset of bilateral upper and lower extremity weakness. Unable to raise self from a seated or lying position. Decline in proprioception for right upper extremity. Computed tomographic myelogram showed complete blackage on contrast flow at C6-C7 consistent with a severe spinal stenosis.	No funds were received in support of this work. No benefi ts in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.	
Anderson CL 2012 USA	Discovered at exploration (in response to presenting complaint): Serosanguineous paraspinal fluid = sterile. Extensive osteolytic process, posterior elements and surrounding posterior hardware. Near complete obstruction of the thecal sac, paraspinal fluid collection with surrounding heterotopic ossification, cortical breach of L4 pedicle screw R side. Heterotopic ossification inferior to lumbodorsal fascia, encapsulating paraspinal musculature in continuity with the fusion mass (nonmalignant mature bone), Serosanguineous fluid collection, no evidence of ongoing leak/infection. Solidly fused lumbar spine. Cortical breach L4.	No funds were received in support of this work. No benefi ts in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.	
Balseiro 2010 USA	**Case1** 3 mos: Increase low back pain, osteolysis affecting L4 and L5, expansion of preoperative defect caused by subchondral cyst 15 mos f/u: no complaints of back pain, solid fusion at L4-L5 **Case 2** 4 mos: increasing low back pain, osteolysis of L4 and L5 bodies, appear to be expansion of a preoperative vertebral defect caused by subchondral cyst 1 and 2 yrs: continued lower back pain, again declined revision surgery	Not reported, 2nd author EWN consulting for Medtronic	End plate violation during disc space preparation, rhBMP-2 overdosing or combo can lead to vertebral osteolysis. In addition, these cases suggest that end plate defects present before surgery may also be a risk factor for osteolysis when rhBMP-2 is placed in the disc space.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Brower 2008 USA	Case Report	Age Diagnosis Fusion Site	69 1 yr Hx of back and right leg pain with foot drop. Multiple level DDD w/ disc space narrowing, anterior spurring, grade 1 degenerative spondylolisthesis. Central canal stenosis narrowing of lateral recesses on right side. L4-L5	rhBMP-2 + PLIF with collagen sponge, wrapped around granules of biphasic calcium phosphate carrier (15% hydroxyapatite and 85% tricalcium phosphate). Pedicle screw instrumentation. Some local graft.	
Chamoun 2009 USA	Case Report	total n **Case 1** Age Diagnosis Fusion Site **Case 2** Age Diagnosis Fusion Site	7 19 mo Pfeiffer syndrome, severe stenosis at the level of the foramen magnum and craniocervical junction instability secondary to a hypoplastic dens Occiput - TF 10 Increased atlantodental interval, ossiculum terminale persistens and spinal instability C1-C2	**Case 1** rhBMP-2 + posterior instrumented fusion with iliac crest bone graft suboccipital craniectomy **Case 2** rhBMP-2 ?? + instrumented fusion with cancellous morselized allograft	NR

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Brower 2008 USA	3 mos: pain along right iliac wing. Large collection of tracer in the right retroperitoneum from the right kidney to the pelves, including involvement of the iliac wing, heterotopic bone formation in the right psoas and iliacus muscles extending down to the iliac wing. 5.5 mos: heterotopic bone visible on anteroposterior film of abdomen and spine, heterotopic bone formation in the right iliopsoas muscle, osteopenia in the rest of the skeleton. 1 yr: continued improvement in pain levels, still required use of solid foot orthosis for foot drop. 2 yrs: Foot drop persists, heterotopic bone still apparent on plain films.	None.	
Chamoun 2009 USA	None reported for either patient.	The authors have no personal or financial interest in any of the drugs, materials, or devices in this article.	Paper is focused on C2 laminar screw fixation. One patient of seven had prolonged dysphagia, but the authors belive this was from a C1 lateral mass screw insertion.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Chen 2010 Taiwan/USA	Case Report	**Case 1** Age Diagnosis Fusion Site **Case 2** Age Diagnosis Fusion Site **Case 3** Age Diagnosis Fusion Site **Case 4** Age Diagnosis Fusion Site	39 Multiyear hx of right leg radiculopathy, back pain. Discography L4-L5 78 Lower back pain, right leg radiculopathy. Grade 1 spondylolisthesis. L4-L5 69 Right leg pain, paresthesias. Grade 1 spondylolisthesis, lateral recess stenosis, 19years post prior L4-L5 spinal fusion. L4-L5 56 Lower back pain, lower-extremity S1 radiculopathy, Loss of disc height at L5-S1, severe bilateral L5-S1 lateral recess stenosis. L3-S1	All cases: rhBMP-2 (1 large kit) + TLIF with single large absorbable collagen sponge, PEEK interbody fusion cage	**Case 1.** Reexploration of fusion mass, large, dense bone mass encountered encasing L4 and L5 nerve roots, removed **Case 2. R**epeat decompression, instrumentation extended to L3-L4 w/ facet arthrodesis **Case 3.** Reoperation, diffuse mass of bone encasing L5 nerve root removed. **Case 4.** No additional surgery.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Chen 2010 Taiwan/USA	**Case 1:** 29 mos, new back pain, right posterolateral thigh pain, weakness in right lower extremity. Opacification of right L4-L5 neural foramen, entrapment of nerve root within bone mass, solid interbody fusion **Case 2**: 1 yr, solid, non-mobile union at L4-L5. 32 mos, recurrent right side radiculopathy, back pain. Bilateral stenosis at L3-L4 and L4-L5, newly formed ectopic bone opacified L4-L5 neural foramen. **Case 3**: 23 mos, left side S1 radiculopathy, left neural foraminal narrowing w/ large endplate bone mass abutting left-exiting L5, transversing S1 nerve roots, stable fused segment w/outtracer uptake. **Case 4**: 51 mos, recurrent left leg pain. New ectopic bone formation in left L5-S1 foramen, moderate neural impingement.	Not reported. No conflicts of interest.	4 cases of delayed ectopic bone formation following MIS-TLIF, cause remains unknown. Key influences of ectopic bone formation: * position of graft and carrier (recommend placement of cage as anteriorly and medially as possible) * barriers to migration of bone-forming material (presence of an intact posterior annulus a likely barrier) * rhBMP-2 dose

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Cho 2011 USA	Case Report	**Case 1** Age Diagnosis Fusion Site **Case 2** Age Diagnosis Fusion Site	17 Type-1 neurofibromatosis. Increasing upper back pain. Increased cervical lordosis and severe upper thoracic kyphosis w/ right-sided posterior prominence. Complete spontaneous dislocation of T3 on T4, angular kyphosis, dural ectasia with widened spinal canal. T2-T7 (other work at C4-C6, T1, T8-T12) 30 Type-1 neurofibromatosis, severe back and lower-right extremity pain. Dural ectasia from L3-L5 and throughout sacrum. T12-L3 (specifically L3-sacrum??)	**Case 1** rhBNP-2 + allograft + autologous iliac bone graft **Case 2** rhBMP-2 (2mg/mL and 40mg/mL)	
Choudhry 2012 USA	Case Report	Age Diagnosis Fusion Site	70 low back pain radiating to left lower extremity in L4-L5 diatribution TLIF at L4-L5	TLIF at L4-L5, laminectomy, excision of herniated disc, PEEK cage with rhBMP-2 (medium kit), pedicle screw-rod construct	**Reoperation at 8 weeks postop to remove a cystic lesion at L4-L5, incision of the cyst revealed collagen sponge material**

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Cho 2011 USA	**Case 1** None reported. 5 yrs: intact spinal instrumentation and robust bone formation.No pain. **Case 2** None reported. 2 yrs, pain in back and right lower-extremities fully resolved, solid fusion.	Not reported. Financial relationship and payments from third party in support of work noted.	Thoracic/Thoracic Lumbar No adverse events reported.
Choudhry 2012 USA	Inflammatory cyst formed around collagen sponge requiring second surgery	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
David 2010 Canada	Case Report	Age Diagnosis Fusion Site	44 Hx of multiple surgeries for scoliosis, developed paraplegia after 1989 surgery. 2001 developed increasing back pain and neuropathic symptoms in left lower limb. Residual scoliosis, solid fusion T4-L2, evidence of Charcot arthropathy below fusion level, progressive destruction of L3-L4 region. T12-S1	rhBMP-2+ PLIF with 6 mm tibial allograft spacer, pedicle screws, unilateral rod, morselized bone and allograft	
Deutsch 2010 USA	*Case Report*	*Age* *Diagnosis* *Previous Surgery* *Comorbidities* *Fusion Site*	*56* *Increased back pain. Evidence of pseudoarthrosis and scre pullout (L1)* *Complex anterior and posterior fusion from T8-pelvis.* *60-pack-a-year cigarette smoking history* *T11- S1*	Anterior: rhBMP-2 (12 mg INFUSE) + ALIF Circumferential with Grafton demineralized bone matrix, crushed allograft, autogenous rib graft, titanium mesh cages. Posterior: rhBMP-2(6mg per level) + rods, autograft, crushed allograft, Grafton putty.	***Removal*** *Anterior abdominal sharp dissection and excision of ectopic bone forming a sheet-like layer between the psoas and retroperitoneum.*
Garrett 2009 USA	Case Series	Total n n reporting swelling % Female Age Average (Range) Fusion Levels mean (range)	130 6 (4.6%) 83.3% (5/6) 58 (34-80) 3.5 (1-8)	2 pts: laminectomy + PLF, 3 pts: also PLIF 2 of 3 PLIF: PEEK cages rhBMP2 (range from 2.1mg - 14.7mg)	6 patients underwent surgical exploration: mean 7.7. days (range 5-13) after initial surgery 4 pts had Hemovac drains placed

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
David 2010 Canada	None reported.3 wks: re-exploration and debridement of surgical wound, no deep infection found. 6 mos back pain resolved significantly. 6-12 mos: twisting and lifting restrictions lifted, pt returned to work. 2 yrs solid fusion, no evidence of hardware loosening.	None. Author disclosures present.	No adverse events reported related to use of rhBMP-2.
Deutsch 2010 USA	*1 month: patient complaint of progressively enlarging mass in left lower quadrant. Seroma noted and drained percutaneously. 7 mos: Patient weight loss of 40 lbs, experiencing early satiety and pain with urination. Enlarging hard mass in the left lower quadrant palpable. Osseous ectopic bone formation in the left abdominal and pelvic cavity wall.*	*Not reported, no author disclosures reported*	*Possible issues with dosing and cages, cages used in the patient were probably more consistent with a smaller kit. Also, seroma noted at 1 month may have been related to the dispersement of rhBMP-2 into the retroperitoneal space.*
Garrett 2009 USA	During surgery: 3 pts incurred durotomy, 2 required direct repair 5-13 days: painful swelling, erythema and tenderness at surgical site, possible infection. Upon inspection serous fluid collection noted, subcutaneous tissues edematous, infection ruled out. In 3 pts with durotomy, CSF from a persistant leak ruled out.	None reported	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Glassman 2011	Case Series	Total n	Case Series 1:	All patients underwent lumbar decompression and instrumented posterolateral fusion with rhBMP-2/absorbable collagen sponge.	
		age (Mean)	Case Series 2:		
		% Male	rhBMP-2 without dural tear		
		%Smoker	rhBMP-2 with dural tear		
		% Worker's compensation	51		
		Fusion Levels (mean)	51		
		Preoperative HRQOL	59.5		
		ODI	60.2		
		Back Pain	35		
		Leg Pain	41		
		SF-36 PCS	20		
		SF-36 MCS	14		
			14		
			12		
			1.8		
			1.9		
			51.7		
			51.7		
			7.8		
			7.3		
			8.0		
			7.8		
			27.1		
			27.1		
			36.7		
Hansen 2006 USA	Case Report	Age	45	rhBMP-2 + ALIF Circumferential with FRA	
		Diagnosis	10 yrs of Discogenic Pain		
			DDD		
		Fusion Site	L5-S1		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Glassman 2011	Postoperatively, three patients in the group with a dural tear had new onset radiculopathy and one needed administration of oral steroids. All three radiculopathy resolved within 6 months postoperatively. No patient in the group without a dural tear had new onset radiculopathy	Medronic paid royalties, consulting fees, reseach support and Trips/tavel expenses for some authors.	From consecutive series of 1,037 patients who underwent decompression and posterolateral lumbar spine fusion using rhBMP-2/absorbable collagen sponge between 2003 and 2006, intraoperative dural tear was reported in 58 cases (5.59%).
Hansen 2006 USA	3 mos: low back/bilateral pain. Dx: degenerative osteophytes S1 joints, erosive changes inferior endplate L5 and superior endplate S1. 5 mos: cont. pain. Cysts on endplates at interbody fusion site. Infection apparent, concern re: osteomyelitis but no infection present. 6 mos: small cysts internal FRA surface, lucencies at graft-host junction, increased density of cancellous bone cranial to FRA. 12 mos: similar findings. 15 mos: no obvious bridging bones, poss pseudo arthrorisis. Upon exploration, solid arthrodesis found.	Not reported	Reabsorptive response w/in interbody space in early months following anterior discectomy and fusion can resemble an infection.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Haque	Case Series	Total n	17	rhBMP-2 + C1-C2 fusion eith rib graft = 5	NR
2009		Total rhBMP-2	9	rhBMP-2 + occipital-cervical fusions	
USA		Pathological entities	posttraumatic rotary subluxation, os odontoideum (3), Down syndome, congenital occipitocervical instability (3), posttraumatic occipitocervical instability		
		Overall fusion sites	O-C3		
Kepler	Case Series	**Case 1**	23	**Case 1**	
2011		Age	Proximal and distal pseudoarthrosis and degenerative breakdown	Lateral approach: rhBMP-2 (8mg) + polyether ether ketone interbody cages, collagen sponge	
USA		Diagnosis			
		Previous Surgery	8 years previousm spinal fusion T2-T12 for Scheuermann kyphosis.	**Case 2**	
		Fusion Site	Posterior spinal fusion (PSF), T1-L1. Lateral approach inter-body fusion T11-L1.	rhBMP2 (8 mg) + expandable cage + collagen sponge	
		Case 2		**Case 3**	
		Age	78	rhBMP2 (6mg) - no other information reported	
		Diagnosis	T12 burst fracture with progressive deformity, pain, and myelopathy.	**Case 4**	
		Medical hx	Osteoporosis	rhBMP-2 (12.5mg) - no other information reported)	
		Fusion Site	PSF T11-L1. Lateral approach T12 corpectomy		
		Case 3			
		Age	Information not provided		
		Diagnosis	Information not provided		
		Fusion Site	Lateral approach T12 copectomy, lateral approach interbody fusion T8-T9		
		Case 4			
		Age	Information not provided		
		Diagnosis	Information not provided		
		Fusion Site	Lateral approach T11 corpectomy (Staged after PSF T4-S1)		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Haque 2009 USA	No complications related to the use of rhBMP-2 in any of these patients.	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.	Verifying sfaety and suitibility of alternative techniques to the C1-2 transarticular screw. Cannot critically evaluate the use of rhBMP-2.
Kepler 2011 USA	**Case 1** Chest tube outputs- day 1: 35 cc., day 2: Removed. Day 3: Patient complained of chest fullness and difficulty breathing. Interval development of large right pleural effusion. Tachypneic (30 breaths per minute), tachycardic (120 beats/min), maintained oxygen saturations in upper 90s. 6 weeks: mild subjective chest fullness, sizeable residual pleural effusion. 3 months: effusion resolved. **Case 2** Chest tube outputs- day 1: 25 cc, removed. Day 2: patient developed dyspnea and a tachyarrhythmia. Large left pleural effusion. Chest tube replaced, output 710, day 3: 200 cc., day 4: 510 cc., day 5: 50 cc., tube removed. No further symptoms, pleural effusion resolved w/in 1 month. **Case 3** Chest tube outputs- day 1: 1030 cc., day 2: 440 cc., day 3: 90 cc., 65 cc, removed. Shortness of breath resolved by day 8, supplemental O2 required for 1 month, pleural effusion resolved w/in 3 months. **Case 4** Chest tube outputs- day 1: 120 cc., day 2: 40 cc., day 3: 140 cc., 140 cc, removed. Chest fullness improved during hospitalization, pleural effusion resolved w/in 5 months.	None	Thoaracic Authors believe effusions were related to use of rhBMP-2 because effusions 1. occurred on side of surgical approach, 2. did not resolve quickly after surgery 3. and similar pleural effusions have not been noted by operating surgeon when rhBMP-2 was not used. Possible link between rhBMP-2 inflamatory properties and pleaural effusion.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Lehman 2011 USA	*Case Report*	*Age* *Diagnosis* *Previous Surgery* *Fusion Site*	*63* *Suprajacent degeneration and radiculopathy.* *L5-S1 fusion* *L5-S1?*	*rhBMP2 (6 mg) + TLIF with absorbable collagen sponge + Capstone cage*	
Lewandrowski 2007 USA	Case Series	Total n Complication, n Age, average yrs Male, n Female, n Diagnosis	68 5 50.2 3 2 (4 pts) DDD, osteophyte formation, sclerosis of end plates (1 pt) adjacent level disease and nonunion following previous surgery (4 pts) single-level disease, (1 pt) L3-L4 and L5-S1	4 pts: rhBMP2 (small INFUSE kit, 4.2 mg) + TLIF with PEEK cage and absorbable collagen sponge 1 pt: rhBMP2 (medium INFUSE kit, 4.2 mg) + TLIF with removal of implants and reinstrumentation with PEEK cages	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Lehman 2011 USA	*Postoperative left lower extremity radiculitis refractory to narcotics and gabapentin several months after surgery.*	*Defense Advanced Research Projects Agency, Defense Medical Research and Development Program*	*Consists of primarily images. Little to no commentary.*
Lewandrowski 2007 USA	4 weeks - 3 mos: New onset severe low back pain. CT scan showed resorption of the inferior aspect of the L5 vertebral body occurred in each of the 5 patients.	Nothing of value received from a commercial entity related to this manuscript.	Vertebral osteolysis can occur with the use of rhBMP-2 in PLIFs. Violation of the end plate during decortication may be a contributing factor.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Lindley 2011 USA	Case Series	n	48	**Case 1** rhBMP2 + dorsal fusion with titanium instrumentation and magnum decompression, laminectomy **Case 2** rhBMP2 + dorsal fusion with titanium instrumentation and magnum decompression **Case 3** rhBMP2 + dorsal fusion with titanium instrumentation and decompression of ventral medulla and expansion of previous suboccipital decompression **Case 4** rhBMP2 + fusion with titanium instrumentation and magnum decompression, laminectomy **Case 5** rhBMP2 + fusion with titanium instrumentation **Case 6** rhBMP2 + fusion with titanium instrumentation and magnum decompression, laminectomy	**Case 1** Emergent tracheostomy, right frontal ventriculostomy, wound exploration, and placement of a drain in the wound. **Case 2** **E**mergency right frontal ventriculostomy and wound exploration. **Case 3** Posterior fossa and repeat decompression, intradural lysis of adhesions, placement of a shunt from the fourth ventricle to the subarachnoid space, and duraplasty
		Total n with rhBMP- 2 complications	6		
		Case 1	14		
		Age	Upward, near-horizontal position of the clivus		
		Diagnosis	with a short basiocciput and a high-riding		
		Fusion Site	anterior arch of the atlas		
		Case 2	O-C2		
		Age			
		Previous Surgery	8		
		Diagnosis	Craniofacial remodeling and cranial release		
		Fusion Site	procedures		
		Case 3	Atlantoaxial instability		
		Age	O-C1-C2		
		Diagnosis			
			16		
			Posterior fossa craniotomy, C-1 laminectomy,		
		Fusion Site	duraplasty		
		Case 4	Hypoplastic clivus with compression of the		
		Age	medulla by the odontoid, tonsillar herniation,		
		Fusion Site	and a cervical syrinx		
		Case 5	O–C2		
		Age			
		Fusion Site	6		
		Case 6	O- C2		
		Age			
		Fusion Site	11		
			O-C3		
			11		
			O-C2		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Lindley 2011 USA	**Case 1** Day 4: Apneic spells, large fluid collection in the operative site with extension into the epidural space within the posterior fossa, and obstructive hydrocephalus **Case 2** Day 3: Worsening ataxic gait and somnolence. Large posterior fossa epidural fluid collection and hydrocephalus **Case 3** 1 + year: Excessive bone growth in the area of previous decompresion **Case 4** 4 weeks: Wound swelling, evidence of seroma formation, no evidence of wound infection **Case 5** 2 weeks: Large fluid collection at the operative site **Case 6** 4 weeks: Fluid collection at the operative site, cultures negative	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.	A significant number of patients (10.4%) developed postoperative complications associated with the use of rhBMP. The most common complication was seroma formation observed in 5 patients and ectopic bone formation in 1 patient.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Lu 2007 USA	Case Study	Age Previous operations Diagnosis Fusion Site	16 mos 4 mos: spinal reduction, placement of halo fixation, C-1 decompression, and occiput–C3 fusion with iliac crest and occipital bone graft. 11mos: Rib grafts were wired to the occiput and C-2 and C-3 and covered with demineralized bone matrix (Grafton). Loss of reduction and nonunion of the construct C2-C3	rhBMP-2 + (5.6 ml) + craniovertebral fusion with iliac crest secured with a titanium cable and instrumentation with 2-mm craniomaxillofacial plates and screws	NR
Madrazo 2006 Mexico	Case Series	**Case 1** Age Diagnosis Fusion Site **Case 2** Age Comorbidities Diagnosis Fusion Site **Case 3** Age Diagnosis Fusion Site	 56 C5-C6 and C6-C7 posterolateral osteophytes, predominantly on the right side, and reduction of the root foramina C5-C7 73 Diabetes, moderate whole body osteoporosis Grade II degenerative listhesis at C3-C4, siginificant degenerative changes at C4-C5, lateral and central osteophyte and spinal cord and root compression C3-C5 44 Significant osteophytes at C4-C5 and C5-C6 with cervical kyphosis with disk protrusion and	**All cases** rhBMP-2 (1.4 mL) + ACDF with PEEK cages and collagen sponge carriers	NR

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Lu 2007 USA	No adverse events reported.	The authors of this study do not have any financial interests in any of the companies mentioned in this paper.	First report of use use of rhBMP-2 to promote bone fusion in an infant with craniovertebral instability after two attempts at arthrodesis had failed.
Madrazo 2006 Mexico	No adverse events reported.	NR	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Mladenov 2010 Germany	Case Series	**Case 1**	6	Thoracic cervical	
		Age	Mucopolysaccharidosis type 1 (Hurler's	**Case 1**	
		Diagnosis	disease). Progressive weakness in lower	rhBMP-2 (12 mg)	
			extremities and sleep apnea. Spinal cord	**Case 2**	
			compression in cranio- cervical junction with	rhBMP-2 (12mg) + repeat posterior	
			myelopathy caused by C1-C2 instability. 4 mos	autologous iliac crest bone grafting	
			after first surgery: local kyphosis and anterior	**Case 3**	
		Previous Surgery	displacement of C1 on C2, unstable non-union	rhBMP-2 (12mg) + repeat autologous iliac	
			confirmed.	crest bone grafting	
		Fusion Site	Widen foramen magnum, C1-C2 laminectomy.		
		Case 2	Autologous iliac crest bone grafting from		
		Age	occiput to C4.		
		Diagnosis	C1-C2		
			2		
			Klippel-Feil deformity, muscle hyptony in both		
			lower extremities. Cervical kyphosis and		
		Previous Surgery	anterior desplacement of upper cervical spine		
		Fusion Site	of 13 mm. 10 mos after first surgery: non-		
		Case 3	union and pin loosening		
		Age	Arthrodesis + autologous iliac crest bone graft.		
		Diagnosis	C2-C4, T2-T4		
			10		
		Previous Surgery	Hereditary sensory autonomic neropathy type		
		Fusion Site	IV, thoraco-lumbar juntional kyphosis of 65°,		
			partial destruction of L1 and L2 vertebra		
			bodies. Following first surgery: concerns about		
			significant bone substance deficiency		
			Posterior decompression of L1-L2,		
			instrumentation T11-L4, iliac crest bone		
			grafting, anterior cage filled with autologous		
			rib bone graft		
			L1-L2?		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Mladenov 2010 Germany	Adverse events related to use of rhBMP-2 not reported.	None reported. No potential conflicts of interest.	Cervical/Thoracic/Lumbar No adverse events reported.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Moshel 2008 USA	Case Report	Age	53	rhBMP-2 + TLIF with 12-mm allograft Capstone spacer and pedicle screw (PS) placement	**2nd Operation** Fusion construct extended to S2, PS revised, autologous bone graft w/out rhBMP-2 **3rd Operation** exploration of previous L5-S1 laminectomy defect, removal of ligamentum flavum, decorticated interspace contralateral to interbody graft and packed it with cancellous iliac crest autograft, replaced loose L5, S1 PS, pack w/ cancellous iliac crest autograft wrapped in collagen and hydroxyapatite sponges soaked in rhBMP-2
		Diagnosis	3-year hx of severe axial low-back pain and progressive bilateral radiculopathy		
		Comorbidities	Hypertension, gout, hepatitis C, and depression, past hx of smoking		
		Fusion Site	L5-S1		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Moshel 2008 USA	Following 1st Operation max creatinine level 1.5mg/dl, BUN 47 mg/dl, levels dropped to .6 mg/dl, 35mg/dl in response to intravenous hydration, fever of 38.6°C, cultures show no signs of growth For year following, continued to report severe low-back pain, lucencies consistent with pseudo-arthrosis Following 2nd Operation creatinine and BUN levels remained w/in normal levels, fever 38.3°C post-op day 1, cultures show no evidence of growth Following 3rd Operation Day 7: Max creatinine = 3.2 mg/dl, max BUN = 53 mg/dl, no evidence of hydronephrosis, creatinine and BUN levels stabilized after 3 mos Day 10: SVT developed, heart rate in 160s, hypoxic w/ oxygen saturation dropped to 70%, fever 38.5°C, Swan-Ganz catheterization demonstrated hyperdynamic cardiac function and low systemic vascular resistance consistent with sepsis, low probability of pulmonary embolism. Intermittent low-and high grade fevers for 3 weeks. Cultures did not show evidence of growth. Day 14: MRI: no evidence of surgical site abscess, thin rim of enhancement adjacent to bone graft placement evident Day 29: MRI: no evidence of infectious disease Given hx of gout + joint pain, aspiration of fluid from knee/elbow on Day 4, 13, 19, no evidence of growth. Concern of immune response to rhBMP-2	Not reported	Pt suffered severe and potentially life-threatening systemic immune toxicity after re-exposure to rhBMP-2 and bovine collagen carrier. Pt may have had mild version of systemic immune toxicity after first exposure to rhBMP-2 and bovine collagen carrier. Possible that reaction was to collagen but data suggest collagen is relatively safe. Suspect reaction to rhBMP-2. Mechanism of reaction unknown, possible hypothesis: nonosteogenic functions of endogenous BMP-2 were affected by the induced antibody response

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Muchow 2010 USA	Case Report	Age Diagnosis Comorbidities Fusion Site	27 Progressive low back pain, radiated into left lower extremity. Slight scoliosis. Radiographs demonstrate rotatory subluxation and levoscoliosis, mild levoscoliosis, and mild degenerative disc disease. MRI demonstrate degenerative disc disease, with a central disc herniation and subarticular stenosis and degenerative disc disease with a bulging disc Smoke 1.5 packages of cigarette/day, obesity. L4-L5	rhBMP-2 (medium INFUSE kit) + TLIF with two #12 22-mm PEEK cages packed	15 wks: Reexplored and decompress L4 nerve root, Instrumentation removal at L4-L5 on right side. 8 mos: microscopic decompression of the left cyst, remaining instrumentation removed
Newman 2012 USA	Case Report	Age Diagnosis Fusion Site	57 Low back and right leg pain in L5 distribution with previous L4-L5 discectomy with later revision L4-L5	TLIF with rhBMP-2 medium kit and morselized local autograph	Repeat surgery to explore the thecal sac; a large amount of clear yellow gel-like material was found and removed; the material was though to be an expansion of the DuraSeal
Oluigbo 2008 UK	Case Study	Age Diagnosis Previous treatments Fusion Site	2 Severe C1–2 level spinal cord injury with cord transection, type I fracture of dens, disruption of the anterior longitudinal, transverse and posterior interspinous ligaments and evidence of joint injury and traumatic effusion at C0–1 and C1–2 joints 12 week course of Halo-Vest immobilization and SOMI type external orthosis C1-C2	rhBMP-2 + non-metal-instrumented posterior spinal fusion with ACS matrix and bicalphos crystals	NR

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Muchow 2010 USA	4 wks: progressive low back pain, radiated into lateral right thigh 9 wks: pain increase in severity (10/10 w/ activity), two epidural fluid collections at L4-L5 involving right and left neural foramen 15 wks: 2d surgery, removal of solid, encapsulated, purplish, mobile mass. Inspection revealed evidence of old hematoma + new organizing bone. Tissue removed from L4 nerve root revealed diffuse osteoid and woven bone, but surrounded by a fibrovascular stroma extensively populated by lymphocytes with occasional eosinophils 2 wks post Surgery 2: low back pain, radiate left lower extremity 3 mos post Surgery 2: enlargement of left side cyst, compression of left L4 nerve root. Surgery 3: Removal of cyst, same findings as at 2nd Surgery	Not reported Multiple author disclosures	Chronic host inflammatory response after off-label use of rhBMP-2. Gross examination revealed mass to be a collection of consolidating fibrous and bony tissue with old hematoma. Concern with supraphysiologic doses of rhBMP-2 is in vivo amplification of the host inflammatory response.
Newman 2012 USA	Cauda equina after expansion of dura seal causing with burning and parathesias in the saddle region	One or more of the authors (JR) has received funding from Medtronic Sofamor Danek Riddle Hospital/Rothman Institute, Media, PA, USA	
Oluigbo 2008 UK	No adverse events reported.	NR	Bony fusion began at 3 week, solid spinal fusion confirmed within 8 weeks. There was no evidence of spinal canal encroachment and no adverse effects related to the rhBMP-2/ACS-carrier matrix. There was no evidence of spinal canal breach or osseous induction within the spinal canal.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Pargament 2009 USA	Case Report	**Case 1**	77	**Case 1**	
		Age	Neurogenic claudication and 10 yrs back pain.	rhBMP-2 + PLF with allograft, local autogenous bone graft	
		Diagnosis	High-grade spinal stenosis L3-L4 and L4-L5	**Case 2**	
		Comorbidities	Exogenous obesity, atherosclerotic cardiovascular disease, gastroesophageal reflux disorder, urinary incontinence, hyperlipidemia, hypertension, hx of . thromboembolic disease	rhBMP-2 + PLF with allograft bone, local bone graft, segmental spinal fixation using polyaxial screws and rods.	
		Fusion Site	L4-S1		
		Case 2	60		
		Age	Grade I degenerative spondylolisthesis (80mm2) at L4-L5 and L3-L4, spinal stenosis at L3-L4, L4-L5 (40mm) and L5-S1 disc collapse with a small central herniation, 12° left convex degenerative type scoliosis and previous bilateral hemilaminotomy defects at L4-L Lumbar discectomy 22 yrs previous Chronic cigarette smoking, asthma, chronic obstructive pulmonary disease, sleep apnea, gastroesophageal reflux disorder, osteoarthritis, essential hypertension, depression, osteopenia, and congestive heart failure		
		Diagnosis			
		Previous Surgery			
		Comorbidities			
		Fusion Site			
			L2-L5 (Infuse from L3-L5 only)		
Perri 2007 USA	Case Study	Age	54	rhBMP-2 + ACDF with Cornerstone- HSR implants and removal of anterior cervical plate for a previous ACDF, subsequent adjacent levels of ACDF an re-application of an anterior cervical plate fixation	Wound reopened, serous fluid aspirated
		Previous surgery	Several years previous: ACDF of C5-C7.		
		Medical hx	HIV, hypertension, gout, gastroesophageal reflux disease		
		Fusion Site	C3-C5		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Pargament 2009 USA	**Patient 1:** 10 days: increasing back and new leg pain. Fluid collection, differential Dx: epidural abscess and "significant" postoperative swelling. No clinical evidence of infection of abscess. Pt afebrile, blood count normal, erythrocyte sedimentation rate and C-reactive protein mildly elevated at 30. Tx: pain control and 6-day SoluMedrol. 5 Weeks: Wound healed, no new leg pain, no swelling. R leg nondermatomal numbness. 12 months: mild low back pain, no leg pain. **Patient 2:** 4 days: hemoglobin decreased, requiring two-unit transfusion 6 days: numbness of R buttock down R leg, preoperative quadriceps and ankle dorsiflexors weaker (3/5), no compressive pathology, notable soft-tissue swelling, edema, and phlegmon in the paraspinal muscles and iliopsoas, no epidural hematoma. Tx: molded ankle-foot orthosis 1 week: right leg strength improving (5/5) in the tibialis anterior, 4/5 in the toe extensors and 4/5 in her quadriceps, continuing complaints of nondermatomal numbness and pain in leg TX: gabapentin, 300mg 3x daily. 1 year: no motor deficits, ill-defined leg global "numbness" intermittent	Not reported	Swelling noted in the cervical spine with high-dose rhBMP-2 may occur in a similar fashion in the lumbar spine and result in clinical symptoms. Be aware of clinical manifestation, avoid more aggressive Tx. Tx should be observation w/ or w/out steroids. While soft-tissue swelling is typical, it is clearly more notable with use of rhBMP-2 in doses of 1-2 Infuse kits.
Perri 2007 USA	3-5 days: Increasing neck swelling and mild difficulty swallowing. Day 5: Massive swelling extending from the mandible to the sternal notch/clavicle border, difficulty swallowing. Several pockets of air within the soft tissue and small fluid collection on ipsilateral side	Nothing of value received from a commercial entity related to this manuscript.	Case report is of the complications and response to complications. Surgery details taken from medical record.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Robin 2010 USA	Case Study	Age Medical hx Diagnosis Fusion Site	66 Diabetes, hypothyroidism, gout, hyperlipidemia Multilevel cervical spondylosis and superimposed stenosis. On examination found to be myelopathic with diffuse hyperreflexia and bilateral Hoffman signs C3-C7	rhBMP-2 + posterior instrumentation with arthrodesis and laminectomy	Day 6: Irrigation and debridement, wound reopened, clear fluid released under pressure. Day 10: Irrigation and debridement, excision of bone graft material, demineralized bone matrix, and tissue around the posterolateral gutters.
Saigal 2012 USA	Case Series	Age Diagnosis Fusion Site Age Diagnosis Fusion Site Age Diagnosis Fusion Site	Case 1 56 Splaying of L4-L5 facet joings with compression of the thecal sac, herniated disc, bilateral facet hypertrophy and ligamentum flavum thickening L4-L5 Case 2 62 Grade 3 L3 over L4 spondylolisthesis L3-L5 Case 3 47 L5-S1 spondylolisthesis with L4-L5 disc degeneration L4-L5	L4-L5 laminectomy, facetectomy, L4-L5 discectomy, PLIF at L4-L5 with rhBMP-2, allograft, and pedicle screws L3-L4 PLIF with allograft wedges without rhBMP-2 and TLIF at L4-L5 with rhBMP-2 L4-L5 laminectomy, discectomy, TLIF with PEEK and BMP collagen with pedicle screws and allograft	Revision surgery for cage removal

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Robin 2010 USA	Day 5: Bilateral dull pain in shoulders. Day 6: Significant loss of strength in right elbow and wrist. MRI showed a large hyperintense fluid collection in the epidural space consistent with seroma. Day 11: (5 days after second surgery) Bilateral pain in shoulders. MRI showed similar hyperintense fluid collection.	No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.	2 other patients were found to have had similar reactions in the last year at the authors' hospital. Analysis of rhBMP-2, pro-inflammatory cytokines, and anti-inflammatory revealed multiple elevations of proinflammatory and anti-inflammatory cytokines, especially IL-6 and IL-8.
Saigal 2012 USA	All three cases developed lumbar spine osteolysis after posterior spinal fusion usint rhBMP-2	The authors decleare that they have no conflicts of interest concerning this article.	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report	Baseline Characteristics		Interventions	Additional Surgeries
Shah 2010 USA	Case Report	Age Diagnosis Fusion Site	45 Sudden severe back pain, weakness in lower extremities, inability to ambulate. Collapse of L5 vertebral body, severe tumor infiltration at L5 and elsewhere. Multiple myloma. L4-S1	rhBMP- 2 (large INFUSE, 12 mg) + ALIF circumferential with posterior spinal instrumentation and sextant pedicle screws. Disectomy L4-L5, L5-S1, corpectomy L5 with reconstruction using a cage.	**Revision** 5 days postoperative: copiour irrigation with pulsatile lavage done on superficial and deeper levels, replacement and repositioning of cage, second large INFUSE kit applied to L5 corpectomy defect.
Shahlaie 2008 USA	Case Study	Age Diagnosis Fusion Site	53 Basilar invagination with stenosis and distortion of the cervicomedullary junction and stenosis at the C3-C4 level resulting in canal compromise and spinal cord compression. 0-C6	rhBMP-2 (large INFUSE, 12 mg) + posterior cervical fusion with occipital plate, lateral mass screws, and a contoured rod. Also laminectomy and sub-occipital craniectomy.	Wound exploration, upon reopening wound a large, dark, thin fluid collection was encountered and evacuated. Tissues appeared to be grossly edematous and swollen.
Whang 2008 USA	Case Report	Age Diagnosis Previous Surgery Fusion Site	42 Severe back pain, muscle spasms L buttock and posterolateral thigh. Degenerative change L-5-S1. 1+ year. TLIF procedure. Graft material: rhBMP-2 (Infuse) + local autogenous bone. 12 mm polyethylethylketone spacer filled with graft material. Percutaneous pedicle screws L5-S1. L5-S1	Revision fusion procedure. Removal of interbody spacer. Placement of structural femoral ring allograft filled with iliac crest allograft.	

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Shah 2010 USA	5 days: Migration of L4-L5 cage. 4 months: Evidence of bone formation bridging L4-S1. Scans show development of osseous mass around vertebral body and anterior to the left psoas muscle. 10 months: Patient experiencing minor back pain and limited truncal flexibility. Scans showed L5 vertebral body largely absent from corpectomy, surgical fusion from L4-S1. Large mass of mature heterotopic ossicifcation identified, arising from left anterior margin of L4, extending inferiorly along anterior surface of te left iliopsas muscle, continuing anteriorly and inferiorly along the left medial pelvic wall to the posterior surface of the anterior abdominal wall.	Not reported.	Left-sided paramedian retroperitoneal approach. Bony overgrowth a mojor concern when using rhBMP-2 to enhance lumbar spinal fusion. Role of cytokines in ossification, second surgery may have increased amount of osteo-inductive cytokines, leading to increased bone formation. Dexamethasone used for multiple myeloma, data does not indicate BMP-potentiating effect of this nature. Off-lable use of rhBMP-2
Shahlaie 2008 USA	Day 3: Numbness and weakness in arms and hands. MRI revealed significant paraspinal muscle edema and a non-enhancing, large fluid collections extending from C2 to C4.	No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.	
Whang 2008 USA	Clinical diagnosis: pseudoarthrosis. Histopathologic analysis of implant: no obvious bone production around or w/in spacer, microscopic findings similar to early fracture callus (cartilage, immature woven bone, smalls amounts of lamellar bone) and abundant osteoclasts and osteoblasts. Following corrective surgery: 12 weeks cleared for physical activity, 6 mos returned to work, 1 yr bridging bone across L5-S1 interspace.	Possibly Medtronic Sofamor Danek, Corresponding author Vaccaro = consultant for Medtronic	RCTS of rhBMP-2 and autogenous iliac crest bone graft show success, but none looked at results of revision surgeries or provide histologic analysis. This case study does not show failure of rhBMP-2, but rhBMP-2 should not be thought of as infallible. Uncertainties exist re: use of rhBMP-2, esp "off-label" use and dosing requirements.

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Type of Report		Baseline Characteristics	Interventions	Additional Surgeries
Wong	Case Series	**Case 1**	29	TLIF	Only reported revision surgeries
2008		Age	Desiccated disc L5-S1, undisplaced L5	**Case 1**	done by senior author
USA		Diagnosis	spondylosis, bulge of disc	rhBMP-2 + sponge carrier, pedicle screw	**Case 1**
		Fusion Site	L5-S1	instrumentation	None
		Case 2		**Case 2**	**Case 2**
		Age	26	rBMP2 sponge, structural allograft and	Retention of ectopic bone in canal
		Diagnosis	Discogenic	cancellous allograft chips	and decompression of nerve roots
		Fusion Site	L5-S1	**Case 3**	**Case 3**
		Case 3		rBMP2 sponge (no further info)	Same as 2
		Age	38	**Case 4**	**Case 4**
		Diagnosis	Discogenic	rBMP2 sponge+ cage	Same as 2
		Fusion Site	L5-S1	**Case 5**	**Case 5**
		Case 4		2 rhBMP-2 + sponge carrier,	None
		Age	35	polyetheretherketone cage	
		Diagnosis	Discogenic		
		Fusion Site	L3-S1		
		Case 5			
		Age	39		
		Diagnosis	Grade I spondylolytic spondylolisthesis		
		Fusion Site	L5-S1		

Evidence Table 11. Case Reports and Case Series

Author Year Country Trial # or Name	Adverse Events	Funding	Comments
Wong 2008 USA	For all Cases: radicular symptoms increase postoperatively over weeks to months, 4/5 increasing radicular pain, 1/5 (pt 3) numbness in radicular pattern. Ectopic Bone Formation: Average time to showing of definitive ectopic bone = 8.35 months	Grant research support from Stryker, Zimmer, Archus, Cervitech	No evidence that ectopic bone formation was preexisting. Factor influencing bone ectopic bone formation include dosage of rhBMP-2, properties of the carrier, any barrier that would resist migraton of rhBMP-2 into the canal. Speculate that adherence of neural structures to the ectopic bone at revision surgery may be a reaction to the inflammatory process involved in bone formation.