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Effectiveness and safety of recombinant human bone morphogenetic protein-2 for adults with lumbar spine pseudarthrosis following spinal fusion surgery

A SYSTEMATIC REVIEW

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Objectives

We performed a systematic review of the literature to determine the safety and efficacy of bone morphogenetic protein (BMP) compared with bone graft when used specifically for revision spinal fusion surgery secondary to pseudarthrosis.

Methods

The MEDLINE, EMBASE and Cochrane Library databases were searched using defined search terms. The primary outcome measure was spinal fusion, assessed as success or failure in accordance with radiograph, MRI or CT scan review at 24-month follow-up. The secondary outcome measure was time to fusion.

Results

A total of six studies (three prospective and three retrospective) reporting on the use of BMP2 met the inclusion criteria (203 patients). Of these, four provided a comparison of BMP2 and bone graft whereas the other two solely investigated the use of BMP2. The primary outcome was seen in 92.3% (108/117) of patients following surgery with BMP2. Although none of the studies showed superiority of BMP2 to bone graft for fusion, its use was associated with a statistically quicker time to achieving fusion. BMP2 did not appear to increase the risk of complication.

Conclusion

The use of BMP2 is both safe and effective within the revision setting, ideally in cases where bone graft is unavailable or undesirable. Further research is required to define its optimum role.

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Keywords: systematic review; BMP; fusion; pseudarthrosis; lumbar; degenerative disc disease; deformity; complications

Article focus

- To perform a systematic review of the literature to determine whether the use of bone morphogenetic protein (BMP) 2 in adults undergoing revision lumbar spinal fusion surgery secondary to pseudarthrosis is effective and safe.

Key messages

- BMP2 provides high fusion rates for both single- and multiple-level fusion within the revision setting.
- BMP2 provides significantly faster time to fusion compared with bone graft.
- BMP2 may be clinically appropriate in high-risk cases when all clinical and societal factors are considered as part of the treatment package for spinal fusion surgery.

Strengths and limitations

- This is the first systematic review which identifies and compares the safety and efficacy of BMP specifically in the revision spinal fusion surgery setting secondary to pseudarthrosis.
- A meta-analysis could not be performed due to differences in study designs, varying quantity of BMP used, and differing methods of surgery.

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Introduction

For patients undergoing spinal fusion surgery, autologous bone graft (ABG) is commonly harvested to stimulate fusion of the required vertebrae. Pseudarthrosis occurs in approximately 5% to 35% of patients following instrumented spinal fusion surgery with autograft,[1] often necessitating revision surgery. Although the use of ABG is regarded as the benchmark for primary surgery, reports are increasingly associating this intervention with significant donor site morbidity in up to 30% of patients, as well as an increase in operative time, blood loss, risk of infection, cosmetic deformity, and arterial and nerve injury.[2-4] Failed surgery causes distress for both patients and spinal surgeons. Not only is the condition difficult to treat appropriately, but recurrent interventions and surgeries yield unpredictable results. In such patients, correcting the pseudarthrosis to achieve a stable spine is the primary goal. The role of revision spinal fusion is still prominent in the United Kingdom as indicated by the Hospital Episode Statistic (HES).[5]

Recombinant human bone morphogenetic protein (BMP) is indicated as an alternative to ABG to promote single-level (L4-S1) fusion in spinal surgery.[6-8] However, its use has grown rapidly, particularly in specialist practice, within various off-label indications and via alternative approaches based on user-reported high fusion rates and a reduction in surgery-related complications and morbidity.[9] Where ABG is not available, non-autologous material is often used to supplement the surgical procedures (including allograft cancellous chips, demineralised bone matrix, ceramics, tricalcium phosphate, and hydroxyapatite products), however, the use of allografts alone results in a slower incorporation into the affected bone and, therefore, decreased fusion rates.[10] Despite advances in the availability of good quality allografts, autologous and synthetic bone grafts (ABG and BMP, respectively) are still considered to deliver better results.[11]

Systematic reviews and meta-analyses to date have achieved differing results with regard to the value of BMP in increasing fusion rates and reducing pain compared with ABG, however, these findings are limited to the use of BMP in the primary setting.[12] Although concerns regarding an association between BMP and an increase in the incidence of complications are unfounded from such reviews, this still remains a concern in practice.

Despite numerous reviews, no formal guidelines exist regarding use of BMP on a national or international basis, with the recent exception of a coverage policy by the North American Spine Society (NASS).[13] Furthermore, despite reference to use of BMP within the revision setting in the NHS standard contract for complex spinal surgery, the commissioning position of BMP for this indication remains unclear across the United Kingdom.[14]

We conducted a systematic review of all published studies which investigated the use of BMP in adult patients with lumbar spine pseudarthrosis following primary fusion surgery to determine its efficacy and safety in this specific setting.

Patients and Methods

Design. We conducted a systematic review of the published literature performed using *a priori* protocol.

Literature search. Clinical studies of any design type that investigated the safety and efficacy of BMP in revision spinal fusion surgery via any surgical approach at the lumbar region only were eligible for inclusion. We performed a systematic literature search using the following databases: Cochrane Central Register of Controlled Trials (Cochrane Library 2009, issue 2) which contains the Back Group, Bone, Joint and Muscle Trauma Group, and Musculoskeletal Group specialised register; MEDLINE (via PubMED) (1950 to September 2014); and EMBASE (1980 to September 2014), adopting PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) recommendations.[15] We supplemented the database search by a hand search of the reference list of the identified studies (Fig. 1). The search terms and limits are provided in the supplementary material (Tables S1 and S2).

Article selection. We included studies if they investigated BMP for revision spinal fusion surgery secondary to pseudarthrosis. Comparative treatments included ABG, allograft and bone graft products. Trials were required to have been conducted in human subjects $\geqslant$ 18 years of age without restriction of gender or surgical approach used except that the location of spine surgery be within the lumbar region. Due to the nature of the intervention and subsequent assessment, it was agreed that studies of open-label and single-blind design should be included in addition to the double-blind design, as well as studies of both prospective and retrospective design.

Data from previous reviews were not used to enable collection of data from original sources, however, any such publications identified served as a comparator to ensure that all relevant studies had been included within this review.

We excluded all studies which were not published as full-text articles and: where BMP was not used (e.g. use of synthetic material other than BMP); which reported on non-spinal fusion (e.g. long-bone); which reported BMP use only in patients undergoing primary spinal fusion surgery; where the location of BMP applied was not clearly reported within the outcome data; where the reason for revision surgery was other than for pseudarthrosis or not clearly stated; and where follow-up data covered less than 24 months.

Outcome measures - effectiveness analysis. Our pre-specified outcomes were those likely to be important for patients and healthcare providers. The primary outcome measure was spinal fusion, assessed as success or failure in accordance with radiograph, MRI or CT scan review at 24-month follow-up. This outcome was chosen on the basis that an assessment of fusion success was the most commonly reported endpoint. The secondary outcome measure was time to fusion. The third outcome measure

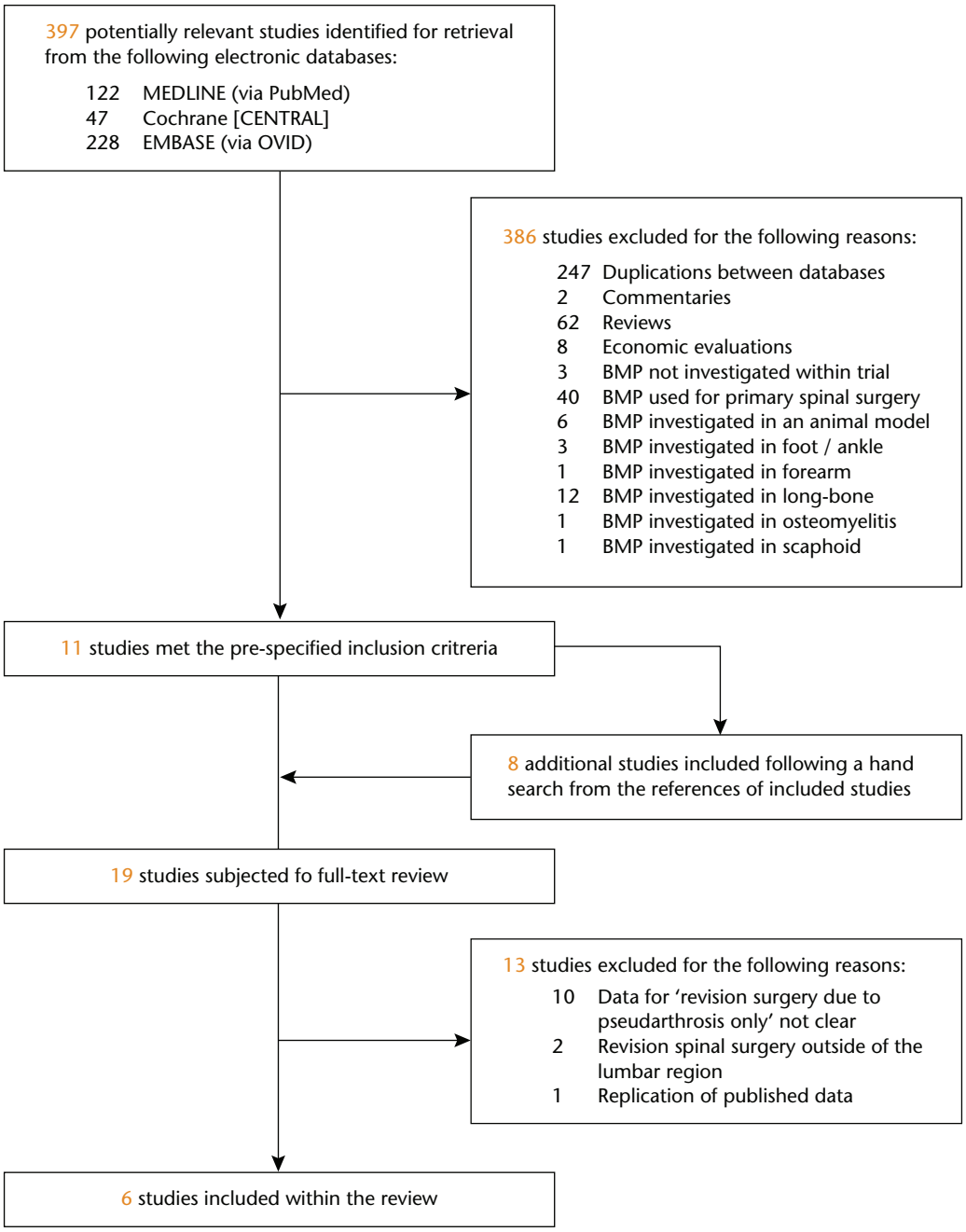

Fig. 1

Flow diagram showing the systematic review.

was the change from baseline to month six in the Oswestry Disability Index (a validated ten-domain index derived from the Oswestry Low Back Pain Questionnaire to quantify disability for low back pain, ranging from 0% (minimal disability) to 100% (bedbound)).[16]

Outcome measures - safety analysis. We extracted data on the number of adverse events from the published studies included for both the BMP and autograft arms.

Quality assessment and data extraction. Two investigators reviewed abstracts and full-text articles retrieved by the search and selected potentially relevant publications against the pre-specified inclusion and exclusion criteria. To ensure consistency of data abstraction for each study a structured form was used. To define the quality of evidence, each article was assigned a level of evidence (LOE) as described by Sackett.[17] Any discrepancies or lack of agreement between the two reviewers were referred to a third independent investigator for arbitration. In accordance with the Cochrane Handbook for Systematic Reviews and Interventions, and the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, the assessment of risk of bias for

Table I. Summary of trials included with the analyses

Author (yr)	Study design (follow-up)	Diagnosis / procedure	Concentration or total dose of BMP2	Additional graft	Total patients	Mean age (range)	Main outcome(s)	Level of evidence
Lee et al (2013)[21]	Retrospective study (24 mths)	Degenerative lumbar spine disease/PLF (BMP2 with allograft or local bone *vs* ICBG)	4.2 mg for 1 level; 8.4 mg for 2 levels; 12 mg for 3 levels and over.	Allograft	195	73 (65 to 91) *vs* 48 (17 to 64)	(1) TLIF, Fusion rate, (2) Time to fusion	III
Taghavi et al (2010)[22]	Retrospective cohort study (24 mths)	Degenerative lumbar spine disease with pseudarthrosis after previous PLF/1) PLF BMP2 and local graft and graft extender 2) PLF BMAA only 3) PLF and ICBG	12 mg total (regardless of number of levels)	Local graft and graft extender	62	57 (21 to 75)	(1) Fusion rate, (2) Time to fusion, (3) Pain score	III
Rogozinski et al (2009)[23]	Prospective non-randomised study (24 mths)	Degenerative lumbar spine disease/PLF (BMP2 & ICBG *vs* ICBG & implantable stimulator)	12 mg total (regardless of number of levels)	ICBG	30	45 (26 to 62)	(1) Fusion rate, (2) Time to fusion, (3), Pain score	III
Mulconrey et al (2008)[24]	Prospective non-blinded, non-randomised study (24 mths)	Multilevel spinal deformity (lumbar and thoracic)/Group 1: ALIF + Post instrumentation (BMP2 only); Group 2: PLF (BMP2/local graft/ graft extender); Group 3: PLF (BMP2 and graft extender)	Group 1: 8 to12 mg/level; Group 2: 20 mg/level; Group 3: 40 mg/ level	TCP/HA, Local graft	98	51 (NR)	(1) Fusion rate, (2) Number of levels fused	IV
Glassman et al (2007)[25]	Retrospective study (24 mths)	Degenerative lumbar spine disease/PLF (active = BMP2 with one or more of the following: allograft / graft extender / local bone) *vs* (control = ICBG)	12 mg total (regardless of number of levels)	Bone graft extenders including local bone, ACC, DBM, and / or TCP-HA at the discretion of the surgeon.	91	60 (27 to 84)	Fusion rate	IV
Vaidya et al (2007)[26]	Prospective non-randomised study (24 mths)	Degenerative lumbar or cervical disease/ALIF or TLIF (BMP2 *vs* allograft)	2 mg/level (for lumbar fusion)	Allograft	54	47 (16 to 77)	(1) Fusion rate, (2) Pain score + Oswestry index, (3) Time to fusion	III

TCP/HA, Tricalcium phosphate / hydroxyapatite; DBM, Demineralised bone matrix; ACC, Allograft cancellous chips; ALIF, Anterior lumbar interbody fusion; PLF, Posterior lumbar fusion; TLIF, Transforaminal lumbar interbody fusion; ICBG, Iliac crest bone graft; BMAA, Bone marrow aspirates in conjunction with allograft; ACS, Absorbable collagen sponge; NR, Not reported; BMP, bone morphogenetic protein

eligible studies was undertaken using the TREND statement.[18-20] Where analyses were not directly reported as intention-to-treat this value was calculated.

Results

Study selection. A total of six studies met the inclusion criteria representing 530 patients, of which 203 underwent revision surgery due to pseudarthrosis (Fig. 1).[21-26] Of the six studies, four provided a comparison of recombinant human (rh) BMP2 and bone graft whereas the other two solely investigated the use of BMP2. No studies investigating the use of BMP-7 met the inclusion criteria. Within the pseudarthrosis population, 117 patients received BMP2 as part of revision surgery while bone graft alone was used in 68 patients (the remaining 18 patients received bone marrow aspirates and are therefore excluded from analyses). All studies were published as full journal articles with a follow-up of 24 months.

Study characteristics. The main characteristics of the studies included are given in Table I. Of the six studies, two were single-arm assessments of BMP2 alone (one retrospective study and one prospective study,[24,25] and four were comparative assessments of BMP2 and bone graft (two retrospective studies and one prospective study).[21-23,26] Reasons for exclusion from the systematic review are provided in Figure 1.

Quality assessment. A common theme across eligible studies was an absence of sample size calculation and the availability of a protocol detailing trial design or planned outcomes. In two of the eligible studies, the authors declare receipt of royalties from the manufacturer of BMP2, although this does relate to involvement in the study design, analysis or publication. Due to study design and differing methods of surgical technique used which increases the potential for methodological diversity, all six studies included were noted as having a moderate risk of bias in accordance with the TREND Statement Checklist, a tool recommended for systematic reviews which include non-randomised studies.

Radiological outcomes - fusion. Successful fusion was observed in 92.3% (108/117) of patients following surgery with BMP2. None of the four studies which

Table II. Summary of results: fusion and time to fusion

Author (yr)				Bone morphogenetic protein (BMP)				Bone graft			
	Pseud population	Blinding (surgeon)	Blinding (radiologist)	BMP total (n)	BMP Fused (n)	Fusion rate (%)	Time to fusion (days)	Bone graft total (n)	Bone graft fused (n)	Fusion rate (%)	Time to fusion (days)
Single-arm studies											
Mulconrey et al(2008)[24]	26/98	Unblinded	Unblinded	26	25	*96.2*	Not reported				
Glassman et al(2007)[25]	16/91	Unblinded	Unblinded	16	12	*75.0*	Not reported				
	42/189			***42***	***37***	***88.1***					
Comparator studies											
Lee et al(2013)[21]	70/195	Unblinded	Unblinded	38	34	*89.5*	244	32	31	96.9	279
Taghavi et al(2010)[22]	62/62	Blinded	Blinded	24	24	*100.0*	218*	20	20	100.0	270
Rogozinski et al(2009)[23]	7/30	Blinded	Blinded	4	4	*100.0*	365*	3	3	100.0	730
Vaidya et al(2007)[26]	22/54	Not stated	Unblinded	9	9	*100.0*	180*	13	12	92.3	274
	161/341			***75***	***71***	***94.7***		***68***	***66***	***97.1***	
BMP population (total)				117	108	***92.3***					

*Statistically significantly faster time to fusion, one-way analysis of variance (three-arm studies) or *t*-test (two-arm studies) were used to compare time to solid fusion ($p < 0.05$)

compared BMP2 with bone graft showed superiority, however, BMP2 was equally effective. Fusion success was determined using radiographs in all but one study where CT grading was used. With the exception of one study where method of fusion assessment by the surgeon was not stated, fusion status was reviewed by the surgeon initially and subsequently confirmed by a radiologist. In three of the studies, radiological review was performed in an unblinded fashion by both surgeon and radiologist; in the remaining two studies, both surgeon and radiologist were blinded (Table II). It is interesting to note that in the one comparator study where both surgeon and radiologist were unblinded, the rate of fusion was lower for subjects who received BMP2 compared with those who received bone graft. However, in the two comparative studies in which the surgeon and radiologist were blinded, a fusion rate of 100% was recorded for subjects within the BMP2 and bone graft arms.

Radiological outcomes - time to fusion. Neither of the single-arm studies collected data for reporting time to fusion analysis. In three of the four comparative studies, subjects who received BMP2 as part of their surgery exhibited a statistically quicker time to achieving fusion (Table II). In the two studies where surgeon and radiologist blinding was used, although there was no difference in fusion rate, the time to fusion was statistically significantly faster in subjects who received BMP2.

Clinical outcomes - pain score. An assessment of BMP2 use on pain was not collected in either of the single-arm studies and in only three of the four comparative studies. Despite the Oswestry Disability Index (ODI) being regarded as the principal condition-specific outcome measure in the management of spinal disorders for measuring degree of disability and quality of life factors in a person with low back pain, this was used in one study only, with the 11-point Visual Analogue Scale (VAS) being used in two studies. Overall, despite a significant reduction in pain from baseline in both the BMP2 and bone graft arms, at no point over the two-year follow-up period was there a significant difference between the two. For studies that recruited patients not exclusively undergoing revision surgery secondary to pseudarthrosis, unlike radiological outcomes, pain scores were not reported separately for this subgroup.

Clinical outcomes - safety and tolerability. Across the six studies, the use of BMP2 was not associated with an increase in the risk of complications over bone graft. The only complication reported was in the study by Mulconrey et al[24] where one patient treated with BMP2 developed a tense subfacial haematoma on post-operative day four, requiring surgical drainage. Reporting of adverse events and complications was poorly described.

Investigation by surgical approach. Spinal fusion surgery via the posterior approach (posterolateral fusion; PLF) appeared to be the most commonly implemented, accounting for 86.7% (176/203) of patients undergoing revision surgery secondary to pseudarthrosis. The remaining 27 patients (13.3%) underwent surgery via the anterior approach (anterior lumbar interbody fusion; ALIF) or transverse approach (transforaminal interbody lumbar fusion; TLIF).

Discussion

Our principal analyses were based on data from 203 patients from six eligible studies, of which 117 received recombinant BMP2. All were of prospective or retrospective case series or cohort design. Although randomised controlled trials are the pinnacle of evidence-based medicine, such a design is not practical for the intervention under question within this review. Radiological assessment of fusion was blinded by the surgeon and radiologist in only two of the six studies, unblinded by both parties in three, and radiologist unblinded in only one. Follow-up was complete at 24 months in all studies. Although there is some potential for bias associated with unblinded radiological assessment.

Table III. Examples of high-risk cases for spinal fusion surgery[13]

High risk criteria	Patient population
No, or inadequate, volume or poor quality of iliac crest	Previous fusion surgery where autograft was harvested from the iliac crest Multilevel fusion requiring large amounts of autograft
High risk for post-harvest iliac crest fracture	Previous fusion surgery where autograft was harvested from the iliac crest Previous radiation therapy or other insult to the fusion bed Poor bone quality (elderly, metabolic disturbance)
High risk of pseudarthrosis	Revision spinal fusion surgery to treat pseudarthrosis Smoker Elderly (including osteoporosis) Multilevel surgery (particularly where extending to the sacrum or pelvis) Previous radiation Metabolic disturbance

Following primary spinal fusion surgery, pseudarthrosis is detected in approximately 70% of patients within the first two years.[27] As such, it was felt important that only studies that performed an assessment of fusion status at month 24 should be included within the review.

The use of ABG is hindered within the revision fusion surgery setting due to limited quantity, especially in multiple-level fusions, and the likelihood of re-failure as a result of poor pathological quality. Furthermore, the environment of revision bone healing is often hostile due to presence of scar tissue and decreased vascularity. Additionally, there are large patient populations, typically excluded from prospective and indeed retrospective studies, in which autograft volumes are inadequate or are associated with unacceptable healing rates.[28,29]

Although the four comparative studies (BMP2 *versus* bone graft) which met the inclusion criteria of this review were unable to demonstrate that BMP2 use provides a superior fusion rate, they did show that BMP2 is associated with a significantly faster time to fusion based on radiological assessment. This is clinically important for high risk cases and in subjects with numerous comorbidity factors. The review also suggests that BMP2 significantly improves pain at 24 months post-operatively, compared with pre-operative pain, however, this difference was not statistically significantly different when compared with patients who received bone graft.

For the single-arm studies, no comparator group was included as the cohort of patients in whom BMP2 was used possessed risk factors such as osteoporosis, insufficient quantity of local bone for harvesting, and previous bone graft resulting in pseudarthrosis. These factors meant that surgery in the absence of a synthetic bone graft could not be considered. The use of BMP2 in these patients still, however, enabled a high fusion rate (88.1%) despite previous fusion failure, thus highlighting its suitability as the most clinically appropriate bone graft in a well-defined population.

The safety concerns reported are articulated well in a number of publications and include retrograde ejaculation, post-operative radiculitis, nerve root injury and theoretical carcinogenesis concerns, the results of which highlight a correlation with high doses and implantation within the cervical spine.[30-32]

The true value of BMP2 therefore lies in scenarios where there is insufficient or poor quality autograft, and where the use of allograft would be considered clinically unsuitable, for example in complex, revision, or multiple-level, fusion surgery and/or where a faster time to fusion is important. Examples of high risk cases in which BMP use could be supported, and those cases in which no other reasonable options exist, are described in Table III. In such cases, a typical alternative to BMP is increased use of interbody devices and instrumentation which themselves are associated with complication and failure rates.[33]

How does this compare with the published literature? This is the first systematic review to be conducted focusing solely on the use of BMP in patients with pseudarthrosis following primary lumbar spinal fusion surgery. We identified the relevant studies by explicit systematic review, and the analysis conformed to PRISMA recommendations. The primary efficacy outcome we selected is established from a surgeon's perspective within the revision setting as a clinically acceptable and informative measure, as well as being of relevance to patients and healthcare providers. Although we acknowledge that other measures of success, such as improvements in disability or pain are also of relevance, the goal of revision spinal surgery is to realise the aim of the primary surgery, which is fusion.

This review differs from others available within the published literature in that it specifically addresses the efficacy and safety profile associated with BMP use within a defined population of patients, i.e. adults undergoing lumbar spinal fusion surgery secondary to pseudarthrosis, where prior use of the considered benchmark, ABG, has failed to result in union.

Of interest, however, is a non-clinical overview of the physical and biological properties of osteoconductive and osteoinductive bone replacement materials and their use in spinal fusion surgery.[34] The authors of this overview included an assessment of ABG, allograft, graft extenders, and BMP, concluding that while satisfactory fusion rates may be obtained with the use of non-autologous material, in comparison with ABG, the vascularisation and remodelling of a fusion mass are delayed using allografts as they possess limited osteoinductive properties. As such,

genuine bone replacement is only currently feasible with BMP. The authors further suggest that their use should be restricted to specific indications, such as complex revision surgery and pseudarthrosis.

A limitation of this systematic review is that the data acquired from the published literature are derived from a mixed population, for example different pathological backgrounds, cause of pseudarthrosis, age, number of levels, and particulars of previous surgery (type, technique, and operating surgeon) as well as varying quantity and type of BMP used. On this basis, it was considered inappropriate to subject the data to meta-analysis.

Lastly, based on the studies identified which reported on BMP2 use within the context of revision spinal surgery secondary to pseudarthrosis, it was not possible to comment on any impact on duration of operating time, duration of hospital stay, time to return to work, or changes in related pharmacotherapy.

Despite the above limitations, the use of BMP was associated with a consistently high fusion rate and demonstrated comparable results with use of bone graft in patients where such alternative intervention was possible. In the absence of a prospectively conducted randomised control trial, the above examples of heterogeneity will continue to be present in published reports.

In conclusion, of the bone grafts available, ABG remains the benchmark by which spinal fusion surgery is performed. The use of BMP2 in revision lumbar spinal fusion surgery provides comparable fusion results at 24 months compared with bone graft, but with a quicker time to fusion and without the potential donor site complications of ABG. This review supports the recommendations of NASS and the Complex Spinal Surgery Clinical Reference Group (NHS England), that BMP2 may be the most suitable bone graft option for adults with lumbar pseudarthrosis requiring revision spinal fusion surgery where ABG is not available, however, future studies, ideally of prospective randomised design, are needed to further clarify its clinical advantages and cost effectiveness.

Supplementary material

Further information showing the search strategy is available alongside this paper at www.bjr.boneandjoint.org.uk

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Author Contribution
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- L. Wilson, Study design, manuscript preparation.

ICMJE conflict of interest
- None declared.