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KR Garrison,[1*] S Donell,[2] J Ryder,[1] I Shemilt,[1] M Mugford,[1] I Harvey[1] and F Song[1,3]

[1] School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK
[2] Norwich and Norfolk University Hospital, Norwich, UK
[3] School of Allied Health Professions, University of East Anglia, Norwich, UK

* Corresponding author

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The research reported in this monograph was commissioned by the HTA Programme as project number 04/34/02. The contractual start date was in November 2005. The draft report began editorial review in August 2006 and was accepted for publication in March 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review

KR Garrison,[1*] S Donell,[2] J Ryder,[1] I Shemilt,[1] M Mugford,[1] I Harvey[1] and F Song[1,3]

[1] School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

[2] Norwich and Norfolk University Hospital, Norwich, UK

[3] School of Allied Health Professions, University of East Anglia, Norwich, UK

* Corresponding author

Objectives: To assess the clinical effectiveness and cost-effectiveness of bone morphogenetic protein (BMP) for the treatment of spinal fusions and the healing of fractures compared with the current standards of care.

Data sources: Electronic databases, related journals and references from identified studies were searched in January 2006, with an updated search only for randomised controlled trials (RCTs) in November 2006.

Review methods: A systematic review of available data was conducted. The data from selected studies were then analysed and graded according to quality and processed to give a value to the efficacy of BMP. Existing models were modified or updated to evaluate the cost-effectiveness of BMP for open tibial fractures and spinal fusion.

Results: All selected trials were found to have several methodological weaknesses. Insufficient sample size in most trials, meant that patient baseline comparability between trial arms was not achieved and the statistical power to detect a moderate effect was low. Data did indicate that BMP increased fracture union among patients with acute tibial fractures and found that high-dose BMP is more effective than a lower dose for open tibial fractures. The healing rate in the BMP group was not found to be statistically significantly different from that in the autogenous bone grafting group for patients with tibial non-union fractures, but BMP reduced the number of secondary interventions in patients with acute tibial fractures compared with controls. There was very limited evidence that BMP in scaphoid non-union was safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft. There was evidence that BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease. No significant difference was found when BMP-7 was compared with autograft for degenerative spondylolisthesis with spinal stenosis and spondylolysis. The use of BMP was associated with a reduced operating time, improvement in clinical outcomes and a shorter hospital stay as compared with autograft. The proportion of secondary interventions tended to be lower in the BMP group than the control, but not of statistical significance. Trial data on time to return to work postoperatively were sometimes difficult to interpret because of unclear or inappropriate data analysis methods. The incremental cost of BMP for open tibial fractures was estimated to be about £3.5 million per year in the UK. The estimated incremental cost per quality-adjusted life-year (QALY) gained is £32,603. The probability that cost per QALY gained is less than £30,000 for open tibial fracture is 35.5%. The cost-effectiveness ratio is sensitive to the price of BMP and the severity of open tibial fractures. The use of recombinant human bone morphogenetic protein for spinal fusion surgery may increase the cost to the UK NHS by about £1.3 million per year. The estimated incremental cost per QALY gained was about £120,390. The probability that BMP is cost-effective (i.e. cost/QALY less than £30,000) was only 6.4%. From the societal perspective, the estimated total cost of using BMP for spinal fusion is about £4.2 million per year in the UK.

Conclusions: Additional BMP treatment plus conventional intervention is more effective than conventional intervention alone for union of acute open tibial fractures. The cost-effectiveness of additional BMP may be improved if the price of BMP is reduced or if BMP is mainly used in severe cases. BMP may eliminate the need for autogenous bone grafting so that costs and complications related to harvesting autograft can be avoided. In non-unions,

there is no evidence that BMP is more or less effective than bone graft; however, it is currently used when bone graft and other treatments have failed. The use of BMP-2 in spinal fusion surgery seems to be more effective than autogenous bone graft in terms of radiographic spinal fusion among patients with single-level degenerative disc disease. There is a lack of evidence about the effectiveness of BMP for other spinal disorders including spondylolisthesis and spinal stenosis. There was limited evidence showing that BMP is associated with greater improvement in clinical outcomes. According to the results of economic evaluation, the use of BMP for spinal fusion is unlikely to be cost-effective. The following areas would benefit from further research: clinical trials of BMP that include formal economic evaluation, a multicentre RCT of fracture non-union and of interbody and/or posterolateral spinal fusion, trials of non-tibial acute long bone fractures, and RCTs comparing BMP-2, BMP-7 and controls.

Contents

List of abbreviations

ACS	absorbable collagen sponge
AICBG	autogenous iliac crest bone graft
BCP	biphasic calcium phosphate
BESTT	BMP-2 Evaluation in Surgery for Tibial Trauma
BMP	bone morphogenetic protein
BSM	bone substitute material
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CRM	compression-resistant matrix
CT	computed tomography
DBM	demineralised bone matrix
FDA	Food and Drug Administration
HA–TCP	hydroxyapatite and tricalcium phosphate
hBMP	human bone morphogenetic protein
ICER	incremental cost-effectiveness ratio
IM	intramedullary
ITT	intention-to-treat
NA	not applicable
NNB	natural non-organic bone
NR	not reported
OP-1	osteogenic protein-1
OR	odds ratio
OTF	open tibial fracture
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
rhBMP	recombinant human bone morphogenetic protein
SC	standard care
SF-36	Short Form with 36 Items
TGF	transforming growth factor
TSRH	Texas Scottish Rite Hospital

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The objectives of this study were to assess the clinical effectiveness and cost-effectiveness of bone morphogenetic protein (BMP) for the treatment of spinal fusions and the healing of fractures compared with the current standards of care.

Methods

Electronic literature databases, related journals and references from identified studies were searched for relevant studies in January 2006, then an updated search was performed only for randomised controlled trials (RCTs) in November 2006. The searches were not restricted by language, publication status or date. Due to the anticipated paucity of relevant studies, all studies that reported on BMP for treatment of spinal fusion or fracture were included. However, in our analyses, we focused on evidence from RCTs because of the poor quality of data from identified case series. All data were extracted by one reviewer and checked by another.

Models developed by ABACUS International were modified or updated to evaluate the cost-effectiveness of BMP for open tibial fractures and spinal fusion.

Results

Quantity and quality of included RCTs

Eight randomised trials of BMP for tibial fractures, one for scaphoid non-union and 12 randomised trials of BMP for spinal fusion were included. These trials had several methodological weaknesses, including unreported randomisation and allocation methods, incomparable baseline characteristics between the groups, failure to perform intention-to-treat analysis or to use independent blinded assessors and failure to report reasons for drop-outs. Some secondary outcomes were not measured and/or reported. Because of insufficient sample size in most trials, patient baseline comparability between trial arms was not achieved and the statistical power to detect a moderate effect was low.

Effectiveness of BMP for tibial fractures

According to the data from three trials (494 patients in total), the use of BMP increased fracture union among patients with acute tibial fractures [pooled odds ratio (OR) 1.65, 95% confidence interval (CI) 1.12 to 2.45]. This pooled analysis was dominated by the data from a large trial (n = 450). Data from the largest trial (n = 450) also indicated that high-dose BMP (1.5 mg/ml) is more effective than a lower dose (0.75 mg/ml) for open tibial fractures. Four small trials (245 patients in total) found that the healing rate in the BMP group was not statistically significantly different from that in the autogenous bone grafting group for patients with tibial non-union fractures (pooled OR for union rate 0.82, 95% CI 0.25 to 2.64). The use of BMP reduced the number of secondary interventions in patients with acute tibial fractures compared with controls.

Effectiveness of BMP for scaphoid non-union

Only one small RCT (n = 18) was identified. Very limited evidence indicated that BMP in scaphoid non-union was safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft.

Effectiveness of BMP for spinal fusion

Evidence from seven trials (n = 631 in total) showed that BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease (pooled OR 3.87, 95% CI 1.74 to 8.59). Two small trials (n = 56 in total) compared BMP-7 and autograft for degenerative spondylolisthesis with spinal stenosis and found no statistically significant difference (pooled OR 0.87, 95% CI 0.15 to 5.08). No statistically significant difference was observed in one small trial (n = 20) that compared BMP-7 and autograft spondylolysis (pooled OR 0.38, 95% CI 0.05 to 2.77). The use of BMP was associated with an average of 25-minute reduction (95% CI 11 to 37 minutes) in operating time and a shorter hospital stay (0.75 days, 95% CI 0.31 to 1.19 days) compared with autograft. BMP may be associated with improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. The proportion of secondary interventions tended to

be lower in the BMP group than that in the control group, but the difference was not statistically significant (pooled OR 0.62, 95% CI 0.28 to 1.39). Data from trials on time to return to work postoperatively were sometimes difficult to interpret because of unclear or inappropriate methods used for data analysis and results presentation.

Cost-effectiveness assessments

The incremental cost of BMP for open tibial fractures is estimated to be about £3.5 million per year in the UK. The estimated incremental cost per quality-adjusted life-year (QALY) gained was £32,603, with a wide 95% CI from £14,085 to £61,257. The probability that cost per QALY gained is less than £30,000 for open tibial fracture was 35.5%. The cost-effectiveness ratio is sensitive to the price of BMP and the severity of open tibial fractures.

The use of rhBMP for spinal fusion surgery may increase the cost to the UK NHS by about £1.3 million per year. The estimated incremental cost per QALY gained was about £120,390. The probability that BMP is cost-effective (i.e. that the cost/QALY is less than £30,000) was only 6.4%. We re-analysed data on time to return to work after spinal surgery, and revealed that patients in the BMP group were not returning to work earlier than those in the control group. From the societal perspective, the estimated total cost of using BMP for spinal fusion is about £4.2 million per year in the UK.

Conclusions

Additional BMP treatment plus conventional interventions is more effective than the conventional intervention alone for union of acute open tibial fractures. The cost-effectiveness of additional BMP may be improved if the price of BMP is reduced or BMP is mainly used in severe cases.

The use of BMP may eliminate the need for autogenous bone grafting so that costs and complications related to harvesting autograft can be avoided. In non-unions, there is no evidence that BMP is more or less effective than bone graft; however, it is currently used when bone graft and other treatments have failed.

The use of BMP-2 in spinal fusion surgery seems more effective than autogenous bone graft in terms of radiographic spinal fusion among patients with single-level degenerative disc disease. There is a lack of evidence about the effectiveness of BMP for other spinal disorders including spondylolisthesis and spinal stenosis. There was limited evidence showing that BMP is associated with greater improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. According to the results of economic evaluation, the use of BMP for spinal fusion is unlikely to be cost-effective.

Recommendations for further research

The following areas are recommended for further research:

- clinical trials of BMP that include formal economic evaluation
- a multicentre RCT covering fracture non-union
- a multicentre RCT covering interbody and/or posterolateral spinal fusion
- RCTs covering non-tibial acute long bone fractures
- RCTs comparing BMP-2, BMP-7 and controls.

Chapter 1
Background

Fractures

A fracture is a broken bone. Most tibial fractures heal within 20 weeks.[1] The rate of fracture union depends on a number of factors, which include:

- violence of injury
- presence of an open wound
- number of fracture fragments
- associated vascular injury
- part of the tibia fractured
- method of fracture treatment.[2–4]

A fracture that does not heal in the time expected is considered a delayed union. The rate of delayed unions varies by fracture severity from 16–60% for less severe fractures (Gustilo–Anderson types I–IIIA) to 43–100% for more severe fractures (Gustilo–Anderson types IIIB and IIIC).[5–7] A fracture that demonstrates motion at the bony ends and is not completely healed within 6 months is considered a non-union.[8] Non-unions can lead to significant pain, inhibition of function and decreases in personal and professional productivity.[9] The rate of non-unions has been reported to range from 4 to 10%.[1,10] The costs for treating non-unions have been poorly reported.[11–14] Some factors that can contribute to delayed union or non-union are:

- severe comminution (broken into small fragments)
- open fractures
- association with tumour
- infection
- insufficient immobilisation
- inadequate blood supply
- poor nutrition
- chronic disease.

A fracture is considered closed when the skin is not breached. A fracture is open when the bone protrudes through the skin or communicates with a wound and therefore has a significant risk of infection. It is estimated that there are 23 open fractures per 100,000 population, of which 54% involve either the phalangeal or tibial diaphysis.[15] The severity of open fractures is graded using the Gustilo–Anderson system. Grade I is a puncture wound and grade IIIC is a large, open, dirty wound with an arterial injury. A higher grade means a higher risk of amputation. In grade IIIB open fractures there can be up to a 50% infection rate.[4] The severity of an open fracture is determined by:[8]

- energy level
- degree of contamination
- degree of soft tissue injury
- complexity of fracture pattern
- vascular injury.

Spinal fusion

Spinal fusion surgery is performed to stop motion at the painful vertebra segment,[16] for a number of conditions, including spinal stenosis, spondylolisthesis and degenerative lumbar disc disease.[17–19] Between 10 and 40% of patients who undergo spinal surgery fail to fuse.[20,21]

Spinal stenosis is caused by enlarged facet joints, which then place pressure on surrounding nerves and cause pain in the back, and sometimes the legs. The usual treatment is modifying activities, such as using a stick or walker to walk and doing low-impact exercise. Patients may also receive epidural injections, of whom 50% will experience temporary relief. In certain patients, spinal surgery is required to remove a portion of the enlarged facet joint to relieve pressure on the nerve in either an open decompression or laminectomy.

Degenerative disc disease occurs when the outer ring of the disc, the annulus fibrosus, becomes damaged or worn. The contents of the disc may then protrude and impinge on a spinal nerve root. This will cause pain in the lower back that radiates to the hips and down the backs of the legs. It usually occurs in healthy, active individuals between 30 and 50 years old. Diagnosis is confirmed by magnetic resonance imaging scans. Cervical degenerative disc disease much less commonly causes symptoms than lumbar degenerative disc disease; however, the treatment when symptomatic is much the same. The results of operations for cervical disc disease are less satisfactory than for lumbar disc disease.[22]

Spondylolysis is a discontinuity (defect) of the pars interarticularis (a part of the bony arch that makes up the spinal canal). It may lead to instability of the spine with movement of one vertebra on another. When symptomatic, it may result in pain, or (when severe) affect leg, bladder, bowel and sexual function. Spondylolisthesis is when one vertebra slips on another. Its causes are:

- dysplastic spondylolisthesis (includes congenital)
- degenerative spondylolisthesis (caused by degenerative disc disease)
- traumatic spondylolisthesis (caused by fracture)
- pathologic spondylolisthesis (caused by disease)
- isthmic spondylolisthesis (includes lytic or stress fracture, an elongated but intact pars or acute fracture of the pars).

The costs of back pain in the UK have been reported to be a greater economic burden than any other disease for which economic analysis has been performed.[23] Spinal fusion surgery is a controversial procedure due to varying levels of fusion success with surgery. Non-surgical treatment is an alternative to surgery and the two have been compared in randomised controlled clinical trials. One randomised controlled trial (RCT)[24] found no clear evidence that surgery was more beneficial than the use of multi-disciplinary rehabilitation. However, the authors reported that it was difficult to implement the multi-disciplinary rehabilitation, and that it is not usually available in the NHS. The advantages to rehabilitation are that it does not carry any risks or surgical costs. Another RCT[25] found a significant improvement in pain and disability in the surgery-treated group compared with those treated with physical therapy. Finally, Möller and Hedlund[26] found that for patients with isthmic spondylolisthesis treated with either different surgical procedures or exercise programmes, those who were treated with surgery reported greater Oswestry score improvement at the 2-year follow-up. From these studies, it is unclear whether non-surgical treatment is comparable to surgical treatment, although there does seem to be greater improvement for those patients who received multi-disciplinary rehabilitation over those who received only physical therapy or exercise programmes.

Bone graft substitutes

Spinal fusion (arthrodesis) is the most common indication for bone graft. Currently, autogenous iliac crest bone graft (AICBG) is considered the 'gold standard' graft for bone induction. Because the bone is taken from the patient, it is both histocompatible and non-immunogenic.[27] It has the three properties required for bone formation; osteogenicity, osteoconductivity and osteoinductivity. However, there are several disadvantages to using autogenous bone. Because the graft is taken from the patient, there is a limited amount. This usually becomes important when they have had previous bone grafts and no longer have an adequate volume of iliac crest bone to donate. They therefore require bone to be harvested from different sites or supplemented with bone graft substitutes.[28] Since harvesting bone creates a second surgical site, the use of autogenous bone also increases operating time and blood loss.[27,29] Complications (morbidity) at the donor site have been reported to be common and enduring.[30] The morbidity associated with AICBG includes patient donor site pain, dissatisfaction with donor site appearance and many other complications, often classified as 'major' and 'minor'. The most common morbidity experienced is donor site pain.[30,31] The rates reported of pain vary from one study to another. In a prospective study by Sasso and colleagues, 99% of 202 patients had donor site pain at the time of discharge from the hospital and some level of donor site pain was reported in 31% of 140 patients at 24 months after surgery.[32] Goulet and colleagues reported that 18.3% of 87 patients still experienced pain at the donor site at 24 months or more postoperatively.[30] Using similar major and minor complication definitions, a retrospective review by Arrington and colleagues[27] and a prospective study by Banwart and colleagues[33] investigated the rate of complications. The studies classified a major complication as needing lengthened hospitalisation or reoperation. Arrington and colleagues included the need for a major change in treatment whereas Banwart and colleagues included a problem that caused a significant disability. Minor complications were defined by both studies as those that responded to minor treatment. Banwart and colleagues also described minor complications as those that resolved without treatment or did not cause permanent disability. Based on these definitions, 10% of 180 patients in the Banwart study and 5.8% of 414 patients in the Arrington study experienced a major complication. The major complications included, but were not limited to, donor defect hernias, vascular injuries, nerve injuries, deep infection haematoma, iliac wing fracture and chronic pain limiting activity. Some 39% of 180 patients in the Banwart study and 10% of 414 patients in the Arrington study

experienced a minor complication. Experienced minor complications included, but were not limited to, superficial infection, superficial seromas, minor haematomas, dysesthesia and scar unsightliness. The morbidities associated with AICBG and its limited supply have led to the development of bone graft substitutes.

Allograft bone (bone from another person), has osteoconductive and weak osteoinductive properties. Its level of osteoinductivity depends on its preparation method. However, with allograft bone, there is an increased rate of infection, greater resorption rate, varying levels of immune response and longer fusion times compared with autograft bone.

Demineralised bone matrix (DBM) is made from allograft bone and is a composite of collagen, non-collagenous proteins and growth factors. Due to its extensive processing, it is the least immunogenic of the types of allograft bone.[34]

Bone morphogenetic protein

Bone morphogenetic proteins (BMPs) are part of the transforming growth factor beta (TGF-β) superfamily. The latter are proteins secreted by cells, which serve as signalling agents that influence cell division, matrix synthesis and tissue differentiation. BMPs have an important role in bone and cartilage formation, fracture healing and repair of other musculoskeletal tissues.

BMPs induce bone through two pathways. They recruit mesenchymal cells from surrounding muscle, bone marrow or blood vessels and either differentiate these cells into osteoblasts and make bone directly or via cartilage cells which subsequently change to bone cells. BMPs also help in matrix production and vascularisation. *In vivo*, multiple BMPs are expressed during bone healing.[35] The combinatorial effects of BMP-2 and BMP-7 have been studied using gene therapy.[36,37] Co-transfection with adenovirus vectors encoding BMP-2 and BMP-7 resulted in significantly greater osteoblastic differentiation and spine fusion than individual gene transfection. Currently, single recombinant human bone morphogenetic proteins (rhBMPs) are used clinically in bone healing; however, the use of multiple BMPs with known osteogenic activity may be more effective at lower doses.

There are two clinical BMPs available; BMP-7 [also known as osteogenic protein-1 or (OP-1)], supplied by Stryker UK Ltd, which uses a bovine collagen carrier in granular form (Osigraft®), and BMP-2, supplied by Wyeth Research (UK) Ltd, which uses a collagen sponge carrier (InductOs™). These collagen carriers allow the slow release of the BMP over time. In simple terms, BMP-2 and BMP-7 are involved in the early stage of fracture repair, but only BMP-2 acts throughout the process. With differentiation of bone cells, BMP-2 is involved in the conversion of stem cells to osteoprogenitor cells and then throughout the differentiation process. BMP-7 is involved in the stages after the formation of osteoprogenitor cells.[38]

BMP has shown good results in preclinical non-human primate studies. In a study by Akamaru and colleagues,[39] rhesus monkeys underwent bilateral posterolateral intertransverse process arthrodesis at L4–L5 and received either collagen sponge 15:85 biphasic calcium phosphate (BCP) granules loaded with rhBMP-2, collagen sponge and allograft chips loaded with rhBMP-2 or AICBG. Both of the groups that received rhBMP-2 achieved 100% fusion at 6 months whereas only 33% of the control group were fused. Seeherman and colleagues[40] found that a single percutaneous injection of rhBMP-2 and α-bone substitute material (α-BSM) could accelerate fibular osteotomy healing by up to 40% in cynomolgus monkeys. In another study by Seeherman and colleagues,[41] they also found that a percutaneous injection of 0.5 ml of 1.5 mg/ml rhBMP-2 and calcium phosphate matrix administered 1 week post-surgery accelerated osteotomy site healing by 40–50% in cynomolgus monkeys.

BMP has also been evaluated for use in cranial defects in non-human primates. Sheehan and colleagues[42] treated bilaterally created critically sized calvarial defects and bilateral rectangular bone flaps with rhBMP-2 on a collagen sponge. Treatment with rhBMP-2 led to 71% closure of defects compared with 28% in the control monkeys. Five of the six bone flaps treated with rhBMP-2 had complete osteointegration whereas the control experienced poor osteointegration of bone flaps. Ferguson and colleagues[43] found that partially purified bovine BMP led to a more complete regeneration of cranial trephine defects than the control bovine serum albumin in rhesus monkeys.

Oral and maxillofacial studies have been performed in both primates and in humans. Blumenthal and colleagues[44] evaluated the use of rhBMP-2 with absorbable collagen sponge (ACS)

or α-BSM for the treatment of three-wall intrabony periodontal defects in the baboon. Compared with the buffer control with both carriers, they found that rhBMP-2 significantly increased regeneration. Specifically, rhBMP-2/ACS led to significantly greater new cementum formation. Chin and colleagues[45] used rhBMP-2 instead of autogenous bone to repair congenital facial clefts. Successful osseous union was achieved in 98% of the cleft sites, and no systemic adverse events were attributed to rhBMP-2.

Licensing

In the UK, Osigraft® (OP-1), produced by Stryker, is licensed for treatment of tibial non-unions of at least 9 months' duration, secondary to trauma, in skeletally mature patients in cases where previous treatment with autograft has failed or the use of autograft is infeasible. In the USA, OP-1 Putty™ is approved by the Food and Drug Administration (FDA) for use in posterolateral spinal fusion in patients who have had failed spinal fusions and are not able to provide their own bone for grafting due to osteoporosis, diabetes or smoking.[46]

In the UK, InductOs™ (rhBMP-2), produced by Wyeth, is licensed for the treatment of acute tibial fractures in adults, as an adjunct to the standard of care using open fracture reduction and intramedullary nail fixation. It is also licensed "for the treatment of single level (L4–S1) anterior lumbar spine fusions as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least six months of non-operative treatment for this condition".[47] In the USA it is FDA approved with the name InFUSE™, Medtronic Sofamor Danek, for use in acute open tibial fractures with internal stabilisation.[48]

Chapter 2

Objectives and methods

Review objectives

The objectives of this review were to assess the clinical effectiveness and cost-effectiveness of BMP for the treatment of spinal fusions and non-healing fractures compared with the current standards of care. The outcomes of interest included healing rate, fusion rate, number of secondary interventions, adverse events, quality of life and any other cost-effectiveness-related outcomes.

Methods

The search strategy was designed to look for any studies that are relevant to the effectiveness and cost-effectiveness of BMP in the treatment of either fractures or spinal fusion, including clinical trials, literature reviews and economic evaluations.

The following electronic databases were initially searched from their default start dates to the end-point, January 2006: Cochrane Library (Central) from 1800, EMBASE (Ovid) from 1980, MEDLINE (Ovid) from 1966, Science Citation Index from 1945, NeLH and the UK National Research Register. Studies were limited to humans, with no language or date restrictions. Details of searches are given in Appendix 1.

The searches were not restricted by language, publication status or date.

A second search was then performed in MEDLINE and EMBASE, to determine the likelihood of BMP being referred to as TGF since it is part of the TGF family of proteins. EMBASE (Ovid) and MEDLINE (Ovid) were both searched from 1980 to week 3 January 2006. Initially, in the BMP–TGF search, a similar number of papers were found as in the BMP search. Therefore, to assess more quickly whether there would be any relevant papers, it was decided to reduce the number of papers by using the highly specific search strategy for identifying RCTs.[49] Thirty-one papers in MEDLINE and EMBASE were found using this refined search. The references were checked for relevance. It was decided not to expand the search or search the other databases when no relevant papers were found.

A second search was then performed in November 2006 for newly available RCTs in Cochrane Library (Central) from 1800, Specialised Register of the Cochrane Bone Joint and Muscle Trauma Group, EMBASE (Ovid) from 1980, MEDLINE (Ovid) from 1966, Science Citation Index from 1945, NeLH and the UK National Research Register using a revised search strategy (see Appendix 1).

Key journals were selected and handsearched from 1995 to the most recently available at the time of search. The following journals were handsearched based on them supplying the largest number of relevant papers identified from the search: *Clinical Orthopaedics and Related Research*, January 1995 to February 2006; *European Spine Journal*, February 1995 to March 2006; *Journal of Bone and Joint Surgery – American*, January 2000 to March 2006; *Journal of Neurosurgery Spine*, January 1999 to March 2006; and *Spine*, April 1995 to March 2006.

References extracted from the references in the papers obtained were also handsearched for any possibly relevant studies.

We also contacted relevant companies (Wyeth and Stryker Biotech) and authors where appropriate to ask for any missing or unpublished data (see Acknowledgements).

Study inclusion and exclusion

We included any clinical trials and full or partial economic evaluation studies that assessed the effectiveness and/or costs and/or cost-effectiveness of BMP for fracture and spinal fusion.

Stage 1

Two reviewers independently assessed the papers for inclusion or exclusion, using the title and, when available, the abstract.

Because it was expected that there would be a limited number of relevant studies and the BMP treatment would vary considerably, including fracture or fusion, degree of fracture or fusion, location, previous failed interventions, dosage,

standard of care treatment method and BMP delivery system, we included all varying BMP interventions for treatment of fracture or fusion in humans.

Stage 2

Full copies of the studies identified in stage 1 were obtained for assessment. Any studies that did not meet the inclusion criteria were excluded at this stage. The list of excluded papers is given in Appendix 5.

Data extraction strategy

Data from included studies were extracted by one reviewer and checked by another reviewer using the predesigned data extraction form. Multiple publications of the same study were extracted as one study, and the sources noted. The effectiveness data extraction forms are shown in Appendix 2, the cost-effectiveness data extraction form in Appendix 3.

Clinical effectiveness review

The following data were extracted:

1. details of study population, including:
   (a) patient diagnoses
   (b) inclusion and exclusion criteria
   (c) surgical interventions
   (d) patient demographics
2. details of intervention, including:
   (a) type of BMP
   (b) dose
   (c) carrier
3. study design quality
4. details of follow-up lengths and patient withdrawals
5. details of outcomes measured, including:
   (a) fusion rates
   (b) clinical scores
   (c) pain improvement
   (d) antibody response
   (e) adverse events
   (f) secondary procedures
   (g) return to work rate.

Cost-effectiveness review

The following data were extracted:

1. details of study characteristics, including:
   (a) type of study
   (b) dates data collected
   (c) setting
2. details on the source of effectiveness data, including:
   (a) where evidence is from
   (b) type of model used, if applicable
   (c) clinical evidence
3. details of economic analysis, including:
   (a) benefits measured and methods of valuation
   (b) costs
   (c) statistical analysis
   (d) sensitivity analysis
4. details of results reported, including:
   (a) intervention and comparator costs
   (b) sensitive parameters.

Quality assessment strategy

Clinical effectiveness

The methodological quality of the selected studies was assessed using the York Centre for Reviews and Dissemination (CRD)[50] criteria for experimental and observational studies. The criteria were tested and the following quality issues were considered to be important for RCTs: randomisation method, allocation concealment, blinding of outcome assessors, similar prognostic baselines, clearly defined inclusion and exclusion criteria, performance of intention-to-treat (ITT) analysis and the numbers lost to follow-up. For the non-RCTs, the following quality criteria were considered: explicit population definition, similar prognostic baselines, appropriate assessment of outcomes and number lost to follow-up. Quality assessment criteria are given in Appendix 4.

Cost-effectiveness

The quality of published economics studies was assessed using the Drummond checklist,[51] which includes evaluation of study design, data collection methods, analysis and interpretation of results. Inclusion/exclusion of studies was based on the researchers' overall judgement of methodological quality, informed by the checklist.

Methods of analysis and synthesis

Descriptive summaries of the included trials were undertaken and relevant evidence was categorised and summarised in tables. Summary tables constructed for trials included study characteristics, interventions, quality of studies, radiographic results, clinical results, adverse events, antibody responses and secondary interventions. When possible, the ITT principles were used to analyse the individual trial data. Where appropriate, results from individual studies were quantitatively pooled by meta-analysis using the random effects model. Odds ratios (ORs) with 95% confidence intervals (CIs) were used as the outcome statistic for dichotomous data. Weighted mean differences with 95% CIs were used for continuous data. Heterogeneity across studies was tested. Publication bias was tested for using funnel plots. Where appropriate, sensitivity and/or

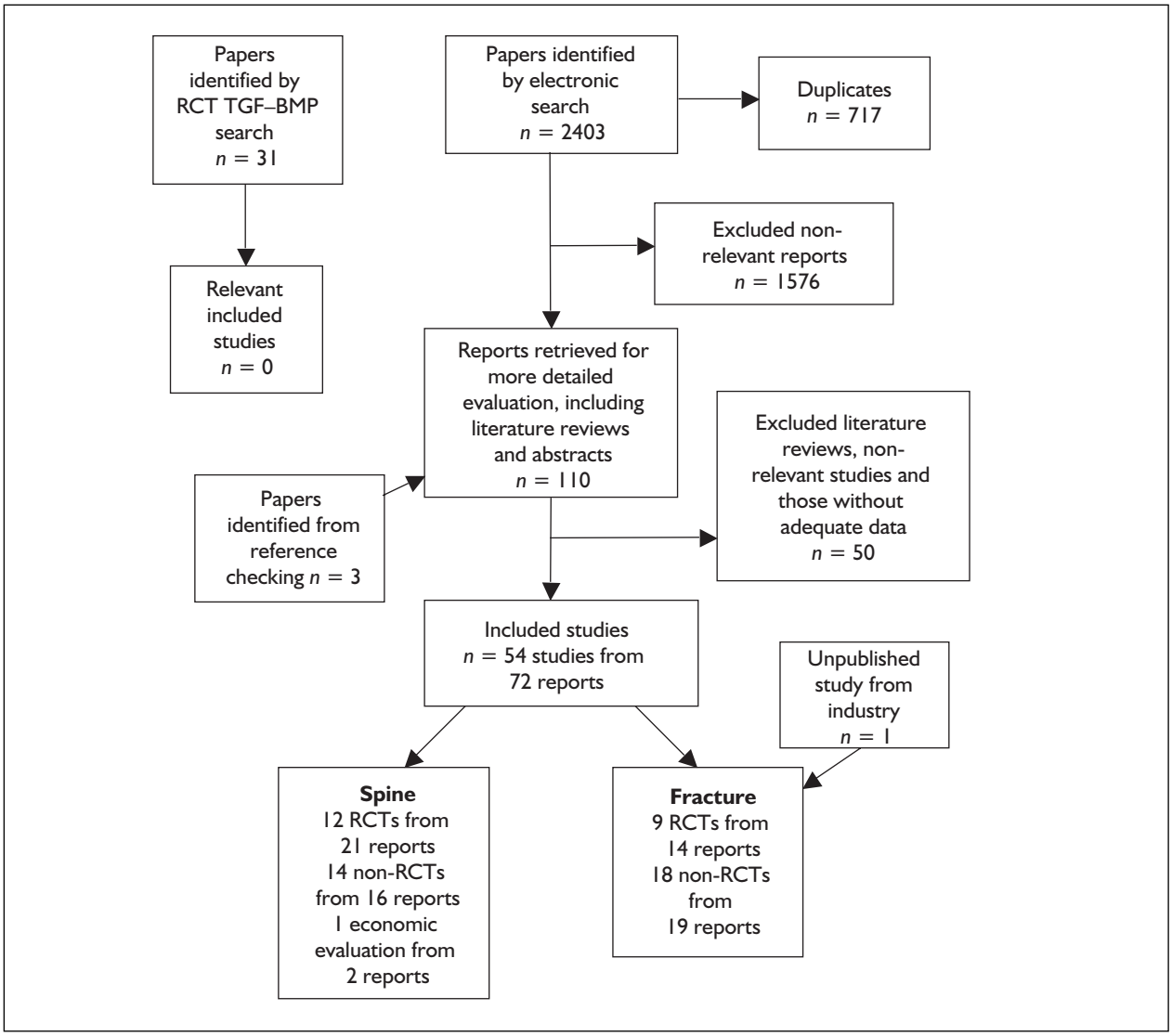

FIGURE 1 *Identification of relevant studies – flow chart*

subgroup analyses were conducted. Results from economic studies were also summarised and put into tables where appropriate.

Quantity of available research

Figure 1 shows the process of identifying studies in each stage of the search.

Number of included studies

Sixty-eight publications reporting relevant trials were identified, including eight abstracts, seven abstracts from conference proceedings and 52 published reports. Data from an unpublished retrospective case series abstract on tibia fractures were provided by Wyeth.[52]

Four publications reporting economic analyses were identified, including one abstract and three published papers.[53–55] Two of the published papers[53,54] reported the same study and were treated as one. The remaining published paper[55] and abstract[56] did not have enough information to be extracted, so the authors were contacted. An abstract by McQueen and colleagues[57] of a randomised clinical trial of radius malunions was identified. However, the results section contained a typo related to union success rates which prevented data extraction; the authors were contacted with no response. An abstract of an ongoing study conducted at the Centre for Musculoskeletal Studies by Speck and Pike was also found; however, it is not included due to lack of data.

The studies were grouped according to study type (RCT or non-RCT), and within those groups by population type (spinal fusion or fracture). Twenty-one reports of 13 RCTs evaluating the use

of BMP for spinal fusion were identified. Sixteen reports of 14 case series for use of BMP in spinal fusion were identified. Fourteen reports of nine RCTs evaluating the use of BMP for use in fractures were identified. Nineteen reports of 18 case series or case report studies for BMP use in fracture non-unions were identified.

Publication bias

Publication bias was tested for using funnel plots (not shown). No significant asymmetry was found, although there were only a small number of studies. The use of BMPs clinically is relatively recent. The risk of publication bias was unlikely due to contact with manufacturers and their knowledge of completed/ongoing trials. The National Research Register was also searched, which would contain any ongoing trials.

Chapter 3

Results of effectiveness assessment: fracture healing

Number and characteristics of included fracture healing RCTs

Nine RCTs are included, by Bilic and colleagues,[58] Chen and colleagues,[59] Cook,[60] Friedlaender and colleagues,[9,10] Govender and colleagues,[61] Jones and colleagues[28] and Maniscalco and colleagues.[62] Abstracts of the study by McKee and colleagues[63] and Perry and colleagues[64] are included. The included studies assessed BMP for use in treatment of fractures or non-unions.

Appendix 6 gives the table of general characteristics of each fracture-healing RCT included in this review. All but one of the studies included patients with either acute or non-union tibial fractures. Due to the different characteristics of the fractures, the studies were assessed based on fracture type.

Five of the studies were conducted in the USA, one in Italy, one in China and one in Croatia and one was a multi-centre trial in 11 countries (Australia, Belgium, Canada, UK, Finland, France, Germany, Israel, The Netherlands, Norway and South Africa). Five of the studies specified that their funding source was industry. One study[59] was government sponsored and three studies[58,62,64] did not state their source of funding.

The Govender study[61] had the most patients, with a total of 450 and the McKee study[63] had the second highest number of patients (124). Friedlaender and colleagues[9,10] reported data on 122 patients with 124 non-unions. The numbers of patients in the remaining studies ranged from 14 to 80.

One RCT[58] assessed BMP in scaphoid non-unions at the proximal pole and the surgical procedure was not described.

The Chen,[59] Cook,[60] Perry[64] and Friedlaender[9,10] studies included patients with tibial non-unions. A fracture is generally considered a tibial non-union after a number of unsuccessful procedures, thus indicating a more difficult fracture to heal successfully. Although these are RCTs, patients may not be convincingly comparable between the BMP and the control groups in terms of certain baseline prognostic factors. The Friedlaender study[9,10] reported a statistically significant difference in the rate of atrophic non-unions at baseline between the intervention and control groups, $p = 0.048$. Atrophic non-unions were found in 26% of the BMP intervention group and 15% of the control group. An atrophic non-union has an impaired blood supply and is therefore even more difficult to heal. Other reported differences between the groups, although not statistically significant, include a higher number of patients smoking tobacco in the intervention group (74%) compared with the control group (57%), $p = 0.057$. There were also more prior autografts in the intervention group (43%) than the control group (31%) ($p = 0.177$) and a higher number of comminuted fractures in the intervention group (67%) than the control group (56%), $p = 0.212$. All of these population characteristics could affect the healing ability of the non-union fractures and hence may affect the comparability of the intervention group.

The remaining studies included patients with acute tibial fractures. The Govender study[61] included patients with open fractures, of which the main component was diaphyseal. The McKee study[63] included patients with open tibial shaft fractures which were suitable for intramedullary nailing procedure. The Jones study[28] included patients with open or closed diaphyseal fractures and the Maniscalco study[62] patients with closed fractures.

The patients with non-unions were treated with either intramedullary (IM) nails[9,60,64] or the treatment used was not reported.[59] In the Govender study,[61] IM nail fixation and routine soft tissue management were used to treat the open tibial fractures (OTFs). The authors reported a statistically significant difference between the groups of those treated with reamed and unreamed IM nails. Totals of 39 (27%) of the control group, 48 (33%) of intervention group A and 59 (41%) of intervention group B received reamed IM nails, $p = 0.0371$. Statically locking IM nailing was used in the McKee study.[63] The Jones study[28] used staged reconstruction of the tibia as its surgical intervention for open or closed tibia fractures. Finally, monolateral external fixator

treatment was performed for treatment of the closed fractures in the Maniscalco study.[62]

Two studies[28,61] reported the severity of the tibia fractures based on the Gustilo–Anderson classification of open wounds. They included all grades of fractures from I to IIIB. The Friedlaender study[9,10] reported different grades of fractures ranging from III to IIIC, but did not specify the grading system used. Finally, the two remaining studies did not give details on the severity of fractures included.

Where reported, the mean age of patients with tibia fractures ranged from 31 to 47 years. In the Govender study,[61] there was a statistically significant difference between the ages of the intervention groups and the control group, with mean ages in the control and 0.75 mg/ml (intervention A) groups of 37 years and a mean age in the 1.5 mg/ml (intervention B) group of 33 years, $p = 0.0384$. The mean ages of patients in the scaphoid non-union study[58] ranged from 19 to 23 years. Most of the studies reported outcomes at multiple points of assessment. The follow-up times ranged from 6 to 24 months. Friedlaender and colleagues[9] specified a 24-month follow-up, but outcomes were reported at the 9-month primary follow-up point, unless specified otherwise. The Maniscalco study[62] did not clearly specify the follow-up length but gave a mean length of follow-up.

Interventions

Table 1 gives details on the interventions investigated in the studies. Two studies[28,61] investigated rhBMP-2 and six studies[9,10,58,60,62–64] investigated BMP-7. One study[59] used unspecified concentrations of BMP and natural non-organic bone (NNB) in a complex.[59] The concentrations of rhBMP-2 used were 0.75 mg/ml[61] and 1.5 mg/ml.[28,61] In the Govender study,[61] there were two intervention groups that received either a 0.75 or 1.50 mg/ml concentration of BMP-2; 91% of patients in the 0.75 mg/ml group (intervention A) received the full dose of 6 g of rhBMP-2 and 90% of intervention group B received the full 1.50 mg/ml dose of 12 g of rhBMP-2. The patients who did not receive the full dose did not because of the inability to close the wound because of the bulk of the BMP carrier. One fracture non-union study[9] reported the concentration of BMP-7 used as 3.5 mg per unit, with a maximum of two units implanted (dependent on fracture size). Bilic and colleagues[58] reported that 3.5 mg of BMP-7 and 1 g of collagen were implanted in one group that also received autograft bone and another group that received allograft bone. The remaining studies did not report the dose of BMP-7 used.[60,62–64] In the Jones study,[28] patients who received BMP-2 also received allograft bone. This is important because it is not possible to assign effectiveness to BMP alone compared with the control group.

Where reported, a collagen sponge was used to deliver the BMP-2 and collagen granules were used to deliver the BMP-7. The control groups of the four studies[9,10,28,60,64] that included patients with non-unions received autograft bone in addition to surgical treatment. One of these studies[59] also had another control group that received a different, unspecified, surgical treatment. Three studies[61–63] that included patients with acute fractures used surgical treatment alone as the control intervention. In the remaining acute fracture study,[28] the control group patients received AICBG. The scaphoid non-union control group received autograft bone only.

Quality assessment of studies

Appendix 7 summarises the quality of the included studies. Two of the studies are preliminary reports[60,62] and two[63,64] are abstracts from conference presentations. The following quality criteria were used to assess study design and methodology: randomisation method, allocation concealment, blinding of outcome assessors, similar prognostic baselines, clearly defined inclusion and exclusion criteria, performance of ITT analysis and the numbers and reasons of patients lost to follow-up reported.

The quality of the studies is variable, ranging from low to moderate, in that none of the studies meet all of the quality criteria. Based on the quality criteria, the studies in order of least to most possible bias is as follows: Govender and colleagues;[61] Bilic and colleagues,[58] Jones and colleagues,[28] Friedlaender and colleagues[9] and Maniscalco and colleagues;[62] Cook[60] and Perry and colleagues;[64] Chen and colleagues[59] and McKee and colleagues.[63]

In seven of the nine studies, the randomisation method was unclear in that they only used the terms ‘randomisation’ or ‘randomised’ and did not specify the method used. For the same seven studies, the method of allocation concealment was not known. The remaining study, by Govender and colleagues[61] used a central, 24-hour automated system, which was considered adequate and thus the allocation concealment was also considered adequate.[65] Bilic and colleagues[58] reported that computer-generated randomisation

TABLE 1 *Fracture RCT interventions*

Study	Intervention(s)				Other
	BMP used	**Dose of BMP**	**Delivery method**	**Control**	
Scaphoid non-unions					
Bilic, 2006[58]	BMP-7	3.5 mg and 1 g collagen	Collagen	Autograft	One BMP group also had autograft and another had allograft
Tibial non-unions					
Chen, 2000[59]	BMP/NNB	NR	NR	A: autograft bone B: different surgical management	
Cook, 1999[60]	BMP-7	NR	Type I collagen	Autogenous iliac crest bone	Both groups had reamed intramedullary nail fixation
Friedlaender, 2001[9,10]	rhBMP-7	3.5 mg and 1 g collagen per unit (max. 2 units)	Type I bovine collagen	Autograft	Both groups had intramedullary nail fixation
Perry, 1997[64]	BMP-7	NR	NR	Autograft	
Open tibial fractures					
Govender, 2002[61]	rhBMP-2	A: 0.75 mg/ml (6-mg dose) or B: 1.50 mg/ml (12-mg dose)	Type I bovine collagen sponge	Surgical treatment and routine soft-tissue management	All groups had surgical treatment which included intramedullary nail fixation and routine soft-tissue management
McKee, 2002[63]	rhBMP-7	NR	NR	Standard wound closure	Both groups underwent statically locked intramedullary nailing
Open and closed tibial fractures					
Jones, 2006[28]	rhBMP-2	1.5 mg/ml (12 mg dose)	Type I collagen sponge with allograft bone	Autogenous iliac crest bone	All groups had staged reconstruction of tibial defect. 11 intervention and 10 control patients had IM nail fixation; 4 intervention and 5 control patients had external fixation
Closed tibial fractures					
Maniscalco, 2002[62]	BMP-7	NR	OP-1 applied to external fixator	External fixator only	All groups had external fixator treatment

NR, not reported.

was used, but did not report the allocation concealment method.

Five of the trials[59,60,62–64] did not use an independent blinded assessor for the primary radiographic outcome. Due to the lack of a clearly established union definition, the use of independent assessors is a particularly important quality measure, given the extremely subjective task of assessing union success.

There were also issues regarding the true nature of assessor 'blindness' in that some aspects of the interventions were apparent during assessment. Autograft is visibly mineralised on radiographs from the start, whereas BMP in collagen is radiolucent. This provides assessors with a way to determine which intervention was used and compromises their 'blind' assessment. Also, on radiographs, mineralised autograft and new bone appear similar, thus allowing for misinterpretation of bone formation. Finally, there is a technical limitation of radiographs to show clearly the space by the internal fixation and irregular gaps, to allow for conclusive assessment. In the Jones study,[28] the difference between allograft and autograft bone

was apparent on the radiographs. Therefore, to test the 'blindness' of the blinded assessors, the radiographs were assessed in reverse chronological order, and the point where the difference was no longer apparent was identified. Six months was determined as the point where 'blindness' was consistent and thus blinded assessors reviewed all of the images from 6 to 12 months.

Clinically, assessors use patient histories and clinical and radiographic outcomes to determine fracture healing.[9] Therefore, relying on only one aspect of clinical assessment may not provide an accurate representation of clinical evaluation. Hence those studies[28,61,62] that included clinical outcomes in their definition of successful healing may provide a better representation of clinical evaluations.

The Friedlaender study[9] had a significantly higher number of atrophic non-unions in the intervention group than control group, $p = 0.048$. Govender and colleagues[61] reported a statistically significant difference in the ages between the intervention groups and control group, where the mean age of intervention group B was lower than those of intervention group A and the control group, $p = 0.0384$. Three trials[9,10,28,62] had a significantly higher number of males than females in their overall populations, but this was known to be balanced between the intervention groups in all but one of the studies.[59] Three studies[60,63,64] did not report any population characteristics. One study[59] reported population characteristics, but did not separate the characteristics between the treatment groups. The inclusion and exclusion criteria were clearly reported in four[9,10,28,58,62] of the nine trials. The studies that did not adequately report the inclusion and exclusion criteria gave only the patient diagnoses, and no further information.

Only two studies[28,61] performed partial ITT analyses in that the patients were assessed in the group to which they were randomised, but not all randomised patients were included in the final analysis. Two studies did not mention patient drop-outs.[59,63] The drop-out rates in the Jones study[28] were 26.7% in the control group and 13.3% in the BMP intervention group. The Govender study[61] reported an 8% drop-out rate in the control group and 6 and 5.4% drop-outs in intervention groups A and B, respectively. Bilic and colleagues[58] reported one patient drop-out in the BMP–allograft group, but did not give a reason. In the remaining studies, there were no patient drop-outs.

Findings from RCTs on tibia fractures

Radiographic results

Table 2 reports the union rates using ITT analysis of the studies and gives each study's definition of a successful union.

The studies that reported a definition of successful union included the parameter of bridging bone seen on a certain number of radiographic views. Three of the studies[28,61,62] also included clinical outcomes in their definition of successful union. Two studies[59,64] did not report the definition of union used. The McKee study[63] did not report the radiographic outcome or give a definition of union.

BMP for non-union tibial fractures: radiographic results

Chen and colleagues[59] reported 100% union rates in both the intervention group ($n = 30$) and autograft control group ($n = 20$). The second control group ($n = 30$) which received a different, unreported, surgical procedure had a 0% union rate. The exact patient numbers are not reported due to the lack of information in the paper regarding drop-outs. Perry and colleagues[64] reported a 95% union rate in the BMP intervention group and 81% in the control group. Two non-union studies[9,10,60] reported higher union rates in the control group. Although Friedlaender and colleagues[9] reported a follow-up of 24 months, they only reported radiographic union rates at the 9-month follow-up point. It may be that BMP is not as effective in severe cases of non-unions. Part of its action is to encourage a blood supply to form, which requires good local soft tissue, especially muscle that may not be present in multiply-treated resistant non-unions.

The lengths of follow-up in these two studies[9,10,60] were shorter than in the other non-union studies: 9 months compared with 19 and 12 months. This shorter follow-up length could possibly have been too short, which therefore excluded some patients who went on to heal within 12 months. Most of the acute fracture studies had a longer follow-up length of 12 months. Data from the Jones study[28] show that at the 8-month radiographic assessment point the independent radiologist determined that 60% (6/10) of control patients and 50% (6/12) of intervention patients were healed. At the 12-month assessment, 67% (10/15) of control patients and 87% (13/15) of intervention patients were considered healed. This example supports the view that a follow-up period of longer than

TABLE 2 *Fracture radiographic results*

Study	% of successful unions (no. of patients)		Statistical significance	Successful union definition
	Intervention	**Control**		
Tibial non-unions				
Chen, 2000[59]	100%[a] (30)	A: 100%[a] (20) in autograft group B: 0%[a] (30) in different surgery group		Not defined
Cook, 1999[60]	85.7% (12/14)	93.8% (15/16)		Bridged with new bone across at least 3 of 4 cortices
Friedlaender, 2001[9,10]	At least 1 view: 75% (47/63) At least 3 views: 62% (39/63)	At least 1 view: 84% (51/61) At least 3 views: 74% (45/61)	At least 1 view: $p = 0.218$ At least 3 views: $p = 0.158$	Assessed whether bridging by new bone existed across the fracture site and in how many views it was apparent
Perry, 1997[64]	95% (19/20)	81% (17/21)		Not defined
Open tibial fractures				
Govender, 2002[61]	A: 49.7% (75/151) B: 61.7% (92/149)	44.7% (67/150)	A vs control: $p = 0.0028$	Cortical bridging and/or disappearance of the fracture lines on at least 3 of the 4 cortices viewed on the anteroposterior and lateral radiographs and fulfilment of clinical criteria (including full weight bearing and lack of tenderness at fracture site on palpation) and no secondary interventions that were considered to promote fracture healing
Open and closed tibial fractures				
Jones, 2006[28]	87% (13/15)	67% (10/15)	Difference in proportion of patients with fracture healing 0.2 (95% CI –0.094 to 0.494)	Extracortical bridging callus on 3 of the 4 cortices viewed on anteroposterior and lateral radiographs, pain-free full weight bearing and lack of tenderness at the fracture site on palpation. Did not require reintervention to promote fracture healing
Closed tibial fractures				
Maniscalco, 2002[62]	100% (7/7)	100% (7/7)		Presence of callus bridging the fracture site on anteroposterior and lateral radiographs and clinically by the absence of pain and motion at fracture site

[a] Unable to calculate ITT data from paper.

9 months could be needed in resistant non-unions, although the role of chance could not be excluded.

The Cook study[60] did not provide patient group characteristic details, so it cannot be determined if there were any significant differences between the groups at baseline. However, the Friedlaender study[9,10] did present differences between the intervention group and the control group. First, the number of atrophic non-unions were significantly higher in the intervention group than the control group (41 vs 25%, $p = 0.048$). Atrophic non-unions are a much more difficult fracture to heal because they lack a blood supply, which is one of the main components necessary for fracture healing. Therefore, this difference could have

affected the healing outcomes of the groups. Other differences to note, although not statistically significant, were higher numbers of smokers ($p = 0.057$), prior autografts ($p = 0.177$), comminuted fractures ($p = 0.212$) and previous IM nail insertions ($p = 0.280$) in the intervention group compared with the control group. All of these characteristics increase the risk of resistant non-union.

Figure 2 gives the ORs with 95% CIs of the union rates for the studies that included patients with non-unions. Because Chen and colleagues[59] did not report data using ITT principles, a sensitivity analysis was performed excluding that study, which did not affect the OR. Heterogeneity across studies is not statistically significant ($I^2 = 32.8\%$, $p = 0.23$). There is no statistically significant superiority of effect with BMP treatment for patients with tibial non-unions who receive IM nailing as compared with patients who receive IM nailing with autograft bone. The overall OR is 0.82 (95% CI 0.25 to 2.64) ($p = 0.74$).

BMP for acute tibial fractures: radiographic results

Govender and colleagues[61] reported higher union rates in both intervention groups than in the control group in OTFs. The union rates were 49.7% in intervention group A, 61.7% in intervention group B and 44.7% in the control group. The union rate in intervention group B (1.5 mg/ml) was significantly higher than the control group, $p = 0.0028$. Based on these results, patients with OTFs treated with IM nailing with 1.5 mg/ml BMP experience higher union rates than patients who receive the same surgical treatment alone. The Jones study[28] also reported higher healing rates in the intervention group than the control group, with 87% in the intervention group and 67% in the control group experiencing successful radiographic union.

Both the intervention and control groups had 100% union rates in the Maniscalco study.[62] The McKee study[63] did not report union rates.

Figure 3 shows the pooled ORs with 95% CIs of the healing rates in patients with acute fractures. The Maniscalco study[62] received no weight in the analysis due to 100% healing rates in both groups. Due to the small size of the Jones study,[28] 95% of the weight is attributed to the Govender study.[61] Because the Govender study included two BMP intervention groups with different concentrations of BMP used, they were separated and compared with the results of half of the control group population each. The heterogeneity across individual studies is not statistically significant ($I^2 = 1.5\%$, $p = 0.36$). Overall, the OR is 1.65 with the 95% CI ranging from 1.12 to 2.45, suggesting a beneficial effect from BMP treatment ($p = 0.01$).

Unfortunately, the studies[9,10,61] that reported the different fracture severities within each group did not separate their union success data between the severity grades, so no conclusions can be drawn regarding BMP treatment within different fracture severities.

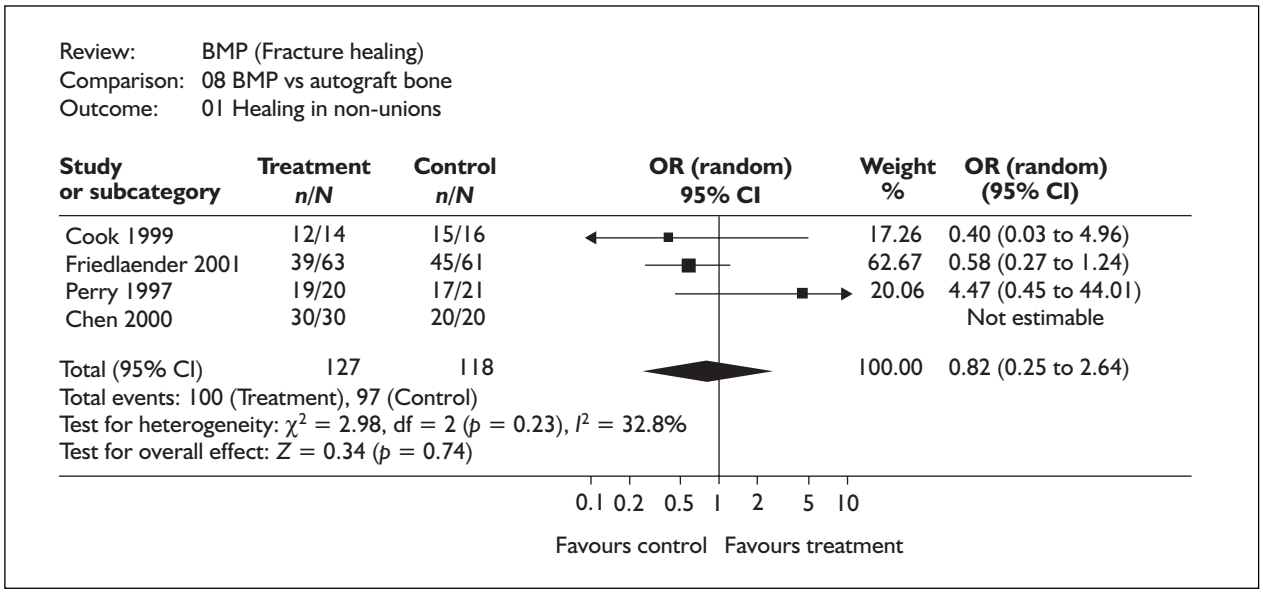

FIGURE 2 *Healing in non-unions*

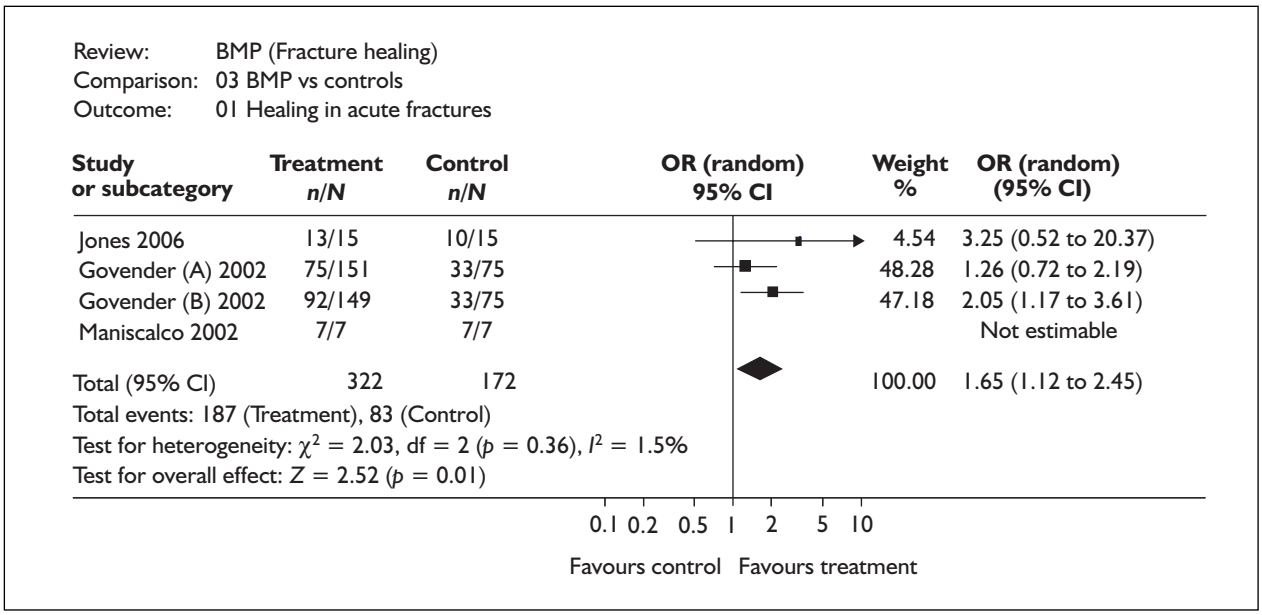

FIGURE 3 *Healing of acute fractures*

TABLE 3 *Time to fracture healing*

Study	Healing rate (days)	
	Intervention	**Control**
Govender, 2002[61a]	Median intervention A: 187 Median intervention B: 145[b]	Median 184[b]
Jones, 2006[28]	Median 184 (95% CI 124 to 295)	Median 176 (95% CI 127 to 263)
Maniscalco, 2002[62]	Mean 135 (range 120–165)	Mean 131 (range 124–164)

[a] As based on 50% of patients.
[b] Authors stated that the difference is statistically significant, $p = 0.002$.

It was also not possible to assess the effect of different BMPs on healing rates due to study heterogeneity and lack of data. Three non-union studies[9,10,60,64] used BMP-7 and one[59] used BMP with NNB. The Govender[61] and McKee[63] studies could have been compared since they have similar treatment groups and used BMP-2 and BMP-7, respectively. However, the McKee abstract did not report this outcome. The remaining studies were considered too heterogenous to allow for comparisons between BMPs.

Time to fracture healing

The reported times to fracture healing are shown in *Table 3*. Govender and colleagues[61] and Jones and colleagues[28] reported the median healing rates whereas Maniscalco and colleagues[62] reported the mean healing rates. The healing rates were all comparable except for the median healing rates of intervention B and the control group in the Govender study. Treatment with 1.5 mg/ml of BMP compared with surgery only (control) was associated with an increase in the median time to healing by 39 days, which the authors reported was statistically significant ($p = 0.0022$). A subgroup analysis by Swiontkowski and colleagues[66] that included Gustilo–Anderson type III fractures from the Govender study[61] and unpublished data from American patients who underwent the same protocol as the Govender study examined only patients who received the 1.50 mg/ml BMP concentration. Sixty-six patients from the BMP group and 65 patients from the control group were included. Due to the subgrouping, and therefore increased risk of statistical error, results from this analysis will only be presented and not included in any final conclusions. The average time to radiographic union as reported by the subgroup analysis (described in the Govender study) was 277 days in the control group and 271 days in the BMP group, $p = 0.43$.

Operation results

Table 4 summarises the reported operation results, including mean operating time, mean blood loss and mean length of hospital stay. For all operation results, *p*-values could not be calculated accurately due to ranges being reported with means instead of standard deviations.

Friedlaender and colleagues[9,10] and Jones and colleagues[28] reported average operating times. In both studies, the control groups' average operating times were similar to those of the interventing groups. The operating times were 2.82 and 2.97 hours for the intervention and control group, respectively, in the Friedlaender study,[9,10] and 2.5 and 2.82 hours for the intervention and control group, respectively, in the Jones study,[28] $p = 0.4309$. In the Friedlaender study,[9,10] both groups received IM nail fixation, whereas the control group received autograft bone and the intervention group received BMP-7. Thus, for patients with tibial non-unions receiving IM nail fixation and BMP there was no reported significant difference in surgical times to those who received the same surgical treatment with autograft bone. Also, for patients with acute tibial fractures who received BMP and allograft bone with staged reconstruction there was no reported significant difference in surgical times compared with patients who received the same surgical treatment and AICBG.

The same two studies[9,10,28] reported average blood loss. Both studies reported that average blood losses were significantly lower in the intervention groups than in the control group. The Friedlaender study[9,10] reported average blood losses of 254 and 345 ml in the intervention and control group, respectively. The mean blood loss reduction in the intervention group was 236 ml, $p = 0.049$. The Jones study[28] reported 117 and 353 ml average blood losses in the intervention and control group, respectively, with a mean blood loss reduction of 91 ml ($p = 0.0073$). In the Jones study,[28] patients with acute tibial fractures received staged reconstruction of the tibial defect by either IM nail fixation or external fixation. The control group patients received autogenous iliac crest bone whereas the intervention patients received BMP-2 with allograft bone. In both studies, the control groups underwent bone graft harvest. It has been reported that the average blood loss at the iliac crest bone graft site is 66 ml (20–200 ml).[29] The reduction in blood loss in the two studies falls between the ranges reported and therefore is likely to be attributable to the elimination of a donor graft site. However, this study was small (30 patients), and a larger study would be recommended to clarify this outcome further.

Finally, the same two studies reported their average lengths of hospital stay. Both studies

TABLE 4 *Fracture RCT operative results*

Study	Mean operating time (hours)		Mean blood loss (ml)		Mean length of hospital stay (days)	
	Intervention	Control	Intervention	Control	Intervention	Control
Tibial non-unions						
Friedlaender, 2001[9,10]	2.82 (range 0.97–7.0)	2.97 (range 0.97–7.0)	254[a] (range 10–1150)	345[a] (range 35–1200), $p = 0.049$	3.7 (range 0–18)	4.1 (range 1–24)
Perry, 1997[64]	States only that times were similar		NR	NR	States only that lengths were similar	
Open and closed tibial fractures						
Jones, 2006[28]	2.5	2.82, $p = 0.0073$	117[a] (range 10–400)	353[a] (range 100–1200), $p = 0.4309$	NR	NR
Closed tibial fractures						
Maniscalco, 2002[62]	NR	NR	NR	NR	11.7 (range 5–21)	12 (range 5–26)

[a] Authors stated that the difference is statistically significant.

reported slightly longer lengths of stay for the control groups compared with the intervention groups, although the criteria for discharging patients was not described in either study. The Friedlaender study[9,10] reported an average hospital stay of 3.7 days for the intervention group and 4.1 days for the control group. The Jones study[28] reported an average hospital stay length of 11.7 days in the intervention group and 12 days in the control group. There is not a significant difference between the reported lengths of hospital stay; therefore, based on reported data, treatment with BMP does not seem to affect this outcome for the included patients who received the specific surgical treatments as compared with their control groups.

For patients with tibial non-unions or acute fractures, there is no evidence to suggest a difference in surgical times or hospital stay lengths with BMP treatment. However, there is a statistically significant reduction in blood loss compared with control autograft.

Other clinical outcomes

Table 5 summarises the clinical outcomes most frequently reported, which were weight bearing and pain upon weight bearing.

Four studies[9,10,60,62,63] reported results on weight bearing. Friedlaender and colleagues[9,10] reported similar percentages of patients' weight bearing at the final end-point (9 months) in the intervention and the control group. The method and parameters used to assess weight bearing were not described. The McKee study[63] reported 11% more patients weight bearing in the intervention versus the control group. However, it did not provide the actual number of patients weight bearing or number of drop-outs, so this result should be treated with caution. The Cook study[60] only reported the total number of patients in the whole study weight bearing at the final end-point and the Maniscalco study[62] reported the average number of days when each group was allowed partial weight bearing. The Swiontkowski subgroup analysis[66] reported that the included patients' time to full weight bearing was shorter in the BMP group (95 ± 38 days) than the control group (126 ± 61 days).

Due to the lack and variability of the data provided, it is not possible to determine whether treatment with BMP affects the patients' ability to weight bear or the time at which they could weight bear.

Five studies[9,10,60,61,63,64] reported on pain outcomes. The patients in the Friedlaender study[9,10] reported mild pain at the surgical site in 89 and 90% of the intervention and control groups, respectively, at the 9-month follow-up point. The Govender study[61] reported the number of patients with overall body pain. The frequency of pain was significantly lower (67 and 68% in intervention groups A and B, respectively) in both intervention groups compared with the control group (79%), $p = 0.0389$. The statistical significance for the intervention B group compared to the control group was $p = 0.0343$. The Govender study suggests that there is an improvement in overall body pain for patients with OTFs who receive surgery with BMP as opposed to surgery alone. McKee and colleagues[63] reported the proportion of patients without pain during activity; 24% fewer patients in the BMP intervention group experienced pain with activity than in the control group, $p = 0.04$. As with the weight bearing outcome, this result should be treated with caution due to missing patient drop-out information. Cook[60] reported the total number of patients with pain and their varying degrees of pain upon weight bearing regardless of their treatment group. Owing to unstandardised methods of collecting data in some studies and lack of data in others, it was not possible to conduct a meta-analysis to draw a better conclusion on the effect of BMP treatment on pain. Due to variable reporting in the non-union studies, it cannot be determined whether or not treatment with BMP affects pain in patients with non-unions compared with treatment with autograft bone.

Three studies[9,10,28,64] reported on donor site pain. Friedlaender and colleagues[9,10] reported that all control patients experienced pain at the donor site and 80% of them reported that their pain was moderate or severe. At the 6-month follow-up, more than 20% still had mild or moderate pain at the donor site, and at 12 months, 13% of patients reported persistent pain. About 93% (14/15) of the control group patients in the Jones study[28] reported pain at the donor site, which ranged from 5 days to 4.5 months. At 12 months, one patient reported residual tenderness at the graft site. Perry and colleagues[64] only reported that the control patients experienced severe but temporary pain at the donor site. BMP has the advantage of eliminating any donor site pain related to harvesting autograft bone.

The inconsistent reporting among the studies raises concern about possible reporting bias. The Cook[60] study reported the weight bearing and pain outcomes of the whole study population, regardless of treatment group.

TABLE 5 *Fracture RCT clinical results*

Study	Weight bearing		Pain	
	Intervention	**Control**	**Intervention**	**Control**
Tibial non-unions				
Cook, 1999[60]	25 of healed non-unions		1 patient had moderate pain, 8 mild pain and 18 no pain (upon weight bearing)	
Friedlaender, 2001[9,10]	86% (54/63)	85% (52/61), $p = 0.941$	89% (56/63) on weight bearing	90% (55/61) on weight bearing, $p = 0.817$ All patients had pain at donor site postoperatively, of whom 80% judged it moderate or severe >20% had persistent mild or moderate pain at donor site at 6 months 13% had persistent pain at donor site at 12 months
Perry, 1997[64]	NR	NR	NR	Severe, but temporary, pain at autograft site
Open tibial fractures				
Govender, 2002[61]	NR	NR	A: 67% (97/145)[a] B: 68% (98/145)[a] (overall body pain)	79% (116/147)[a] (overall body pain), $p = 0.0389$
McKee, 2002[63]	95%[b]	84%[b], $p = 0.11$	80%[a,b] had no pain with activity	56%[a,b] had no pain with activity, $p = 0.04$
Open and closed tibial fractures				
Jones, 2006[28]	NR	NR	NR	14/15 reported acute onset pain at donor site ranging from 5 days to 4.5 months; 1 reported residual tenderness at donor site at 12 months
Closed tibial fractures				
Maniscalco, 2002[62]	Partial weight bearing from average of 19 days (range 14–24 days) postoperatively	Partial weight bearing from average of 21 days (range 14–28 days) postoperatively	NR	NR

[a] Authors stated that the relationship is statistically significant.
[b] *n/N* not reported.

The Jones study[28] used the Short Musculo-skeletal Function Assessment to assess the 'function' and 'bother' status of the patients. The function index included assessment of daily activities, emotional status, arm and hand function and mobility, whereas the bother index assessed how much the patient was bothered in certain situations, such as recreation and leisure, sleep, work and family. The score was out of a possible 100, with 100 equating to the worst function and most bother. The difference in the preoperative and 12-month function index was –22.2 in the control autograft group and –23.9 in the BMP–allograft group. The bother index change at 12 months was –20.3 in

TABLE 6 *Fracture RCT antibody response results*

Study	Antibody response to BMP		Antibody response to bovine collagen	
	Intervention	**Control**	**Intervention**	**Control**
Tibial non-unions				
Friedlaender, 2001[9,10]	10% (6/63)	0	5% (3/61)[a]	0
Open tibial fractures				
Govender, 2002[61]	A: 2% (3/151) B: 6% (9/149)	1% (1/150)	A: 15% (22/151) B: 20% (29/149)	6% (9/150)
Open and closed tibial fractures				
Jones, 2006[28]	0	0	6.6% (1/15)	26.7% (4/15)

[a] Approximation from percentage as *n*/*N* not reported.

the control autograft group and –24.6 in the BMP–allograft group from preoperative scores. The improvements were similar between the groups.

Antibody response

Table 6 shows the antibody responses to BMP and bovine collagen.

Three studies[9,10,28,61] reported data on antibody responses to either BMP or bovine collagen. Friedlaender and colleagues[9,10] did not check the antibody levels before surgery, therefore it cannot be determined if there were any patients with preoperative antibodies to BMP. There are two studies[9,10,61] where the antibody response to BMP was higher in the intervention group than the control, and one study[28] where there was no BMP antibody response in either group. Interestingly, in the Govender study,[61] one patient in the control group was reported to have antibodies to BMP. This raises the issue of whether or not the addition of BMP is responsible for all of the antibody responses reported and which physiological responses are occurring that lead to an antibody response to BMP.

Of the studies that reported antibody responses to bovine collagen, two[9,10,61] reported higher responses in the intervention group and one study[28] reported higher responses in the control group.

Unsurprisingly, there is a higher number of patients with an antibody response to BMP in the intervention group than the control group. However, the antibody responses were not reported to be linked to any symptoms or adverse events and therefore did not seem to have a major effect on the safety of the patient.

Adverse events

Appendix 8 shows all adverse events experienced in the intervention and control groups.

There was considerable variation in the way in which studies reported the presence of adverse events. Some authors[63] reported only that no adverse events were attributable to BMP, with no further explanation, whereas others[9,10,28,61,62] reported the number of patients affected and type of adverse event. Govender and colleagues[61] and Jones and colleagues[28] both continuously monitored the number of adverse events. These two studies defined adverse events as any sign, symptom or abnormal laboratory finding that occurred or worsened after treatment. Govender and colleagues[61] also specified an adverse event as any illness or medical condition, whereas Jones and colleagues[28] also included any disease, radiographic finding or physiological observation that occurred or worsened after treatment. Both studies[28,61] defined infection as "any suspected or confirmed superficial or deep infection involving soft tissue or bone, with or without bacteriological confirmation".

The Govender study[61] reported fewer adverse events in the intervention group than the control group for all reported events except the rate of infection in Gustilo–Anderson type I and II fractures, where the rate was the same between the intervention A and control groups and slightly higher in the intervention B group. The rate of fracture site infection was significantly lower in intervention B (24%) patients with Gustilo–Anderson type IIIA and IIIB fractures than control patients (44%) with the same fracture grades, $p = 0.0219$. It was also significantly lower in both intervention groups compared with the control group, $p = 0.047$. The Jones study[28]

supported the results in the Govender study[61] by also reporting fewer adverse events. The groups had similar adverse events in the Jones study,[28] except for five patients who developed epidermal erythemas and one patient who had heterotopic bone formation in the BMP group and two patients who had hardware failure in the control group. The erythemas in BMP patients were reported to be mild or moderate and to have resolved within 6–12 weeks postoperatively. The heterotopic bone was described as an 'anterior bone spur' and did not require removal. McKee and colleagues[63] did not report any specifics regarding adverse events but did say that any adverse events were not related to BMP. Friedlaender and colleagues[9,10] retrospectively classified all adverse events as serious or non-serious according to the International Conference of Harmonization Guidelines.[67] In both groups 44% of patients had serious adverse events. The study[9,10] also reported a statistically significant difference in the number of postoperative osteomyelitis (bone infection) events, with 3% ($n = 2$) occurring in the BMP intervention group and 21% ($n = 13$) in the control group, $p = 0.002$. The Maniscalco study[62] reported that one patient in the BMP group had calcification of the tibio-fibular ligament and one control patient fell 1 month after fixator removal and refractured the bone. The remaining studies reported more adverse events in the intervention groups than the control groups.

As previously reported, pain at the donor site was a major issue for patients who underwent bone grafting. Three patients in the control group of the Jones study[28] also developed pustules or drainage at the donor graft site, which lasted up to 2 weeks.

Overall, the evidence suggests that BMP reduces osteomyelitis in non-union fractures compared with autograft. It also reduces infections and pain in Gustilo–Anderson type IIIA and IIIB open fractures compared with surgery alone. In studies where autograft bone was used as the control, BMP eliminated donor site pain and morbidity. Generally, the number and type of adverse events reported were similar between intervention groups, apart from one case of heterotopic bone formation, five cases of epidermal erythema and one case of tibio-fibular ligament calcification in BMP groups.

Secondary interventions

Table 7 gives the numbers and percentages of patients requiring secondary interventions reported in the included RCTs of BMP for tibial fractures. It also gives any details that were provided in the papers regarding the surgical interventions performed.

Four studies reported data on the number of secondary interventions in each group. In the Jones study,[28] the proportions of patients requiring secondary interventions were similar between the groups. In three studies,[9,10,61,63] the proportion of secondary interventions was higher in the control group than the intervention groups. Govender and colleagues[61] classified the secondary procedures as most, less or non-invasive. The most invasive procedures included bone graft, exchange nailing, plate fixation, fibular osteotomy or bone transport; less invasive procedures included nail dynamisation or exchange from internal fixation to functional brace; and non-invasive procedures included ultrasound, electric stimulation or magnetic field stimulation. Fewer intervention patients required either the most and less-invasive procedures than the control patients. There was a statistically significant difference in the need for secondary interventions between the intervention groups[66] (36 and 24% of BMP intervention groups A and B, respectively) and the control group (42%), $p = 0.0326$. There was also a statistically significant difference between the number of 'most invasive' procedures required between the groups, $p = 0.0264$. The Swiontkowski subgroup analysis[66] reported significantly more control patients who received invasive secondary procedures, with 28% (18/65) of the control group and 9% (6/66) of the BMP group, $p = 0.0065$. Similar statistically significant findings were reported in the McKee study[63] ($p = 0.02$). The Jones study[28] reported similar rates of secondary interventions in each group; however, this study may lack power due to small sample sizes. From the above studies, there is some evidence that BMP treatment is associated with fewer secondary interventions compared with surgery alone for patients with acute OTFs.

The Govender study[61] also reported the proportion of secondary interventions based on wound severity classification and smoking history. There were significantly fewer secondary interventions in patients with both Gustilo–Anderson type IIIB and I, II and type IIIA fractures in intervention group B compared with the control group, $p < 0.01$. In patients with a recent history of smoking, there was a significantly lower rate of secondary interventions in intervention group B compared with the control group, $p = 0.0138$.

Among the patients with non-union fractures, the Friedlaender study[9,10] reported a 2% difference in

TABLE 7 *Fracture RCT secondary interventions*

Study	% (*n*/*N*) secondary interventions		Surgical procedures	
	Intervention	Control	Intervention	Control
Non-unions				
Friedlaender, 2001[9,10]	18% (11/61)	16% (10/61)	NR	NR
Open tibial fractures				
Govender, 2002[61]	A: 36% (47/130)[a] B: 24% (32/135)[a]	42% (58/139)[a], $p = 0.0326$	20% (26/130) of intervention A and 19% (12/135) of intervention B – most invasive procedures 16% (21/130) of intervention A and 13% (18/135) of intervention B – less invasive procedures. 1% (2/135) intervention B – non-invasive procedures	21% (29/139) – most invasive, $p = 0.0264$ 21% (29/139) – less invasive, $p = 0.3074$
McKee, 2002[63]	13% (8)[b]	27% (17)[b], $p = 0.02$	NR	NR
Open and closed tibial fractures				
Jones, 2006[28]	13% (2/15)	20% (3/15)	Two patients developed deep infection, requiring surgical intervention. For one patient, removal of non-incorporated portion of allograft was required	One patient developed deep infection, requiring surgical intervention. Two patients received IM nail dynamisation for interlocking screw breakage

[a] Authors stated that the relationship is statistically significant.
[b] Drop-outs not reported.

secondary interventions at the 24-month follow-up between the intervention group compared with the control group who received autograft.

Figure 4 shows the pooled meta-analysis of the number of secondary interventions in fractures, in which the Govender study's intervention groups and control group were again separated for analysis. For non-union fractures there is no statistically significant effect ($p = 0.81$), based on the one study that reported data. The pooled OR for acute fractures is 1.58 (95% CI 1.01 to 2.46), which was significant, $p = 0.04$. There is no significant heterogeneity between the studies, $I^2 = 25.1\%$, $p = 0.26$. It should be stressed that this is based mostly on the Govender study,[61] which attributed 77% of the weight. Again, based on the Govender study,[61] there seems to be a dose-dependent effect on the number of secondary interventions, with intervention group B, who received 1.5 mg/ml, experiencing fewer secondary interventions than group A, who received 0.75 mg/ml, OR 0.55 (95% CI 0.34 to 0.87, $p = 0.01$) (not shown). Because McKee and colleagues[63] report the number of drop-outs and ITT data could not be used, a sensitivity analysis (not shown) was performed excluding the McKee study. The OR for acute fracture studies changed to 1.41 (95% CI 0.87 to 2.30), $p = 0.16$.

Findings from RCT on scaphoid non-union

Radiographic results

In the one RCT on scaphoid non-union, by Bilic and colleagues,[58] radiographs taken from four views were assessed by two blinded radiologists. The percentage of remodelled scaphoid bone surface was reported. At 4 weeks, the percentage of bridging bone in BMP–autograft-treated patients (70–95%) was significantly greater than in both BMP–allograft and autograft-only patients (60–80%), $p < 0.05$. By 9 months, 90–100% bridging bone was seen in BMP–autograft patients compared with 75–90% in both BMP–allograft and autograft-only patients. All available patients at 24 months were fully healed.

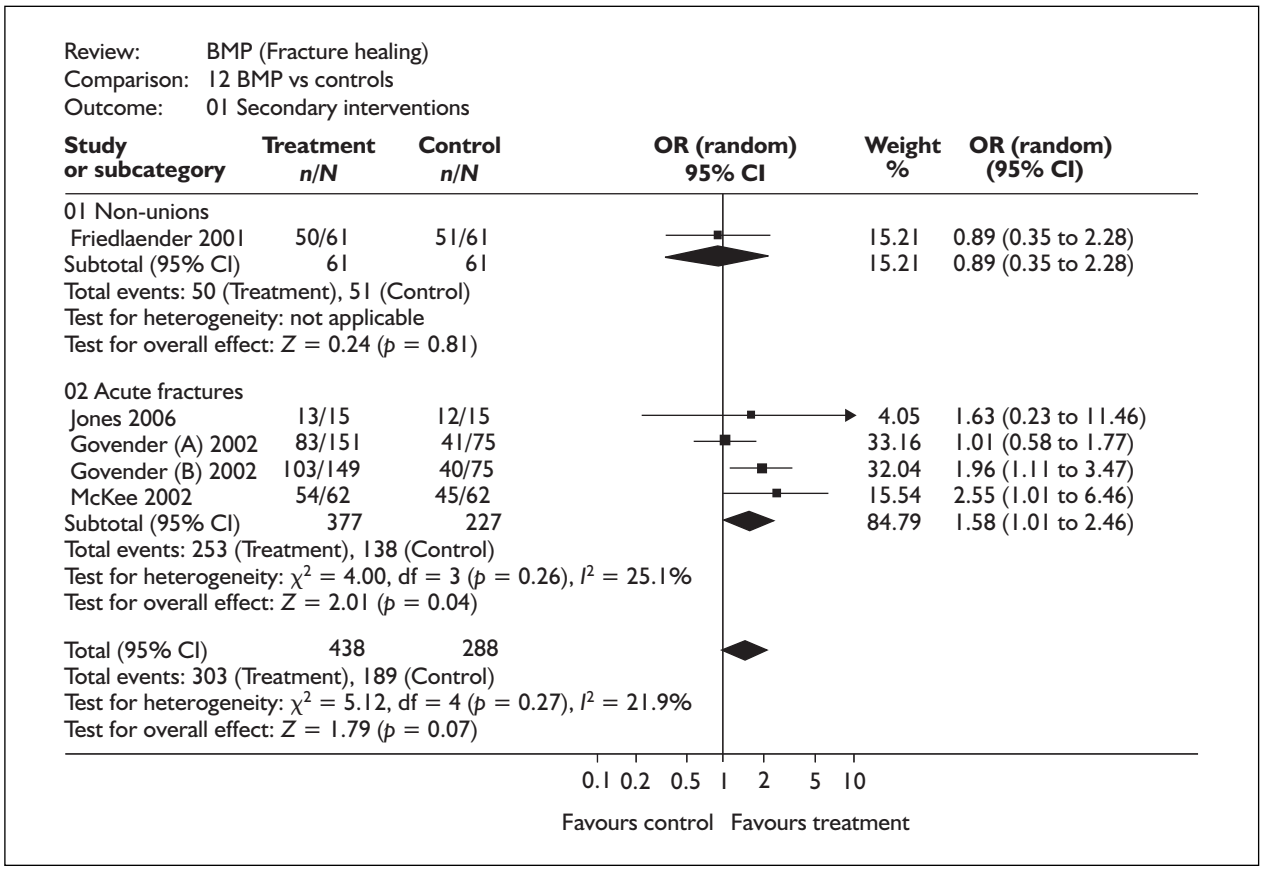

FIGURE 4 *Number of secondary interventions for fractures*

The area (mm^2) of sclerotic bone was measured at varying intervals in each group. At 24 months, the reduction in sclerotic bone from immediately postoperatively in both the BMP–autograft and BMP–allograft groups was significantly better than in the autograft-only group.

Operation results

The exact data for operation length and blood loss were not reported. The authors did report that the BMP–allograft group lost 50 ml less blood due to the elimination of the donor site graft. Also, the BMP–allograft patients were under anaesthesia for 45 fewer minutes than both the BMP–autograft and autograft-only groups.

Other clinical outcomes

Functional tests that assessed the degrees of deviation and flexion and grip strength and pain during different activities were reported at 4 and 12 months. At 4 months, the BMP–autograft group had 91% functioning of that of a normal hand and had significantly greater improvement over autograft in the areas of ulnar and radial deviation, palmar and dorsal flexion, pinch strength and pain during maximal dorsi-flexion and during maximal grip. The BMP–allograft group had 85% functioning of a normal hand and had significant improvement over the autograft group in radial deviation and pain during maximal grip tests. Autograft-treated patients had 75% normal hand function. By 24 months, the authors reported that all patients had good functional results.

All patients who received autograft experienced donor site pain.

Adverse events

There were no reported adverse events in any group.

Summary of evidence on BMP for fractures

There are several methodological limitations in the included RCTs, as none met all of the quality criteria. The main weaknesses in the studies include lack of reporting of randomisation and allocation methods, failure to adjust for differences in baseline characteristics between intervention and control groups, lack of reporting of explicit inclusion/exclusion criteria, failure to

perform ITT analysis or to use independent blinded assessors and failure to report reasons for drop-outs. Some outcomes were not measured and/or reported in every included trial.

Tibial acute and non-union fractures

There is no evidence that BMP treatment is associated with shorter operating times or hospital stays. There is evidence, however, that BMP intervention may be associated with a reduction in operation blood loss, with reported mean decreases of 91 and 236 ml ($p < 0.05$). In patients with non-unions, this may be attributable to elimination of blood loss from autograft removal from the donor site, which was conducted in the control group.

According to evidence from three trials, BMP treatment is associated with increased radiographic healing amongst patients with acute tibial fractures (pooled OR 1.65, 95% CI 1.12 to 2.45). This is based mainly on the data from one larger study which carries 95% of the weight.

The available data from four clinical trials on non-union tibial fracture showed no statistically significant difference between BMP and standard treatment with autograft bone (pooled OR for radiographical union 0.82, 95% CI 0.25 to 2.64).

Furthermore, treatment with BMP eliminates the need for bone grafting, where autograft bone would normally be used, and thus eliminates donor site morbidities. The use of BMP reduces the number of secondary interventions in patients with acute tibial fractures compared with controls.

It was difficult to draw a conclusion on the impact of BMP treatment on weight bearing ability and/or pain as the data were scarce or collected in an unstandardised manner across the studies. There is some evidence that BMP treatment is associated with a lower number of adverse events experienced in patients with non-unions and acute fractures in comparison with autograft and surgery alone, respectively.

Appendix 24 reports a patient's perspective on his experience and his suggestions regarding acute tibial fractures.

Scaphoid non-union

There is little evidence on BMP in scaphoid non-union, although the evidence available suggests that BMP is safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft. When used with allograft it eliminates the need for a donor site, thus preventing any associated morbidity.

Chapter 4

Results of effectiveness assessment: spinal fusion

Number and characteristics of included spinal fusion RCTs

Twelve RCTs are included, by Baskin and colleagues,[68] Boden and colleagues,[69] Boden and colleagues,[70] Burkus and colleagues,[71–73] Burkus and colleagues,[74–76] Dimar and colleagues,[77,78] Haid and colleagues,[79] Johnsson and colleagues,[80] Kanayama and colleagues[81] and Vaccaro and colleagues.[82] Also included are abstracts by Assiri and colleagues[83] and Shapiro and colleagues.[84] The studies assess either BMP-2 or BMP-7 for use in spinal fusions. Appendix 15 reports the general study characteristics of each included study.

Nine of the studies were conducted in the USA, one[80] in Sweden and one[83] in Canada.[83] In one study,[81] it was not clear where it was conducted, but the authors were from Japan and the USA. One study reported it was sponsored by Norton Healthcare[78] and another stated that its funding was from a National Institutes of Health (NIH) award.[81] Three studies[74,83,84] did not state their sources of funding and one study reported that it did not receive any funds.[77] The remaining studies were sponsored by industry.

Seven studies included patients diagnosed with single-level degenerative disc disease. Four[71–74,76,85] of these studies used anterior fusion and three[69,78,83] used posterolateral fusion. Another study[80] included patients with L5 spondylolysis who were treated with non-instrumented posterolateral lumbar fusion. Three studies[81,82,84,86] included patients with spinal stenosis and degenerative spondylolisthesis who were treated with posterolateral fusion. Another study[68] included patients with one- or two-level cervical disc disease who underwent anterior cervical discectomy. The remaining study[77] included patients with a variety of diagnoses, with the majority including degenerative disc disease ($n = 27$) and grade I spondylolisthesis ($n = 27$). Also included were patients with herniation of nucleus pulposus ($n = 6$), instability ($n = 13$), spondylosis ($n = 4$) and stenosis ($n = 21$). All patients in this study were treated with posterolateral instrumented fusion.

The mean age of patients ranged from 40 to 70 years. The length of follow-up for most trials that included patients with disc disease was 24 months. Although the Boden (2002) study[69] specified a 24-month follow-up length, the mean follow-up length was 17 months (range 12–27 months). In the Kanayama study,[81] the mean follow-up lengths were 16 months for the BMP intervention group and 13 months for the autograft control group. The follow-up time was 12 months in the study with spondylolysis patients. For patients with degenerative spondylolisthesis with spinal stenosis, the follow-up time was 12 months.

Interventions

Table 8 shows the interventions investigated in the studies. Nine studies investigated BMP-2 and three investigated BMP-7. Six studies[68,71–74,76,79,85] used a BMP-2 concentration of 1.5 mg/ml. Where reported, the doses used ranged from 8.4 to 12 mg in the Burkus (2005) study,[71–73] from 4.2 to 8.4 mg in the Burkus (2002) study[74,76] and from 4 to 8 mg in the Haid (2004) study.[79] Also used was 2 mg/ml (dose of 20 mg each side of the spine) in the Boden (2002)[69] and Dimar Studies.[77,78] The Shapiro study[84] reported 4.2 mg/interspace used. The doses of BMP-7 used were 3.5 mg BMP-7/g collagen vials on each side of the spine,[81] 3.5 mg per 3.5 ml[80] and 3.5 mg per side of spine.[82,86]

Five BMP-2 studies[68,71–74,76,79,85] used a collagen sponge to deliver the BMP. The Shapiro study[84] stated that it used BMP-2-soaked sponges, which presumably would have been made of collagen. One BMP-2 study used ceramic granules made of hydroxyapatite and tricalcium phosphate (HA–TCP)[69] and one used a compression resistant matrix made of HA–TCP and collagen sponges.[77,78] HA–TCP, in the proportions of 15% hydroxyapatite and 85% tricalcium phosphate, has been shown to enhance fusion in non-human primates.[39] The ratio used in the Boden (2002) study[69] was 60% hydroxyapatite and 40% tricalcium phosphate and was not specified in the Dimar study.[77,78] The carriers used in the BMP-7 studies were a paste made of BMP-7, collagen and saline,[80] and a putty made of BMP-7, collagen and carboxymethylcellulose.[81,82,86] Eight studies used AICBG as a control and the remaining two studies[81,84] used local autograft bone as the control. The control group in the Kanayama

TABLE 8 *BMP interventions used in spine RCTs*

Study	BMP used	Dose of BMP	Delivery method	Control	Other
Assiri, 2004[83]	rhBMP-2	NR	NR	Autogenous bone	Both groups received Texas Scottish Rite Hospital instrumentation
Baskin, 2003[68]	rhBMP-2	1.5 mg/ml in 3.2 ml water then 0.4 ml solution on collagen sponge	Collagen sponge in allograft	Autograft bone in allograft	Both groups received ATLANTIS anterior cervical plate
Boden, 2002[69]	rhBMP-2	2 mg/ml (20 mg per side of spine)	Ceramic granules distributed from a glass syringe	AICBG with Texas Scottish Rite Hospital pedicle screw instrumentation	Intervention groups received (A) Texas Scottish Rite Hospital pedicle screw instrumentation or (B) no instrumentation
Boden, 2000[85]	rhBMP-2	1.5 mg/ml (2.6 ml used)	Collagen sponge in fusion cage	Autogenous iliac crest bone	Both control and intervention groups had tapered cylindrical threaded fusion cages
Burkus, 2005[71–73]	rhBMP-2	1.5 mg/ml (dose range 8.4–12 mg)	Collagen sponge	Autogenous iliac crest bone	Both groups received a pair of threaded cortical allograft bone dowels
Burkus, 2002[74–76]	rhBMP-2	1.5 mg/ml (dose range 4.2–8.4 mg)	Collagen sponge	Morcellised AICBG	Both control and intervention groups received LT-CAGEs
Dimar, 2006[77]	rhBMP-2	2 mg/ml (20 mg in each lateral gutter)	Compression resistant matrix consisting of HA–TCP with collagen sponge	Iliac crest graft harvest	
Haid, 2004[79,87]	rhBMP-2	1.5 mg/ml (dose range 4.0–8.0 mg)	Collagen sponges	Morcellised AICBG	Both control and intervention groups received stand-alone cylindrical threaded titanium fusion cages (INTER FIX cages)
Johnsson, 2002[80]	BMP-7	3.5 mg (one implant per side of spine)	BMP-7 paste made of 3.5 mg BMP-7 with 1 g of collagen and 2.5 ml saline	Autograft iliac crest bone paste	
Kanayama, 2006[81]	BMP-7	1 vial of 3.5 mg BMP-7/g collagen per side of spine	Collagen matrix and sodium carboxymethylcellulose	Autograft bone with 5 g HA–TCP granules per side of spine	Both control and intervention groups received pedicle screw instrumentation
Shapiro, 2005[84]	rhBMP-2	4.2 mg/interspace	Local bone wrapped in rhBMP-2 sponges	Local bone	Both interventions placed in interspace between two wedges
Vaccaro, 2004[82,86,88]	BMP-7	3.5 mg per side of spine	rhOP-1 with type I collagen and 200 mg carboxymethylcellulose (OP-1 Putty)	Iliac crest autograft	

study[81] also received 5 g of HA–TCP on each side of the spine. In the Burkus (2005)[71–73] and Baskin[68] studies, both groups received allograft bone.

Quality assessment of included RCTs

Appendix 16 summarises the quality of the included studies. One of the studies was published in a preliminary report[85] and two were abstracts.[83,84] We were unable to identify any further publications from these trials.

The overall quality of the studies included in this review is substantially variable, ranging from low to moderate. Based on the quality criteria, the studies in order of least to most possible bias are as follows: Burkus and colleagues 2005[71–73] and Burkus and colleagues (2002);[74–76] Boden and colleagues (2000)[85] and Vaccaro and colleagues[82,86,88] Boden and colleagues (2002)[69] and Johnsson and colleagues (2002);[80] Kanayama and colleagues,[81] Dimar and colleagues[77] and Baskin and colleagues (2003);[68] Haid and colleagues;[79,87] and finally Shapiro and colleagues[84] and Assiri and colleagues.[83] It was not possible to determine whether the quality criteria were satisfied in the studies described in the abstracts[83,84] due to the lack of information. The Boden (2000)[85] and Burkus (2005)[71–73] studies both met all but one of the quality criteria.

In eight of the 12 studies, the randomisation method was unclear in that they only used the terms 'randomisation' or 'randomised', with no further explanation of the method used. In the other four studies, three different methods of randomisation were used and are considered adequate and one method was found to be inadequate. The three methods of randomisation that were considered adequate are the marginal balancing method,[85] sequentially numbered envelopes[71] and SAS PROC Plan.[74] Assigning the patients' group at the time of surgery[82] as a randomisation method was considered inadequate. In the Burkus (2005)[71–73] and Burkus (2002)[74–76] studies, the allocation concealments were considered adequate based on their randomisation methods as according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions.[65]

One or more blinded independent assessors were used to review radiographs in all but three trials. The Shapiro[84] and Assiri[83] studies did not report the assessment methods used and the Kanayama study[81] did not report whether or not independent assessors were used. However, the actual 'blinding' of assessors is questionable due to the ability of assessors to visualise certain treatment elements on the radiographs and computed tomography (CT) scans. In the Boden (2002) study,[69] the biphasic calcium phosphate carrier and instrumentation were visible on both radiographs and CT scans, thus allowing bias during assessment.

The inclusion and exclusion criteria were clearly stated in six[69,71–73,77,78,81,82,85,86] of the 10 trials. For the studies that did not explicitly report the inclusion and exclusion criteria, they only reported patient diagnoses and possibly broad inclusion criteria, but no exclusion criteria. The Shapiro[84] and Assiri[83] studies did not report any group characteristics.

There was a statistically significant difference between the BMP intervention group's and control group's age in the Kanayama study,[81] with a mean age of 70 ± 8.0 years in the BMP group and 58.7 ± 9.0 years in the control group ($p < 0.05$). In the Boden (2002) study,[69] two of the five patients in the control group had diabetes whereas none in the intervention group did. Diabetes leads to an increased risk of infection and this may cause a decreased fusion rate. The infection rate was not reported; therefore, the effect of diabetes in this study cannot be inferred.

Three studies[79,83,84] reported no data on drop-outs whereas other studies reported comparable drop-outs. One exception is the Boden (2002) study,[69] which reported an 18% drop-out rate in the BMP-only intervention group and 0% in both the BMP with Texas Scottish Rite Hospital (TSRH) pedicle screw instrumentation and control groups. The 18% drop-out rate was due to post-randomisation patient exclusion when the investigators discovered that the exclusion criterion of greater than Grade 1 spondylolisthesis was met. One of the excluded patients had a solid bilateral fusion and the other developed a non-union. In the fusion analysis, these patients and their reported fusion states were included in the assessment. Four studies[69,74,76,81,82] reported the number and reasons patients were lost to follow-up. Two studies[68,71–73] gave the numbers lost to follow-up, but no reasons. Two studies[80,85] did not lose any patients to follow-up and three studies[79,83,84,87] did not report on whether any patients were lost to follow-up. The Dimar study[77] only reported the total number of patients initially randomised in the whole study and the number of patients available in each group at the final end-point. Therefore, the number of drop-outs and ITT data were not calculable.

In summary, there were many methodological quality issues with the studies. Overall, the studies failed to meet many of the basic quality expectations of an RCT, such as describing the randomisation and allocation methods, analysing data on an ITT basis, clearly defining inclusion and exclusion criteria and reporting reasons for any drop-outs.

Findings from RCTs on spinal fusions

Findings from RCTs for lumbar spinal fusion

Radiographic results

Table 9 shows the fusion rates of the spine studies at their final end-points. It also gives the definition of successful fusion in each study. Due to varying fusion rates and number of patients available at each follow-up, the final radiographic assessments at the end-points of each study were determined to be the most reliable. Fusion rates are shown based on an intention-to treat (numbers lost considered failures) basis, when data were reported that allowed this.

Of the 11 studies, seven[69,71–76,79,85,87] had a similar definition of successful fusion. This definition includes; <5° angulation on flexion–extension radiographs, ≤3 mm translation, radiolucent lines covering 50% or more of the implant and evidence of bridging trabecular bone. The Vaccaro study[82,86] had a minor difference in its definition which included complete bridging bone and ≤2 mm translation. The Kanayama study[81] also included <2 mm translation on radiographs and evidence of bridging bone on CT scan images. The Dimar study[77] did not report a fusion definition, but instead classified fusion status with a grading system ranging from 1 (not fused) to 5 (solid bilateral fusion). The authors did not report the exact scores of fusion at any end-points throughout the study, but instead reported the number of patients with 'solid fusions' at the final end-point. However, it was not specified which grades of fusion were considered solid fusions. Also included in two studies' definition of successful fusion was the requirement that no secondary surgeries were performed for either persistent low back symptoms and clinical suspected non-unions[74,76] or revision, removal or supplemental fixations.[71–73] It has been reported that a successful fusion does not always guarantee improvement in clinical outcomes.[89–91] Therefore, it may not be appropriate to assess the success or failure of fusion based on the fusion outcome alone. The remaining study[84] did not report its definition of successful fusion.

Three small studies[80–82,86] reported higher (but statistically non-significant) fusion rates in the control group versus the intervention group. The remaining nine studies reported higher or equal fusion rates in the intervention versus control group. Of these, two studies[69,71] reported statistically significant differences between the fusion rates of intervention and control groups. Boden and colleagues[69] reported that both intervention groups had statistically significantly higher fusion rates than the control group with $p = 0.018$ and 0.028 for intervention groups A and B, respectively. Burkus and colleagues (2005)[71–73] reported a significantly higher fusion rate in the intervention group compared with the control group ($p < 0.001$).

Assessing the study characteristics and interventions used there are a few differences between the Johnsson study[80] and the others. First, a BMP-7 paste made of BMP-7, collagen and saline was used instead of the more common granules. It could be that the paste is not a suitable carrier and therefore BMP-7 was not as effective as it would have been with a different carrier. Also, the Johnsson study[80] had the least specific definition of fusion success, which leaves more room for interpretation by the assessors, which could have led to inconsistent assessment. The Vaccaro study[82,86] had the highest drop-out rate, with 20.8% in the intervention group and 16.7% in the control group. Since drop-outs were considered failures, this could have affected the results. In the Kanayama study,[81] one patient in the BMP group dropped out and for this analysis was counted as a failure. Also, the authors reported that it was difficult to assess the status of new bone formation in the control group because the hydroxyapatite particles were slow to resorb. The investigators surgically explored the fusion area of those with successful fusions when removing the screw instrumentation and solid arthrodesis was found in seven of nine control patients and four out of seven intervention patients. New bone formation was seen in six of seven of the intervention patients. As with other studies, HA–TCP has been shown to enhance fusion, and therefore ideally would have been used in both treatment groups. In both treatment groups the authors suspected beneficial effects from HA–TCP, although this cannot be supported by their findings.

Several papers[69,71–74,76] have reported a tendency for fusion rates to decline over time. Possible

TABLE 9 *Spine RCT radiographic results*

Study	% Successful fusions (no. of patients)		Successful fusion definition
	Intervention	Control	
Assiri, 2004[83]	62.5% (5/8)	14.3% (1/7)	Presence of continuous bridging trabecular bone bilaterally on both modalities (radiograph and CT scans) with absence of motion on flexion–extension radiographs
Boden, 2002[69]	A: 100% (11/11)[a] B: 91% (10/11)[a]	40% (2/5)[a]	Evidence of bilateral continuous bridging trabecular bone and ⩽3 mm of translation and <5° of angular motion on lateral flexion-extension radiographs
Boden, 2000[85]	100% (11/11)	66.7% (2/3)	Less than 5° of angular motion and absence of radiolucent lines covering at least 50% of implant surfaces
Burkus, 2005[71–73]	96.2% (76/79)[a]	71.1%(37/52)[a]	Presence of bridging trabecular bone connecting vertebral bodies through or around dowels, angular motion of 5°, sagittal translation of 3 mm and no radiolucent area involving >50% of the interface between dowels and end plates. No secondary surgeries required
Burkus, 2002[74–76]	83.9% (120/143)	75% (102/136)	An absence of radiolucent lines covering >50% of either implant, translation of ⩽3 mm and angulation of <5° on flexion–extension radiographs and continuous trabecular bone growth connecting the vertebral bodies on CT scan. No secondary surgeries due to persistent low back symptoms or clinically suspected non-union
Dimar, 2006[77b]	90.6% (48/53)[b,c]	73.3% (33/45)[b,c]	Grade 1: no fusion Grade 2: partial or limited unilateral fusion Grade 3: partial or limited bilateral fusion Grade 4: solid unilateral fusion Grade 5: solid bilateral fusion
Haid, 2004[79,87]	82.5% (28/34)[d]	78.8% (26/33)[d]	Absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion–extension radiographs and continuous bone growth connecting vertebral bodies
Johnsson, 2002[80]	60% (6/10)	80% (8/10)	Bilaterally bridging bone
Kanayama, 2006[81]	70% (7/10)	90% (9/10)	Less than 5° of angular motion and less than 2 mm translation on radiographs. Evidence of bridging bone on CT scans
Shapiro, 2005[84]	100% (20/20)[c]	100% (20/20)[c]	NR
Vaccaro, 2004[82,86]	45.8% (11/24)	33.3% (4/12)	Complete bridging bone between transverse processes at the spondylolisthetic segment and measurements taken from flexion–extension lateral radiograph films showing ⩽5° angulation and ⩽2 mm of translation

[a] Authors stated that the difference is statistically significant.
[b] Reported as 'solid fusion'.
[c] Unable to calculate ITT, data from paper reported.
[d] Data estimated from drop-outs and union rates reported as percentages.

explanations for this occurrence were described in the Burkus (2002) paper.[74] The reasons given were radiolucency seen at the implant–bone interface and that the autogenous bone became atrophic over time. This raises concern about the accuracy of the studies with short follow-up, which could have improperly designated patients as fused when they were not. Among the control group of the study by Burkus and colleagues (2005),[71–73] some patients who had appeared to be fused at

the 12-month follow-up point were found not to be fused at the 24-month follow-up. This was due to previously unseen lucencies around the implants that were thought to be obscured by the tightly packed autograft bone. The authors reported that in the BMP group this was not observed due to early integration of the allograft bone. Not all patients in the Boden (2002) study[69] were followed up for 24 months, and hence there is a chance of uncertainty regarding fusion deterioration in patients who were not followed up for the complete follow-up length.

In a report published by Glassman and colleagues,[78] the fusion results of 72 patients from one centre of the multi-centre Dimar trial[77] trial were analysed based on the number of smokers. The numbers of smokers were comparable between the groups, with 22% in the BMP intervention group and 23% in the control group. At the 12-month final end-point, the mean fusion grade in the control group was 3.25 for smokers and 3.93 for non-smokers. In the BMP group, the mean fusion grades were 3.75 for smokers and 4.86 for non-smokers. When both groups were combined, smokers had a mean fusion grade of 3.5 and non-smokers 4.42. Previous studies[92] have found evidence that smoking inhibits fusion and although not statistically significant, the data here support the prior findings.

Figure 5 shows data from individual trials and pooled estimates for fusion success outcome, according to subgroups of different patient diagnoses. There is evidence for the effectiveness of BMP-2 with comparison with autograft bone for patients with single-level degenerative disc disease. The pooled OR is 3.87 (95% CI 1.74 to 8.59, $p = 0.0009$). However, there is also statistically significant heterogeneity in this analysis ($I^2\% = 53.8\%$, $p = 0.04$). This heterogeneity may not be important, since the results of these trials were consistently in favour of BMP-2. It is also interesting that the largest trial, (the Burkus (2002) study,[69] showed the smallest treatment effect in *Figure 5* (Egger's test for funnel plot, $p = 0.027$; Begg's test, $p = 0.81$). Some of the heterogeneity could be attributed to different interventions used. The Boden (2002)[69] and Dimar[77] studies used HA–TCP granules in different proportions as bulking agents in the BMP group. HA–TCP has been shown to enhance fusion in non-human primates.[39] Therefore, because HA–TCP was only used in the BMP group, the difference in the fusion rates should be treated with caution. The Assiri study[83] was excluded in a sensitivity analysis (not shown) because the ITT data were not reported and could not be calculated. The exclusion of this study made no difference to the overall effect for single-level degenerative disc disease studies, so it was included.

Among patients with degenerative spondylolisthesis with spinal stenosis or spondylolysis, there is not enough evidence on the effect of BMP-7 treatment compared with autograft bone in this analysis. The pooled OR is 0.87 (95% CI 0.15 to 5.08, $p = 0.88$). Again, a sensitivity analysis (not shown), excluding the Shapiro study[84] because it did not report ITT data, did not affect the OR.

A sensitivity analysis (not shown) was conducted to investigate possible heterogeneity from combining the two BMP intervention groups in the Boden (2002) study.[69] As mentioned above, the intervention group A and the control group both received instrumentation whereas intervention group B did not. As a result, patients in intervention group B were excluded from the sensitivity analysis. This reduced the numbers in the intervention group to 11/11. The conclusion on the overall effect in single-level degenerative disc disease was the same when intervention group B was excluded, so all intervention patients are included. Overall, the analysis suggests that BMP-2 is more effective than autograft for patients with single-level degenerative disc disease. However, for patients with degenerative spondylolisthesis with spinal stenosis and spondylolysis treated with BMP-7, the data provide no statistically significant effect.

A sensitivity analysis was performed based on study quality (*Figure 6*). The analysis included four studies[69,71–74,76,85] which met more than half of the quality criteria. The sensitivity analysis produced an OR of 6.55 (95% CI 1.48 to 29.06).

Anterior fusions are easier to define radiographically because the fusion mass is visible on the radiographs. Posterolateral fusions are more difficult to define, and can be more accurately assessed using CT scans. All but two of the studies that used the posterolateral approach used CT scans to assess fusion. The Johnsson study[80] used radiostereometric analysis to measure the vertebral movement which was considered an adequate assessment method. The Vaccaro study[82,86] only used standard radiographs to assess the fusion status, which may not have been adequate to assess the fusion status clearly.

Figure 7 shows the analysis of spinal fusion success by the anterior approach. It is further

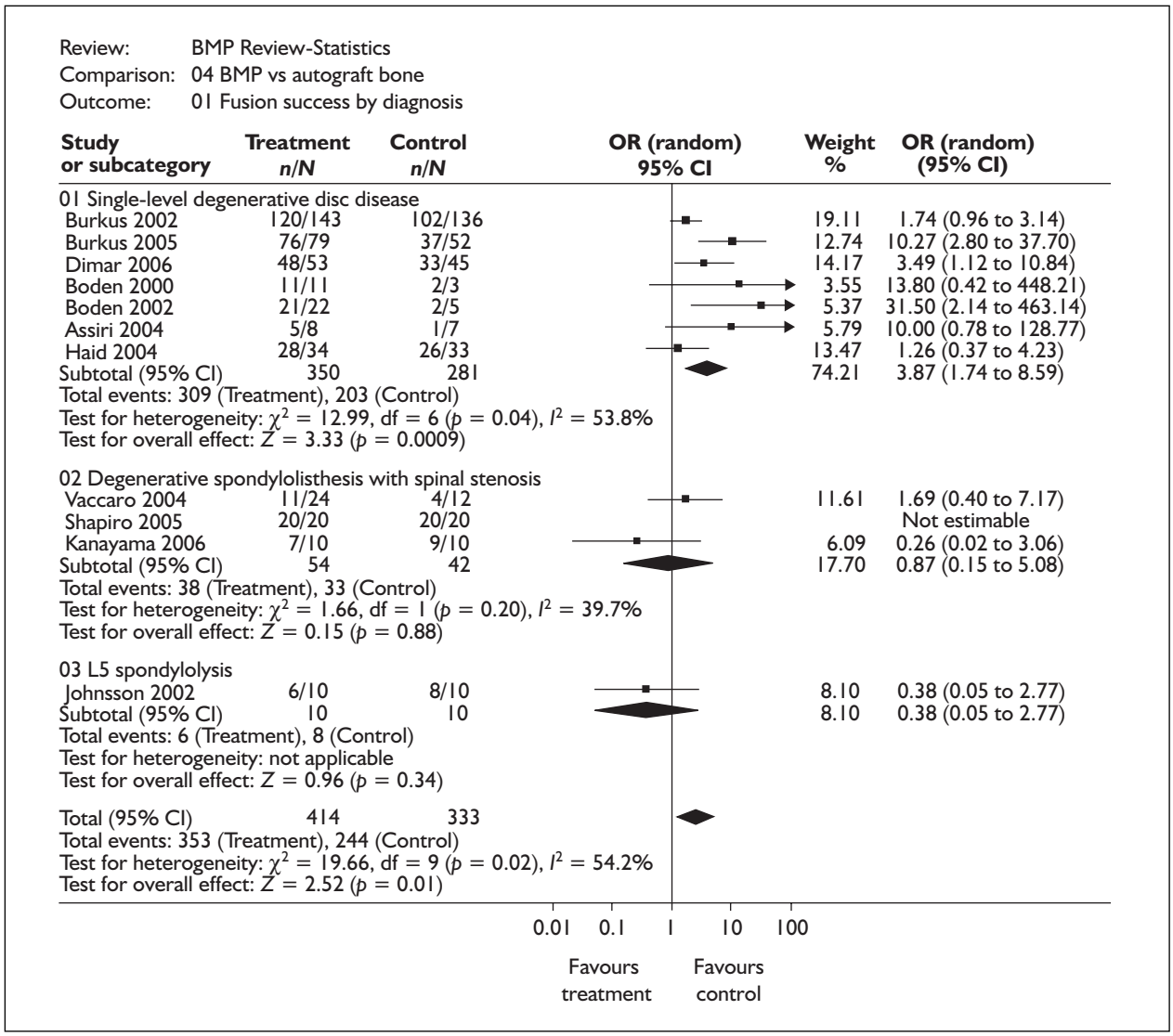

FIGURE 5 *BMP versus autograft bone by diagnosis*

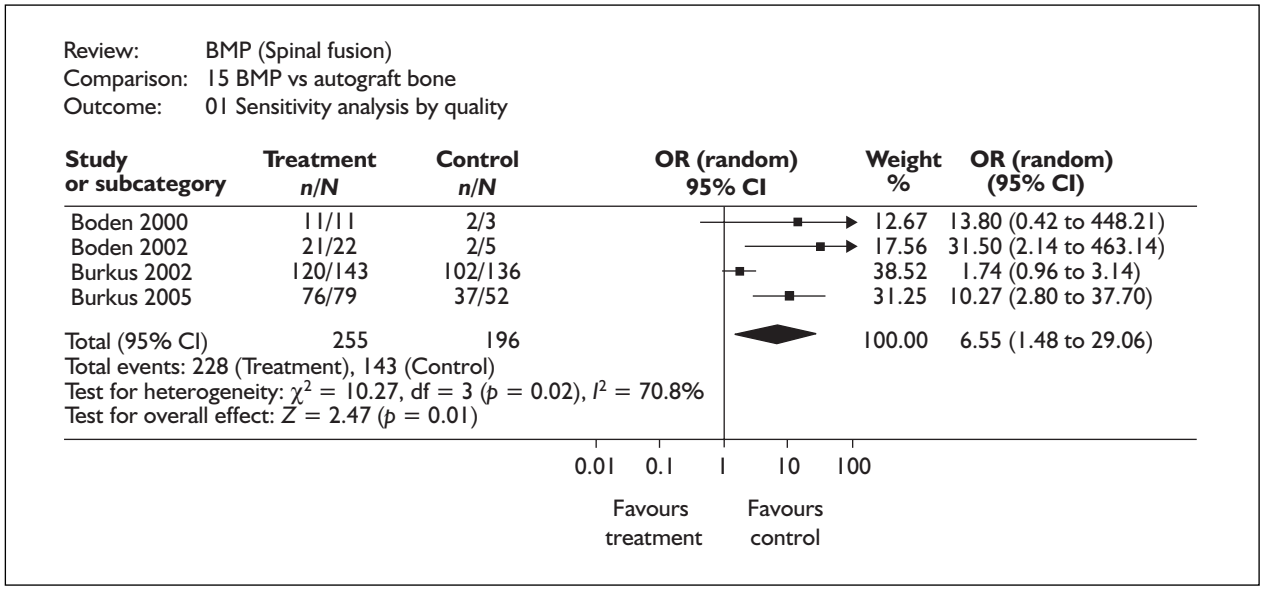

FIGURE 6 *Sensitivity analysis by study quality*

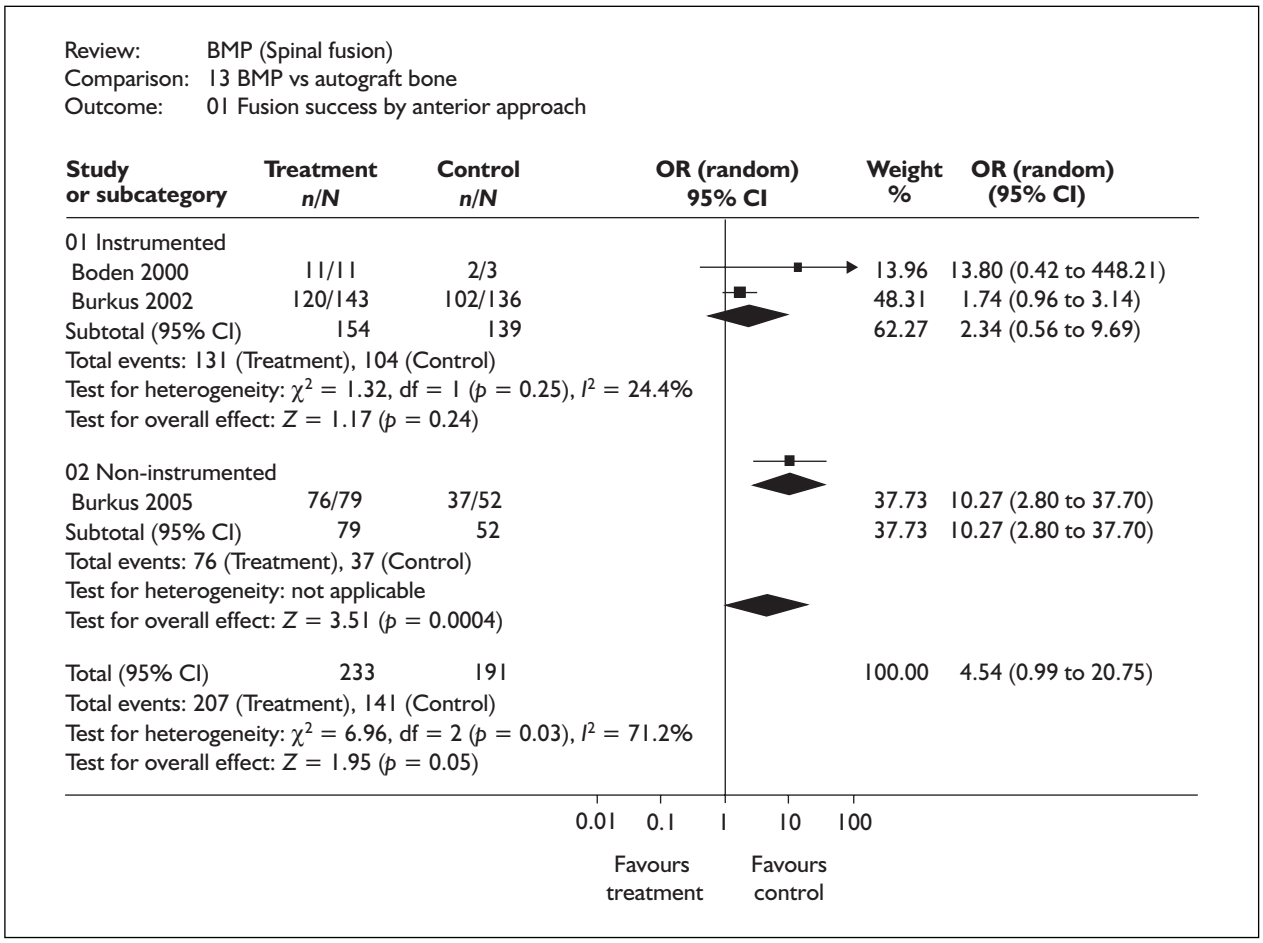

FIGURE 7 *Spinal fusion success by anterior approach*

subcategorised into those studies that used instrumentation and those that did not. There was no evidence from the data provided for BMP treatment versus autograft bone among those who received an instrumented anterior fusion. The OR is 2.34 (95% CI 0.56 to 9.69, $p = 0.24$). There is also statistically significant heterogeneity among this group of studies ($p = 0.03$, $I^2 = 71.2\%$).

Only one study, the Burkus (2005) study,[71–73] used non-instrumented anterior fusion study and reported a statistically significant effect. The OR is 10.27 (95% CI 2.80 to 37.70, $p = 0.0004$). Both intervention groups in this study received threaded cortical bone dowels, the effect of which is unknown. It may be that BMP is only more effective than iliac bone crest when bone dowels are added. The conclusion that could be drawn, based on the data available, is that BMP is probably effective for patients with non-instrumented anterior fusions. However, there is not enough evidence to determine BMP's effectiveness for instrumented anterior fusions.

Figure 8 shows the analysis of fusion success by posterior approach, subcategorised by whether or not instrumentation was used. As the fusion success between the two groups was not very different (11/11 patients fused in one group and 10/11 patients in the second group), and the control group received instrumentation and was too small to be split in the analysis, the two BMP intervention groups in the Boden (2002) study[69] were both included in the instrumented subcategory, although one group received instrumentation. Among the studies that used instrumented posterior fusion, there was no evidence that BMP was more effective. The pooled OR was 1.93 (95% CI 0.62 to 6.00), with heterogeneity $I^2 = 46.8\%$ ($p = 0.13$). For studies that used non-instrumented posterior fusion, the pooled OR was 0.94 (95% CI, 0.22 to 3.97, $p = 0.93$). Again, a sensitivity analysis excluding both Assiri[83] and Shapiro[84] studies showed no significant change to the overall effects, so both studies are included in the analysis. Both non-instrumented fusion studies that counted towards

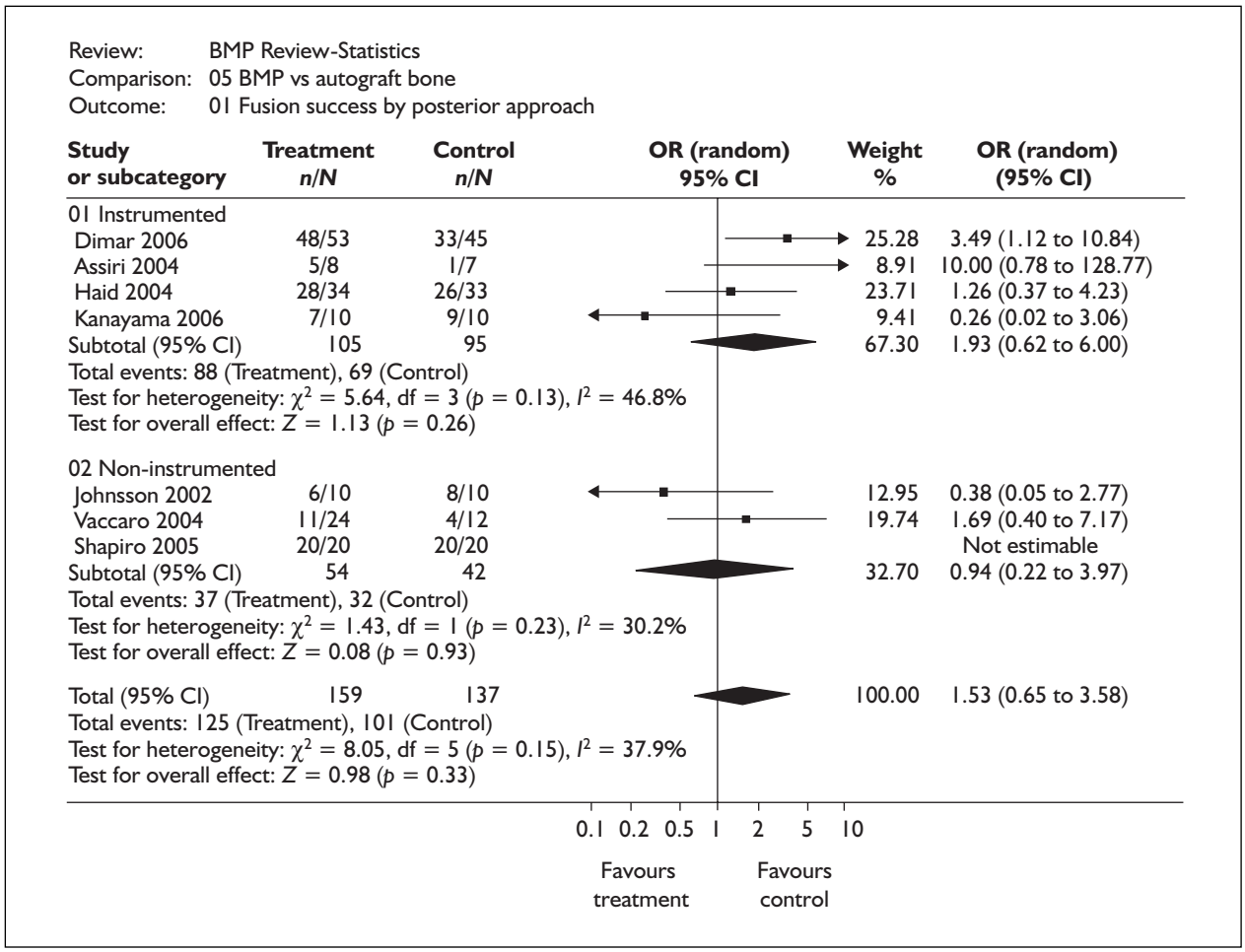

FIGURE 8 *Spinal fusion success by posterior approach*

the odds ratio used BMP-7 in the dose of 3.5 mg per side of the spine. Where reported, the instrumented fusion studies used BMP-2 in the doses of 20 mg per side of spine and 4.2 mg per interspace. The Kanayama study[81] used BMP-7 in a dose of 3.5 mg per side of the spine also, and the fusion rates were 20% lower in the intervention group versus the control group. It could be that a higher dose of BMP-7 is needed for fusion or that BMP-7 is not as effective for spinal fusions. Based on the data presented, there is no evidence of the effect of BMP for posterior spinal fusion, instrumented or not.

It was not appropriate to analyse the studies based on the BMP used (BMP-2 or BMP-7) due to high heterogeneity in the studies. All of the studies that used BMP-2, except the Shapiro study,[84] included patients with single-level degenerative disc disease. The Shapiro study[84] included patients with degenerative spondylolisthesis, similar to two studies treated with BMP-7. However, in addition to BMP-2, intervention patients received local bone with machined cortical wedges in the Shapiro (2005) study.[84] Patients who received BMP-7 were diagnosed with either degenerative spondylolisthesis or spondylolysis. Therefore, due to the separation of diagnoses between BMPs, it is not possible to compare effectiveness of BMP-2 and BMP-7 for different diagnoses.

Operative results

Table 10 summarises the reported operation results, including mean operating time, mean blood loss and mean length of hospital stay.

Seven studies[69,71,74,77,79,82,85] reported mean operating times. In all but one intervention group [intervention A in the Boden (2002) study[69]] the reported mean operating time was equal to, or shorter than, the control group's. Four studies[69,71,77,85] reported statistically significant different operating times, although the validity of the statistical tests is questionable. Due to different surgical procedures, there is a wide range of mean operating times reported (1.4–3.7 hours).

TABLE 10 *Spine RCT operation results*

Study	No. of patients		Mean operating time (hours)		Mean blood loss (ml)		Mean length of hospital stay (days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Boden, 2002[69]	A: 11 B: 9	5	A: 3.7 ± 0.3 B: 2.0 ± 0.2	3.1 ± 0.4, $p = 0.002$	A: 577.3 ± 113.1 B: 333.3 ± 121.3	430.0 ± 81.5, $p = 0.301$	A: 3.3 ± 0.1 B: 4.0 ± 0.9	4.4 ± 0.5, $p = 0.443$
Boden, 2000[85]	11	3	1.9 ± 0.2	3.3 ± 0.6, $p = 0.006$ (95% CI 0.4 to 2.4)	95 ± 31	67 ± 117, $p = 0.4$	2.0 ± 0.6	2.3 ± 1.4, $p = 0.18$
Burkus, 2005[71–73]	79	52	1.4	1.8, $p < 0.001$	87.4	184.7, $p < 0.001$	2.9	3.3, $p = 0.02$
Burkus, 2002[74–76]	143	136	1.6 ± 0.6	2.0 ± 0.7	109.3 ± 117.3	153.8 ± 179.1	3.1 ± 1.6	3.3 ± 1.3
Dimar, 2006[77]	53	45	2.4	2.9, $p = 0.003$	273	465, $p < 0.001$	3.9	4, $p = 0.801$
Haid, 2004[79,87]	34	33	2.6	3.0, $p = 0.065$	322.8	372.7	3.4	5.2
Vaccaro, 2004[82,86]	24	12	2.3 ± 0.72	2.6 ± 0.47, $p = 0.24$	NR	NR	3.9 ± 1.7	4.3 ± 2, $p = 0.59$

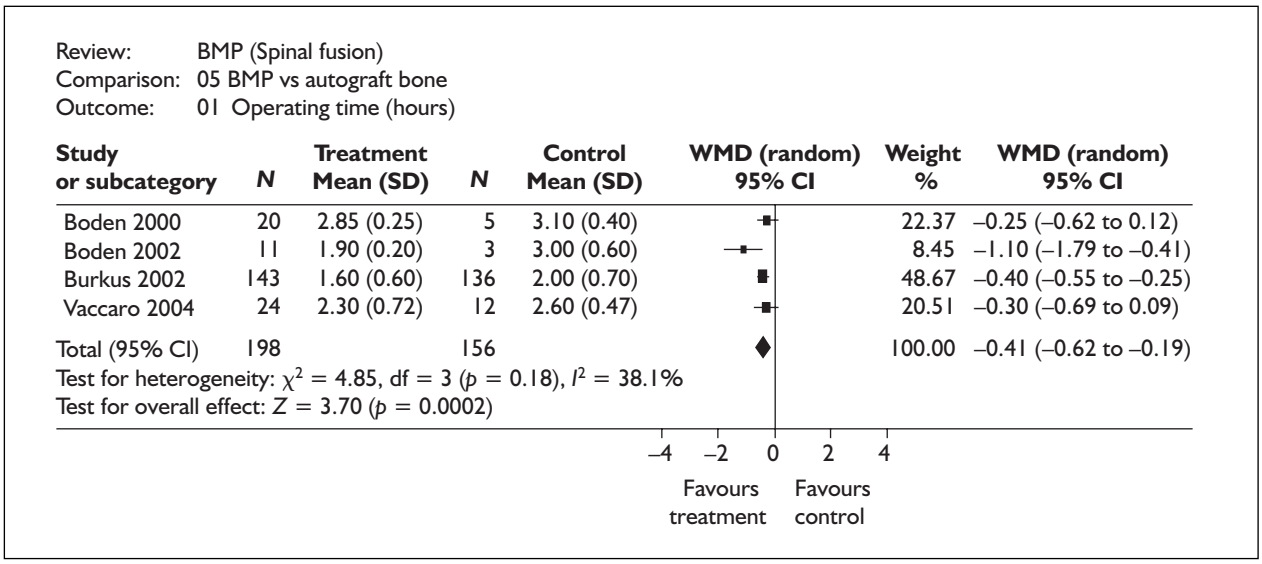

FIGURE 9 *Spine operating times*

Figure 9 shows the fixed weighted mean difference with the 95% CI of the operating times, where the standard deviations were reported. There is no strong evidence for statistically significant heterogeneity ($p = 0.18$, $I^2 = 38.1\%$), although clinical heterogeneity cannot be ruled out. Overall, the weighted mean difference is –0.41 (95% CI –0.62 to –0.19) in favour of BMP intervention. This suggests that BMP reduces the operating time by about 25 minutes (range 11–37 minutes). The reduction in operating time can most likely be attributed to the elimination of autograft bone harvesting. Dhawan and colleagues[29] reported a mean time to harvest iliac crest bone of 37 minutes (20–51 minutes).

Six studies[69,71–74,76,78,79,85] reported the mean blood loss. Again, all but one intervention group [intervention A in the Boden (2002) study[69] reported lower mean blood loss in the BMP group than the control group, which was statistically significant in two trials.[71,78] There is a wide range of mean blood loss reported amongst both groups (87.4–577.3 ml), which also could be due to different surgical procedures. There is not sufficient evidence to determine BMP's effect on blood loss.

Finally, seven studies[69,71–74,76,77,79,82,85,86] reported the mean length of hospital stay. One study[71] reported a statistically significant difference. The mean length of hospital stay ranged from 1.1 to 5.2 days in the control groups and from 1.4 to 3.9 days in the intervention groups.

Figure 10 shows the weighted mean difference of the length of hospital stay, where reported. There is no statistically significant heterogeneity across studies ($I^2 = 0\%$). Overall, the weighted mean difference is statistically significant (–0.75, 95% CI –1.19 to –0.3), that is, the use of BMP shortened hospital stay by 0.75 days (ranging from 0.31 to 1.19 (days).

Other clinical results

The most frequently reported clinical outcomes in the studies included mean Oswestry Low Back Pain Disability Questionnaire score,[93] mean Short Form with 36 Items (SF-36) score[94] (general health status measuring questionnaire), mean back pain score improvement, mean leg pain score improvement and work status.

Table 11 shows the reported mean Oswestry score improvements by treatment group. Out of the nine studies[69,71–77,79,81,84,85,87] that gave full data for mean Oswestry score improvement, six reported greater improvement in the intervention group versus the control group. The Boden (2002) study[69] did not report specific Oswestry scores at the end-point but instead showed them in a graph, so the values shown in *Table 11* are estimates. Both studies by Boden and colleagues,[69,85] defined a clinically significant success as a 15% improvement in Oswestry score over the preoperative score. However, the authors defined this as a fairly 'strict' definition and noted that patients often feel they have significant functional improvement with any Oswestry score improvement. Using this definition of clinical success, 90.9% (10/11) of intervention patients and 66.7% (2/3) of control patients were a clinical success in the Boden (2000) study.[85] Estimates from a graph in the Boden (2002) study[69] show a

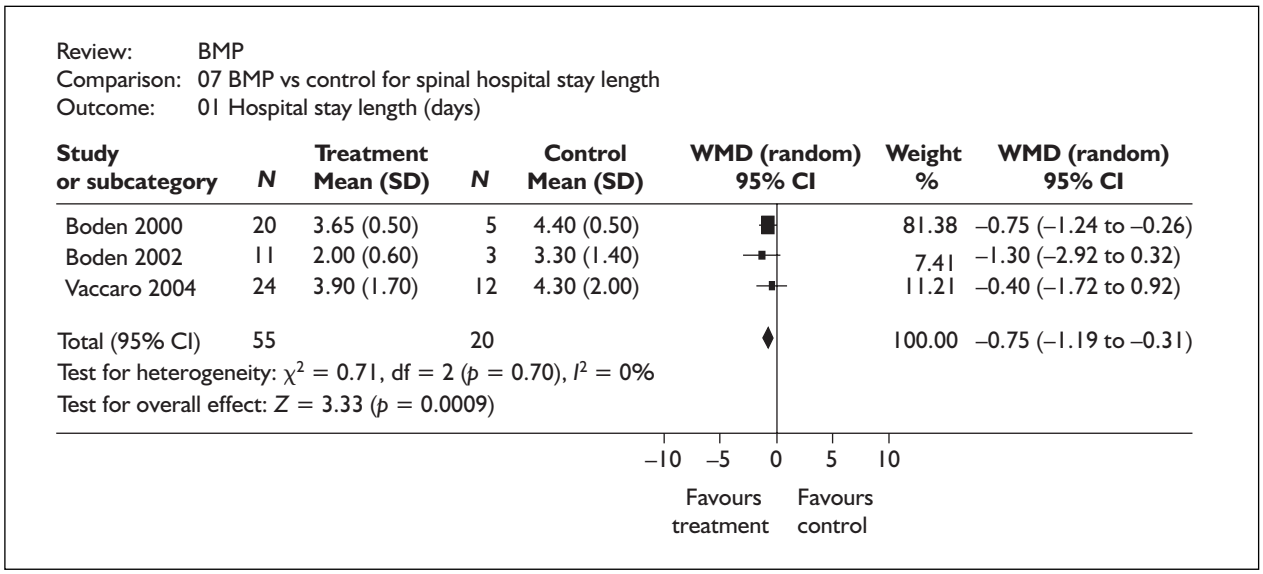

FIGURE 10 *Spine hospital stay length*

TABLE 11 *Spinal studies mean Oswestry score improvement*

Study	Mean Oswestry score improvement		
	Intervention	**Control**	***p*-Value**
Assiri, 2004[83]	–31.1	–17.6	
Boden, 2002[69]	A: –12[a] B: –28.7±3.1	–22[a]	A vs control: < 0.05
Boden, 2000[85]	–25	–15	0.12
Burkus, 2005[71–73]	–33.4	–27.0	0.12
Burkus, 2002[74–76]	–29.0	–29.5	
Dimar, 2006[77]	–24.5	–21.4	0.455
Haid, 2004[79,87]	–29.6	–24.9	
Kanayama, 2006[81]	–17.1	–24.1	0.05
Shapiro, 2005[84]	–23	–22	

[a] Estimate from graph.

90% success rate in the BMP-2-only (intervention B) group, 65% in the BMP-2 with instrumentation group and 80% in the control group. Statistically significant improvements over the mean preoperative scores were seen at 6 weeks in the BMP-2-only group ($p = 0.009$), 3 months in the BMP-2–TSRH group ($p = 0.003$) and 6 months in the control autograft group ($p = 0.041$). At the final 24-month follow-up, the greatest mean improvement was seen in the BMP-2-only group ($p = 0.001$). The Burkus (2005) study[71–73] reported that the improvements in Oswestry scores were greater in the intervention group than the control group at all follow-up times and reached statistical significance at 3 months ($p = 0.021$) and 6 months ($p = 0.031$). The Burkus (2002) study[74,76] reported that both groups showed a statistically significant improvement over their mean preoperative scores at all follow-up points ($p < 0.001$). In the Haid study,[79] from 3 months onwards the intervention group's mean score improvement was higher than the controls. Kanayama and colleagues[81] reported statistically significant reductions in mean Oswestry scores in both groups starting at the 3-month follow-up ($p < 0.05$), although the difference between the groups was not statistically significant ($p > 0.05$). The Vaccaro study[82,86] (not shown) did not report specific Oswestry score improvements, but instead defined 'clinical success' as a 20% Oswestry score improvement. Based on this definition, 75% (18/24) of intervention patients and 67% (8/12) of control patients were a clinical success.

As shown in *Table 12*, six studies[69,71–73,77,79,82,85,86] reported mean SF-36 score improvements. All but

TABLE 12 *Spinal studies mean SF-36 score improvements*

Study	Mean SF-36 score improvement		
	Intervention	**Control**	***p*-Value**
Boden, 2002[69]	A: Physical = 6[a] Bodily pain = 16[a] B: Physical = 16[a] Bodily pain = 37[a]	Physical = 7[a] Bodily pain = 16[a]	0.049
Boden, 2000[85]	Physical = 37.7 Role–physical = 65.9 Pain index = 43.5 General health perception = 5.7 Vitality = 25 Social function = 44.3 Role–emotional = 51.5 Mental health = 15.6	Physical = 36.7 Role–physical = 41.7 Pain index = 27 General health perception = 8.3 Vitality = 23.4 Social function = 37.5 Role–emotional = 44.5 Mental health = 13.3	
Burkus, 2005[71–73]	15.7	11.6	0.015
Dimar, 2006[77]	Physical = 8.6 Bodily pain = 29.7	Physical = 10.7 Bodily pain = 28.7	0.378 0.861
Haid, 2004[79,87]	Physical = 14[a]	Physical = 12[a]	
Vaccaro, 2004[82,86]	Physical = 15.3 Mental health = 9.6	Physical = 7.9 Mental health = 6.8	

[a] Estimate from graph.

two [intervention A group in the Boden (2002) study[69] and physical component in the Dimar study[77]] studies showed higher mean score improvement in the intervention versus control groups. Again, in the Boden (2002) study,[69] the values were estimated from a graph. In the Boden (2002) study,[69] statistically significant improvements in the mean SF-36 physical component score over the preoperative values were seen at 3 months in intervention group B ($p = 0.039$) and 6 months in intervention group A ($p = 0.033$). At the last follow-up, the mean physical score for intervention group B was greater than for the control group ($p = 0.07$). In the same study, significant improvement in the bodily pain index score was seen at 6 weeks in intervention group B ($p = 0.010$), 3 months in intervention group B ($p < 0.001$) and 6 months in the control group ($p = 0.034$). However, this study is very small, with only five patients in the control group and 11 in each of the two intervention groups. In the Burkus (2005) study,[71–73] mean score improvement for the intervention groups reached statistical significance at 6 months ($p = 0.001$) and was significantly higher than the control group's score ($p = 0.017$). The difference maintained significance at the final 24-month follow-up, $p = 0.015$. The Boden (2000) study[85] reported the mean improvements in all eight SF-36 categories; however, this study is also very small (14 patients). There is no significant evidence to determine the effect of BMP treatment compared with autograft bone.

Table 13 provides data reported on mean back pain score improvement. Out of the five studies[69,71,74,77,79] that reported results for mean back pain, the score improvement was better in the BMP intervention groups, except for an intervention group in the Boden (2002) study.[69] All but one[77] of the studies reported they used a 20-point numerical rating scale to assess the intensity of the pain and either the type[69] or duration[71–74,76,79] of pain. Three of the studies reported that the difference was statistically significant.[69,71,79] The Burkus (2005)[71–73] and Burkus (2002)[74,76] studies reported statistically significant improvements in back pain scores in both groups at all follow-up points. The interventions group's mean score improvement in the Burkus (2005) study[71–73] was significantly better than that for the control group from the 3-month follow-up onwards ($p < 0.05$). Haid and colleagues[79,87] reported greater mean back pain scores in the intervention group than the control group at all follow-up points, with a significant difference in the final follow-up mean score improvement, $p = 0.009$. The available evidence points to a slightly greater improvement in back pain score in those treated with BMP compared with autograft.

TABLE 13 *Spinal studies mean back pain score improvements*

Study	Mean back pain score improvement		
	Intervention	Control	*p*-Value
Boden, 2002[69]	A: –5.1 ± 2.1[a] B: –10.4 ± 1.7	–6.2 ± 2.1	0.025
Burkus, 2005[71–73]	–8.6	–7.1	0.032
Burkus, 2002[74–76]	–8.4	–8.1	
Dimar, 2006[77]	–7.4	–6.6	0.685
Haid, 2004[79,87]	–9	–4.5	0.009

[a] Estimate from graph.

TABLE 14 *Spinal studies mean leg score improvement*

Study	Mean leg pain score improvement		
	Intervention	Control	*p*-Value
Boden, 2002[69]	A: –3[a] B: –9.9±1.9	–4[a]	0.042
Burkus, 2005[71-73]	–6.8	–4.9	0.011
Burkus, 2002[74–76]	–6.5	–5.9	
Dimar, 2006[77]	–5.7	–5.2	0.567
Haid, 2004[79,87]	–7.7	–6.5	

[a] Estimate from graph.

As shown in *Table 14*, five studies[69,71–77,79,87] reported results for the mean improvement in leg pain scores. As with back pain, all but one of the studies[77] reported that they used numerical rating scales of pain intensity and either type[69] or duration[71–74,76,79] of pain to assess leg pain. All but the Boden (2002) study[69] reported greater score improvements in the intervention groups versus the control groups. The Burkus (2005)[71–73] and Burkus (2002)[74,76] studies reported statistically significant mean improvements in leg pain scores in both groups at all follow-up points. The Burkus (2005) study[71–73] reported a statistically better improvement in the intervention group than in the control groups for mean leg pain score at 6 ($p = 0.043$), 12 ($p = 0.011$) and 24 months ($p = 0.011$). In this study, the control group saw a worsened score at the 12- and 24-month follow-ups. The Haid study[79] reported greater mean leg pain scores in the intervention group than the control group at all follow-up points. Overall, the evidence for mean leg pain score improvements suggests that BMP treatment is at the least comparable to autograft control.

Four studies[69,74,76,79,85] reported on various neurological outcomes measured, as shown in *Table 15*. The Boden (2002),[69] Boden (2000),[85] Burkus (2002)[74,76] and Haid[79] studies all included motor and sensory functions in their assessment, with success measured as postoperative scores being greater than or equal to the preoperative scores. Also evaluated were reflex and straight-leg raise measurements,[69,79,85] deep tendon reflexes and sciatic tension signs[74,76] and straight-leg tension causing pain.[82,86] The evidence from the four studies that assessed neurological outcomes suggests that treatment with BMP is comparable to treatment with autograft bone.

Overall, the studies that reported clinical results suggest that treatment with BMP is at least comparable to treatment with control (autograft). There is some evidence to suggest that BMP treatment leads to faster improvement in Oswestry and SF-36 scores. There is also some evidence that suggests that BMP is linked to greater improvements in Oswestry, SF-36, back and leg pain scores. There is limited evidence of the effects of BMP on neurological status compared with control; however, from the evidence available, treatment with BMP appears to be comparable for this outcome.

Table 16 shows the details of reported work status outcome in four studies.[71–77,79,87] Two of the

TABLE 15 *Spinal studies neurological status*

Study	Neurological status at end-point		Parameters assessed
	Intervention	Control	
Boden, 2002[69]	Slightly improved in all three groups compared with preop.		Motor and sensory function, reflex and straight-leg raise measurements
Boden, 2000[85]	All parameter scores ⩾preop. scores at all follow-up times At 24 months, reflex in one patient noted to be normal to hyporeflexic		Motor and sensory function, reflex and straight-leg raise measurements
Burkus, 2002[74,76]	82.8% (101/122) success	83.3% (90/108) success	Motor and sensory function, deep tendon reflexes and sciatic tension signs
Haid, 2004[79]	100% success	100% success	Motor and sensory function, reflex and straight-leg raise measurements

TABLE 16 *Spinal studies work status*

Study	Work status			
	Intervention		Control	
Burkus, 2005[71–73]	60% working preoperatively	Mean return 89 days	48% working preoperatively	Mean return to work 96 days
Burkus, 2002[74–76]	47.6% (68/143) working preoperatively	66.1% (80/121) working at 24 months Median return to work 63.5 days[a]	36.8% (50/136) working preoperatively	56.1% (60/107) working at 24 months Median return to work 64.5 days[a]
Dimar, 2006[77]	40% (18/45) working preoperatively	40% (18/45) returned to work at 24 months	32% (17/53) working preoperatively	30% (16/53) returned to work at 24 months
Haid, 2004[79,87]	26.5% working preoperatively	+8.8%[b] Median return to work 43 days[a,c]	45.5% working preoperatively	–3.1%[b] Median return to work 137 days[a,c]

[a] For patients working preoperatively.
[b] Percentage change of patients working at study end-point compared with presurgically.
[c] Authors stated that the difference is not statistically significant.

studies calculated the average time it took the patients to return to work, another study used survival analysis [71] and the remaining study[77] did not report on return to work rates. Where reported, the apparent average time of return to work rate was shorter in the intervention group than in the control group. The Burkus (2002) study[74–76] provided the proportion of patients working before surgery and at the final end-point. The percentage increase in patients working at the final end-point was comparable between the treatment groups, 18.5% in the intervention group and 19.3% in the control group. The Haid study[79,87] provided the change in the proportion of those working at the study end-point compared with presurgically, which increased in the intervention group by 8.8% and decreased in the control group by 3.1%.

Antibody response

Table 17 shows the antibody responses to BMP and bovine collagen.

Antibody response to BMP was reported in five studies.[69,71–74,76,79,85] All but one study[85] reported that antibody titres were measured preoperatively and at the 3-month follow-up point. In the Baskin[68] and Boden (2002)[69] studies, an 'authentic' antibody response was defined as such when the preoperative titre level was <50 and the

TABLE 17 *Spine RCT antibody response results*

Study	Antibody response to BMP		Antibody response to bovine collagen	
	Intervention	Control	Intervention	Control
Boden, 2002[69]	4.5% (1/22)	0% (0/4)	NR	NR
Boden, 2000[85]	0	0	27% (3/11)	NA
Burkus, 2005[71–73]	0	0	9% (7/78)	8% (4/49)
Burkus, 2002[74–76]	0.7%	0.8%	NR	NR
Haid, 2004[79,87]	0	0	8.8% (3/34)	15.1% (5/33)

NA, not applicable.

3-month level was ⩾50; or, if the preoperative level was >50, for it to be considered an antibody response, the antibody titre level had to be three times greater than the preoperative level. In the Haid study,[79] the postoperative antibody titre level had to be three times greater than the preoperative level to be counted as an antibody response. The Boden (2000)[85] and Burkus (2005)[71–73] studies reported only that the patients with antibody responses had increased antibody titres. In one study,[69] the antibody response to BMP was higher in the intervention group: one of 22 (4.5%) patients compared with no patients in the control group. In another study,[74] the BMP antibody response was slightly lower in the intervention group at 0.7% compared with 0.8% in the control group. The remaining three studies[72,73,79,85] reported no BMP antibody response in either group.

Of the three studies[71,72,79,85] that reported antibody responses to bovine collagen, two[71–73,85] reported higher responses in the intervention group and one[79,87] reported a higher response in the control group.

None of the studies reported any symptoms caused by elevated antibody titres to either BMP or bovine collagen.

Adverse events

Appendix 17 shows the details of any reported adverse events.

All but three of the studies[81,83,84] reported some sort of adverse events data. The details reported vary from only the frequency of adverse events in each group to both the frequency and description of each experienced adverse event. In the Boden (2002) study,[69] four adverse events were reported in the intervention group and none in the control group. These included left and right leg pain that required decompression 1 level above the intervention level, epidural haematoma which led to decompression surgery 1 year later, persistent lower back and leg pain which led to anterior lumber interbody fusion procedure at 8 months and a superficial haematoma that was evacuated on day four. In the Boden (2000) study,[85] four intervention patients and two control patients experienced adverse events. The Dimar study[77] reported 61 adverse events experienced by intervention patients and 66 by control patients. In the Vaccaro study,[82,86] 23/24 (96%) intervention patients and 12/12 (100%) control patients experienced an adverse event, although the authors stated the adverse events in the intervention group were deemed to be unrelated to BMP, except for perhaps a pseudoarthrosis (non-union). Six male patients in the Burkus (2002) study[74,76] experienced postoperative retrograde ejaculation (number in each group not specified). There was a statistically significant difference between transperitoneal and retroperitoneal approach, with 13.3% (4/30) of men undergoing transperitoneal and 1.8% (2/116) of men undergoing retroperitoneal approaches experiencing retrograde ejaculation, $p = 0.017$. If graft site pain is taken into account, three studies[71–74,76,82,86] reported more adverse events in the control group, three[69,80,85] reported more intervention group adverse events, one[79,87] had an equal number of adverse events in each group and three[78,84] did not report this outcome.

In the Burkus (2005) study,[71–73] 46.5% of the control group experienced pain at the donor site pain at the 24-month follow-up. The Burkus (2002) study[74,76] reported eight adverse events related to iliac crest graft harvesting, none of which required additional surgery. There were three lateral femoral cutaneous nerve injuries, two avulsion fractures of the anterior superior iliac crest, one infection and one haematoma. Postoperatively, all patients experienced donor site pain and 32% suffered pain at the donor site at

TABLE 18 *Number of spinal fusion secondary interventions*

Study	Type of secondary interventions	BMP (%) (*n*/*N*)	Autograft (%) (*n*/*N*)	Notes
Boden, 2002[69]	Revision decompression Revision surgery Evacuation of epidural haematoma	A: 18 (2/11) B: 11 (1/9) A: 9 (1/11) B: 11 (1/9)	0 (0/5)	At time of all revision surgeries, fusion was noted to be bilaterally solid
Burkus, 2005[71–73]	Supplemental fixation	2.5 (2/79)	15 (8/52)	
Burkus, 2002[74–76]	Implant removal Supplemental fixation Reoperations	1 (2/143) 7 (10/143) 4 (6/143)	0 (0/136) 10 (14/136) 3 (4/136)	One patient in BMP group underwent both a removal and supplemental fixation
Dimar, 2006[77]	Revision of malpositioned screws	0	3	
Haid, 2004[79,87]	Spinal surgical procedure Spinal fusion at different level	18 (6/34) 9 (3/34)	18 (6/33) 9 (3/33)	
Johnsson, 2002[80]	Decompression Instrumented fusion	10 (1/10) 10 (1/10)	10 (1/10)	

the 2-year follow-up. Also, 16% of patients were bothered by their graft site appearance at the final end-point. The Dimar study[77] reported the mean hip pain score improvement in the control autograft group. By 6 weeks the score had improved from 11.6 to 8.0, and by 24 months the score was 7.6. The Haid study[79] reported two adverse events that were related to the iliac crest graft harvesting. One patient experienced pain and one had a haematoma, neither of which required additional surgery. All patients experienced donor site pain postoperatively, and 60% of patients had some level of pain at 24 months. Four (13.3%) of patients felt that the graft site appearance bothered them at 24 months. One patient in the Johnsson study[80] had persistent minor graft site pain. In the Vaccaro study,[82,86] 58% of patients reported mild or moderate graft site pain 6 weeks postoperatively. At the 24-month follow-up, 66% of patients reported mild or moderate donor site pain.

The Kanayama study[81] reported the presence of necrotic bone during histological assessment in one BMP-7 patient and 'most' control specimens. The authors attributed this to residual host bone segments following decortication in the BMP treatment group and autograft bone in the control group.

In the Haid study[79,87] patient enrolment was stopped when excess bone formation was seen in 24 of 32 BMP patients and four of 31 control patients, $p < 0.0001$. The bone extended outside the disc space into the spinal canal or neuroforamina. The difference between the number of patients experiencing excess bone is statistically significant, $p < 0.0001$. The authors reported that the excess bone formation was dependent on the procedural approach. Although the rate of excess bone formation was high, the authors reported no apparent effects on patient outcomes due to it.

Secondary interventions

Table 18 shows the number of patients in each study who required secondary interventions, and any details that were provided in the papers regarding the surgical interventions performed.

Six studies[69,71,74,77,79,80] reported data on the number of secondary interventions in each group. In two small studies,[69,80] the percentage of patients requiring secondary interventions was higher in the intervention group than the control group, but the difference may not be statistically significant. In the remaining four studies, the proportion was higher in the control group than the intervention group.

Figure 11 shows the ORs with 95% CIs for the number of secondary interventions performed. There is not statistically significant heterogeneity ($I^2 = 29.7\%$, $p = 0.21$). The pooled OR is 0.62 (95% CI 0.28 to 1.39) in favour of BMP treatment. This effect, however, is not statistically significant ($p = 0.24$). From the evidence reported in the included studies, the effect of BMP treatment compared with control on the number of secondary interventions is unconvincing.

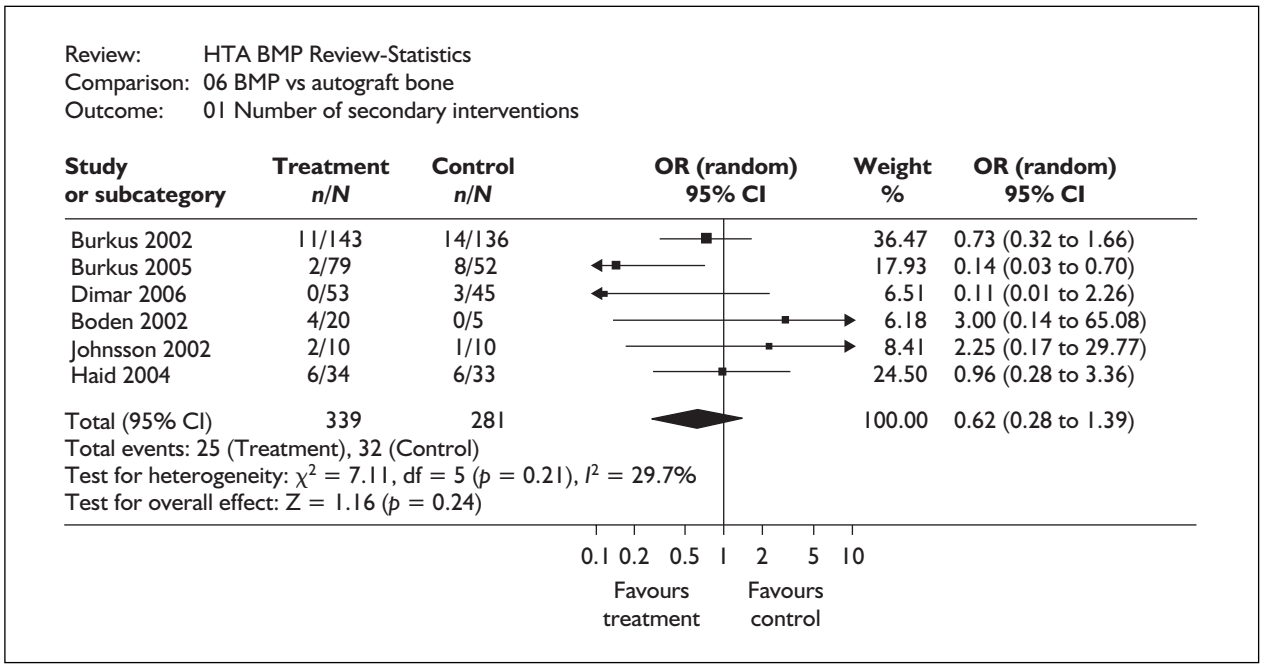

FIGURE 11 *Spine secondary interventions*

Findings from RCT for cervical spinal fusion

The Baskin study[68] is the only RCT that assessed BMP in cervical spinal fusion.

Radiographic findings

Successful fusion was defined on radiographs and CT scans as a <4º difference in angular motion between flexion and extension seen on lateral flexion extension radiographs, no radiolucency more than 2 mm thick covering more than 50% of the superior or inferior surface of the graft and evidence of bridging trabecular bone. Using ITT and assuming that drop-outs were failures, by 6 months there was fusion in 15/18 BMP patients and 13/15 control patients. Out of the number of patients available, 10/18 BMP patients and 10/15 control patients showed successful fusion at 24 months, $p = 0.52$.

Operation results

The mean length of operation was 1.8 hours in both groups. The mean blood loss was 91.4 ml in the BMP group and 123.3 ml in the control group. Mean hospital stay length was 1.4 and 1.1 days in the BMP and control groups, respectively. None of these results were significant.

Other clinical outcomes

The SF-36 questionnaire measured any physical and mental improvement changes in the groups. At 24 months the mean physical component score improvement in the BMP group was 16.7 points and in the control group 14.7 points. The mean mental component score improvement at 24 months was 21.8 in the BMP group and 7.2 in the control group.

Neck pain and intensity was assessed using a 20-point numerical rating scale. At 24 months the mean improvement in the BMP group's score from preoperation was 13 points and in the control group 9 points, $p = 0.055$.

A 20-point numerical rating scale was also used to assess arm pain and intensity. At 24 months the mean score improvement was 14 points in the BMP group and 8.5 points in the control group, $p < 0.03$.

Motor and sensory function were assessed to determine neurological status and reported as either success (maintenance or improvement of both functions) or failure. For the patients available at the 24-month follow-up there was a 100% success rate in both groups (14 BMP and 12 control patients).

Antibody response

An 'authentic' antibody response was defined as a negative preoperative titre (<50) and a positive 3-month titre (≥50), or if the preoperative titre was positive then the 3-month titre was three times greater. There were no authentic antibody

responses to BMP-2. One BMP and one control patient had responses to bovine type I collagen at 3 months.

Adverse events

Pain at the donor site was measured using numerical rating scales. The control autograft group experienced significant graft site pain, $p < 0.007$, and were unhappy with the graft site appearance. By 6 months, the groups were comparable in terms of graft site pain and appearance. By 24 months an unreported number of patients were still experiencing residual donor site pain and rated the graft site appearance as 'fair'.

In two BMP group and one autograft control group patients, bone formation anterior to the segments adjacent to the treated level was visible at the 12-month follow-up. The authors report that all three patients who experienced bone formation were treated by the same surgeon, and the results may therefore be related to technique. Other possible explanations discussed were acceleration of spondylitic bone growth in adjacent degenerated discs or blood at the surgical trauma site channelling BMP from the carrier.

Secondary interventions

There was one reported secondary intervention in a BMP-treated patient that was deemed unrelated to the original procedure. A segment adjacent to the original surgical site was operated on, requiring removal of the anterior cervical plate.

Summary of evidence from randomised trials of BMP for spinal fusion

The included RCTs have many methodological weaknesses as none met all of the quality criteria. The main methodological limitations of the studies are lack of reporting of randomisation and allocation concealment methods, failure to analyse data using ITT analysis, unclear inclusion and exclusion criteria and failure to report reasons for patient drop-outs. Some secondary outcomes were not measured and/or reported in every trial.

Lumbar spinal fusion

According to evidence from seven trials, the use of BMP-2 increased radiographical fusion among patients with single-level degenerative disc disease (pooled OR: 3.87, 95% CI 1.59 to 9.46). Data available from four trials of other spinal disorders were insufficient to determine any difference in effect between BMP and control treatments. The pooled OR for patients with degenerative spondylolisthesis with spinal stenosis is 0.87 (95% CI 0.15 to 5.08) and for patients with spondylosis the OR is 0.38 (95%C CI 0.05 to 2.77).

The evidence suggests that BMP is associated with a 25-minute (range 11–37 minutes) reduction in operating time compared with controls, which is probably attributable to elimination of bone graft harvesting. BMP is also associated with a shorter hospital stay (pooled OR –0.75, 95% CI –0.31 to –1.19). There is no convincing evidence that the use of BMP reduced blood loss.

Treatment with BMP eliminates donor site morbidities by replacing bone grafting. There was some evidence to suggest that BMP is associated with greater improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. Available data on the impact of BMP on the proportion of patients who returned to work was limited, unstandardised and sometime difficult to interpret. From the evidence reported in the studies, it was not possible to determine convincingly the effect of BMP on the number of adverse events or secondary interventions. Further research and longer follow-up are required to evaluate the clinical importance of excess bone formation seen in the Haid study.[79]

Cervical spinal fusion

There is little evidence for BMP in cervical spinal fusion. The evidence available indicates that BMP with allograft is comparable to autograft with allograft for fusion rates, length of operation, blood loss, hospital stay length, SF-36 score and neurological improvement. However, there is some evidence to suggest that BMP may improve neck and arm pain scores over autograft control. Finally, the use of BMP with allograft eliminates the need for a donor site and thus consequently any donor site morbidity.

Chapter 5

Economic evaluation of BMP for tibial fracture and spinal fusion

In this chapter, findings are presented from a critical review of published economic evaluations on the use of BMP for fracture and spinal fusion. Two economic evaluation models provided by ABACUS are then assessed and modified.

Review of published economic studies

Three published papers[53–55] and one abstract[56] were identified. However, one published short study[55] and the abstract[56] did not provide enough information for data extraction. The remaining two published papers reported the same set of data and were therefore treated as one study. In this review, we included only one study on the economic evaluation of BMP for spinal fusion,[50,51] and we identified no published economic evaluations of BMP for fracture.

Data from the included study were extracted by one reviewer and checked by another. The objectives of the economic evaluation[50,51] were (a) to compare the costs of stand-alone anterior lumbar interbody fusion using either rhBMP-2 on a collagen sponge or autogenous iliac crest bone graft in a tapered cylindrical cage or threaded cortical bone dowel and (b) to conduct a threshold analysis to estimate the cost (price) of BMP at which direct medical costs are entirely offset. The paper reported that it was conducted in a primary care setting in the USA.

The study was judged to be of high methodological quality based on assessment using the Drummond checklist.[51] The only applicable checklist items that were not met related to a failure to report whether discounting had been undertaken, although this may be due to the short time horizon (2 years) considered by the model. All of the remaining quality criteria were either met or not applicable.

The study aimed to develop cost-offset models (i.e. a threshold analysis). Clinical outcomes considered in the models were those relevant to medical resource use, including fusion success rates, pain and complications at the bone graft site. Data from two trials,[75,95] along with peer-reviewed literature and expert opinion, were used to create two different models comparing costs of BMP and costs of AICBG. One model included hospital costs incurred during index hospitalisation only and the other additionally took into account direct medical costs 2 years after surgery.

Table 19 shows that a base price cost of BMP at $3380 was found to offset the index hospital resources and 2-year resources (US$, 2001). Based on effectiveness data extracted from the Burkus (2002) study,[74–76] intervention with BMP over a 2-year period was found to cost $9 less than AICBG intervention (US$, 2001).

Polly and colleagues[54] included a sensitivity analysis that was performed using data from the Burkus (2005) study.[71–73,95] Costs were insensitive to changes in complication rates associated with bone harvesting, length of stay, autograft extender/harvester use, time horizon, autologous blood use and external electrical stimulation use. *Table 20* shows results of the sensitivity analysis to changes in BMP price and fusion rate assumptions. The cost was found to be sensitive to increases in the price of BMP and decreases of fusion rates in the BMP patients. Based on the model presented in this study, cost neutrality of BMP treatment compared with AICBG is reached at a BMP cost of $3389 (US$, 2001).

In summary, the economic evaluation by Polly and colleagues[54] suggests that the initial cost of using BMP for spinal fusion is likely to be offset by avoiding autogenous bone graft and related complications and improved successful fusion. However, the models described in published papers were not available electronically for us to assess detailed structures. The input estimates were heavily based on expert opinion. In addition, the results of this US study may not be generalisable to the UK setting.

TABLE 19 *Index hospital resources and 2-year medical costs*

Resource	Improvement by BMP	Cost offset in US$ (2001)	
		Estimated cost savings	Cost/unit
Index hospital resources			
Operating time, anaesthesia time	Reduced 30 minutes (24–30)	540	18/minute operating room 2/minute anaesthesia
Recovery room	Reduced 15 minutes	45	3/minute
Blood	Reduced probability of 1-unit blood transfusion by 5%	4	84/unit
Autograft extenders Autograft harvesters	Reduced probability of use by 35% Reduced probability of use by 65%	474	935/unit extender 225/unit harvester
Length of stay	Reduced 0.5 days (0.2–1.2)	231	462/night
Drain	Reduced probability of use by 33%	NR	28.97/unit
Iliac crest backfill	Reduced probability by 2%	NR	1000/unit
2-year direct medical costs			
Inpatient physician services	NR	337	NR
Medical/surgical supplies	NR	125	NR
Severe pain	8%	93	1161
Minor pain	25%	79	315
Infection, haematoma, wound dehiscence, prolonged wound drainage	Combined rate of 4%	302	11,984/infection 5824/haematoma 6237/wound dehiscence 6166/prolonged wound drainage
Vascular injury, herniation, iliac crest fracture	Combined rate of 1%	75	11,375/vascular injury 12,361/herniation 6397/iliac crest fracture
Follow-up care		1024	2052/after successful index surgery 3705/after unsuccessful index surgery 14,896/pseudarthrosis repair 2552/after successful pseudarthrosis repair 4204/after unsuccessful pseudarthrosis repair

Adapted from data in Tables 1–4 in the paper by Polly *et al*. 2003.[54]

Assessment of ABACUS models: economic evaluation of BMP for open tibial fractures

ABACUS International is a healthcare consultancy specialising in strategic marketing, health economics and medical communications. Sponsored by Medtronic (producer of rhBMP-2), ABACUS developed an economic evaluation model using Microsoft Excel to evaluate cost-effectiveness of rhBMP-2 in the treatment of OTFs. For a selected population, the model could be used to estimate the number of annual OTFs by severity, the cost of adding rhBMP-2 to standard care, secondary interventions and infections avoided and the net budget impact of using rhBMP-2 for OTFs.

ABACUS provided a copy of the Microsoft Excel model to the HTA team at the University of East

TABLE 20 *Sensitivity analysis*

Parameters		Cost (saving) of BMP use in index hospitalisation model (US$)	Cost (saving) of BMP use in 2-year model (US$)
Base case	**Changed to**		
$3380/BMP	$3000/BMP	1354	(389)
$3380/BMP	$8000/BMP	6354	4611
BMP fusion rate of 94.5%			
AICBG fusion rate of 88.7%	BMP fusion rate of 100%		
AICBG fusion rate of 68.4%	NA	(4564)	
BMP fusion rate of 94.5%	BMP fusion rate of 90%	NA	785
BMP fusion rate of 94.5%	BMP fusion rate of 85%	NA	1668

Adapted from data in Table 5 in the paper by Polly and colleagues.[54]

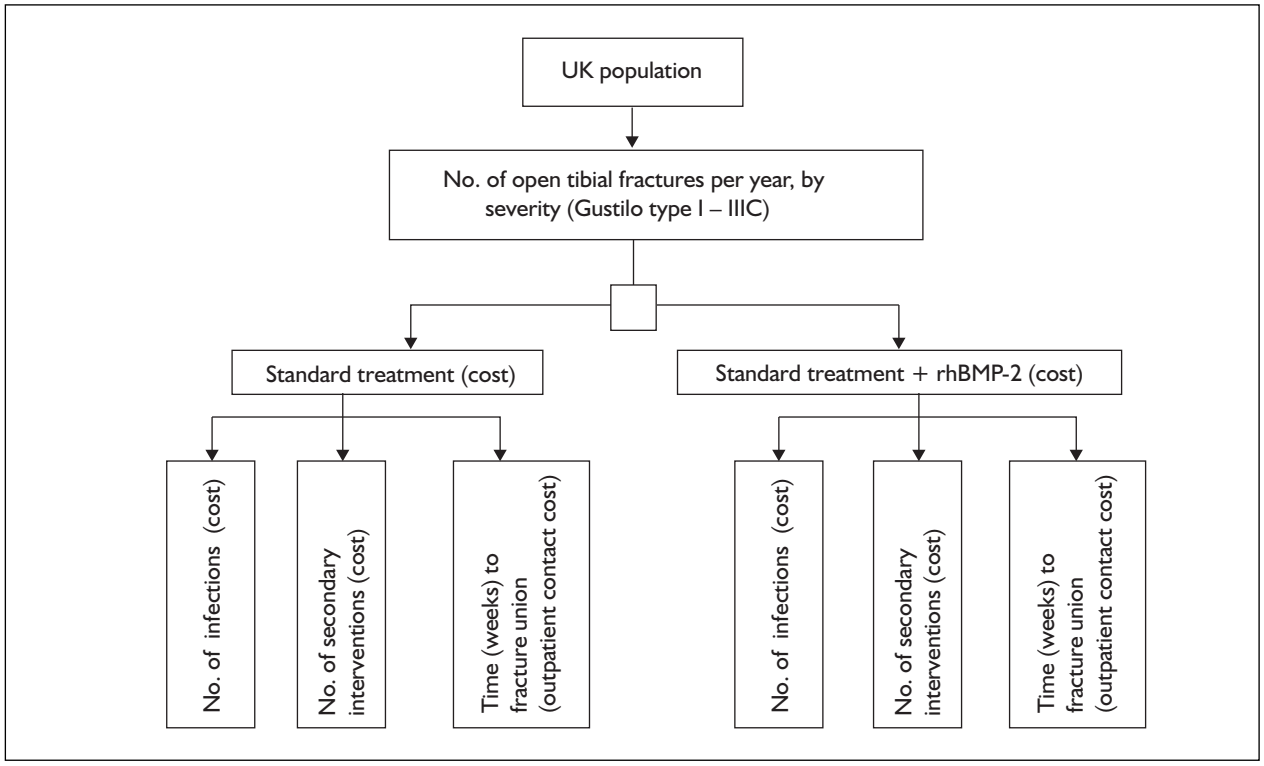

FIGURE 12 *Basic ABACUS model structure*

Anglia in September 2005, without a formal written report. A revised version of the model was received from ABACUS in November 2006, with some minor changes made to input parameters. The data reported below are from the revised version. In this section, the model will be referred to as the ABACUS BMP–OTF model. Details about the original model's structure and input parameters are first described, then the main concerns about the model's structural validity and the credibility of input data are summarised. Finally, the model is modified in terms of structure and input data when judged helpful to obtain new results.

The ABACUS BMP–OTF model's structure

The basic structure of the model is summarised in *Figure 12*. The model compares the cost and clinical consequences of two intervention approaches: standard care versus standard care plus the use of rhBMP-2 in the treatment of OTFs. The clinical consequences included in the model are: (1) infections, (2) secondary interventions and (3) time to fracture union (*Figure 12*). Then cost consequences of any infections, secondary interventions and time to fracture union are estimated.

BMP-OTF model: data sources and key input values

Burden of disease

A document from the British Orthopaedic Association and British Association of Plastic Surgeon[96] provided data to estimate the burden of disease. The annual incidence of OTFs is 5.53 per 100,000, and the population in the UK is 58,789,194. Thus, it was estimated that the total number of OTFs is 3251 in the UK. These OTF patients are further classified into different severity groups, ranging from Gustilo–Anderson ('Gustilo') type I to type IIIC, according to distribution profile shown in *Table 21*.

Data sources for clinical outcome parameters

Data from an RCT by Govender and colleagues[61] were used to estimate model parameters for clinical outcomes, including infection rate, secondary interventions and time to fracture union. The trial is also named the BESTT trial (the BMP-2 Evaluation in Surgery for Tibial Trauma trial), which compared the standard of care and the additional use of BMP-2 for OTF. It is the largest trial ($n = 450$) among the trials of BMP for tibial fracture reviewed in Chapter 3. Data from the BESTT trial contributed more than 75% of the weight to meta-analyses (in *Figures 3* and *4*). The quality of the trial is relatively good, with appropriate allocation concealment, independent radiology panel, ITT analysis and data on drop-outs (Appendix 7).

TABLE 21 *Data used in the BMP–OTF model: distribution of patients with OTF by fracture severity grade*

Severity category	% of patients	No. of patients
Gustilo type I	24.10	783.5
Gustilo type II	21.70	705.5
Gustilo type IIIA	22.50	731.5
Gustilo type IIIB	27.90	907.0
Gustilo type IIIC	3.80	123.5
All OTF	100	3251

TABLE 22 *Data used in the BMP–OTF model: infection rates by fracture severity grade*

Severity category	% SC group	% SC + BMP group
Gustilo type I	15.63	17.14
Gustilo type II	14.55	15.56
Gustilo type IIIA	35.71	15.79
Gustilo type IIIB	52.94	29.63
Gustilo type IIIC	52.94	29.63

Infection rate

The model used data in *Table 22* to estimate the number of infections for the standard care (SC) group and for the SC plus rhBMP group. The infection rates were derived from data from the BESTT trial.[61] From these data, we can see that there was no significant difference in infection rate for patients with Gustilo type I or II OTFs. The infection rates were lower in the BMP group than in the SC group for Gustilo type III patients.

Secondary interventions

Data from the BESTT trial[61] were used to estimate the rate of secondary interventions (*Table 23*). The use of BMP was associated with a lower rate of secondary interventions than the standard care group.

Secondary interventions were classified as the most invasive and less invasive (*Table 24*). Then the most and less invasive secondary interventions were further separated according to surgical procedures (*Table 25*).

Average time to fracture union

According to data from the BESTT trial,[61] the average time to fracture union was from 27 to 44 weeks in the SC group and from 21 to 33 weeks in the BMP group (*Table 26*). In the BESTT study,[61] fracture union was defined by the participating clinicians on a combination of clinical findings (pain-free weight bearing and lack of tenderness at fracture site), plus radiological union (three out of four cortices with bridging callus). This is more stringent than most studies which use two bridged cortices.

The model estimates that a total of 20,937 well-patient weeks would be gained (or fracture non-union weeks avoided) by using BMP. Assuming that there was one outpatient contact every 4 weeks before fracture union, 5234 (that is, 20,937/4) outpatient contacts would be avoided.

TABLE 23 *Data used in the BMP-OTF model: secondary intervention rates by fracture severity grade*

Severity category	% SC group	% SC + BMP group
Gustilo type I	31.25	17.14
Gustilo type II	21.82	8.89
Gustilo type IIIA	38.10	18.42
Gustilo type IIIB	64.71	40.74
Gustilo type IIIC	64.71	40.74

TABLE 24 *Data used in the BMP–OTF model: secondary intervention rates by degree of invasiveness*

Severity category	SC group		SC + BMP group	
	Most invasive (%)	Less invasive (%)	Most invasive (%)	Less invasive (%)
Gustilo type I	20.00	80.00	16.67	83.33
Gustilo type II	50.00	50.00	50.00	50.00
Gustilo type IIIA	43.75	56.25	42.86	57.14
Gustilo type IIIB	72.73	27.27	36.36	63.64
Gustilo type IIIC	72.73	27.27	36.36	63.64

TABLE 25 *Data used in the BMP–OTF model: distribution of secondary surgical procedures*

Procedure	% of patients
Most invasive	
Bone graft	39.39
Exchange nailing	36.36
Plate fixation	9.09
Fibular osteotomy	15.15
Bone transport	0.0
Less invasive	
Nail dynamisation	95.45
Internal fixation to brace	4.55

TABLE 27 *Data used in the BMP–OTF model: average disutility values by fracture severity grade*

Severity category	Average disutility due to delayed fracture union	Total disutility (or QALYs gained)
Gustilo type I	0.13	4.19
Gustilo type II	0.24	18.62
Gustilo type IIIA	0.35	23.19
Gustilo type IIIB	0.46	91.21
Gustilo type IIIC	0.46	12.49
All OTFs		150.21

Utility and quality of life

Table 27 shows estimated disutility values due to fracture non-union. It was not explicit in the model about how the disutility values were estimated. According to a personal communication from A Bentley (Senior Analyst, ABACUS International, Bicester, UK: 2006), disutility values were extrapolated from estimates for hip fractures[67] and general fractures.[97] We looked at the two references cited[67,97] and will discuss them in detail in the section 'Comments on the original ABACUS model' (p. 51).

The quality-adjusted life-years (QALYs) gained by the use of BMP were then estimated based on the number of OTF patients (*Table 21*), the additional well-patient weeks per patient (*Table 26*) and assumed disutility values (*Table 27*). That is, for each OTF severity category, the QALYs gained are calculated by

$$\text{QALY} = (Ntf \times Wpw/52) \times Duv$$

where Ntf is the number of OTF patients, Wpw is the number of well-patient weeks gained per patient by the use of BMP and Duv is the disutility value because of fracture non-union.

Unit costs and data sources

Table 28 summarises unit costs used in the ABACUS model. Unit costs of standard treatment of OTFs, infections of the fracture sites, secondary interventions, outpatient contacts and rehabilitation care were based on data derived from the UK NHS National Schedule of Reference Costs 2003. A personal communication from Wyeth Pharmaceuticals estimated that the use of

TABLE 26 *Data used in the BMP–OTF model: average time to fracture union and well-patient weeks gained per patient by use of BMP*

Severity category	SC group (weeks)	SC + BMP group (weeks)	Well-patient weeks gained per patient
Gustilo type I	29.71	27.57	2.14
Gustilo type II	26.86	21.14	5.72
Gustilo type IIIA	35.57	30.86	4.71
Gustilo type IIIB	44.00	32.57	11.43
Gustilo type IIIC	44.00	32.57	11.43

TABLE 28 *Unit cost data in the ABACUS BMP–OTF model (and updated data when available)*

Cost item	Unit	Unit cost (£)	Source[a]
Standard treatment of OTF (by type)			
Gustilo type I	Cost per fracture	2205 (1827)	National Schedule of Reference Costs 2003 (2005) – NHS Trusts – Non Elective In Patient HRG Data – H35: Open Lower Limb Fractures or Dislocations – lower quartile value
Gustilo type II	Cost per fracture	2551 (2674)	National Schedule of Reference Costs 2003 (2005) – NHS Trusts – Non Elective In Patient HRG Data – H35: Open Lower Limb Fractures or Dislocations – midpoint of lower quartile and national average values
Gustilo type IIIA	Cost per fracture	2897 (3521)	National Schedule of Reference Costs 2003 (2005) – NHS Trusts – Non Elective In Patient HRG Data – H35: Open Lower Limb Fractures or Dislocations – national average value
Gustilo type IIIB	Cost per fracture	3196 (3768)	National Schedule of Reference Costs 2003 (2005) – NHS Trusts – Non Elective In Patient HRG Data – H35: Open Lower Limb Fractures or Dislocations – midpoint of national average and upper quartile values
Gustilo type IIIC	Cost per fracture	3494 (4014)	National Schedule of Reference Costs 2003 (2005) – NHS Trusts – Non Elective In Patient HRG Data – H35: Open Lower Limb Fractures or Dislocations – upper quartile value
		1790	Personal communication (Wyeth Pharmaceuticals)
rhBMP-2 (Inductos Sponge – 1.5 mg/ml) Infection			
Less severe	Cost per infection	976	National Schedule of Reference Costs 2003 – NHS Trusts – Elective In Patient HRG Data – S20: Postoperative Infections: 50% of national average value
Intermediate	Cost per infection	1952	National Schedule of Reference Costs 2003 – NHS Trusts – Elective In Patient HRG Data – S20: Postoperative Infections: national average value
Severe	Cost per infection	2928	National Schedule of Reference Costs 2003 – NHS Trusts – Elective In Patient HRG Data – S20: Postoperative Infections: 150% of national average value
Secondary interventions			
Most invasive			
Bone graft	Cost per intervention	4963 (3971)	National Tariff 2005/06 (2006/07) – Admitted Patient Care Tariff – HRG Code H16 – Soft tissue or other bone procedures: Category 1: >69 or w cc – Non-elective spell tariff
Exchange nailing	Cost per intervention	2580 (2186)	National Tariff 2005/06 (2006/07) – Admitted Patient Care Tariff – HRG Code H17 – Soft tissue or other bone procedures: Category 1: <70 w/o cc – Non-elective spell tariff
Plate fixation	Cost per intervention	4963 (3971)	National Tariff 2005/06 (2006/07) – Admitted Patient Care Tariff – HRG Code H16 – Soft tissue or other bone procedures: Category 1: >69 or w cc – Non-elective spell tariff
Fibular osteotomy	Cost per intervention	2580 (2186)	National Tariff 2005/06 (2006/07) – Admitted Patient Care Tariff – HRG Code H17 – Soft tissue or other bone procedures: Category 1: <70 w/o cc – Non-elective spell tariff
Bone transport	Cost per intervention	4963 (3971)	Estimate as plate fixation
Less invasive			
Nail dynamisation	Cost per intervention	1300 (1439)	National Tariff 2005/06 (2006/07) – Admitted Patient Care Tariff – HRG Code H52 – Removal or fixation device <70 w/o cc – Non-elective spell tariff
Internal fixation to brace	Cost per intervention	1300 (1439)	Estimate as nail dynamisation
Outpatient contacts	Cost per outpatient contact	67 (71)	National Tariff 2005/06 (2006/07) – Mandatory Outpatient Tariff – Speciality Code 110 – Trauma and orthopaedics – Adult follow-up attendance tariff

[a] HRG code S20 (postoperative infection) is no longer available in National Schedule of Reference Costs since 2004.

TABLE 29 *Main results of the original BMP–OTF model*

	Point estimate (£)	95% CI (£) (based on 10,000 simulations)
Net cost impact in the UK	3,058,795	1,823,722 to 4,159,112
Cost per OTF	941	561 to 1,279
Incremental cost/QALY	20,364	11,683 to 31,321

rhBMP-2 would cost £1790 per fracture additional to the standard treatment.

Uncertainty and probabilistic simulation

A range of values for important input parameters were estimated for probabilistic simulations by the ABACUS model. The model parameters that were randomly investigated included severity distribution of OTFs, infection rate, secondary intervention rates/types, time to fracture union, disutility values and unit costs of interventions and clinical outcomes. In probabilistic simulations, the range (95% CIs) of input parameters could be from 25% (or 50%) smaller and greater than the point estimates. Then input values were randomly sampled from a gamma or beta distribution to obtain random estimates for cost-effectiveness outcomes. The random simulations were repeated many times to generate a large number of random estimates, and the simulation results were used to calculate average estimates and corresponding CIs. For estimating the incremental cost-effectiveness ratio (ICER), a cost-effectiveness acceptability curve (CEAC) can be created using the results of simulations.[98]

The BMP–OTF model's original outputs

The main results of the original ABACUS model are shown in *Table 29*. Based on input data described above, the model estimated that there were about 3251 OTFs in the UK each year. The SC of these patients cost £8,976,951 and the SC plus rhBMP-2 cost £14,796,317. Hence the use of rhBMP for the treatment of OTFs would cost the NHS an additional £5,819,366 each year.

However, the use of rhBMP-2 might prevent 367 infections and 593 secondary interventions, which would result in saving of £497,906 and £1,911,972, respectively (*Table 29*). In addition, £350,692 could be saved by the use of BMP because reduced time to fracture union would avoid 5234 outpatient contacts. After taking away savings from the total costs, the use of rhBMP-2 will cost the NHS £921 per OTF, or a total of £3,058,795 each year in the UK.

The original ABACUS model estimated that the costs per QALYs gained by additional use of BMP for OTFs is £20,364 (95% CI 11,683 to 31,321).

Comments on the original ABACUS model

ABACUS International sent a copy of the model, so the model can be considered as transparent generally in terms of its structure and input parameters. The model was well developed and programmed; the ABACUS model was assessed and no programming and other errors were found. The model's structure seems reasonable, given the currently available research evidence. Clinical data for input parameters of the model was mainly from the BESTT trial[61] and cost data from National Schedule of Reference costs (2003). Perhaps these are currently the best available data sources, although unit cost could be updated by data from National Schedule of Reference costs 2005.

The model could be used to conduct probabilistic simulations. The range of input parameters was arbitrarily decided to be 25% or 50% smaller or greater than the point estimates of input parameters. Therefore, it is unclear whether uncertainty in estimates of input values had been adequately accommodated in the analysis.

Possible duplicate counting of events and related costs

The effects of the use of BMP were measured by its impact on infections of the fracture sites, secondary interventions and time to fracture union, which reflect outcome measures used in clinical trials. However, the three outcomes may not be completely independent. For example, a patient with infection may more likely require secondary interventions, and also with delayed fracture union. By personal communication (V Alt, Clinical Advisor, University Hospital Giessen-Marburg, Giessen, Germany: 2006), we received further data on secondary intervention and infections for 44 patients in the BESTT trial. Of these patients, there were 18 who received secondary interventions and 17 with infection

events. Seven of the patients had both secondary intervention and infection, although it is difficult to decide whether the two events were directly associated.

According to the Department of Health, England, the fundamental principle for costing in the NHS is that "reference costs should be produced using full absorption costing".[99] This means that each reported unit cost will include the direct, indirect and overhead costs associated with providing that treatment/care. Therefore, the cost of postoperative infection may already include the cost of corresponding secondary interventions required due to infection. If so, savings related to infections and secondary interventions may have been overestimated by duplicate counting.

Utility values

Delayed union of an OTF will inevitably impact on a patient's quality of life (QoL) (Appendix 24). There is a lack of objective data on patient utility. Utility values used in the ABACUS model were extrapolated from estimates for older women with hip fractures[67] and women with long-standing vertebral osteoporotic fractures.[97] The two studies were reviewed; more details and discussions are provided below.

Salkeld and colleagues[67] used the time trade-off technique to estimate the utility associated with hip fracture and fear of falling among older women (aged ⩾75 years). The baseline utility value (EQ-50) was 0.77 for interviewed women. They found that a 'bad' hip fracture (which results in admission to a nursing home) was valued at 0.05 and a 'good' hip fracture (maintaining independent living in the community) 0.31. The dis-utility value for a 'good' hip fracture could be estimated as 0.46 = 0.77 – 0.31, on which it seems that the disutility value used for Gustilo type IIIB/C OTF non-union in the model was based.

Hall and colleagues[97] measured QoL in women with long-standing vertebral osteoporotic fracture and age-matched normal women, using the SF-36. Then SF-36 scores were transformed to a utility score by the Fryback technique. It was found that the utility score was 0.64 for women with vertebral fracture and 0.72 for controls. The difference in the utility scores between the two groups is 0.08 (0.72–0.64). However, it is not clear how this estimate has been used to estimate disutility values in the ABACUS model.

It is highly questionable whether the results from Salkeld and colleagues' study[67] of hip fracture and Hall and colleagues' study[97] of vertebral osteoporotic fracture are generalisable to patients with OTF. We identified a further study of economic evaluation of patients with closed tibial shaft fractures.[100] Based on expert opinion, the utility value estimated was 0.9 for returning to normal activities, 0.5 for non-union, 0.6 for delayed union and 0.5 for experiencing a postoperative complication. This study estimated the utility value based on expert opinion, which was subjective and may not truly reflect patient opinion.

Fracture union in the BESTT trial was defined by a combination of pain-free weight bearing and lack of tenderness at fracture site plus radiological union (three out of four cortices with bridging callus). Hence the QoL of patients may not be much different from normal many weeks before the defined fracture union. For example, a patient with pain-free weight bearing and lack of tenderness at the fracture site did not meet the criteria for fracture union if radiological union was not achieved. Therefore, the original ABACUS model may has overestimated the disutility values due to delayed union.

Modified and updated ABACUS model

The following changes were made in the modified ABACUS model:

1. The population in the UK was 60,209,500 in 2005.
2. Unit costs were updated by data from National Schedule of Reference Costs 2005/06 and National Tariff 2006/07 when available.
3. Since the disutility values might be much overestimated in the original ABACUS model but there is no alternative objective data, we arbitrarily assumed the values to be 30% smaller.
4. To deal with possible multiple counting of savings, estimated costs of infections and outpatient contacts were assumed to be 10% lower than those in the original model.
5. Considering great uncertainty, probabilistic simulations were conducted by using a wider range of input values: 50% greater or smaller than the point estimates.

The results of the modified ABACUS model are shown in *Table 30* and *Figures 13* and *14*.

The estimated direct cost of using rhBMP-2 is £5,959,958 each year in the UK. After considering savings from fewer clinical complications (infections and secondary interventions) and fewer

TABLE 30 *Results of modified ABACUS model for open tibial fracture in the UK*

	Point estimate (£)	95% CI (£) (based on 10,000 simulations)	
Main analysis			
Net cost impact in the UK	3,510,952	1,512,916 to 5,081,078	
Cost per OTF	1,054	454 to 1,526	
Incremental cost/QALY	32,603	14,085 to 61,257[a]	
Sensitivity analyses		**Net cost impact in UK (£)**	**Cost per OTF (£)**	**Cost/QALY (£)**
BMP-2 price reduced by 20% (from £1790 to £1432 per case)		2,318,960	696	21,534
BMP-2 price reduced by 40% (from £1790 to £1074 per case)		1,126,969	338	10,465
BMP only for Gustilo type III		1,243,502	689	13,616

[a] Based on the CEAC.

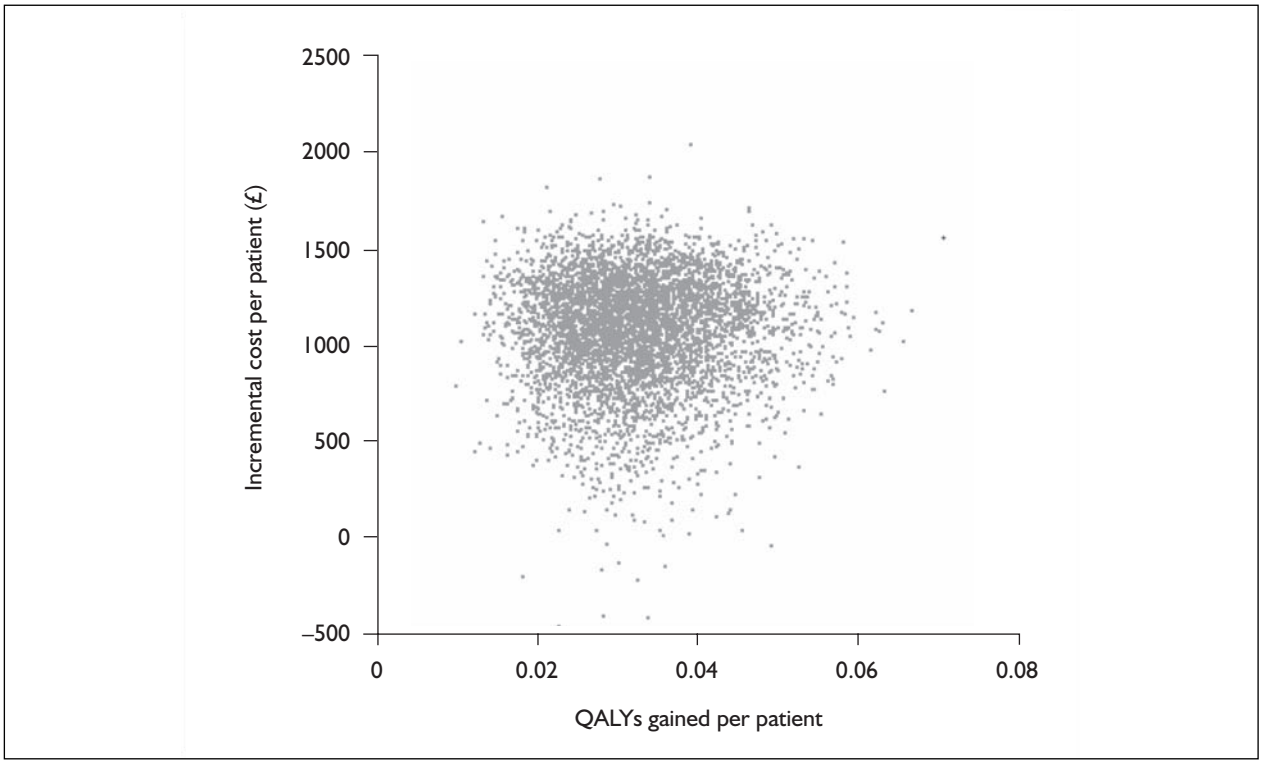

FIGURE 13 *Incremental cost and QALYs gained by the use of BMP for open tibial fractures in the UK: results of Monte Carlo simulations (n = 5000)*

outpatient contacts due to delayed fracture union, the net cost of using rhBMP-2 is £3,510,952, which is greater than the £3,058,795 estimated by the original ABACUS model. The cost per QALY gained will be £32,603, with a wide 95% CI from £14,085 to £61,257. The CEAC obtained by 10,000 Monte Carlo simulations is presented in *Figure 14*. There is a 35.5% probability that the cost per QALY gained by the use of BMP for OTF is less than £30,000.

The ICER is highly sensitive to the price of rhBMP-2. If the price of rhBMP-2 is reduced by about 20% (that is, from £1790 to £1432), the estimated cost per QALY gained will be £21,534, based on the input values used in the modified model.

ICERs may be improved if BMP is used only for Gustilo type III OTFs. The total number of eligible patients will be reduced by about 46%

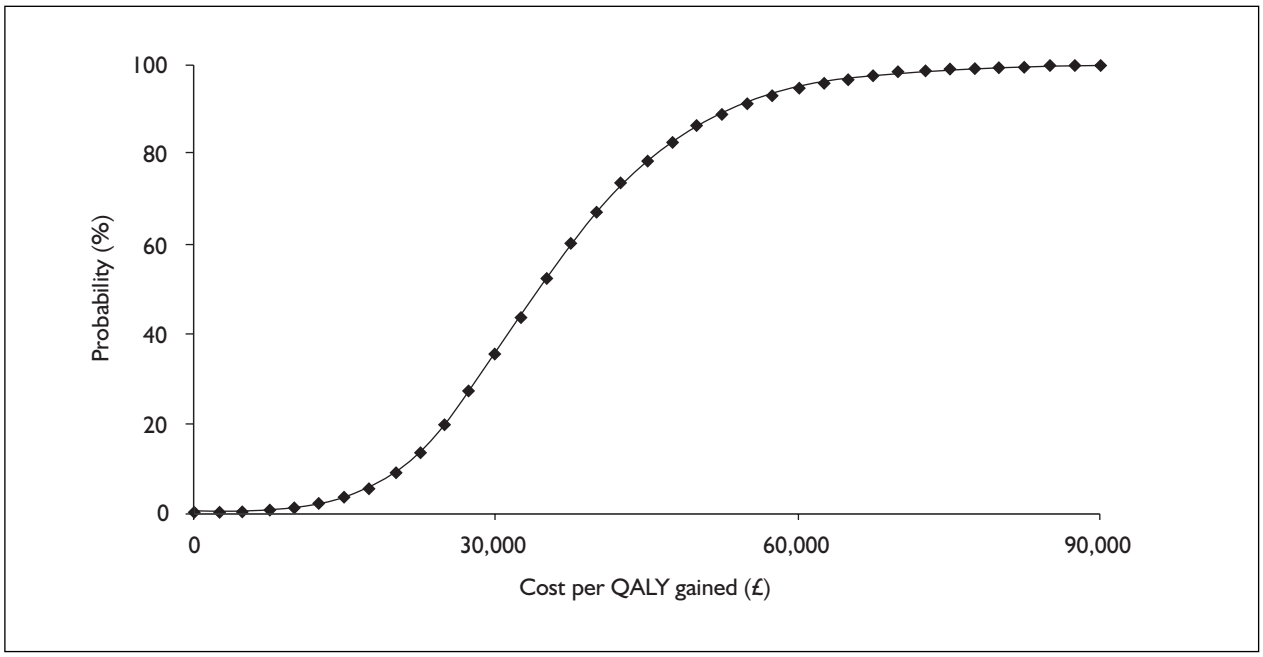

FIGURE 14 *CEAC: BMP for open tibial fractures (Monte Carlo simulation results using ABACUS model)*

from 3330 to 1805 each year in the UK. It will cost the UK NHS about £1.24 million extra per year. The estimated cost per QALY gained is £13,616.

Assessment of ABACUS model: economic evaluation of BMP for spinal fusion

Original ABACUS model of rhBMP-2 for spinal fusion

ABACUS International sent us a copy of a model for the evaluation of cost-effective management of spinal fusions in September 2005 and a revised version in November 2006. The model estimates the net budget impact of BMP, by integrating data on the number of annual spinal fusions in a given population, costs of current treatment (the use of autograft) and costs for additional BMP treatment in spinal fusion surgery. The model includes the following components:

- population and incidence of spinal fusion surgery procedures
- costs of current treatment and additional BMP
- savings by the use of rhBMP due to reduced operating time, length of hospital stay, and secondary interventions
- savings from reduced sick payment due to earlier return to work
- fusion rate and utility.

Input estimates used in the original BMP spinal fusion model

This model is referred to as the ABACUS BMP to SF model. The assessment of the ABACUS spinal fusion model was based on the version received in November 2006. *Tables 31* and *32* summarise model parameters for the number of patients and procedures and show unit cost estimates.

Population, incidence and number of spinal fusion procedures

The model estimated that there are 1000 single anterior level fusion cases per year in England. These spinal fusion surgeries were further separated into two groups: open spinal fusion procedures (41.09%) and laparoscopic procedures (58.91%), based on the study by Burkus and colleagues.[101] This proportion is questionable since the Burkus study[101] was not a population-based study; it reported data from one RCT of patients treated with open spinal fusion surgery and two prospective cohort studies of laparoscopic spinal fusion.

Costs of current treatment and additional rhBMP-2

The estimated cost for a spinal fusion procedure (both open and laparoscopic) without severe clinical complications was £5930 and the additional cost of rhBMP-2 was £1790 per case (*Table 32*).

Operating time, length of stay and revisional spinal procedures

The use of rhBMP-2 reduced operating time because harvesting autogenous bone graft is no longer required. The ABACUS model used data from Burkus and colleagues[101] in which the use of rhBMP-2 on average reduced the operating time by 0.4 hours in open procedure and by 1.2 hours in laparoscopic procedure. According to data from Burkus and colleagues,[101] the use of rhBMP-2 was associated with a shorter hospital stay, reduced by 0.2 days in patients with the open fusion procedure and by 1.8 days with the laparoscopic procedure. The reported rate of second surgeries was generally lower in the rhBMP-2 group (*Table 31*).

Time to return to work

According to the ABACUS model, 75% of patients working preoperatively and 35% of patients not working preoperatively in the rhBMP-2 group started working after fusion surgery, which were higher than 65 and 31%, respectively, in the autograft group. However, it is not clear how these estimates were derived, since they were not directly available in the paper by Burkus and colleagues.[101] Burkus and colleagues[101] reported that the median time to return to work was 386.5 days in autograft and 165.0 days in the rhBMP-2 group for open procedures, and 154.0 days in autograft and 89.0 days in the rhBMP-2 group for laparoscopic procedures. Patients working postoperatively in the rhBMP group

TABLE 31 *Data used in the original BMP-SF model: number of patients and procedures*

Parameter	Input value				Data source
Population (England)	58,789,194				
Spinal fusions per year	17.01/1,000,000 (n = 1,000)				Fairbank *et al.*, 2005[24]
Open procedure	41.09%				Burkus *et al.*, 2003[101]
Laparoscopic procedure	58.91%				
	Open		**Laparoscopic**		
	BMP	**Control**	**BMP**	**Control**	
Surgery parameters					
Operating time (hours)	1.6 (0.6)	2.0 (0.7)	1.9 (0.9)	3.1 (1.4)	Burkus *et al.*, 2003[101]
Hospital stay (days)	3.1 (1.6)	3.3 (1.3)	1.2 (1.1)	3.0 (0.8)	
Re-surgery rates					
Revisions (%)	0.00	0.00	0.75	3.01	Burkus *et al.*, 2003[101]
Removals (%)	1.39	0.00	1.44	2.63	
Supplemental fixations (%)	6.99	10.29	6.14	5.26	
Reoperations (%)	4.19	2.94	2.89	10.53	
Preoperative work status					
Working (%)	52.20	47.60	44.50	36.80	Burkus *et al.*, 2003[101]
Not working (%)	47.80	52.40	55.50	63.20	
Postoperative work status					
Of patients working preoperatively (%)	74.60	64.90	74.60	64.90	
Of patients not working preoperatively (%)	35.30	31.30	35.30	31.30	
Time to return to work (median) (days)	165.0	386.5	89.0	154.0	
Fusion rate					
6 months (%)	97.00	95.80	92.60	95.50	Burkus *et al.*, 2003[101]
12 months (%)	96.90	92.60	94.10	93.10	
24 months (%)	94.50	88.70	94.20	89.80	
Utility score					
Preoperative	0.5387	0.5417	0.5508	0.5571	Unpublished data, Brazier Index calculated from SF-36 health survey score
3 months	0.5948	0.5861	0.6062	0.5870	
6 months	0.6191	0.6161	0.6313	0.6047	
12 months	0.6332	0.6314	0.6478	0.6186	
24 months	0.6537	0.6481	0.6690	0.6526	

TABLE 32 *Data used in the original BMP-SF model: unit costs*

Parameter	Unit cost (£)	Data source
Open spinal fusion surgery	5930	National Tariff 05-06 HRG Code: R04 Vertebral Column Injury with Fusion or Decompression
Laparoscopic fusion procedure	5930	
Cost of rhBMP per case	1790	Wyeth Pharmaceuticals
Cost of per hour of operating time	965	Rivero-Arias *et al*., 2005[102]
Cost per bed day	389	Cost per surgery bed. Personal Social Services Research Unit, *Unit costs of health and social care*, 2002. This has been inflated to 2004 costs using the Hospital and Community Health Services Pay and Price Inflation Indices
Cost per revisional procedure:		
Revisions	3520	Not described in the model
Removals	3520	
Supplemental fixations	3520	
Reoperations	3520	
Average sickness pay per day	95	Office of National Statistics: Patterns of pay: results of the 2003 New Earnings Survey (Weekly = £476 = £95 per day)

returned to work 221.5 days earlier than those in the control group after open fusion surgery and 65.0 days earlier after laparoscopic fusion surgery.

Fusion rates and utility scores

The rates of radiographic fusion at 24 months were 94.5% in the BMP group and 88.7% in the control group for the open procedure and 94.2% in the BMP group and 89.8% in the control group for the laparoscopic procedure.[101] The model used reported fusion rate without considering possible bias due to drop-outs. If patients who dropped out before the follow-up at 24 months are considered to have a failure outcome, the success rates will be lowered to 84% versus 75% for open fusion and to 60% versus 57% for laparoscopic fusion.

Utility values used in the ABACUS model were unpublished, calculated from SF-36 health survey scores. The data on SF-36 scores were from three studies (one RCT and two cohort studies) reported by Burkus and colleagues.[101]

Results of the original BMP–SF model

The original ABACUS model estimated that, every year in England, the use of BMP-2 in spinal surgery would reduce operating time by 900 hours, length of hospital stay by 1143 days and number of revisional surgeries by 78. The use of BMP-2 was also associated with 51 more successful fusions by month 24 and 56 additional QALYs.

The original model estimated that the initial cost of current treatment was £5,930,025 for 1000 spinal fusion surgeries per year in England. The use of rhBMP would increase the annual cost by £1,790,007. However, the cost of rhBMP was offset by reduced operating time and hospital stay (by £1,311,965) and fewer revisional procedures (by £275,617). These savings reduced the incremental cost of rhBMP from £1,790,007 (£1790 per case) to £202,425 (£202 per case).

The original ABACUS model estimated that the use of rhBMP-2 avoided payment for 48,369 sickness days, which saves £4,595,055 per year in England. After taking savings of reduced sickness payment into account, the use of rhBMP could save £4,392,630 in total (i.e., saving £4393 per case).

Comments on the original BMP–SF model

Clinical data used in the ABACUS model was mainly derived from the 2003 paper by Burkus and colleagues.[101] This paper reported data from one RCT of the open fusion procedure,[74,76] and two separate cohort studies of laparoscopic fusion procedures. The RCT[74,76] compared BMP and autograft treatment in patients who underwent open anterior lumbar interbody fusion surgery for degenerative lumbar disc disease. It was a multi-centre trial, with adequate patient allocation concealment and comparable to patients in the BMP and the autograft group at baseline (Appendix 16). Therefore, data from the RCT for the open fusion procedure seem unbiased. However, the RCT[74,76] included only 279 patients and aimed to establish statistical equivalence (non-inferiority) between the BMP and autograft treatment. To investigate whether BMP was

TABLE 33 *Work status from Burkus* et al. *(2002) study*[74]

	% of patients			
	Autograft		rhBMP-2	
	Burkus, 2002[74]	Standardised	Burkus, 2002[74]	Standardised
Preoperative	36.80	42.30	47.60	42.30
1.5 months	11.30	12.99	15.60	13.86
3 months	28.40	32.64	38.30	34.04
6 months	45.50	52.30	50.70	45.05
12 months	50.40	57.93	55.00	48.88
24 months	56.10	64.48	66.10	58.74

statistically superior to autograft, Burkus and colleagues[101] combined data from the RCT of the open procedure and data from two additional cohort studies of laparoscopic surgical procedures. One of the two cohort studies of laparoscopic procedures used BMP and one used autograft in patients similar to those in the RCT. However, the baseline characteristics of patients in the two different laparoscopic studies may not be comparable. For example, 41% of patients in the laparoscopic autograft group had previous back surgery compared with only 25% in the laparoscopic BMP group.[101] The differences in operating time, hospital stay and second surgeries between the BMP and control group were much greater according to data from the two separate laparoscopic studies, compared with that based on the RCT of open procedures. Consequently, the relative effect of BMP compared with autograft may have been overestimated by using data from the two cohort studies.

The inclusion of sickness payment had a dramatic impact on the result in the original ABACUS model. After including estimated savings due to reduced sickness payment, the use of BMP was no longer a cost, but a saving, from a societal perspective. The estimated reduction in sickness payment by BMP depended on time of return to work reported by Burkus and colleagues.[101] The difference in days to return to work between the BMP and control groups was enormous (165 versus 386 days for open procedures and 89 versus 154 days for laparoscopic procedures). The Burkus (2002) study[74,76] reported that the median return to work time was 63.5 days in the BMP group and 64.5 days in the autograft group, in the same trial included in the Burkus (2003) study.[101] Reasons for this huge discrepancy are unclear.

More detailed data for work status between groups is available from the Burkus (2002) study[74] (*Table 33*). Since the proportion of patients working preoperatively in the BMP group was considerably higher than that in the control group (48% versus 37%), the proportions of patients working after surgery should be adjusted accordingly. The average proportion of patients working was 42.3% in all patients before the surgery. This baseline proportion was changed according to the observed relative changes (ratio of the neighbouring proportions) in the corresponding groups. According to the standardised estimates, there was no longer an advantage by using BMP-2 in spinal fusions.

Modified BMP–SF model

Based on the above assessment, we modified the ABACUS model to evaluate the use of BMP for spinal fusion in the UK. *Table 34* shows input values for clinical parameters and shows unit costs used in the modified BMP–SF model. Detailed modifications are described below.

1. Since the estimates for laparoscopic procedures in the original model may be biased or inaccurate, we assumed that all procedures are open fusions and use data only from the RCT[74] (*Table 34*).
2. Unit costs used in the model were updated (*Table 35*). NHS unit costs were mainly from National Schedule of Reference Costs 2005 or National Tariff (2006/07). Cost per hour of operating time was based on data from Rivero-Arias and colleagues.[102] Cost is not discounted due to the short time horizon (24 months).
3. The standardised proportions of patients working after surgery were used in the analysis of sickness payments.
4. The original ABACUS model was a deterministic version. We modified it to conduct Monte Carlo (probabilistic) simulations. Data from the trial were available to estimate standard errors for operating time, hospital stay and utility values. For other input

TABLE 34 *Input values for the modified BMP–SF model: number of procedures and clinical parameters*

Parameters	Value		Source
Population (2005, UK)	60,209,500		National Statistics UK
Spinal fusion	17.01 per million		As in the original ABACUS model
Open fusion surgery	100%		
	BMP	**Control**	
Surgery parameters			
Operating time (hours)	1.6 (0.6)	2.0 (0.7)	Burkus *et al.*, 2002[74]
Hospital stay (days)	3.1 (1.6)	3.3 (1.3)	
Resurgery rates			
Revisions (%)	0.00	0.00	Burkus *et al.*, 2002[74]
Removals (%)	1.39	0.00	
Supplemental fixations (%)	6.99	10.29	
Reoperations (%)	4.19	2.94	
Working after operations			
1.5 months (%)	13.86	12.99	Based on data from Burkus *et al*., 2002,[74] adjusted by the baseline working status
3 months (%)	34.04	32.64	
6 months (%)	45.05	52.30	
12 months (%)	48.88	57.93	
24 months (%)	58.74	64.48	
Fusion rate			
6 months	90.00	85.00	Based on data from Burkus *et al*., 2002.[74] ITT analysis: assuming drop-outs = failures
12 months	89.00	82.00	
24 months	84.00	75.00	
Utility score			
Preoperative	0.5387	0.5417	Unpublished data, Brazier Index calculated from SF-36 Health Survey[103]
3 months	0.5948	0.5861	
6 months	0.6191	0.6161	
12 months	0.6332	0.6314	
24 months	0.6537	0.6481	

TABLE 35 *Input values for the modified BMP-SF model: unit costs*

Parameter	Unit cost (£)	Source
Initial current treatment	5283 (IQR 2923 to 5631)	Average unit cost for decompression and fusion for degenerative spinal disorders; from National Schedule of Reference Costs 2005
BMP (InductOs 12-mg Implant kit)	1790	Wyeth Pharmaceuticals
Revisional spinal procedures	4452 (IQR 2400 to 4860)	National Schedule of Reference Costs 2004/05, NHS Trust, TELIP, R09 – Revisional spinal procedures
Cost per hour of operating time	1034.07	Rivero-Arias *et al.*, 2005:[102] total costs related to theatre duration in spinal stabilisation operation = £2,863.07 (including cost of theatre *per se*, personnel and anaesthetics). The average duration of the operations = 182 minutes. Hence 944 = 2863.07/(182/60). Inflated to 2005
Cost per bed day	264	National Tariff 2006/07, R03 – Decompression and fusion for degenerative spinal disorders, cost per day long-stay payment (for days exceeding trimpoint)
Annual mean gross salary for all employee jobs, UK 2005	23,400	National Statistics UK

IQR, interquartile range.

TABLE 36 *Results of modified/updated BMP–SF model: clinical benefit and cost-effectiveness of BMP for spinal fusion procedures (95% CI estimated by 10,000 Monte Carlo simulations)*

Parameter	Estimate (95% CI)		
No. of spinal fusion procedures in the UK	1024 (510 to 1553)		
Clinical outcomes			
Reduced operating time	410 (178 to 695)		
Reduced length of hospital stay	205 (–140 to 620)		
Reduced revisional procedures	7 (–64 to 84)		
Additional fusions at month 24	92 (46 to 140)		
Additional QALYs	11 (–30 to 56)		
Costs	**Control**	**BMP**	**Difference**
Initial treatment costs (£)	5,410,656	7,243,909	1,833,253 (913,722 to 2,780,476)
Avoided bone grafting cost offsets (£)	–	–477,699	–477,699 (–922,042 to –165,781)
Cost of revisional procedures (£)	603,232	573,139	–30,093 (–420,074 to –291,986)
Total incremental costs to NHS (UK) (£)	6,013,888	7,339,349	1,325,461 (583,547 to 2,192,916)

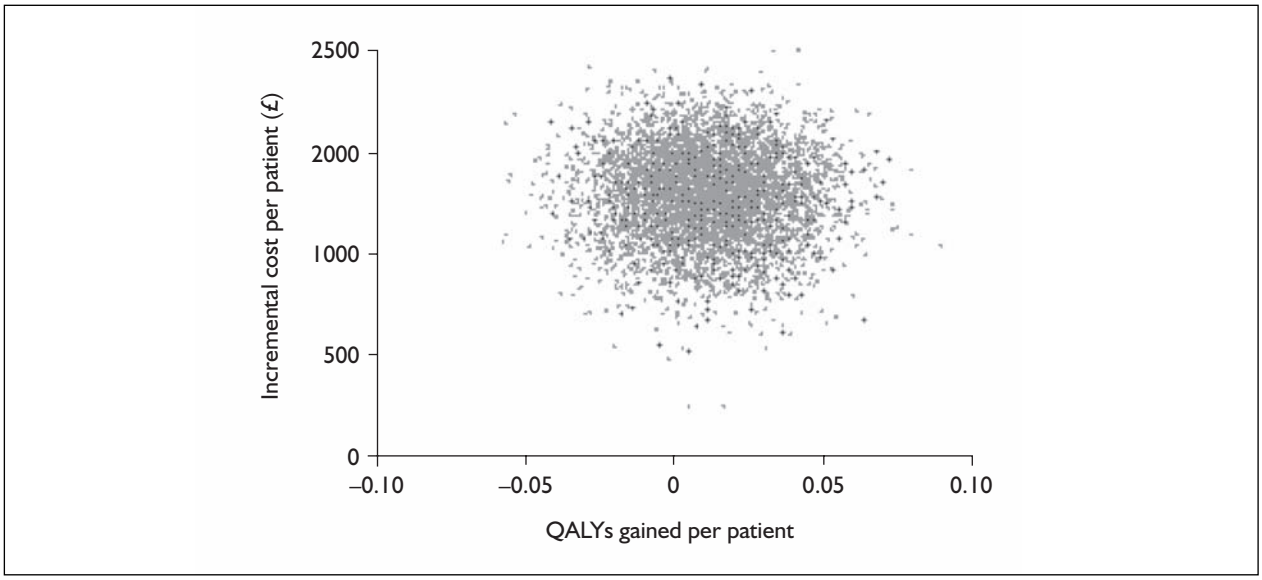

FIGURE 15 *Incremental cost and QALYs gained per patient by the use of BMP for spinal fusion surgery in the UK: results of simulations (n = 5000)*

parameters, a range (i.e. 95% CI) is assumed to be 50% smaller or greater than the point estimates.

Results of modified economic evaluation of BMP for spinal fusion

Results of the modified BMP–SF model for economic evaluation of BMP for spinal fusion in the UK are shown in *Table 36* and *Figures 15* and *16*.

The use of BMP in 1024 patients undergoing spinal fusion surgery reduces the operating time by 410 hours (95% CI 178 to 695 hours), length of hospital stay by 205 days (95% CI –140 to 620 days) and revisional spinal procedures by seven (95% CI –84 to 64). It is associated with 11 additional QALYs (95% CI –30 to 56).

The use of rhBMP will increase the initial treatment cost to the UK NHS by approximately

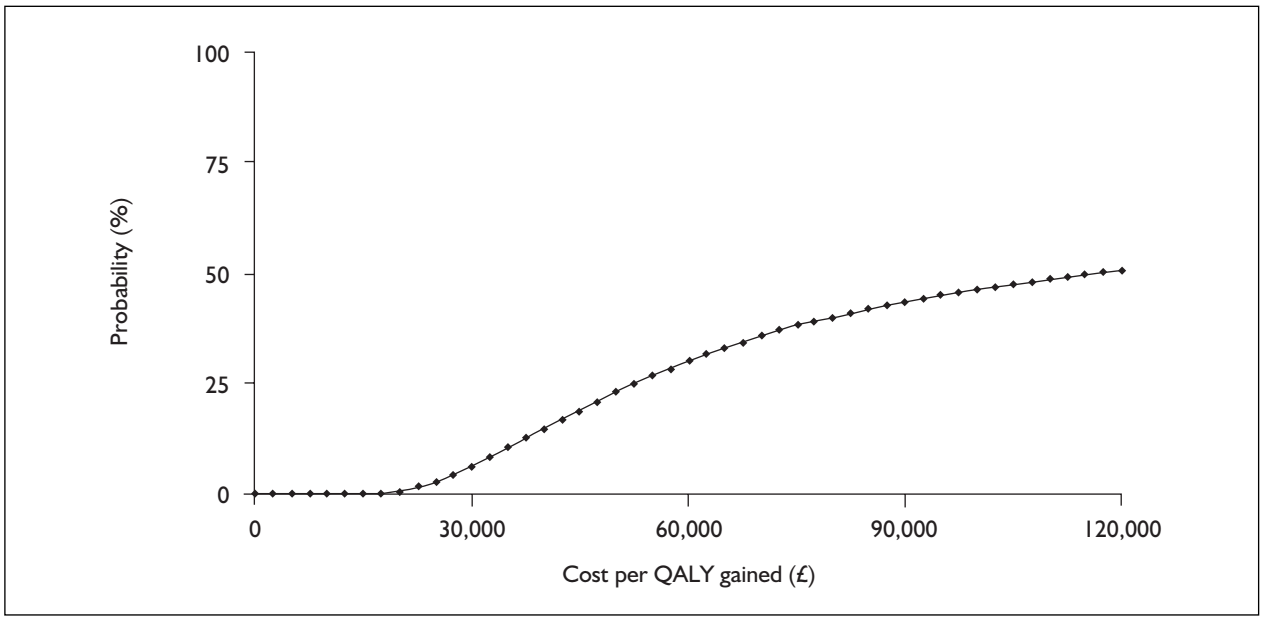

FIGURE 16 *CEAC: BMP for spinal fusion (results of 10,000 Monte Carlo simulations)*

£1.8 million per year. After taking into account savings due to reduced operating time, shorter hospital stay and less revisional surgery, the incremental cost to the NHS in the UK is approximately £1.3 million.

Estimated cost per QALY gained is on average £120,390. The probability that BMP is cost-effective (cost/QALY <£30,000) is only 6.4%, according to the CEAC (*Figure 16*).

According to standardised rate of working after surgery, patients in the BMP group actually tend to return to work later than those in the control group. This is associated with an increase in societal costs of £2.9 million. Inclusion of this societal cost will increase the total incremental cost of using BMP for spinal fusion from £1.3 million to £4.2 million per year in the UK.

Summary of economic evaluations

The literature review identified no published economic evaluation of BMP for fracture healing and only one study for evaluating BMP for spinal fusion. The included study suggests that the initial cost of using BMP for spinal fusion is likely to be offset by avoiding autogenous bone graft and related complications and improved successful fusion. However, the models described in published papers were not available electronically for detailed structures to be assessed. The input estimates were heavily based on expert opinion. In addition, the results of this US study may not be generalisable to the UK setting.

ABACUS International provided two models for the economic evaluation of BMP for acute OTF and the use of BMP for spinal fusion. These models were appropriately structured and programmed and sufficiently transparent in terms of links between inputs and results.

The ABACUS models were assessed and modified or updated. According to the results of the modified and updated analysis, the initial cost of using rhBMP-2 for OTFs is approximately £6 million each year in the UK. After considering savings resulting from fewer clinical complications (infections and secondary interventions) and fewer outpatient contacts due to delayed fracture union, the net cost of using rhBMP-2 reduces to £3.5 million. The estimated incremental cost per QALY gained is £32,603 with a wide 95% CI from £14,085 to £61,257. The probability that BMP is cost-effective (cost/QALY gained <£30,000) for OTF is 35.5%. The ICER is sensitive to the price of BMP and the severity of OTFs. If BMP is used only for Gustilo type III OTFs, the estimated incremental cost per QALY gained is £13,616.

According to our analyses, the use of rhBMP for spinal fusion surgery increases the initial treatment cost to the UK NHS by about £1.8 million per year. After taking into account savings due to reduced operating time, shorter hospital

stay and less revisional surgery, the incremental cost to the NHS in the UK is about £1.3 million. The estimated incremental cost per QALY gained is on average £120,390. The probability that BMP is cost-effective (cost/QALY <£30,000) is only 6.4%. In contrast to the original ABACUS model, patients in the BMP group actually tended to return to work later than those in the control group after standardisation by employment status before spinal surgery. This is associated with an increased societal cost of £2.9 million. From the societal perspective, the estimated total incremental cost of using BMP for spinal fusion is about £4.2 million per year in the UK.

Chapter 6

Discussion and conclusions

The main purpose of this review was to evaluate the effectiveness and cost-effectiveness of BMP for the treatment of spinal fusions and fracture healing. Although all types of studies were sought, only RCTs were used for analysis. This was because case series or case reports included heterogeneous patient populations, had small sample sizes and were generally of low quality. Also, some of the non-RCTs included patients with serious co-morbidities and many received either autograft bone or other bone substitutes in addition to BMP. We decided not to include data from case series in the analyses.

Methodological quality of included RCTs

We identified eight RCTs of BMP for tibial fractures, one of scaphoid non-union and 12 of BMP for spinal fusion. The included trials have some methodological weaknesses, including unreported randomisation and allocation methods, incomparable baseline characteristics between the groups, failure to perform ITT analysis or to use independent blinded assessors and failure to report reasons for drop-outs. Some secondary outcomes were not measured and/or not reported. The sample size was small in most of the included trials, ranging from 14 to 450 in trials of tibial fracture and from 14 to 279 in trials of spinal fusion. Because of insufficient sample size, patient baseline comparability between trial arms may not be achieved and statistical power to detect moderate effect and/or to establish equivalence between different interventions is low.

Effectiveness of BMP for tibial fractures

Among the eight identified trials, the BMP intervention was evaluated in two trials for OTFs, one trial for closed tibial fracture, one trial for both open and closed tibial fracture and four trials for tibial fracture non-union. Data from three trials indicated that the use of BMP increased fracture union among patients with acute tibial fractures (pooled OR 1.65, 95% CI 1.12 to 2.45). This pooled estimate is dominated by a large multi-centre trial of acute OTF.[61] Also in this large trial, the high-dose BMP (1.5 mg/ml) showed a higher union rate than the lower dose (0.75 mg/ml) (OR 1.64, 95% CI 1.03 to 2.59). The proportion of secondary interventions in the BMP group is lower than that in the control group for patients with acute tibial fractures (pooled OR 0.53, 95% CI 0.37 to 0.78).

Evidence from four small trials provided insufficient evidence to be certain whether BMP treatment is more or less effective than autogenous bone grafting for patients with tibial fracture non-union (pooled OR for union rate 0.82, 95% CI 0.25 to 2.64). There are several possible explanations for this lack of effectiveness of BMP in fracture non-union. First, BMP may not be more effective than autograft in atrophic non-union because of inadequate local blood supply. The trials included in the analysis were small (total number of patients 30, 41 and 124), and patients between trial arms may not be comparable. There were more atrophic non-unions at baseline in the BMP group than that in the control group in the largest trial (n = 124). In addition, the length of follow-up (9 months) in some trials may not be sufficiently long. However, the use of BMP avoids the need for autogenous bone grafting so that costs and complications related to harvesting autograft (e.g. pain, blood loss) can be prevented.

Effectiveness of BMP for scaphoid non-union

Only one small RCT (n = 18) was identified. Very limited evidence indicated that BMP in scaphoid non-union was safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft.

Effectiveness of BMP for spinal fusion

There are seven trials of BMP-2 in spinal fusion for patients with symptomatic single-level degenerative disc disease, including four trials that used anterior fusion and three that used posterolateral fusion. One trial[80] of BMP-7

included patients with L5 spondylolysis who were treated with non-instrumented posterolateral lumbar fusion. Three trials[81,82,84,86] of BMP-7 included patients with spinal stenosis and degenerative spondylolisthesis who were treated with posterolateral fusion. Evidence shows that the use of BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease (pooled OR 3.87, 95% CI 1.74 to 8.59). The pooled OR for patients with degenerative spondylolisthesis with spinal stenosis is 0.87 (95% CI 0.15 to 5.08) and for patients with spondylolysis 0.38 (95% CI 0.05 to 2.77).

BMP treatment replaces autogenous bone grafting and prevents donor site morbidities. The evidence suggests that BMP is associated with a 25-minute (11–37 minutes) reduction in operating time compared with controls, and a shorter hospital stay (0.75 days, from 0.31 to 1.19 days). BMP treatment may also be associated with improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. The proportion of secondary interventions tends to be lower in the BMP group than that in the control group, but the overall difference is not statistically significant (pooled OR 0.62, 95% CI 0.28 to 1.39). Data from trials on time to return to work after spinal fusion were sometimes difficult to interpret because of unclear or inappropriate methods used for data analysis and results presentation.

Several trials[69,71–74,76] reported a tendency for fusion rates to decline over time. Possible explanations for this occurrence were described in the Burkus (2002) study.[74] The reasons given were radiolucency seen at the implant–bone interface and that the autogenous bone became atrophic over time. In addition, patients who required a secondary operation for continuing low back pain despite evidence of radiographic fusion were considered as a fusion failure. A secondary operation, not lack of new bone formation, was reported as the reason for all fusion failures in the BMP group in the by Burkus (2002) trial.[74]

The effectiveness of BMP in spinal fusion also depends on the effectiveness of spinal fusion surgery compared with other non-surgical interventions. A Cochrane systematic review[104] concluded that there was only limited and heterogeneous evidence to support the use of surgery for degenerative lumbar spondylosis. A recently published study in the UK found that "no clear evidence emerged that primary spinal fusion surgery was any more beneficial than intensive rehabilitation" for patients with chronic low back pain, although 28% of patients initially allocated to the rehabilitation group underwent spinal fusion surgery within 2 years.[24] Therefore, future trials that compare BMP and autogenous bone graft for spinal fusion should also include a control of intensive rehabilitation without surgery.

Adverse effects and safety of BMP

More patients in the BMP group developed antibody responses to BMP or bovine collagen. The clinical relevance of the antibody responses is not clear. Carlisle and Fischgrund[105] suggested that, because of these antibody responses, BMP should not be used in pregnant women, and repeat use of BMP should be avoided.

The largest trial of BMP for OTF[61] provided no data but mentioned that the use of BMP did not increase soft-tissue calcification or heterotopic ossification at remote sites. One case of heterotopic bone formation was reported among 15 BMP-treated patients with open or closed tibial fracture in the Jones trial.[28] The patient had a solid tibiofibular synostosis, or joining of the tibia and fibula bones. This event was a concern, but also occurs in patients with severe fractures that do not receive BMP. In the Maniscalco trial,[62] calcification of the tibio-fibular ligament was observed in one case among seven patients who received BMP applied to external fixator for closed tibial fracture. In a trial[79,87] of BMP for spinal fusion, patient enrolment was stopped when excess bone formation was seen in 24 of 32 BMP patients and four of 31 control patients ($p < 0.001$), although the authors reported no apparent effects on patient outcomes. Other trials of spinal fusion did not mention excess bone formation, and it is unclear whether excess bone formation was not investigated or not reported.

It is difficult to assess adverse effects and safety of BMP for fracture and spinal fusion, partly because different trials often investigated and reported different adverse event outcomes.

Different doses and types of BMPs

According to limited evidence, adequate concentration is important for BMP to be effective. The effect of different concentrations of BMP for OTF was directly compared in one

study.[61] It was found that high-dose BMP (1.5 mg/ml) is more effective than lower dose BMP (0.75 mg/ml) (OR 1.64, 95% CI 1.03 to 2.59).

Apart from one trial,[59] which did not identify which BMP was used, two clinically available BMP products were used in the identified clinical trials: BMP-2 and BMP-7. They have not been directly compared in randomised trials. For the treatment of fractures, BMP-2 has been evaluated in two trials (including one large trial with 450 patients, $n = 480$ total) and BMP-7 in six small trials ($n = 351$). For spinal fusion surgeries, BMP-2 was evaluated in seven trials of 631 patients with single-level degenerative disc disease and one trial of 40 patients with degenerative spondylolisthesis and stenosis. BMP-7 was evaluated in two trials of 56 patients with degenerative spondylolisthesis with spinal stenosis and in one trial of 20 patients with spondylolysis. Because great heterogeneity in patients and surgical procedures, it is not possible to make an indirect comparison of BMP-2 and BMP-7. Different doses/concentrations and types of BMP should be compared in further RCTs.

Cost-effectiveness

We assessed and modified two economic models developed by ABACUS International to evaluate cost-effectiveness of BMP for OTF and spinal fusion.

The incremental cost of adopting the use of BMP in the treatment of OTFs is estimated to be approximately £3.5 million per year from a UK NHS perspective. The estimated incremental cost per QALY gained is £32,603 with a wide 95% CI from £14,085 to £61,257. The ICER is highly sensitive to the price of BMP and the severity of OTFs. It should also be noted that utility values used in the model were extrapolated from studies of general fractures (and elderly women for hip fractures). The estimate of health-related QoL used in the economic model may therefore be inaccurate. The effect of BMP on QoL needs to be directly evaluated with further research.

The use of rhBMP for spinal fusion surgery may increase the cost to the UK NHS by approximately £1.3 million per year. Estimated incremental cost per QALY gained is about £120,390. We re-analysed data on time to return to work after spinal surgery, and found that patients in the BMP group actually tended to return to work later than those in the control group. From a societal perspective, the estimated incremental total cost of adopting use of BMP for spinal fusion is approximately £4.2 million per year in the UK.

Conclusions

For both fracture and spinal fusion indications, the use of BMP may eliminate the need for autogenous bone grafting, so that costs and complications related to harvesting autograft can be avoided.

The main concerns about adverse effects and safety of the use of BMP include antibody responses and soft-tissue calcification or heterotopic ossification. No other serious adverse events or safety concerns about the use of BMP have been consistently reported in the identified clinical trials, although we may not be able to rule out rare but severe adverse events from using BMP.

BMP for tibial fracture

Additional BMP treatment plus conventional interventions is more effective than the conventional intervention alone for successful union of acute OTFs. There is no evidence showing that the use of BMP is more or less effective than conventional treatment for tibial fracture non-union or closed tibial fracture. The cost-effectiveness of additional BMP for open tibial fracture may be improved if the price of BMP is reduced or BMP is mainly used in severe cases.

BMP for spinal fusion

The use of BMP in spinal fusion surgery seems more effective than autogenous bone graft in terms of radiographic spinal fusion among patients with single-level degenerative disc disease. There is a lack of evidence about the effectiveness of BMP for other spinal disorders, including spondylolisthesis and spinal stenosis. There was limited evidence showing that BMP is associated with greater improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. According to the results of economic evaluation, the use of BMP for spinal fusion is unlikely to be cost-effective.

Recommendations for further research

The following are our recommendations for additional research:

- Clinical trials of BMP should include formal economic evaluation. More detailed data need to be collected on both costs (including relevant

societal costs) and QoL (utilities) to inform such economic evaluation.

- Multi-centre RCT of fracture non-union. Only one RCT of poor quality using BMP-7 has been performed. Since each study centre has small recruitment numbers, a non-inferiority design is needed. Either BMP-2 or BMP-7 should be studied, with autograft as control. Previous studies have mixed BMP with other products. It is recommended that BMP alone is tested against autograft, to demonstrate the true BMP effect. It is also recommended that BMP is tested in new non-union cases and not just where other therapies have failed. If equivalence can be shown between BMP and autograft, then donor site morbidity can be eliminated, decreasing pain and discomfort for patients.
- Multi-centre RCT of interbody and/or posterolateral spinal fusion. Existing RCTs using BMP-2 have methodological weaknesses. Further studies are recommended comparing BMP-2 against autograft. So far there have been no RCTs using BMP-7. It is recommended that these should be undertaken. If equivalence can be shown between BMP and autograft, then donor site morbidity can be eliminated, decreasing pain and discomfort for patients.
- RCTs of non-tibial acute long bone fractures. One good-quality RCT has been performed of BMP-2 in OTFs. Further similar studies on fractures at other sites are recommended. We are aware that company-sponsored Phase 2 and 3 studies of injectable BMP-2 are being undertaken. The aim should be to demonstrate accelerated fracture healing, reduction in secondary procedures and reduction in healthcare and/or societal costs.
- RCTs comparing BMP-2/BMP-7/controls. There are no studies currently showing the relative efficacy of BMP-2 versus BMP-7. Their different mechanism of action may mean that they have important clinical differences in different circumstances. Studies should be undertaken comparing these two products against controls.

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Contribution of authors

Kimberly Garrison (Research Associate), Simon Donell (Consultant and Honorary Reader), Fujian Song (Reader in Research Synthesis), Miranda Mugford (Professor of Health Economics) and Ian Harvey (Professor of Epidemiology) developed and commented on the review protocol. Jon Ryder (Support Post in Information and Quantitative Methods) and Kimberly Garrison developed the search strategies and searched electronic databases. Kimberly Garrison and Fujian Song reviewed and assessed the studies. Fujian Song, Ian Shemilt (Research Coordinator for Campbell and Cochrane Economics Methods Group) and Miranda Mugford assessed and modified the ABACUS model. Simon Dorell, Miranda Mugford and Ian Harvey provided advice on the interpretation of evidence. Kimberly Garrison and Fujian Song prepared the report. All authors commented on the draft manuscript.

Publication information

A protocol of Cochrane Systematic Review has been accepted by Cochrane Collaboration, to develop a Cochrane Systematic Review based on part of the report (review of RCTs of the use of BMP for tibial fracture).

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Appendix 1

Search strategies

BMP for treatment of fractures or fusion

MEDLINE (Ovid) 1966 to week 3 January 2006 and EMBASE (Ovid) 1980 to week 3 January 2006

1 bone morphogen$.ti,ab.
2 osteogen$.ti,ab.
3 osteoinduct$.ti,ab.
4 protein$.ti,ab.
5 factor$.ti,ab.
6 polypeptide$.ti,ab.
7 poly-peptide$.ti,ab.
8 ((bone morphogen$ or osteogen$ or osteoinduct$) adj (protein$ or factor$ or polypeptide$ or poly-peptide$)).ti,ab.
9 (BMP or BMP2 or BMP-2 or BMP7 or BMP-7).ti,ab.
10 (rhBMP or rhBMP2 or rhBMP-2 or rhBMP7 or rhBMP-7).ti,ab.
11 (rh-BMP or rh-BMP2 or rh-BMP-2 or rh-BMP7 or rh-BMP-7).ti,ab.
12 (rhop1 or rhop-1).ti,ab.
13 (op1 or op-1).ti,ab.
14 exp Bone Morphogenetic Proteins/
15 fracture$.ti,ab.
16 exp Fractures, Ununited/ or exp Skull Fractures/ or exp Fractures, Malunited/ or exp Zygomatic Fractures/ or exp Orbital Fractures/ or exp Fractures, Bone/ or exp Spinal Fractures/ or exp Femoral Neck Fractures/ or exp Radius Fractures/ or exp Femoral Fractures/ or exp Tibial Fractures/ or exp Maxillary Fractures/ or exp Humeral Fractures/ or exp Ulna Fractures/ or exp Fractures, Compression/ or exp Fractures, Cartilage/ or exp Fractures, Spontaneous/ or exp Hip Fractures/ or exp Shoulder Fractures/ or exp Jaw Fractures/ or exp Mandibular Fractures/ or exp Fractures, Open/ or exp Fractures, Closed/ or exp Tooth Fractures/ or exp Rib Fractures/ or exp Fractures, Stress/ or exp Fractures, Comminuted/
17 (nonunion or nonunion).ti,ab.
18 (non-fusion or nonfusion).ti,ab.
19 non-heal$.ti,ab.
20 fusion.ti,ab.
21 union.ti,ab.
22 heal$.ti,ab.
23 (allograft$ or autograft$).ti,ab.
24 spin$.ti,ab.
25 tibial.ti,ab.
26 or/8-14
27 or/15-25
28 26 and 27
29 limit 28 to humans

Science Citation Index 1945 to week 2 January 2006

1 TS=bone morphogen*
2 TS=osteogen*
3 TS=osteoinduct*
4 TS=bmp or bmp2 or bmp-2 or bmp7 or bmp-7
5 TS=rhbmp or rhbmp2 or rhbmp-2 or rhbmp7 or rhbmp-7
6 TS=rh-bmp or rh-bmp2 or rh-bmp-2 or rh-bmp7 or rh-bmp-7
7 TS=rhop1 or rhop-1
8 TS=op1 or op-1
9 TS=fracture*
10 TS=nonunion or nonunion
11 TS=non-fusion or nonfusion
12 TS=non-heal*
13 TS=fusion
14 TS=union
15 TS=heal*
16 TS=allograft or autograft
17 TS=spin*
18 TS=tibial
19 #8 or #7 or #6 or #5 or #4
20 #18 or #17 or #16 or #15 or #14 or #13 or #12 or #11 or #10 or #9
21 #20 and #19

NeLH on 19 January 2006

Search terms:

- Bmp
- Op-1
- Op1
- Rhop-1
- Rhop1
- Rhbmp
- Rhbmp2
- Rhbmp-2
- Rh-bmp
- Rh-bmp-2
- Rhop-1
- Rhop1
- Nonfusion

- Non-fusion
- Allograft*
- Tibia
- Bone morphogen*
- Osteogen*
- Bmp2
- Bmp-2
- Bmp7
- Bmp-7
- Rhbmp7
- Rhbmp-7
- Rh-bmp-7
- Fracture*
- Nonunion
- Nonunion
- Non-heal*
- Fusion
- Autograft*
- Spin*

Cochrane Library Central 1800 to week 2 January 2006 (all in title and abstract)

1 bone morphogen*
2 osteogen*
3 osteoinduct*
4 protein*
5 factor*
6 polypeptide*
7 poly-peptide*
8 (bone morphogen* or osteogen* or osteoinduct*) next (protein* or factor* or polypeptide* or poly-peptide)
9 bmp or bmp2 or bmp-2 or bmp7 or bmp-7
10 rhbmp, rhbmp2, rhbmp-2, rhbmp7, rhbmp-7
11 rh-bmp, rh-bmp2, rh-bmp-2, rh-bmp7, rh-bmp-7
12 rhop1 or rhop-1
13 op1 or op-1
14 MeSH descriptor Bone Morphogenetic Proteins
15 fracture*
16 MeSH descriptor Fractures
17 Non-union, nonunion
18 non-fusion, nonfusion
19 non-heal*
20 fusion
21 union
22 heal*
23 allograft* or autograft*
24 spin*
25 tibial
26 #8 or #9 or #10 or #11 or #12 or #13 or #14
27 #15 or #16 or (#17 AND or#18) OR #19 or #20 or #21 or #22 or #23 or #24 or #25
28 #26 AND #27

BMP/TGF/RCT and clinical trial filter

MEDLINE (Ovid) 1980 to week 3 January 2006 and EMBASE (Ovid) 1980 to week 3 January 2006

1 bone morphogen$.ti,ab.
2 osteogen$.ti,ab.
3 osteoinduct$.ti,ab.
4 protein$.ti,ab.
5 factor$.ti,ab.
6 polypeptide$.ti,ab.
7 poly-peptide$.ti,ab.
8 ((bone morphogen$ or osteogen$ or osteoinduct$) adj (protein$ or factor$ or polypeptide$ or poly-peptide$)).ti,ab.
9 (BMP or BMP2 or BMP-2 or BMP7 or BMP-7).ti,ab.
10 (rhBMP or rhBMP2 or rhBMP-2 or rhBMP7 or rhBMP-7).ti,ab.
11 (rh-BMP or rh-BMP2 or rh-BMP-2 or rh-BMP7 or rh-BMP-7).ti,ab.
12 (rhop1 or rhop-1).ti,ab.
13 (op1 or op-1).ti,ab.
14 exp Bone Morphogenetic Proteins/
15 fracture$.ti,ab.
16 exp Fractures, Ununited/ or exp Skull Fractures/ or exp Fractures, Malunited/ or exp Zygomatic Fractures/ or exp Orbital Fractures/ or exp Fractures, Bone/ or exp Spinal Fractures/ or exp Femoral Neck Fractures/ or exp Radius Fractures/ or exp Femoral Fractures/ or exp Tibial Fractures/ or exp Maxillary Fractures/ or exp Humeral Fractures/ or exp Ulna Fractures/ or exp Fractures, Compression/ or exp Fractures, Cartilage/ or exp Fractures, Spontaneous/ or exp Hip Fractures/ or exp Shoulder Fractures/ or exp Jaw Fractures/ or exp Mandibular Fractures/ or exp Fractures, Open/ or exp Fractures, Closed/ or exp Tooth Fractures/ or exp Rib Fractures/ or exp Fractures, Stress/ or exp Fractures, Comminuted/
17 (nonunion or nonunion).ti,ab.
18 (non-fusion or nonfusion).ti,ab.
19 non-heal$.ti,ab.
20 fusion.ti,ab.
21 union.ti,ab.
22 (heal or healed or heals or healing).ti,ab.
23 (allograft$ or autograft$).ti,ab.
24 (spine or spinal).ti,ab.
25 tibial.ti,ab.
26 or/8-14
27 or/15-25
28 26 and 27
29 limit 28 to humans
30 bone morphogen$.ti,ab.

31 osteogen$.ti,ab.
32 osteoinduct$.ti,ab.
33 protein$.ti,ab.
34 factor$.ti,ab.
35 polypeptide$.ti,ab.
36 poly-peptide$.ti,ab.
37 ((bone morphogen$ or osteogen$ or osteoinduct$) adj (protein$ or factor$ or polypeptide$ or poly-peptide$)).ti,ab.
38 (BMP or BMP2 or BMP-2 or BMP7 or BMP-7).ti,ab.
39 (rhBMP or rhBMP2 or rhBMP-2 or rhBMP7 or rhBMP-7).ti,ab.
40 (rh-BMP or rh-BMP2 or rh-BMP-2 or rh-BMP7 or rh-BMP-7).ti,ab.
41 (rhop1 or rhop-1).ti,ab.
42 (op1 or op-1).ti,ab.
43 (TGF or TGF-beta or transforming growth factor beta or transforming growth factor).ti,ab.
44 exp Bone Morphogenetic Proteins/
45 fracture$.ti,ab.
46 exp Fractures, Ununited/ or exp Skull Fractures/ or exp Fractures, Malunited/ or exp Zygomatic Fractures/ or exp Orbital Fractures/ or exp Fractures, Bone/ or exp Spinal Fractures/ or exp Femoral Neck Fractures/ or exp Radius Fractures/ or exp Femoral Fractures/ or exp Tibial Fractures/ or exp Maxillary Fractures/ or exp Humeral Fractures/ or exp Ulna Fractures/ or exp Fractures, Compression/ or exp Fractures, Cartilage/ or exp Fractures, Spontaneous/ or exp Hip Fractures/ or exp Shoulder Fractures/ or exp Jaw Fractures/ or exp Mandibular Fractures/ or exp Fractures, Open/ or exp Fractures, Closed/ or exp Tooth Fractures/ or exp Rib Fractures/ or exp Fractures, Stress/ or exp Fractures, Comminuted/
47 (nonunion or nonunion).ti,ab.
48 (non-fusion or nonfusion).ti,ab.
49 non-heal$.ti,ab.
50 fusion.ti,ab.
51 union.ti,ab.
52 (heal or healed or heals or healing).ti,ab.
53 (allograft$ or autograft$).ti,ab.
54 (spine or spinal).ti,ab.
55 tibial.ti,ab.
56 or/37-44
57 or/45-55
58 56 and 57
59 limit 58 to humans
60 59 not 29
61 randomized controlled trial.pt.
62 controlled clinical trial.pt.
63 exp Randomized Controlled Trials/
64 exp Random Allocation/
65 exp Double-Blind Method/
66 exp Single-Blind Method/
67 or/61-66
68 animal/ not human/
"70 exp "Clinical Trial [Publicati"n Type]"/
71 clinical-trial in PT.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
72 (clin$ adj6 trial$).ti,ab.
73 ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
74 ((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ti,ab.
75 exp Placebos/
76 placebo$.ti,ab.
77 random.ti,ab.
78 exp Research Design/
79 or/70-78
80 animal/ not human/
81 79 not (80 or 69)
82 81 and 60
83 Comparative Study/
84 exp Evaluation Studies/
85 exp Follow-Up Studies/
86 exp Prospective Studies/
87 (control$ or prospectiv$ or volunteer$).ti,ab.
88 or/83-87
89 animal/ not human/
90 88 not (89 or 81 or 69)
91 90 and 60
92 from 91 keep 1-10
93 from 82 keep 1-41

MEDLINE (Ovid) 1966 to week 2 November 2006 and EMBASE (Ovid) 1980 to week 2 November 2006

1 bone morphogen$.ti,ab.
2 osteogen$.ti,ab.
3 osteoinduct$.ti,ab.
4 protein$.ti,ab.
5 factor$.ti,ab.
6 polypeptide$.ti,ab.
7 poly-peptide$.ti,ab.
8 ((bone morphogen$ or osteogen$ or osteoinduct$) adj (protein$ or factor$ or polypeptide$ or poly-peptide$)).ti,ab.
9 (BMP or BMP2 or BMP-2 or BMP7 or BMP-7).ti,ab.
10 (rhBMP or rhBMP2 or rhBMP-2 or rhBMP7 or rhBMP-7).ti,ab.
11 (rh-BMP or rh-BMP2 or rh-BMP-2 or rh-BMP7 or rh-BMP-7).ti,ab.
12 (rhop1 or rhop-1).ti,ab.
13 (op1 or op-1).ti,ab.
14 exp Bone Morphogenetic Proteins/

15 fracture$.ti,ab.
16 exp Fractures, Ununited/ or exp Skull Fractures/ or exp Fractures, Malunited/ or exp Zygomatic Fractures/ or exp Orbital Fractures/ or exp Fractures, Bone/ or exp Spinal Fractures/ or exp Femoral Neck Fractures/ or exp Radius Fractures/ or exp Femoral Fractures/ or exp Tibial Fractures/ or exp Maxillary Fractures/ or exp Humeral Fractures/ or exp Ulna Fractures/ or exp Fractures, Compression/ or exp Fractures, Cartilage/ or exp Fractures, Spontaneous/ or exp Hip Fractures/ or exp Shoulder Fractures/ or exp Jaw Fractures/ or exp Mandibular Fractures/ or exp Fractures, Open/ or exp Fractures, Closed/ or exp Tooth Fractures/ or exp Rib Fractures/ or exp Fractures, Stress/ or exp Fractures, Comminuted/
17 (nonunion or non-union).ti,ab.
18 (non-fusion or nonfusion).ti,ab.
19 non-heal$.ti,ab.
20 fusion.ti,ab.
21 union.ti,ab.
22 (heal or healed or heals or healing).ti,ab.
23 (allograft$ or autograft$).ti,ab.
24 spin$.ti,ab.
25 tibial.ti,ab.
26 or/8-14
27 26 and (or/15-25)
28 Randomized controlled trial.pt.
29 Controlled clinical trial.pt.
30 exp Randomized Controlled Trials/
31 exp Random Allocation/
32 exp Double-Blind Method/
33 exp Single-Blind Method/
34 or/28-33
35 animal/ not human/
36 34 not 35
37 exp "Clinical Trial [Publication Type]"/
38 clinical-trial in PT.mp.
39 (clin$ adj6 trial$).ti,ab.
40 ((singl$ or doubl$ or treb$ or trip$) adj6 (blind$ or mask$)).mp.
41 exp Placebos/
42 placebo$.ti,ab.
43 random.ti,ab.
44 exp Research Design/
45 or/37-44
46 animal/ not human/
47 45 not (46 or 36)
48 Comparative Study/
49 exp Evaluation Studies/
50 exp Follow-Up Studies/
51 exp Prospective Studies/
52 (control$ or prospectiv$ or volunteer$).ti,ab.
53 or/ 48-52
54 animal/ not human/
55 53 not (54 or 47 or 32)
56 27 and ((or/47,55) or 36)

Appendix 2

Effectiveness data extraction forms

RCT data extraction form

Reviewer: _____ Date: _____

Author (year)			
Title and source			
Study objectives			
Study characteristics			
Country conducted			
Patient diagnosis			
Surgical interventions			
Inclusion and exclusion criteria			
	Intervention A	**Intervention B**	**Control**
Interventions (mode of delivery, dose, duration, etc.)			
No. of patients			
Age			
M/F			
Weight			
Length of follow-up			
Principal outcome measure			
Other outcome measures			

Study design and quality (using the checklist Appendix 4)			
1. Randomisation method			
Allocation concealment?			
2. Blinding			
3. Baseline comparability			
4. Inclusion/exclusion criteria explicit?			
5. Intention-to-treat analysis?			
6. Drop-outs			
Patient withdrawals			
Reasons			
Total drop-outs:	**Intervention A**	**Intervention B**	**Control**
Study results (including QoL and any adverse effects)			
Outcome measures	**Intervention A**	**Intervention B**	**Control**
Investigators' conclusions			
Reviewer's comments and notes			
Funding source			
References checked			

Non-RCT data extraction form

Reviewer: _____ Date: _____

Author (year)			
Title and source			
Country conducted			
Study type			
Study objectives			
Study characteristics			
Patient diagnosis			
Surgical intervention			
	BMP used	**Concentration**	**Carrier**
Inclusion/exclusion criteria			
Follow-up length			
Outcomes measured			
Population characteristics			
Number of patients			
Age			
M/F			
Weigh			
Quality assessment			
Explicit population definition			
Similar prognostic baseline			
Appropriate assessment of outcomes			
Study results			
Outcome measures	Outcome	Statistical significance	

Investigator's conclusions	
Reviewer's comments and notes	
Funding source	
References checked	

Appendix 3

Cost-effectiveness data extraction form

Reviewer: _____ Date: _____

Author (year)		
Title and source		
Study objectives		
Study characteristics		
Economic study type (cost-effectiveness analysis; cost–utility analysis; cost–benefit analysis)		
Setting:		
Practice setting		
Geographical location		
Dates data collected:		
Effectiveness analysis		
Resources used		
Prices used		
Sources of effectiveness data		
Evidence from (single study, expert opinion, peer reviewed literature)		
Modelling used (if so, type)		
Clinical evidence:	Study 1	Study 2
Author		
Title		
Study design		
Allocation method		
Trial/study size		
Follow-up duration		
Loss to follow-up		
Blinding methods (if any)		

Primary outcomes	
How primary outcomes were assessed	
Trial summary	
Confidence intervals	
Clinical conclusions	
Expert opinion:	
Methods used to derive estimates of effectiveness	
Estimates and assumptions made	
Economic analysis	
Health benefit measured	
Basic method of valuation of intervention	
When valued	
Valuation tool used	
Costs	
Were resource quantities and costs reported separately?	
Whose direct costs were analysed?	
Source of direct cost data	
Date which price data refer to	
Estimation of prices from: (a guess, based on data, derived using modelling techniques)	
Costs stated:	
Discounting relevant?	
Cost reported was (marginal, incremental or average)	
Differential costing used	

Adjustments made to costs (i.e. new technology cost)		
Costs adjusted for inflation (if so, method)		
Statistical analysis		
How resource use and/or costs were treated (i.e. point estimates or in a stochastic manner) give details		
Descriptive statistics (if given, provide methodology)		
Sensitivity analysis		
Parameters (discount rate, estimates of effectiveness or cost data, etc.)		
Areas of uncertainty investigated		
Method used		
Results		
Estimated benefits	Reported benefits	*p*-Value and/or confidence interval
Duration of benefits		
Side-effects considered in economic analysis		
Total intervention cost and discount rate (in original currency)		
Total comparator cost and discount rate (in original currency)		
Statistical analysis results		
Currency conversion		
Incremental quantities/costs (discounted and not discounted)		
Duration of intervention quantities/costs		
Duration of comparator quantities/costs		
How estimated benefits and costs were combined		

Incremental analysis performed?	
Summary findings	
Any differences in cost-effectiveness of sub-populations?	
Sensitive parameters	
Authors' comments on sensitive parameters and variation	
Statistical testing results	
Authors' conclusions	
Comments	
Source of funding	

Appendix 4

Checklist for quality assessment

Quality assessment coding manual for RCTs

(yes, no, unknown/unclear, not applicable)

1. *Was the randomisation method adequate?*
   Yes: Random number tables
   Computer and central office
   Coded packages
   Serially numbered sealed opaque envelopes
   No: Alternation
   Case record numbers, birth dates, or similar approaches
   Unknown/Unclear: only term 'randomised' or 'randomly allocated'

2. *Were the outcome assessors blinded?*
   Yes: There was a separate blinded panel of assessors or independent assessor
   No: No assessors were blinded
   Unknown/Unclear: No statements on procedures and not deducible

3. *Did patients have similar prognostic baselines?*
   Yes: Groups are demonstrably comparable
   No: Patient groups are not comparable

4. *Were inclusion criteria explicitly stated?*
   Yes: Clearly defined inclusion criteria
   No: Inclusion criteria not clearly defined, unable to determine how sample was made up
   Unknown/Unclear: Inadequately defined

5. *Was an intention-to-treat analysis performed?*
   Yes: Intention-to-treat analysis performed according to ITT principle
   No: No intention-to-treat analysis performed
   Unknown/Unclear: Intention-to-treat analysis not performed to ITT principle

6. *Loss to follow-up*
   Yes: Number of randomised stated. Numbers lost stated (or calculable) from each group with reasons
   Partial: Numbers stated, but no reasons
   No: Number randomised not stated or specified
   Unknown: Not mentioned

Non-RCT quality assessment form

(yes, no, unknown/unclear, not applicable)

1. Explicit group definition?
   Yes: There is a clear description of the group characteristics
   No: The group is not clearly described

2. Similar prognostic baselines?
   Yes: Patients within group are comparable
   No: Patients within group are not comparable
   Unknown/Unclear: Unsure whether patient group is comparable

3. Appropriate assessment of outcomes?
   Yes: Independent assessor(s) used to determine outcome
   No: No independent assessor(s) used
   Unknown/Unclear: No statements on outcome assessment procedure or not deducible

4. Lost to follow-up?
   Yes: Number lost to follow-up and reasons described
   No: Number lost to follow-up not given
   Partial: Number stated but no reasons given

Checklist for assessment of methodological quality in economic studies

Item		Yes	No	Not clear	Not appropriate
Study design					
1	The research question is stated	☐	☐	☐	
2	The economic importance of the research question is stated	☐	☐	☐	
3	The viewpoint(s) of the analysis are clearly stated and justified	☐	☐	☐	
4	The rationale for choosing alternative programmes or interventions compared is stated	☐	☐	☐	
5	The alternatives being compared are clearly described	☐	☐	☐	
6	The form of economic evaluation used is stated	☐	☐	☐	
7	The choice of form of economic evaluation is justified in relation to the questions addressed	☐	☐	☐	
Data collection			☐	☐	
8	The source(s) of effectiveness estimates used are stated	☐	☐	☐	
9	Details of the design and results of effectiveness study are given (if based on a single study)	☐	☐	☐	☐
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	☐	☐	☐	☐
11	The primary outcome measure(s) for the economic evaluation are clearly stated	☐	☐	☐	
12	Methods to value benefits are stated	☐	☐	☐	☐
13	Details of the subjects from whom valuations were obtained were given	☐	☐	☐	☐
14	Productivity changes (if included) are reported separately	☐	☐	☐	☐
15	The relevance of productivity changes to the study question is discussed	☐	☐	☐	☐
16	Quantities of resource use are reported separately from their unit costs	☐	☐	☐	
17	Methods for the estimation of quantities and unit costs are described	☐	☐	☐	
18	Currency and price data are recorded	☐	☐	☐	
19	Details of currency of price adjustments for inflation or currency conversion are given	☐	☐	☐	
20	Details of any model used are given	☐	☐	☐	☐
21	The choice of model used and the key parameters on which it is based are justified.	☐	☐	☐	☐
Analysis and interpretation of results			☐	☐	
22	Time horizon of costs and benefits is stated	☐	☐	☐	
23	The discount rate(s) is stated	☐	☐	☐	☐
24	The choice of discount rate(s) is justified	☐	☐	☐	☐
25	An explanation is given if costs and benefits are not discounted	☐	☐	☐	☐
26	Details of statistical tests and confidence intervals are given for stochastic data	☐	☐	☐	☐
27	The approach to sensitivity analysis is given	☐	☐	☐	☐
28	The choice of variables for sensitivity analysis is justified	☐	☐	☐	☐
29	The ranges over which the variables are varied are justified	☐	☐	☐	☐
30	Relevant alternatives are compared	☐	☐	☐	☐
31	Incremental analysis is reported	☐	☐	☐	☐
32	Major outcomes are presented in a disaggregated as well as aggregated form	☐	☐	☐	
33	The answer to the study question is given	☐	☐	☐	
34	Conclusions follow from the data reported	☐	☐	☐	
35	Conclusions are accompanied by the appropriate caveats	☐	☐	☐	

Source: Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. *BMJ* 1996;**313**:275–83.

Appendix 5

List of excluded studies

Paper	Reason for exclusion
Alden TD, Varady P, Kallmes DF, Jane JA Jr, Helm GA. Bone morphogenetic protein gene therapy. *Spine* 2002;**27**(16 Suppl 1):S87–93.	Review
An HS, Phillips FM. Editorial. Are spine biologics the future in spinal surgery? *Spine J* 2005;**5**(6 Suppl):207S–8S.	Review
Anderson DG, Andersson GBJ, Boden SD, Damien C, Ebara S, Helm G, *et al*. Summary statement: clinical BMP programs. *Spine* 2002;27(16 Suppl.):S49.	Review
Bailon-Plaza A, van der Meulen MC. A mathematical framework to study the effects of growth factor influences on fracture healing. *J Theor Biol* 2001;**212**:191–209	Mathematical model
Baltzer AWA, Lieberman JR. Regional gene therapy to enhance bone repair. *Gene Ther* 2004;**11**:344–50.	Review
Becker W, Clokie C, Sennerby L, Urist MR, Becker BE. Histologic findings after implantation and evaluation of different grafting materials and titanium micro screws into extraction sockets: case reports. *J Periodontol* 1998;**69**:414–21.	Diagnosis (extraction socket)
Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine* 2002;**27**(16 Suppl 1):S26–31.	Review
Boden SD. The ABCs of BMPs. *Orthop Nurs* 2005;**24**:49–52; quiz 53-4.	Review
Burkus JK, Schuler TC, Gornet MF, Zdeblick TA. Anterior lumbar interbody fusion for the management of chronic lower back pain: current strategies and concepts. *Orthop Clin North Am* 2004;**35**:25.	Review
Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. *Spine J* 2005;**5**(6 Suppl):240S–9S.	Review
Chin M, Ng T, Tom WK, Carstens M. Repair of alveolar clefts with recombinant human bone morphogenetic protein (rhBMP-2) in patients with clefts. *J Craniofac Surg* 2005;**16**:778–89.	Diagnosis (alveolar clefts)
Cochran DL, Jones AA, Lilly LC, Fiorellini JP, Howell H. Evaluation of recombinant human bone morphogenetic protein-2 in oral applications including the use of endosseous implants: 3-year results of a pilot study in humans. *J Periodontol* 2000;**71**:1241–57.	Diagnosis (extraction sites)
Csimma C, Swiontkowski MF. Large clinical trials in musculoskeletal trauma: are they possible? Lessons learned from the international study of the use of rhBMP-2 in open tibial fractures. *J Bone Joint Surg Am* 2005;**87**:218–22.	Review
De Biase P, Capanna R. Clinical applications of BMP. *Injury* 2005;**36**:43–6.	Review
Derner R, Anderson AC. The bone morphogenic protein. *Clin Podiatr Med Surg* 2005;**22**:607–18.	Review
Dickman CA. 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: point of view. *Spine* 2003;**28**:1225.	Point of view
Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future development. *J Bone Joint Surg Am* 2003;**85** Suppl 3:82–8.	Review
Geesink RGT, Hoefnagels NHM, Bulstra SK. Bone healing with OP-1 device in a human model. *Bone* 1999;**24**:423.	Unable to find in journal (does not exist)
Geesink RG, Hoefnagels NH, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. *J Bone Joint Surg* 1999;**81**:710–18.	Diagnosis (critically sized defect)
Giannoudis PV, Tzioupis C. Clinical applications of BMP-7 – the UK perspective. *Injury* 2005;**36**:47–50.	Retrospective analysis of included studies

continued

Paper	Reason for exclusion
Granjeiro JM, Oliveira RC, Bustos-Valenzuela JC, Sogayar MC, Taga R. Bone morphogenetic proteins: From structure to clinical use. *Braz J Med Biol Res* 2005;**38**:1463–73.	Review
Gupta MC, Maitra S. Bone grafts and bone morphogenetic proteins in spine fusion. *Cell Tissue Banking* 2002;**3**:255–267.	Review
Gupta MC, Khan SN. Application of bone morphogenetic proteins in spinal fusion. *Cytokine Growth Factor Rev* 2005;**16**(3 Spec. Iss.):347–55.	Review
Harwood PJ, Giannoudis PV. Application of bone morphogenetic proteins in orthopaedic practice: their efficacy and side effects. *Expert Opin Drug Saf* 2005;**4**:75–89.	Review
Jones AL. Recombinant human bone morphogenic protein-2 in fracture care. *J Orthop Trauma* 2005;**19**:S23–5.	Inadequate data for extraction (cost analysis)
Khan SN, Lane JM. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in orthopaedic applications. *Expert Opin Biol Ther* 2004;**4**:741–8.	Review
Kim DH, Jenis L, Berta SC, Vaccaro AR. Bone graft alternatives in spinal fusion surgery. *Curr Opin Orthop* 2003;**14**:127–37.	Review
Kirker-Head CA. Development and application of bone morphogenetic proteins for the enhancement of bone healing. *J Orthop Traumatol* 2005;**6**:1–9.	Review
Lieberman JR, Conduah A, Urist MR. Treatment of osteonecrosis of the femoral head with core decompression and human bone morphogenetic protein. *Clin Orthop Relat Res* 2004:139–45.	Diagnosis (hip osteonecrosis)
Meisel HJ. Cost variances in G-DRG groups. The example of rhBMP-2 in spine fusion surgery. *Value Health* 2004;**7**:712.	Inadequate data for extraction (abstract of cost study)
McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. *Spine* 2002;**27**(16 Suppl 1):S66–85.	Review
McKee MD. Recombinant human bone morphogenic protein-7 – applications for clinical trauma. *J Orthop Trauma* 2005;**19**:S26–8.	2006 data requested from author
McQueen MM, Hajducka C, Court-Brown CM. A comparison of rhBMP-7 (ossigraft) and autogenous graft for treatment of metaphyseal defects after osteotomy of the distal radius. In: Orthopaedic Trauma Association; Salt Lake City, UT: 2003.	Unable to extract data (RCT)
Mont MA, Ragland PS, Biggins B, Friedlaender G, Patel T, Cook S, *et al*. Use of bone morphogenetic proteins for musculoskeletal applications. An overview. *J Bone Joint Surg Am* 2004;**86** Suppl 2:41–55.	Review
Obert L, Deschaseaux F, Garbuio P. Critical analysis and efficacy of BMPs in long bones non-union. *Injury* 2005;**36**:38–42.	Review
Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. *Spine* 2002;**27**(16 Suppl 1):S40–8.	Review
Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG, *et al*. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes. *J Neurosurg Spine* 2005;**2**:733–6.	Review
Samartzis D, Khanna N, Shen FH, An HS. Update on bone morphogenetic proteins and their application in spine surgery. *J Am Coll Surg* 2005;**200**:236–48.	Review
Sandhu HS, Anderson DG, Andersson GBJ, Boden SD, Damien C, Ebara S, *et al*. Summary statement: Alternative delivery by gene therapy and cost justification of bone morphogenetic proteins for spine fusion. *Spine* 2002;27(16 Suppl):S86.	Comment
Sandhu H. Spinal fusion using bone morphogenetic proteins. *Orthopedics* 2004;**27**:717–18.	Review
Sasso RC, LeHuec JC, Shaffrey C. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion – a prospective patient satisfaction outcome assessment. *J Spinal Disord Tech* 2005;**18**:S77–81.	Contacted author about unreferenced studies
Seeherman H, Li R, Li XJ, Wozney J. Injectable rhBMP-2/CPM paste for closed fracture and minimally invasive orthopaedic repairs. *J Musculoskel Neuronal Interact* 2003;**3**:317–19.	Animal study

continued

Paper	Reason for exclusion
Starr AJ. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures. *J Bone Joint Surg Am* 2003;**85**:2049; author replies, 2049–50.	Comment
Szpalski M, Gunzburg R. Recombinant human bone morphogenetic protein-2: a novel osteoinductive alternative to autogenous bone graft? *Acta Orthop Belg* 2005;**71**:133–48.	Review
Termaat MF, Den Boer FC, Bakker FC, Patka P, Haarman HJTM. Bone morphogenetic proteins. Development and clinical efficacy in the treatment of fractures and bone defects. *J Bone Joint Surg Am* 2005;**87**:1367–78.	Review
Termaat MF, Den Boer FC, Barker FC, Patka P, Haarman H. Current concepts review bone morphogenetic proteins development and clinical efficacy in the treatment of fractures and bone defects. *J Bone Joint Surg Am* 2005;**87**:1367–78.	Review
Vaccaro AR, Chiba K, Heller JG, Patel TC, Thalgott JS, Truumees E, *et al*. Bone grafting alternatives in spinal surgery. *Spine J* 2002;**2**:206–15.	Review
Valentin-Opran A, Wozney J, Csimma C, Lilly L, Riedel GE. Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Orthop Relat Res* 2002:110–20.	Review
Yin S. Use of OP-1 (BMP-7) in human tibial nonunions. *Bone* 1999;**24**:423.	Not in journal referenced

Appendix 6

RCT fracture study characteristics

Study	Country	Length of follow-up (months)	Sample size		Patient diagnosis	Fracture severity/degree		Surgical intervention	Mean age (years)	Male %	Funding source
			Intervention	Control		Intervention	Control				
Scaphoid non-unions											
Bilic, 2006[58]	Croatia	24	(6, 6)	6	Scaphoid non-union	NR	NR	NR	23/19/22	NR	NR
Non-unions											
Chen, 2000[59]	China	19	30	(20, 30)	Non-union tibia fracture	NR	NR	NR	35 (25–50)	72.5	Government
Cook, 1999[60]	USA	9	14	16	Tibial non-union	NR	NR	Reamed IM nails	NR	NR	Industry (Stryker)
Friedlaender, 2001[9,10]	USA	9	63	61	Tibial non-union	30% grade III, IIIA, IIIB or IIIC	36% grade III, IIIA, IIIB or IIIC	IM nail fixation	38/31	71.8	Industry (Stryker)
Perry, 1997[64]	USA	Minimum of 12	20	21	Tibial non-union	NR	NR	IM nailing	NR	NR	NR
Open tibial fractures											
Govender, 1998[61]	11 countries	12	(151, 149)	150	Open tibial fracture, of which the main component was diaphyseal	*Intervention A:* Stratum A I: 29 (20%) II: 51 (35%) IIIA: 43 (30%) Stratum IIIB: 22 (15%) *Intervention B:* Stratum A I: 32 (22%) II: 50 (34%) IIIA: 38 (26%) Stratum IIIB: 25 (17%)	Stratum A: I: 34 (23%) II: 54 (37%) IIIA: 42 (29%) Stratum IIIB: 17 (12%)	IM nail fixation and routine soft-tissue management	31/33/37	80.9	Industry (Wyeth)
McKee, 2002[63]	USA	6	62	62	Open tibial shaft fractures	NR	NR	Statically locked IM nailing	NR	NR	Industry (Stryker)

continued

Study	Country	Length of follow-up (months)	Sample size		Patient diagnosis	Fracture severity/degree		Surgical intervention	Mean age (years)	Male %	Funding source
			Intervention	Control		Intervention	Control				
Open and closed tibial fractures											
Jones, 2006[28]	USA	12	15	15	Diaphyseal tibia fracture (open or closed) with residual fracture defect	13 open and 2 closed fractures Grades: I or II: 2 (15%) IIIA: 8 (62%) IIIB: 3 (23%)	14 open and 1 closed fracture Grades: I or II: 1 (7%) IIIA: 9 (64%) IIIB: 4 (29%)	Staged reconstruction of tibia with cortical defects	36/38	90	Industry (Wyeth)
Closed tibial fractures											
Maniscalco, 2002[62]	Italy	7 (mean)	7	7	Closed fracture of the tibial shaft	Type A1 or A2 (numbers not specified)	Type A1 or A2 (numbers not specified)	Monolateral external fixator treatment	47/40	92.9	NR

Appendix 7

RCT fracture quality assessment

Study	Randomisation	Allocation concealment	Blinding	Baseline comparability	Explicit inclusion/ exclusion criteria	ITT analysis	Drop-outs		Reasons for drop-outs given	Other notes
							Intervention	Control		
Scaphoid non-unions										
Bilic, 2006[58]	Computer generated	NR	2 assessors blinded	Similar	Yes	No	0/1	0	No	
Tibial non-unions										
Chen, 2000[59]	Unclear	Unknown	No	Unclear	No	Unable to determine	NR	NR	NR	
Cook, 1999[60]	Unclear	Unknown	No assessors blinded	Population characteristics not reported	No	NA	0	0	NA	
Friedlaender, 2001[9,10]	Unclear	Unknown	3 musculo-skeletal radiologists assessed radiographs	No. Significantly higher number atrophic of non-unions in intervention group	Yes	NA	0	0	NA	
Perry, 1997[64]	Unclear	Unknown	Unknown	Unclear	No	NA	0	0	NA	Abstract only
Open tibial fractures										
Govender, 2002[61]	Central, 24-hour automated system	Adequate based on randomisation method	Independent radiology panel	No, statistically significant difference among ages	No	Yes	6.0%/5.4%	8%	Yes	
McKee, 2002[63]	Unclear	Unknown	Not reported	Unclear	No	Unable to determine	NR	NR	NR	Abstract only
Open and closed tibial fractures										
Jones, 2006[28]	Unclear	Unknown	Blinded independent musculoskeletal radiologist reviewed digitised images of radiographs	Similar		Yes	Yes	13.3%	26.7%	No
Closed tibial fractures										
Maniscalco, 2002[62]	Unclear	Unknown	No assessors blinded	Similar	Yes	NA	0	0	NA	Follow-up length unclear

Appendix 8

RCT fracture adverse events

Study	Adverse events	
	Intervention	**Control**
Tibial non-unions		
Friedlaender, 2001[9,10]	8 patients had lower leg arthralgia 8 patients had pain at multiple sites 2 patients had acute or subacute osteomyelitis of the lower leg[a] 31 patients had pyrexia 5 patients had oedema 25 patients had mechanical complication of the internal orthopaedic device 5 patients had haematoma that complicated a procedure 14 patients had postoperative infection 56 patients had mild pain at fracture site	5 patients had lower leg arthralgia 9 patients had pain at multiple sites 13 patients had acute or subacute osteomyelitis of the lower leg[a] 28 patients had pyrexia 7 patients had oedema 34 patients had mechanical complications of the internal orthopaedic device 8 patients had haematomas that complicated a procedure 12 patients had postoperative infection 55 patients had mild pain at fracture site All patients had pain at donor site (80% judged pain mild or moderate) 13% had persistent donor site pain at 12 months
Perry, 1997[64]	NR	Severe but temporary pain at autograft site
Open tibial fractures		
Govender, 1998[61]	17% (25/145) of the intervention A group and 11% (16/145) of intervention B had hardware failure[a] 15% (12/80) of intervention A and 21% (15/70) of intervention B of patients classed as having Gustilo–Anderson type I and II had fracture site infections 29% (19/65) of intervention A and 24% (15/63) of intervention B patients with the Gustilo–Anderson type IIIA and IIIB developed fracture site infection[a] 67% (97/145) intervention A and 68% (98/145) intervention B patients had overall pain[a]	22% (32/147) had hardware failure[a] 15% (13/88) of patients classed as having Gustilo–Anderson type I and II had fracture site infections 44% (26/59) patients with the Gustilo–Anderson type IIIA and IIIB developed fracture site infection[a] 79% (116/147) patients had overall pain[a]
McKee 2002[63]	Only reported that no events were related to BMP	
Open and closed tibial fractures		
Jones, 2006[28]	12 patients had soft tissue swelling 5 patients had epidermal erythema 2 patients[b] developed infection that required surgical intervention, which failed to unite 1 patient[b] developed infection 1 patient had heterotopic bone formation	9 patients had soft tissue swelling 1 patient[b] developed infection that required surgical intervention, which failed to unite 2 patients had hardware failure 14 patients had acute-onset iliac crest donor site pain 3 patients developed pustules or drainage which lasted up to 2 weeks

continued

Study	Adverse events	
	Intervention	**Control**
Closed tibial fractures		
Maniscalco, 2002[62]	1 patient had calcification of the tibio-fibular ligament	1 patient fell 1 month after fixator removal and refractured the bone, which was treated with a cast

[a] Authors state that the relationship is statistically significant.
[b] Patients with Gustilo–Anderson type-III.

Appendix 9

Fracture case series and case report findings

Number and characteristics of included studies

One case report, by Jones and colleagues[106] and 14 case series, by Bai and colleagues,[107] Benke and Gorecki,[108] Bong and colleagues,[109] Delloye and colleagues,[110] Dimitriou and colleagues,[111] Johnson and Urist (1998),[112] Johnson and Urist (2000),[113] Johnson and colleagues (1988),[123] Johnson and colleagues (1988),[114] Johnson and colleagues (1990)[115,116] Johnson and colleagues (1992),[117] Kujala and colleagues (2002),[118] Kujala and colleagues (2004)[119] Riedel and Valentin-Opran,[120] were included. In addition three abstracts from conference proceedings, by Kuklo and colleagues,[121] McKee and colleagues,[52] and Schwartz and Hicks[122] were also included.

Appendix 10 shows the main characteristics of the included studies. Thirteen of the studies were conducted in the USA. The remaining studies were conducted in England,[111] Germany,[108] Finland,[118] China,[107] and Belgium and the USA.[110] Of the studies that reported their funding source, three[52,109,120] were sponsored by industry and two stated that they received no benefits from any related commercial party.[106,111] The remaining 13 studies did not specify their funding source.

Four of the studies included patients with non-unions of the femur.[112–114,122] The remaining studies included non-unions of the tibia ($n = 4$), scaphoid ($n = 2$), humerus ($n = 1$), ulnar ($n = 1$) and a variety of different non-unions ($n = 8$). Eleven of the included studies performed some type of internal fixation. Another study[121] performed both external and internal fixation. Two studies performed one-stage lengthening[112,113] and five studies did not clearly state their surgical methods.

The study sizes ranged from one patient to 653 patients. The follow-up lengths ranged from 3 months to six years and the mean ages ranged from 16 to 56.6 years.

Quality

Table 37 shows the quality assessment of the included studies. Fifteen of the studies clearly described their population. Nine of the studies had similar patient populations. Only one study stated that an independent assessor was used for outcome assessment. The Dimitriou study[111] gave the number and reasons for patients lost to follow-up. Two studies[108,113] gave only the numbers of patients lost and two[109,121] did not report on whether any patients were lost to follow-up. The remaining 11 studies did not lose any patients to follow-up.

Interventions

Appendix 11 shows the interventions used in the non-union studies.

Two studies[108,109] used BMP-7 on collagen granules at a dose of 3.5 mg. The Dimitriou study[111] also used BMP-7 at a dose of 3.5 mg but did not report the carrier used. Two studies[52,124] used rhBMP-7, but did not report the carrier or dose. Two studies[110,120] used rhBMP-2 on a collagen sponge at doses ranging from 3.4 to 12 mg. One study[121] used rhBMP-2 but did not specify the carrier or concentration used. Two studies[118,119] used bovine BMP on a collagen sponge with doses ranging from 2 to 5 mg/cm^3. Another study,[107] used bovine BMP on a plaster of Paris carrier with a concentration range of 50–200 mg. The remaining seven studies used human BMP (hBMP), a BMP composite thought to contain mostly BMP-2 and BMP-7, at doses between 50 and 100 mg, where reported. The carrier most used for hBMP was non-collagenous proteins ($n = 5$). Also used as a carrier were allogenic, autolysed antigen-free cortical bone ($n = 1$) and gelatine capsules ($n = 1$). The case study, which used 50 mg of hBMP, also fixed the scaphoid with a K-wire and the patient was immobilised in a cast for 12 weeks.

In 12 of the studies, an additional bone graft or bone substitute was used in all or part of the patient population. This included allograft bone, autograft bone or demineralised bone matrix (DBM). In the Delloye study,[110] patients also received adjuvant chemotherapy and/or radiation. Two studies[118,119] included biocoral frames in their interventions.

TABLE 37 *Fracture case series and case report quality*

Study	Explicit population definition	Similar prognostic baseline	Appropriate outcome assessment	Number and reasons lost to follow-up
Bai, 1996[107]	Yes	Yes	No	NA
Benke and Gorecki, 2004[108]	No	No, different non-union sites	No	Partial
Bong, 2005[109]	Yes	Yes	Yes	No
Delloye, 2004[110]	Yes	No, different diagnoses and cancers	No	NA
Dimitriou, 2005[111]	Yes	No, different non-union sites	No	Yes
Johnson and Urist, 1998[112]	Yes	Yes	No	NA
Johnson and Urist, 2000[113]	Yes	No, different diagnoses	No	Partial
Johnson, 1988[123]	Yes	Yes	No	NA
Johnson, 1988[114]	Yes	Yes	No	NA
Johnson, 1990[115,116]	Yes	Yes	No	NA
Johnson, 1992[117]	Yes	No, different diagnoses	No	NA
Jones, 2005[106]	Yes	NA	No	NA
Kujala, 2004[119]	Yes	Yes	No	NA
Kujala, 2002[118]	Yes	No, different non-union sites and patient with HIV	No	NA
Kuklo, 2005[121]	Yes	No, different fracture severities requiring different surgical procedures	NR	No
McKee, 2002[52]	No	Yes	Unclear	NA
Riedel and Valentin-Opran, 1999[120]	Yes	Yes	No	NA
Schwartz and Hicks, 2006[122]	No	No, different fracture sites	NR	NA

The follow-up times ranged from 3 months to 6 years. These extremely variable follow-up times could have meant that for those studies with shorter follow-up times, patients that went on to heal later were not accounted for. All but two studies[109,120] did not determine a follow-up length prior to the study. There were some remarkable differences in the baseline characteristics of patients, one of which is the number of previous procedures performed on the fracture. Eight studies reported this and it ranged from zero to as many as 14 previous procedures per patient.

Findings from fracture case series and case report

Radiographic union results

Appendix 12 reports the radiographic union success as defined in the study. It is reported using the ITT basis where possible, meaning that drop-outs are considered treatment failures. It also gives any reported mean times to union.

Eight studies[106,107,109,112,114,115,123,125] reported a successful union rate of 90% or higher. Five studies[52,111,113,117,122,124] reported a union success

TABLE 38 *Johnson[114] anatomical grading*

	0	1	2	3	4
Anatomic (A)	Pseudoarthrosis	Unilateral pseudoarthrosis	Insufficient unilateral bone mass	Contiguous union without hypertrophy	Solid union of the fracture site
Economic (E)	Complete invalid	No gainful employment	Able to work but did not return to previous occupation	Returned to previous occupation on a part-time or limited status	Returned to previous occupation without restrictions
Functional (F)	Motion at the fracture site	Level of pain is same as before operation but able to perform all daily tasks of living	Occasional extremity pain and able to perform activities of daily living	No pain and able to perform all activities except sports	Complete recovery, no recurrent episodes of pain and unrestricted activity

rate between 80 and 89%. Two studies[108,120] reported a union success rate of 75%. Kuklo[121] reported a union rate of 63%. Another study[118] reported a success rate of 20% and the remaining study[110] reported a 0% union success rate. In the Kujala (2002)[118] and Delloye[110] studies, the patient populations had a decreased likelihood of fracture healing due to previous bone tumours[110] and sclerosis and long delay from injury to operation (average of 7 years).[118]

The definitions of union used were considerably variable. Four studies[111,112,119,124] included bone bridging in their definition. The case report by Jones and colleagues[106] described success as "signs of bony healing" and the Delloye study[110] referred to Mankin's criteria.[126] Johnson[114] used an anatomical grading scale to assess union (*Table 38*). For the remaining studies, there was no clear description of union success. All of the studies used standard radiographs to assess union success except for the Jones case study,[106] which used radiographs and CT scans.

The mean time to union was reported in 13 of the 18 studies. The mean time to union ranged from 6 weeks to 8.4 months.

Clinical and other outcomes

Appendix 13 reports any clinical or other reported outcomes given.

Nine studies[52,108,109,111,118–120,122,124] did not report any clinical outcomes. Of those that did, the most common was the Johnson and Urist method of anatomical grading, which included three grades; anatomic, economic and functional (see *Table 38* for descriptions). Nevertheless, the preoperative grades were not reported and it is therefore impossible to determine whether any improvements had occurred. Union was seen at 12 weeks after K-wire removal in the case study patient and he regained full motion in his wrist by 5 months.

Another reported outcome was the antibody levels to BMP or bovine collagen. In one[120] of the two studies that reported these outcomes, there was a transient positive response to rhBMP-2 in two patients. In the other study[110] there was no response to rhBMP-2 in three of the three patients tested and a low antibody titre to bovine collagen in one patient. Finally, the other outcome that was frequently reported is the number of patients who returned to work. However, this was of little importance as the authors did not report the number of patients who were able to work prior to surgery.

Secondary procedures and adverse events results

Appendix 14 shows the details of any secondary procedures or adverse events described in the studies.

Four studies[106,109,115,119] reported that no additional surgical procedures were done, and eight studies[110–114,117,120,123] reported conducting secondary surgical interventions, mostly repeating fixation.

Summary

There were 17 case series and one case report on the impact on BMP treatment on healing of fractures (see Appendix 10 for a descriptive summary). These studies were small and suffered

from several limitations in their designs. Of particular concern is the lack of a standard definition of the primary outcome and considerably different diagnoses. No concrete evidence can be obtained from these studies on the effectiveness of BMP treatment as many patients had extreme co-morbidities, highly variable diagnoses and lack of a valid control.

Appendix 10

Fracture case series and case report study characteristics

Study	Country	Study type	Study size	Length of follow-up (months)	Average no. of previous procedures	Patient diagnosis	Surgical intervention	Mean age	Male %	Funding source
Bai, 1996[107]	China	Case series	16	18–39	1–4 (24 total)	Roentgenographic discontinued gaps with abnormal mobility and pain at fracture site	Internal fixation of non-union	37 (15–75)	67.8	NR
Benke and Gorecki, 2004[108]	Germany	Case series	8	3	NR	Non-unions of long bones (6), delayed bone formation during distraction osteogenesis (1) and non-union of the neck of the femur (1)	BMP-7 only (3), plate fixation with BMP-7 (1), exchange of IM nail (1) or nail plate (2), or BMP-7 IM (1)	NR	NR	NR
Bong, 2005[109]	USA	Case series	23	9	NR	Humeral non-unions	Plate and screw or IM nail fixation with allograft, autograft or DBM with rhBMP-7 and type I collagen	56.6 (21–87)	39	Industry (Stryker)
Delloye, 2004[110]	Belgium and USA	Case series	5	Average 39	NR	Fracture (2) and non-union (3) including osteoarticular allografts (2) and intercalary allograft at the femur (3)	rhBMP-2 application only (3) and rhBMP-7, corticocancellous allografts (1) and revision of internal fixation with additional plating and rhBMP-7 application mixed with corticocancellous allografts (1)	32 (14–56)	20	NR
Dimitriou, 2005[111]	England	Case series	26	Average 15.3	3.2	Fracture non-unions (10 tibial, 8 femoral, 3 humeral, 3 ulnar, 1 patellar and 1 clavicular)	Open reduction and internal fixation (ORIF) (5), revision and ORIF (3), exchange nail (3), Ilizarov frame (3), less invasive stabilisation system plate (1), IM nail (1), revision fusion (1), screw fixation (1), no additional fixation (8)	39.4 (18–79)	73	No benefits from commercial party
Johnson and Urist, 1998[112]	USA	Case series	15	Average 56	2 (1–5)	Post-traumatic shortened atrophic femoral non-unions	One-stage lengthening with hBMP on non-collagenous protein and 6 patients with additional iliac crest bone autograft	48 (28–75)	33	NR

continued

Study	Country	Study type	Study size	Length of follow-up (months)	Average no. of previous procedures	Patient diagnosis	Surgical intervention	Mean age	Male %	Funding source
Johnson and Urist, 2000[113]	USA	Case series	30	Average 55	NR	Atrophic shortened femoral non-unions (24), equal length femoral non-unions (4) and femoral mal-unions (2)	One-stage lengthening of extremity with hBMP and 13 patients receiving additional autogeneic cancellous bone graft	47 (28–75)	33	NR
Johnson, 1988[123]	USA	Case series	6	NR	NR	Segmental defect of the tibia	Intercalary autogeneic cancellous bone graft with BMP/insoluble non-collagenous protein only	31.8 (22–42)	83.3	NR
Johnson, 1988[114]	USA	Case series	12	Average 27.7 (9.3–48.9)	4.3	Intractable femoral non-union of the femoral diaphyseal or metaphyseal–diaphyseal shaft	Internal fixation and hBMP implant	48.4 (16–75)	25	NR
Johnson, 1990[115]	USA	Case series	4	Average 33 (9.7–57.3)	5.8	Severely deformed non-unions of the tibia	Debridement of fibrous tissue, sequestrectomy, correction of angulatory deformities, internal stabilisation and implantation of hBMP	35 (29–39)	75	NR
Johnson, 1992[117]	USA	Case series	25	Average 21 (5–82)	3	Resistant non-unions including partial or complete segmental defects of femur (12), tibia (7) or humerus (6)	Composite implant as onlay (15) and as an inlay graft supported by internal fixation (1), with 7 patients receiving autogeneic cancellous bone grafting	45 (13–75)	36	NR
Jones, 2005[106]	USA	Case report	1	6 years	NR	Proximal pole scaphoid non-union	Curettage of the non-union through a standard volar approach fixed with a single K-wire and hBMP	16	NA	No benefits from commercial party
Kujala, 2002[118]	Finland	Case series	10	Average 14.3 (6–23)	NR	Established scaphoid non-unions	Varying procedures decided on by individual surgeons	40 (23–66)	100	NR

continued

Study	Country	Study type	Study size	Length of follow-up (months)	Average no. of previous procedures	Patient diagnosis	Surgical intervention	Mean age	Male %	Funding source
Kujala, 2004[119]	Finland	Case series	5	14 (8–27)	NR	Resistant ulnar non-unions	Internal fixation with composite implant of BMP, coral and collagen	46 (31–61)	60	NR
Kuklo, 2005[121]	USA	Case series	54	15.6	2–14	Open grade III tibial fractures sustained during Operation Iraqi Freedom	Supplemental external fixation (14), definitive internal fixation (18) and primary external fixation (9)	27.3 (20–42)	100	NR
McKee, 2002[52]	USA	Case series	15	Average 22 (6–52)	2.8 (0–6)	Complex, recalcitrant long-bone non-unions	Removal of any prior implant, debridement of non-union, correction of deformity, stable internal fixation and rhBMP-7 addition	52.8 (38–76)	60	Industry (Stryker)
Riedel and Valentin–Opran, 1999[120]	USA	Case series	12	9	NR	OTF with wound classification of II or higher	Fracture reduction within 24 hours of injury, repeated wound debridement and definitive fracture coverage within 14 days with rhBMP-2 on collagen sponge at time of coverage	37 (21–64)	75	Industry (Genetics Institute)
Schwartz and Hicks, 2006[122]	USA	Retrospective case series	18	NR	NR	Segmental bone defects (9 femur fractures, 6 tibial fractures, 2 clavicle fractures, 1 humerus fracture and 1 ulnar fracture)	NR	NR	61	NR

Appendix 11

Fracture case series and case report interventions

Study	BMP used	Dose/concentration	Carrier	Other	How used
Bai, 1996[107]	bBMP	50–200 mg	Plaster of Paris	6 had additional autogenous bone	Composite applied directly to fill interfragmentary defects and pack around fracture line
Benke and Gorecki 2004[108]	BMP-7	3.5 mg	Collagen sponge	NA	NR
Bong, 2005[109]	rhBMP-7	3.5 mg	Collagen granules	Also received allograft bone, autograft bone or DBM	NR
Delloye, 2004[110]	rhBMP-2	3.5–12 mg	Collagen granules	Four patients received adjuvant chemotherapy and three received radiation therapy	Local application or implantation
Dimitriou, 2005[111]	rhBMP-7	3.5 mg	NR	17/25 patients received BMP and autologous bone graft	NR
Johnson and Urist, 1998[112]	hBMP (composite thought to contain mostly BMP-2 and BP-7)	NR	NCP	6/15 patients had additional autogeneic iliac crest cancellous bone graft	Placed along medial side of intercalary defect
Johnson and Urist, 2000[113]	hBMP	100 mg	AAA cortical bone	13/30 additional autogeneic cancellous bone graft	hBMP/AAA implants placed across medial intercalary femoral shaft defect
Johnson, 1988[123]	hBMP	50–100 mg	iNCP	All patients had iliac crest bone autograft	Placed underneath the medial periosteal sleeve of the defect
Johnson, 1988[114]	hBMP	50–100 mg	iNCP	4/12 patients received autogeneic cancellous bone autograft. 4 patients received allogeneic bone graft	Placed as an onlay across the non-union gap
Johnson, 1990[115]	hBMP	50–100 mg	NCP	1/4 patients had cortical allogeneic bone	Implanted across fracture site
Johnson, 1992[117]	hBMP	NR	NCP	All had AAA bone. 5/25 patients received AICBG. 2/25 patients had reamings from the canal used as additional graft	Implant incorporated as onlay (15) and inlay (10)
Jones, 2005[106]	hBMP	50 mg	Gelatine capsule	K-wire to fix	Implanted into scaphoid non-union

continued

Study	BMP used	Dose/concentration	Carrier	Other	How used
Kujala, 2002[118]	bBMP	2–5 mg/cm^3	Collagen sponge	Biocoral frame. 9 patients received autograft	NR
Kujala, 2004[119]	bBMP	2–5 mg/cm^3	Collagen	Biocoral frame. 3 patients received autograft	NR
Kuklo, 2005[121]	rhBMP-2	NR	NR	Some patients received supplemental allograft, one received AICBG	NR
McKee, 2002[52]	rhBMP-7	NR	NR	NA	Implanted with stable internal fixation
Riedel and Valentin-Opran, 1999[120]	rhBMP-2	3.4–6.8 mg	Collagen sponge	NA	Implanted at time of definitive fracture coverage
Schwartz and Hicks, 2006[122]	rhBMP-2	NR	Collagen sponge	NA	NR

AAA, allogeneic, autolysed, antigen-free; bBMP, bovine bone morphogenetic protein; iNCP, insoluble non-collagenous protein; NCP, non-collagenous protein.

Appendix 12

Fracture case series and case report radiographic results

Study	Successful radiographic union (%)	Mean time to union	Successful union definition
Bai, 1996[107]	94.1 (16/17)	5.7 months	NR
Benke and Gorecki, 2004[108]	75 (6/8)	6–8 weeks	NR
Bong, 2005[109a]	100 (23/23)	144.3 days (69–356 days)	Absence of pain at fracture site, no motion at fracture site on manual three-point stressing in the sagittal and coronal planes and functional recovery of range of motion with the involved extremity
Delloye, 2004[110]	0 (0/5)	NA	Mankin's criteria[126]
Dimitriou, 2005[111]	88 (23/26)	4.2 months (2–9 months)	Painless full weight bearing and presence of bridging callous of two cortices visible on two X-ray views (clinical and radiographic)
Johnson and Urist, 1998[112]	93 (14/15)	5.6 months (5–7 months)	Host bridging callus and full weight bearing
Johnson and Urist, 2000[113]	80 (24/30)	6 months (3–9 months)	NR
Johnson, 1988[123]	100 (6/6)	5.7 months (4–9 months)	All patients were classified as A4 ('solid union of the fracture site') by the anatomical grading system[b]
Johnson, 1988[114]	91.7 (11/12)	4.7 months (3–6 months)	11 patients classified as A4, one patient was considered a failure, but later went on to unite with further surgery[b]
Johnson, 1990[115]	100 (4/4)	4.4 months (4–5.2 months)	NR
Johnson, 1992[117]	80 (20/25)	6 months (3–14 months)	20 patients classified as A4, four went on to heal with revision surgery[b]
Jones, 2005[106]	100 (1/1)	3 months	Signs of bony healing
Kujala, 2002[118]	20 (2/10)	NR	NR
Kujala, 2004[119]	100 (5/5)	6.6 months (3–12 months	Bridging trabeculae of bone seen on radiographs
Kuklo, 2005[121]	63 (34/54)	NR	NR
McKee, 2002[52]	87 (13/15)	NR	NR
Riedel and Valentin-Opran, 1999[120]	75 (9/12)	NR	NR
Schwartz and Hicks, 2006[122]	84.2 (16/19)	8.4 months (3.5–13.5 months)	NR

[a] Unable to calculate ITT data.
[b] See *Table 38* for grading definitions.

Appendix 13

Fracture case series and case report clinical and other outcomes

Study	Clinical outcomes	Other reported outcomes
Bai, 1996[107]	6 patients considered excellent, 6 good and 4 fair based on anatomical grading system	NR
Benke and Gorecki, 2004[108]	NR	Reported the serum levels of growth and angiogenic factors (ANG, IL-8, bFGF and IGF-1) were in the physiological range during observation period. IL-8 levels were elevated in the 1st, 2nd and 6th weeks. VEGF (vascular endothelial growth factor) level was elevated in the 1st week only
Delloye, 2004[110]	No improvement in clinical outcome following intervention	0/3 developed Ab to rhBMP-2. 1 patient developed low Ab titre to bovine collagen
Johnson and Urist, 1998[112]	9/15 considered results excellent. 4/15 good and 2 were satisfied with healing, absence of pain and reduction in limb discrepancy but would have preferred additional femoral length	Average length increase of femoral non-unions = 2.8 cm (1.5–5 cm) Average percentage increase in femur length compared with shortened femur = 8% (4–13%) 10 patients returned to full employment, 5 were retired
Johnson and Urist, 2000[113]	Patient satisfaction was especially high in patients with equalised leg lengths. All patients resumed full weight bearing and resumed functional use	Average femur length increase was 2.7 cm (1.5–5 cm)
Johnson, 1988[123]	F4: 4/6[a] F3: 2/6	E4: 5/6[a] E1: 1/6
Johnson, 1988[114]	F4: 8/12[a] F3: 4/12	E4: 9/12[a] E3: 2/12 E1: 1/12
Johnson, 1990[115]	2/4 patients had unlimited function of activities of daily living and only insignificant pain with excessive ambulation. 1 was limited to ambulation with a cane	2/4 patients returned to full employment
Johnson, 1992[117]	F4: 14/24[a] F3: 8/24 F2: 2/24	E4: 16/24[a] E3: 4/24 E2: 4/24
Jones, 2005[106]	At 5 months patient had regained full wrist motion and had no tenderness over scaphoid	NR
Kuklo, 2005[121]	96.9% (31/32) patients fully weight bearing	NR
McKee, 2002[52]	NR	1 tibia patient had recurring deep infection and required below-knee amputation 1 clavicular defect patient had delayed radiographic union at 6 months, but declined further intervention because clinically stable
Riedel and Valentin-Opran, 1999[120]	NR	Transient positive antibody titres to rhBMP-2 in 2 patients

[a] See *Table 38* for grading definitions.

Appendix 14

Fracture case series and case report secondary procedures and adverse events

Study	Secondary surgical procedures	Adverse events
Bong, 2005[109]	None	3 serious perioperative events (2 radial nerve palsies and one bracialis muscle contracture) and 1 non-serious perioperative event of superficial cellulitis. 4 late serious adverse events (severe elbow stiffness, superficial wound infection, heterotopic ossification near shoulder and late ulnar nerve palsy)
Delloye, 2004[110]	2/5 revision surgeries	Resorption of allograft (1) and sterile drainage (2) which stopped spontaneously
Dimitriou, 2005[111]	Further fixation with LISS plate and rhBMP-7 reapplication (2)	Superficial wound infection (2) and recurrence of deep infection requiring below-knee amputation (1)
Johnson and Urist, 1998[112]	Repeat stabilisation without hBMP implantation	Plate fatigue fracture
Johnson and Urist, 2000[113]	Repeat fixation (4)	Three patients died at 6, 8 and 10 years after treatment
Johnson, 1988[123]	Repeat implantation of hBMP/iNCP due to temporary failure. Two soft tissue procedures attempting coverage failed. Associated injuries required traumatic high contralateral above-knee amputation	Osteonecrosis and osteomyelitis of the entire tibial diaphyseal shaft significant loss of soft tissue occurred
Johnson, 1988[114]	Exchange fixation with tension band 95° angled blade plate and osteosynthesis and repeat onlay of hBMP/iNCP/PLA	Subtrochanteric sclerotic atrophic femoral pseudoarthrosis
Johnson, 1990[115]	None	Wound haematoma which required drainage
Johnson, 1992[117]	Revision of failed fixation and second composite alloimplant (4/5 healed)	Secondary infection that led to removal of composite alloimplant. Large anteromedial sequestrum (1)
Jones, 2005[106]	None	None
Kujala, 2002[118]	NR	Postoperative infection in HIV patient. Migration of fixation material at 6 and 8 months in two patients
Kujala, 2004[119]	None	None
Kuklo, 2005[121]	NR	1 superficial skin infection, 1 osteomyelitis
Riedel and Valentin-Opran, 1999[120]	3 patients required second surgical intervention for delayed union and underwent bone grafting and were healed by end of study	5 infections in 4 patients. 1 patient died at 6 months unrelated to treatment
Schwartz and Hicks, 2006[122]	Specifics NR	2 patients had premature resorption of graft and 1 had fixation failure at 6 weeks due to non-compliance

PLA, polylactic copolymer.

Appendix 15

RCT spine study characteristics

Study	Country	Length of follow-up (months)	Sample size		Patient diagnosis	Surgical intervention	Mean age (years)	Male (%)	Funding source
			Intervention(s)	Control					
Assiri, 2004[83]	Canada	NR	8	7	Degenerative disc disease	Posterolateral lumbar fusion	NR	NR	NR
Baskin, 2003[68]	USA	24	18	15	One- or two-level cervical disc disease producing radiculopathy, myelopathy or both	One- or two-level anterior cervical discectomy	51.3/47.1	44/88	Industry
Boden, 2002[69]	USA	24 (mean 17)	(11, 11)	5	Symptomatic single-level degenerative disc disease with ⩽grade I spondylolisthesis	Single-level posterolateral lumbar arthrodesis	57.6/51.8/52.9	40	Industry
Boden, 2000[85]	USA	24	11	3	Symptomatic single-level lumbar degenerative disc disease	Lumbar interbody arthrodesis with tapered cylindrical threaded fusion cage	42.5/40.2	50	Industry (Medtronic)
Burkus, 2005[71–73]	USA	24	79	52	Symptomatic single-level degenerative disc disease	Single-level stand-alone anterior lumbar interbody arthrodesis with a pair of threaded cortical bone dowels	40.2/43.6	38.9	Industry (Medtronic)
Burkus, 2002[74–76]	USA	24	143	136	Symptomatic single-level degenerative lumbar disc disease	Single-level anterior lumbar fusion with LT-CAGE lumbar tapered fusion device	43.3/42.3	52.7	NR
Dimar, 2006[77]	USA	24	53	45	Single-level degenerative disc disease	Instrumented posterolateral fusion	50.9/5.7	41.5/44.4	Not funded
Haid, 2004[79,87]	USA	24	34	33	Symptomatic single-level degenerative disc disease with ⩽grade I spondylolisthesis	Single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices	46.3/46.1	47.8	Industry (Medtronic)
Johnsson, 2002[80]	Sweden	12	10	10	L5 spondylolysis	Non-instrumented posterolateral lumbar fusion	44.8/40.8	40	Industry

continued

Study	Country	Length of follow-up (months)	Sample size		Patient diagnosis	Surgical intervention	Mean age (years)	Male (%)	Funding source
			Intervention(s)	Control					
Kanayama, 2006[81]	Japan and USA	12	10	10	Symptomatic degenerative spondylolisthesis with spinal stenosis	Single-level posterolateral fusion with pedicle screw instrumentation	70.3/58.7	57.9	NIH award
Shapiro, 2005[84]	NR	12	20	20	Severe spinal stenosis and grade I degenerative spondylolisthesis	Decompressive laminectomy of L4 and L5 and bilateral posterior lumber interbody fusion	NR	NR	NR
Vaccaro, 2004[82,86]	USA	12	24	12	Symptomatic degenerative spondylolisthesis with spinal stenosis	One-level non-instrumented posterolateral fusion of the lumbar spine following decompressive laminectomy	63/66	44.4	Industry

Appendix 16

RCT spine quality assessment

Study	Randomisation	Allocation concealment	Blinding	Baseline comparability	Explicit inclusion/ exclusion criteria	ITT analysis	Drop-outs (%)		
							Intervention	Control	Reasons given
Assiri, 2004[83]	Unclear	Unknown	Not reported	Population characteristics not reported	No	No	NR	NR	NR
Baskin, 2003[68]	Unclear	Unknown	Two independent radiologists reviewed radiographs and CT scans	Similar	No	No	3	1	No
Boden, 2002[69]	Unclear	Unknown	Two independent neuroradiologists reviewed radiographs and CT scans	Similar except statistically significant difference in diabetes rate (40% in control group, 0% in intervention groups) and education >high school (40% in control, 100% in intervention A and 87.5% in intervention B)	Yes	No	A: 0 B: 18	0	Yes
Boden, 2000[85]	Marginal balancing method	Unknown	Three radiologists reviewed radiographs. Three neuroradiologists and two surgeons reviewed CT scans	Similar except for statistically significant difference in mean weight (211 lb in control group and 166 lb in intervention group)	Yes	No	0	0	NA
Burkus, 2005[71–73]	Sequentially numbered envelopes	Adequate (based on randomisation method)	Two independent radiologists reviewed radiographs and CT scans	Similar	Yes	No	3.8	5.8	No
Burkus, 2002[74–76]	SAS PROC plan stratified by investigator site	Adequate (based on randomisation method)	Two independent radiologists reviewed radiograph and CT scans	Similar	No	No	6.3	8.8	Yes
Dimar, 2006[77]	Unclear	Unknown	One radiologist and two orthopaedists reviewed radiograph and CT scans	Similar	Yes	No	NR	NR	NR

continued

Study	Randomisation	Allocation concealment	Blinding	Baseline comparability	Explicit inclusion/ exclusion criteria	ITT analysis	Drop-outs (%)		
							Intervention	Control	Reasons given
Haid, 2004[79,87]	Unclear	Unknown	Two independent radiologists reviewed radiographs and CT scans	Similar	No	No	NR	NR	NR
Johnsson, 2002[80]	Unclear	Unknown	Three people blinded to radiostereometric results reviewed radiographs	Similar	No	No	0	0	NA
Kanayama, 2006[81]	Unclear	Unknown	No assessors blinded	Statistically significant, ($p = 0.05$) difference in age	Yes	No	1	0	Yes
Shapiro, 2005[84]	Unclear	Unknown	No assessors blinded	Population characteristics not reported	No	No	NR	NR	NR
Vaccaro, 2004[82,86]	Study representative assigned patient's group at time of surgery	Unknown	Two independent neuroradiologists assessed radiographs	Similar	Yes	No	20.8	16.7	Yes

Appendix 17

RCT spine adverse events

Study	Adverse events	
	Intervention	**Control**
Boden, 2002[69]	1 patient in intervention A developed left leg pain then right leg pain and underwent decompression one level above previous 1 patient had an epidural haematoma evacuated 5 days post-surgery with numbness in both legs leading to 1-year revision decompression performed up to 3 levels above previous level 1 patient in intervention B had persistent low back and leg pain resulting in revision with anterior lumbar interbody fusion 8 months postoperatively 1 patient had a superficial haematoma that required evacuation on day 4	
Boden, 2000[85]	1 experienced postoperative ileus and delay in gait training 1 patient had wound dehiscence, 1 had an episode of low back pain 3 had post-traumatic events (2 fell down stairs and 1 fell from building)	1 patient experienced postoperative ileus and delay in gait training 1 patient had urinary retention
Burkus, 2005[71–73]	NR	46.5% of control group still experienced donor site pain at 24 months
Burkus, 2002[74–76]	6 (4.2%) intraoperative vascular events	5 (3.7%) intraoperative vascular events 8 (5.9%) iliac crest graft site adverse events which included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac crest, 1 infection and 1 haematoma All patients had postoperative graft site pain At 24 months 32% still had graft site pain At 24 months 16% were bothered by graft site appearance
Dimar, 2006[77]	9 gastrointestinal 14 traumas 9 cardiovascular 6 urogenital 3 dural tears 6 non-surgical infections 14 other	10 gastrointestinal 9 traumas 6 cardiovascular 6 urogenital 5 dural tears 4 non-surgical infections 3 malpositioned implants 1 surgical infections 2 non-unions 1 respiratory 1 vertebral fractures 17 other
Haid, 2004[79,87]	3 patients had dural tears 14 patients had neurological complications 24 patients developed excess bone in spinal canal or neurofamina	1 patient developed deep vein thrombosis 2 patients had dural tears 14 patients had neurological complications 4 patients developed excess bone in spinal canal or neurofamina All patients had postoperative graft site pain

continued

Study	Adverse events	
	Intervention	**Control**
		At 24 months 60% still had pain At 24 months 13% were bothered by graft site appearance
Johnsson, 2002[80]	2 patients had major back pain at 12 months 4 patients had mild back pain 1 patient had reoperation with instrumented fusion and L5 nerve root decompression 1 had reoperation instrumented fusion	3 patients had major back pain at 12 months 2 patients had mild back pain 1 patient had reoperation with LF nerve root decompression 1 patient's pain persisted 1 patient had persistent minor graft site pain
Vaccaro, 2004[82,86]	96% (23/24) intervention group patients (all deemed unrelated to OP-1 putty, except for possibly pseudoarthrosis)	100% (12/12) control patients experienced an adverse event

Appendix 18

Spine fusion case series findings

Spine case series studies: number and characteristics

Fourteen case series, by Boakye and colleagues,[127] Boden and colleagues,[128] Govender and colleagues,[129] Jeppsson and colleagues,[130] Kleeman and colleagues,[131] Kuklo and colleagues,[125] Lanman and Hopkins (2004),[132] Lanman and Hopkins (2004),[133] Laursen and colleagues,[134] Luhmann and colleagues,[135] Mummaneni and colleagues,[136] Vaccaro and colleagues[137] and Villavicencio and colleagues,[138] and Buttermann[139] (abstract only) were included.

General study characteristics

Appendix 19 shows the general study characteristics of each included spine case series study. Nine out of 14 studies were conducted in the USA. The remaining studies were conducted in Switzerland,[128] Sweden,[130] Canada[129] and Denmark.[134] It was not clear where the conference abstract study[139] was conducted. Two studies[128,129] specified they were sponsored by industry and one[130] by the Swedish Medical Research Council and another[135] stated that it received no funding. The remaining 10 studies did not report their source of funding.

The diagnoses included in the studies are highly variable between and within each study. Six studies[125,131,132,136,138–140] included some type of disc disease in their patient population, and four[125,131,136,138,140] of those also included a level of spondylolisthesis. The Buttermann abstract[139] also included patients with herniated nucleus pulposus or stenosis. The Govender study[129] used the following definition to describe their patient population: "some form of spinal disease requiring spinal fusion with medical risk factors known to inhibit spinal fusion". Of the remaining studies, the diagnoses included radiculopathy, myeloradiculopathy or profound quadriparesis,[127] lumbar spinal stenosis or spondylolisthesis,[128] rheumatoid disease or psoriatic arthritis,[130] discogenic pain, grade I spondylolisthesis or non-union from previous surgery[132] and unstable thoracolumbar spine fractures.[134] The Luhmann study[135] did not specify patients' diagnoses but reported only that it included patients, requiring the specific surgical procedures used.

The surgical interventions are also highly variable between and within the studies. Four studies[125,133,136,138,140] used transforaminal lumbar interbody fusion. The Lanman and Hopkins (2004)[132] and Buttermann[139] studies performed anterior cervical interbody fusion. The Kleeman study[131] performed anterior lumbar interbody fusion. Because of the variability in diagnoses in the Govender study[129] there were equally variable surgical interventions performed. These included lumbar decompression (1), lumbar decompression, posterior lumbar interbody fusion and pedicle screw fixation (1), craniocervical decompression and fixation (1), suboccipital decompression, duraplasty and occipitocervical fusion (2), spinal cord untethering and lumbar pedicle screw fixation (1), atlantoaxial stabilisation (1), cervical laminectomy and occipitocervical fusion (1) and lumbar pedicle subtraction osteotomy and pedicle screw fixation (1). The remaining studies used discectomy, anterior cervical discectomy and fusion at varying number of levels,[127] one- or two-level spinal arthrodesis,[128] atlanto-axial posterior fusions,[130] transpendicular BMP implantation, short segment instrumentation and posterolateral fusion,[134] anterior, posterior or both fusions[135] and decompression following laminectomy and facetectomy followed by intertransverse process fusions.[137,141]

The study sizes ranged from four to 74 patients. The follow-up lengths varied from 5 to 24 months. The mean ages ranged from 38 to 56.9 years.

Quality

Table 39 summarises the quality of the included studies. Two are preliminary reports[134,136,140] and one is an abstract from a conference.[139]

The quality of the studies is low. Six of the studies[125,128,131,134,135,137,141] meet at least three of the four quality criteria assessed.

Ten of the studies[125,127,129,131,133–138,140,141] clearly described their patient populations, whereas only

TABLE 39 *Spine case series quality*

Study	Explicit population definition	Similar prognostic baseline	Appropriate assessment of outcomes	Numbers lost to follow-up
Boakye, 2005[127]	Yes	No	No	Yes
Boden, 2004[128]	No	Yes	Yes	NA
Buttermann, 2005[139]	No	Unable to determine	Unable to determine	Unable to determine
Govender, 2002[129]	Yes	No	No	NA
Jeppsson, 1999[130]	No	Yes	No	NA
Kleeman, 2001[131]	Yes	Yes	Yes	Yes
Kuklo, 2004[125]	Yes	No	Yes	NA
Lanman and Hopkins, 2004[132]	No	Yes	No	No
Lanman and Hopkins, 2004[133]	Yes	No	No	Partial
Laursen, 1999[134]	Yes	Yes	No	NA
Luhmann, 2005[135]	Yes	Yes	Yes	NA
Mummaneni, 2004[135,136,140]	Yes	Yes	No	Partial
Vaccaro, 2005[137,141]	Yes	Yes	Yes	Yes
Villavicencio, 2005[138]	Yes	No	Yes	Partial

eight of the studies[128,130–132,134,136,137,140,141] had patients with similar prognostic baselines within their respective studies. Six of the studies[125,128,131,135,137,138,141] used one or more independent assessors to assess radiographic outcomes. Finally, three studies[127,131,137,141] gave the numbers and reasons for patients lost to follow-up, three[132,133,136,138,140] gave only the numbers lost but no reasons, one study[132] did not give loss to follow-up data and six studies[125,128–130,134,135] did not lose any patients to follow-up.

Interventions

Appendix 20 shows the specific BMP interventions used in each study.

Eight studies used rhBMP-2 in varying doses of 1.5 mg/ml[127,135] 2 mg/ml,[135] 4.9 mg in 3.2 ml,[131] 3.5 mg[137] and 4.2 or 12 mg,[138] with all but one study[135] using only a collagen sponge for the carrier. The remaining study[135] used either a collagen sponge and BCP granules or a compression-resistant matrix (CRM) sponge and BCP granules. Three studies[125,132,133] that used rhBMP-2 did not give the dose used. Three studies used BMP-7 with reported doses of either 2.5 mg[130] or 3.5 mg.[129,137,141] The remaining study[134] did not report the dose of BMP-7 that was used. BMP-7 was delivered on a collagen sponge, collagen granules or an unspecified form of collagen. In the Boden study,[128] a mixture of collagen and growth factors called Ne-Osteo was used. The growth factor mixture contained BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-b1, TGF-b2, TGF-b3, acidic FGF-I, osteocalcin and osteonectin. The Buttermann abstract[139] did not specify which BMP was used or the carrier, but said the dose was 0.9 mg per level.

Eight of the studies[128,129,134–141] had additional bone graft treatment in some form, for all or part of their patient population. The additional treatments included allograft bone, autograft bone and DBM.

Findings from spine case series studies

Appendix 21 gives the radiographic fusion success of each study, average time to fusion and each study's definition of a successful fusion, where reported.

The studies' definitions of successful fusion varied considerably. Three studies[128,134,136,140] reported no fusion definition. Another study[130] reported that if the assessor could detect visible bone formation on radiographs, then it was considered a successful fusion. The Govender study[129] referred to the criteria for fusion of Blount and colleagues.[142] The Luhmann study[135] used the grading systems of Eck and colleagues[143] and Lenke and colleagues[144] to assess fusion. The remaining six studies included some sort of

bridging bone criteria in their definition, with varying degrees of specificity for other criteria. The Buttermann abstract[139] did not report that is assessed fusion status.

In seven of the studies,[125,127,131–133,135,138] there was a 90% or higher fusion rate. The Laursen study[134] did not report fusion success rates and the Boden study[128] gave no numerical data, but reported that the side of the spine the autograft was used on showed better bone morphology, fusion quality and fusion success than the other side. Three studies reported fusion rates of 25%,[130] 42%[137,141] and 44%.[129] Of the studies that reported lower fusion rates, two studies[129,130] included populations with high-risk patients, including rheumatoid disease, psoriatic arthritis, those taking steroids and those with "medical risk factors known to inhibit spinal fusion". Four studies[129,131,136,138,140] reported the mean times to fusion, which ranged from 3 to 6 months.

In a retrospective integrated analysis by Burkus and colleagues,[101] the data from the Kleeman study[131] along with unpublished data from other sites in the same study were compared with a similar study using autograft bone. Both studies included patients with single-level degenerative disc disease and used an LT-CAGE inserted using a laparoscopic approach. The inclusion and exclusion criteria were the same. The preoperative characteristics were similar except for the preoperative working status, where 52% of patients who received InFUSE™ were working preoperatively, whereas only 45% of patients in the autograft study were working preoperatively.

The fusion rates in the InFUSE study were 94% (81/86) compared with 90% (150/167) in the autograft group at 24 months. Good fusion rates were seen in both studies, although slightly higher in the study where patients received BMP.

Clinical and adverse events results

Appendix 22 shows any clinical or other reported outcomes.

As reported in the Burkus integrated analysis,[101] the mean operating time in the InFUSE study (1.9 ± 0.9 hours) was significantly lower than in the autograft study (3.1 ± 1.4 hours). There was also less blood loss in the InFUSE study, with an average reduction of 146.1 ± 406.2 ml, compared with 213.6 ± 493 ml in the autograft study. The hospital stay length was also lower in the InFUSE study at 1.2 ± 1.1 days compared with 3.0 ± 3.8 days in the autograft study.

In the Burkus analysis,[101] the reported improvement in Oswestry score was greater in the InFUSE study than the autograft study, with a mean reduction of 33.6 in the InFUSE study and 23.9 in the autograft study. The SF-36 physical component score improvement was also greater in the InFUSE study (+16.7) than the autograft study (+12.9). The SF-36 pain index was also improved more in the InFUSE study (+41.3) compared with the autograft study (+32.7). The clinical outcomes and the way in which they were reported were insufficient to come to any conclusions regarding BMP's effect on clinical outcomes. However, the trend in the clinical outcomes reported is an overall improvement in function and pain, with the exception of the donor sites of iliac crest graft patients. In the two studies[136,137,140] that reported donor site pain, 25–58% of patients reported pain at the last follow-up.

Appendix 23 shows the details of any secondary surgical procedures and adverse events reported in the studies.

Of the studies that reported data on the number of secondary surgical procedures, three studies[125,132,137,141] reported one secondary procedure each, two[131,138] reported two secondary surgeries, one[129] reported three second surgeries and one[128] reported four revision surgeries.

The Burkus analysis[101] reported fewer secondary interventions in the InFUSE study, with 12 secondary surgeries being performed in 134 patients compared with the autograft study, where 57 secondary surgeries were performed in 266 patients. Also reported was the return to work rate in both studies. The InFUSE study reported a mean return to work rate of 89 days whereas the autograft study reported a mean of 154 days, although it does not say from how many patients this was determined.

Summary

There were 14 case series on the effect of BMP treatment on spinal fusion (see Appendix 19 for a descriptive summary). These studies were small and had many methodological weaknesses. No clear conclusions can be inferred from these studies as many patients had extremely variable diagnoses and received differing surgical procedures.

Appendix 19

Spine case series characteristics

Study	Country	Study type	Study size	Length of follow-up (months)	Patient diagnosis	Surgical intervention	Mean age (years)	Male (%)	Funding source
Boakye, 2005[127]	USA	Case series (retrospective?)	24	13 (12–16)	Radiculopathy (16), myeloradiculopathy (8) and profound quadriparesis (1)	Single-level discectomy (12), two-level anterior cervical discectomy and fusion (ACDF) (9) and three-level ACDF (3) with rhBMP-2 PEEK filled spacer	52 (35–70)	50	NR
Boden, 2004[128]	Switzerland	Case series	22	24	Lumbar spinal stenosis and/or spondylolisthesis	One- or two-level spinal arthrodesis with Ne-Osteo (with varying amounts of Growth Factor mixture) and varying amounts of DBM on one side and iliac crest autograft on the other side of the spine	NR	NR	Industry
Buttermann, 2005[139]	NR	Case series	66	24	Degenerative disc disease, herniated nucleus pulposus or stenosis	Anterior cervical discectomy and fusion	NR	NR	NR
Govender, 2002[129]	Canada	Case series	9	Average 5.22 (2–15)	Spinal disease requiring spinal fusion with medical risk factors known to inhibit spinal fusion	Lumbar decompression (1), lumbar decompression, posterior lumbar interbody fusion and pedicle screw fixation (1), craniocervical decompression and fixation (1), suboccipital decompression, duraplasty and occipitocervical fusion (2), spinal cord untethering and lumbar pedicle screw fixation (1), atlantoaxial stabilisation (1), cervical laminectomy and occipitocervical fusion (1) and lumbar pedicle subtraction osteotomy and pedicle screw fixation (1)	47 (21–74)	44.4	Industry (Stryker)
Jeppsson, 1999[130]	Sweden	Case series	4	10	Rheumatoid disease (3) and psoriatic arthritis (1)	Atlanto-axial posterior fusions with BMP-7 on collagen granules	NR	NR	Swedish Medical Research Council

continued

Study	Country	Study type	Study size	Length of follow-up (months)	Patient diagnosis	Surgical intervention	Mean age (years)	Male (%)	Funding source
Kleeman, 2001[131]	USA	Case series	22	12	Single-level degenerative disc disease or low-grade spondylolisthesis	Anterior lumbar interbody fusion using a laparoscopic approach with a BMP/collagen sponge inserted in NOVUS LT cage	38 (21–56)	36	NR
Kuklo, 2004[125]	USA	Case series	35	Average 12.4 (6–18)	Degenerative disc disease (6), isthmic spondylolisthesis (5), adult degenerative scoliosis (4), degenerative spondylolisthesis (4), failed back syndrome (2) and congenital scoliosis (1)	Single- or multiple-level TLIF with segmental pedicle screw fixation and BMP/collagen sponge implantation	41.6 (23–70)	77.3	NR
Lanman 2004[132]	USA	Case series	20	6	One- to three-level cervical disc disease	Anterior cervical interbody fusion with interbody spacer containing InFUSE	46.2 (22–62)	70	NR
Lanman, 2004[133]	USA	Case series	43	12	Discogenic pain (34), grade I spondylolisthesis (5) and non-union from previous surgery (4)	TLIF with InFUSE, except for one patient who had anterior procedure	48.6 (17–68)	55.8	NR
Laursen, 1999[134]	Denmark	Case series	5	12–18	Unstable thoracolumbar spine fractures	Transpendicular BMP-7 transplantation, short segment instrumentation and posterolateral fusion	49.4 (28–76)	80	NR
Luhmann, 2005[135]	USA	Case series	70	Minimum 12, average 17.9 (12–60)	Patients requiring anterior, posterior or "compassionate use" posterior fusion	Anterior, posterior or both fusions	55.4 (21–80)	20	No funds received
Mummaneni, 2004[136,140]	USA	Case series	44	Average 6	Degenerative disc disease or grade I or II spondylolisthesis	TLIF with iliac crest autograft or BMP-2	53 (33–76)	56	NR
Vaccaro, 2005[137,141]	USA	Case series	12	12	Single-level, grade I or II degenerative spondylolisthesis and symptoms of neurogenic claudication	Decompression following laminectomy and partial or complete medial facetectomy followed by intertransverse process fusion with BMP-7 on collagen and autograft bone	68 (45–79)	25	NR

continued

Study	Country	Study type	Study size	Length of follow-up (months)	Patient diagnosis	Surgical intervention	Mean age (years)	Male (%)	Funding source
Villavicencio, 2005[138]	USA	Case series	74	12	Degenerative disc disease	TLIF with rhBMP-2 on collagen with autograft bone and one or two structural bone allografts	56.9 (20–82)	37.8	NR

TLIF, transforaminal lumbar interbody fusion.

Appendix 20

Spine case series interventions

Study	BMP used	Concentration/dose	Carrier	Other	How used
Boakye, 2005[127]	rhBMP-2	1.5 mg/ml	Collagen sponge	NA	rhBMP-2/sponge put into PEEK spacer then implanted in interbody space
Boden, 2004[128]	Ne-Osteo [bovine type I tendon collagen, with growth factor mixture (known to contain BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-b1, TGF-b2, TGF-b3, acidic FGF-I, osteocalcin and osteonectin) in 5 mmol/l sodium phosphate buffer]	169 mg	Mixed with DBM	6/22 patients received additional demineralised cortical allograft powder. 10/22 patients received additional cancellous chips or local bone	Ne-Osteo mixed with DBM then formed into cylinder and implanted
Buttermann, 2005[139]	NR	0.9 mg per level	NR	Also received allograft. Control group received autograft bone	NR
Govender, 2002[129]	BMP-7	3.5 mg	Collagen granules	Autologous bone harvested from iliac crest and/or from site of local spinal decompression	NR
Jeppsson, 1999[130]	BMP-7	2.5 mg	1.0 g collagen granules	NA	Implant placed on roughened cortical surface between spinous processes
Kleeman, 2001[131]	rhBMP-2	4.9 mg in 3.2 mL	Collagen sponge	NA	rhBMP-2/sponge rolled and inserted in NOVUS LT cage
Kuklo, 2004[125]	rhBMP-2	NR	Collagen sponge	NA	NR
Lanman, 2004[132]	rhBMP-2	NR	Collagen sponge	NA	InFUSE contained within the Cornerstone-HSR absorbable interbody implants
Lanman, 2004[133]	rhBMP-2	NR	Collagen sponge	NA	InFUSE contained within HYDROSORB Telamon bioresorbable orthopaedic implant
Laursen, 1999[134]	BMP-7	NR	Collagen sponge	4/5 patients received additional autogenous bone	Unclear

continued

Study	BMP used	Concentration/dose	Carrier	Other	How used
Luhmann, 2005[135]	rhBMP-2	1.5–2 mg/ml	Collagen sponge or CRM sponge, both with BCP granules	Anterior fusion patients received local bone	
Mummaneni, 2004[136,140]	rhBMP-2	"Medium kit"	Collagen sponge	19/44 received iliac crest autograft, 12 received iliac crest autograft and 9 received local autograft	One sponge placed anterior to interbody cage and one inside
Vaccaro, 2005[137,141]	BMP-7	3.5 mg	Collagen	All patients received iliac crest autograft	One implant each side of spine
Villavicencio, 2005[138]	rhBMP-2	4.2 or 12 mg	Collagen sponge	Structural bone allografts and locally harvested autograft bone were used in all patients	Positioned anteriorly along the annulus fibrosis

Appendix 21

Spine case series fusion results

Study	Successful radiographic fusion	Mean time to fusion (months)	Successful fusion definition
Boakye, 2005[127]	92% (22/24)	NR	Evidence of solid bridging bone and no instability on flexion–extension radiographs
Boden, 2004[128]	No numerical data, says only that autograft showed better results in 3 categories (bone morphology, fusion quality and fusion success)	NR	NR
Govender, 2002[129]	44.4% (4/9)	4.25 (3–6)	Criteria of Blount *et al.*[142]
Jeppsson, 1999[130]	1/4 (25%) showed bone formation	NA	Detect visible bone formation by radiographs
Kleeman, 2001[131]	95% (21/22)	6 (seen in all patients)	Evidence of bridging trabeculae on radiograph or CT scan in at least one of the following areas: lateral, medial, anterior, posterior and/or through either or both of the implants. No more than 3 mm difference in translation or 5° difference in angulation on flexion–extension radiographs and no evidence of radiolucency surrounding >50% of either device on radiographs
Kuklo, 2004[125]	97.4% (38/39)	NR	Presence of continuous bridging bone observed on lateral radiographs
Lanman, 2004[132]	100% (20/20)	NR	Bridging bone in the interbody space from the vertebra through the graft to the adjacent vertebra
Lanman, 2004[133]	93% (40/43)	NR	Bridging bone in the interbody space from the vertebra through the graft to the adjacent vertebra
Luhmann, 2005[135a]	95.4% (251/263 levels fused)	NR	Grades 1 and 2 of *Eck et al.*[143] and Lenke *et al.*[144] fusion grading systems which included definite, with obvious trabeculations apparent crossing vertebral endplates or probable, with intact graft and no lucencies but without full remodelling and incorporation
Mummaneni, 2004[136,140]	Group 1 95% (18/19) Group 2 95% (19/20)	3 (fusion in all patients)	NR
Vaccaro, 2005[137,141]	42% (5/12)	NR	Presence of bridging bone between the transverse processes at the spondylolisthetic segment ⩽5° angulation and ⩽2 mm translation on flexion–extension radiographs
Villavicencio, 2005[138]	96% (71/74)	4.1 (2–10)	Evidence of trabecular bone bridging on CT scans. On radiographs, less than 5° difference in angular motion between flexion and extension and absence of radiolucent lines greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of grafts

[a]Not able to calculate based on ITT.

Appendix 22

Spine case series study clinical and other outcomes

Study	Clinical outcomes	Other reported outcomes
Boakye, 2005[127]	Evaluated using Odom criteria: Good/excellent: 21/22 (5%) Fair: 1/22 (5%)	NR
Boden, 2004[128]	Visual analogue scale for low back pain decrease (10-point scale): Phase I: 2.5 points Phase II: 4.0 Phase III:2.9	
	No meaningful results found for patient assessment helpfulness of surgery for symptoms, or of assessment of results or if they would undergo surgery again	NR
Buttermann, 2005[139]	Neurological deficits resolved in both groups	NR
Govender, 2002[129]	Mean Oswestry score improvement: –12.3 (+49 to –33) points SF-36 scores: overall there were more patients whose scores increased after treatment in physical functioning (7/9), bodily pain (5/9) and mental health (7/9) categories	NR
Jeppsson, 1999[130]	2-month follow-up all patients reported improvement in neurological symptoms and neck pain	NR
Kleeman, 2001[131]	Improved back pain 100% (21/21) Improved leg pain 100% Improved function 100% Full function 48% (10/21) All patients showed improvement in all eight SF-36 categories	Return to work 100% (21/21) Satisfaction 100%
Lanman, 2004[132]	SF-36 physical functioning scores improved by 5.7 points and bodily pain score improved by 2.2 points	NR
Lanman, 2004[133]	Mean Oswestry score improvement: 5.1 points	NR
Laursen, 1999[134]	1 patient reported pain and 2 reported "tiredness" in their backs	Increase in bone mineral density in all but one case (4/5)
Mummaneni, 2004[136,140]	58% complained of donor site pain in iliac crest autograft patients	NR
Vaccaro, 2005[137,141]	25% reported moderate donor site pain Oswestry score and SF-36 functional improvement was achieved in 8/9 patients	NR

Appendix 23

Spine case series secondary procedures and adverse events

Study	Secondary surgical procedures	Adverse events
Boakye, 2005[127]	NR	1 patient died 4 weeks postoperatively of medical complications including sepsis and respiratory distress. Transient dysphagia (2), CSF leakage with ossification of posterior longitudinal ligament (1), transient C-5 paresis (1) and transient vocal cord paresis (1). Clinically asymptomatic heterotopic bone formation (1)
Boden, 2004[128]	4/22 revision surgery	Wound dehiscence, nerve root irritation, revision due to adjacent segment degeneration, pseudarthrosis caused by absent bone formation and dural tear (one each)
Buttermann, 2005[139]		Control group had 1 pseudoarthrosis and 2 donor site complications Neck swelling was 4 times as likely in BMP group
Govender, 2002[129]	Halo vest immobilisation for 3 months (1), further surgical intervention not specified (1), insertion of temporary lumbar spinal drain (1)	Cerebrospinal fluid leak and further spinal cord compression leading to further deterioration
Jeppsson, 1999[130]	NR	Impaired motion at neck (1), 8 mm redislocation in patient who removed neck collar
Kleeman, 2001[131]	Laparoscopic repair of two adverse events	Bowel injury (1) and vascular injury (1) related to laparoscopic technique
Kuklo, 2004[125]	Foraminal decompression to relieve radiculopathy	2 transient neurapraxia or mild motor weakness and persistent right-sided L-5 neurodynia. 1 intraoperative dural tear
Lanman, 2004[132]	Second surgery for non-union	Severe dysphagia
Lanman, 2004[133]	NR	Dural tear on nerve root sleeve which led to numbness of right leg which resolved in 3 weeks
Laursen, 1999[134]	NR	Screw loosening. Resorption of whole anterior column at fracture level
Luhmann, 2005[135]	NR	1 superficial wound dehiscence, 1 deep wound infection and 1 wound haematoma
Mummaneni, 2004[136,140]	NR	Pseudoarthrosis (1)
Vaccaro, 2005[137,141]	Revision instrumented surgical fusion	Pseudoarthrosis (1)
Villavicencio, 2005[138]	Reoperation for screw position. Removal of allograft at 15 months due to migration into epidural space. Second surgery to extend fusion to an adjacent level (2 minimally invasive and 3 open)	

CSF, cerebrospinal fluid.

Appendix 24

Patient statement

The following is a statement by Adam Frere-Smith, consumer representative.

On the 9th of October, 2003, I had a sporting accident that resulted in a double open compound fracture to my left tibia and fibula. My fracture was treated using intramedullary nail fixation. At the time of the accident I was leading a very active lifestyle that revolved around surfing, mountain biking, mountain boarding, fitness training and martial arts, in which I was an assistant instructor. I was working as a hygiene technician and also studying at college. I had no car and travelled by bicycle and public transport.

After my release from hospital I spent 2 weeks convalescing with family as I was living in a second floor flat; the first week I was confined to bed as I was still on pain management medication. I had been issued with a pair of 'walking sticks', but found these very difficult to use at first.

During the first couple of weeks back home many friends and family helped with transport and shopping, etc.; however, I was beginning to feel very dependent and missed the social interaction of my hobbies. My income dropped to statutory sick pay, which hugely impacted my standard of living and quality of life.

During the study I had to attend regular checks at the orthopaedic clinic in the Norfolk and Norwich University Hospital (NNUH) where my progress was measured by X-ray. The two high points were when the clinician told me I had union of the fracture, although this had no affect on my ability to walk, and when I was given the go-ahead to start load bearing on my leg.

As a patient, I think these two moments were pivotal to my perceived recovery rate. The first, because I was feeling so low at the time, missing work and activities, that it was a real boost to be told and to see on the X-ray, that my bone was getting 'whole' again; and the second, because learning to walk again felt like the end was nearly in sight. It wasn't though; it took many more weeks before I could walk without the sticks.

One aspect of my treatment that I think helped was the use of an internal fixation (intramedullary nail). It allowed me to wear my normal clothes, as opposed to patients who had casts or external cages that are more obtrusive. Because of this, I believe that I engaged in 'normal' lifestyle and social activities that helped my recovery, such as swimming, social outings and trips to the countryside and beach, at a much earlier time, which I believe hastened my return to work and improved my well-being.

After reading the draft report I was pleased to see that it has highlighted some very encouraging points, from a patient's point of view. Pain from the injured area over a prolonged period of time can be very depressing and to have this compounded by additional pain from the donor site when grafting is used would be doubly distressing and also increase the possibility of infections. If an alternative to grafting is available, and is shown to be just as effective, I believe it should be used at every opportunity for the benefit of the patient's recovery, well-being and their quality of life.

It was very encouraging to read that BMP may be able to lower operation times, reduce blood loss, fracture and donor site pain, length of hospital stay, reduce the risk of site infections and speed return to work and has no adverse affects on patients. I feel these are all areas of distress for the patient and their families and further investigation into the use of BMP should be carried out if progress can be made to improve these outcomes, especially operation times, hospital stay and infection risk, which are three major concerns to patients and their families.

As previously mentioned, the time of fracture union and load bearing was to me, a major factor in my mental and physical recovery. To be able to accelerate the time to union would be a very welcome aspect. To be able to start to engage in 'normal' activities again is very uplifting, to all parties involved, and no doubt speeds recovery further.

Outpatient visits are another source of distress to both patient and family, and as it will usually

involve a third party for transportation reasons, incurs further economic hardship through the third party's loss of work that day and the patient's feelings of guilt and burden. The possibility of a reduction in outpatient visits through accelerated union, reduction of the risk of infection and lower secondary intervention rates are areas that I feel most patients would like to see reduced.

I believe that research, which can help develop good or new practices and procedures, should be a necessity. From a patient's point of view, if research can result in the improvement of front line services that will increase patient comfort and accelerate healing then it should be carried out. Although I am not in the position to comment on the economic findings of the report (how much is too much to pay for a QALY and who is to decide this figure), I believe the reasons for exploring this area of treatment are justified (societal costs and improving patient recovery). Further research would be a worthwhile investment especially if it would clarify the discrepancies in the economic modelling and bring greater uniformity when comparing study results to identify good practice.

Although this study is looking at the economics of BMP use, I feel strongly that the patient's quality of life is important in recovery and may also impact on the economics of a treatment by facilitating earlier return to work times.

Any treatments that can reduce areas such as pain, blood loss, treatment time, and the use of 'visible' aids over similar treatments are important from a patient's perspective, not only from the medical point of view, but also in the way they can improve the quality of the patient's life. I believe that research that includes investigation into quality of life has the ability to highlight practices, procedures and treatments that may enhance medical recovery due to their psychological affect.

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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