



Evidence Review: Bone morphogenetic protein-2 in spinal fusion

NHS England

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1. Introduction

NHS England is responsible for commissioning complex spinal surgery as set out within the Manual for Prescribed Services (NHS England, November 2012). The commissioning criteria for complex spinal surgery which is commissioned by NHS England is documented within NHSE Policy D14/S/a.

Spinal fusion surgery permanently joins bones in the spine to ensure that there is no movement between them. The aim of a successful fusion is to reduce pain and disability. Fusions can be performed by removing the intervertebral disc and replacing it with a cage designed to maintain (or correct) the anatomical alignment of the lumbar spine. The cage is filled with material to encourage a fusion to occur.

Primary anterior lumbar surgery and revision surgery and posterior instrumented lumbar spinal surgery of more than 2 levels is commissioned by NHS England specialised commissioning teams.

A lumbar spinal fusion is performed (a) when the pain is thought to be due to degenerative change at one or two levels in the lumbar spine (b) to stabilise the spine following decompression of neurological structures where the decompression results in potential instability (c) to correct and stabilise a spinal deformity which is usually performed at multiple levels and may require decompression of the neurological structures.

The use of autologous bone graft (ABG), typically an iliac crest bone graft (ICBG), as an adjunct to spinal fusion surgery is considered the gold standard. Whilst the use of bone graft possesses the three key properties required for bone formation: osteoconductivity (acts as a scaffold allowing native bone to perpetuate), osteoinductivity (stimulates osteoprogenitor cells to differentiate into osteoblasts that then begin new bone formation) and osteogenicity (osteoblasts originating from the bone graft material contribute to new bone growth along with bone growth generated via the other two mechanisms) it may not be suitable for all patients, especially those who do not have sufficient quality iliac of crest bone material, where it has been harvested for previous surgery or where the bone is required for secure fixation as part of the spinal instrumentation.

Bone morphogenetic protein (BMP) is a graft substitute. Currently, the BMP with the widest clinical application is recombinant human bone morphogenetic protein-2 (rhBMP-2), an osteoinductive bone growth factor that is a member of the transforming growth factor-b superfamily.

2. Summary of results

The evidence review has sought to establish the clinical effectiveness, safety and cost effectiveness of rhBMP-2 in comparison with iliac crest bone graft for anterior lumber spinal fusion surgery and posterior instrumented spinal surgery to inform the NHS England policy.

Clinical effectiveness:

The evidence for clinical effectiveness of BMP is based on five good quality independent systematic reviews and meta-analyses (Chen et al., 2012; Fu et al., 2013; Simmonds et al., 2013; Zhang et al., 2014; Noshchenko et al., 2014). The number of studies included in the reviews varied depending on the inclusion and exclusion criteria but all included 8 RCTs evaluating rhBMP-2 with ICBG for lumbar fusion (including anterior lumber spinal fusion). All reviews compared rhBMP-2 with ICBG for spinal fusion and the primary outcomes were rate of fusion and improvement of clinical symptoms based on the ODI and the SF-36, physical scale. The quality of reporting secondary outcomes varied across studies.

Fu et al. (2013) and Simmonds et al. (2013) systematic reviews were conducted as part of The Yale University Open Data Access (YODA) Project. In addition to the published studies, individual-participant data was obtained from sponsors or investigators to address the issue of publication bias.

The results of the analysis on the primary outcome measure indicate that compared with ICBG, rhBMP-2 in lumbar fusion (single level anterior or posterior fusion) has higher rates of radiographic fusion at 2 years follow up period. The Relative Risk (RR) for radiographic fusion varied from 1.13 to 1.19, with 2 reviews showing a statistically significant difference.

Successful fusion was not, however, correlated with improvement in clinical outcomes as measured by: the Oswestry Disability Index (ODI), return to work, back pain, leg pain and SF-36. Both groups had significant

improvements in clinical outcomes but at 2 years follow up there was no statistically significant difference between the two groups. Similar results were observed in a recently published RCT of 197 patients with a 4 years follow up (Hurlbert et al., 2013). After 4 years of follow up, radiographical fusion rates remained significantly higher in patients treated with rhBMP-2 (94%) than those who received autograft (69%) (P = 0.007). However, SF-36, ODI and leg/back pain scores were comparable between the 2 groups.

The rate of non-union at 2 years postoperative was significantly lower in the rhBMP-2 groups (including off-label use) and was approximately half that of the ICBG groups. However, this did not lead to similar improvement for patient centred outcomes and funnel plot analysis indicated an asymmetry of published results, with a tendency to underestimate the non-union risk for rhBMP-2, this may be suggestive of a publication bias (Noshchenko et al., 2014).

Subgroup analysis by type of surgery: anterior lumbar spine (ALIF) and posterior lumbar spine (PLF or PLIF) found similar results for fusion rates and clinical outcomes (Fu et al., 2013).

Radiological fusion and patient related clinical outcomes:

As radiological fusion is used as the primary outcome measure, the clinical relevance of successful fusion after lumbar arthrodesis with rhBMP-2 or ICBG was studied in a meta-analysis by Noshchenko et al. (2015). This study concluded that patients who had radiological fusion had significantly better clinical outcome measures (ODI and Numeric Rating Scales (NRS) for back and leg pain) but fusion used on its own was a poor predictor of clinical outcomes, indicating that other factors contributed to patient related clinical outcome measures.

Overall, it can be concluded that successful fusion using rhBMP-2 is not strongly correlated with improvement in clinical outcomes and it should be noted that no trials were independent of industry sponsorship.

Safety:

The initial reports from industry sponsored trials reported low levels of side effects resulting from the use of rhBMP-2. However, a systematic review by Carragee et al. (2011) reported that adverse events associated with rhBMP-2 use in spine fusion ranged from 10% to 50% (depending on approach) in comparison to the 0% reported in some industry sponsored trials.

Adverse events for ALIF were not directly reported however anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events in the early postoperative period, including life-threatening events. Posterior lumbar interbody fusion (PLIF) use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to, or greater than, that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early adverse events of back pain and leg pain. Higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy (Carragee et al., 2011).

Similar levels of side effects from rhBMP-2 have been reported in other reviews. A meta-analysis, involving 184,324 patients (28,815 rhBMP-2 group, 155,509 ICBG group) from 26 studies published between 2002-2013 by Vavken et al. (2015), reported significantly higher risk of general complications with rhBMP-2 compared to iliac crest bone graft (ICBG) with an odds ratio (OR) of 1.78 (95% CI 1.20–2.63, p = 0.004). The OR for heterotrophic ossification (HO) was 5.57 (95% CI 1.90–16.36, p = 0.002), for retrograde ejaculation 3.31 (95% CI 1.20–9.09, p = 0.020), and for cervical swelling 4.72 (95%CI 1.42–15.67, p = 0.011), all significantly higher in the rhBMP-2 group. Other outcomes such as perioperative clinical outcomes including blood loss, complications/adverse events, and hospital stay were not significantly different between the rhBMP-2 and ICBG groups.

A recent study retrospectively analysed data from 460,773 patients who underwent lumbar spine fusion either without rhBMP-2 (69.3%) or with (30.7%) (Savage et al, 2015). A slightly lower complication rate was reported with rhBMP-2 group (18.2%) compared to the control group (18.7%). This difference did not appear to be very significant (Relative Risk (RR) 0.976 (CI 0.963–0.989) (p < 0.001). In both treatment groups, patients older than 65 years had a significantly higher risk of postoperative complications than the younger patients (p < 0.001). However in patients younger than 65 years, those treated with rhBMP-2 had higher rate of complications compared to control group (Relative Risk (RR)1.042 (CI 1.017–1.067, p<0.001), whereas in the patients ≥ 65 years old, the opposite was true i.e. lower complication rates in rhBMP-2 group (Relative Risk (RR) 0.950 (CI 0.935–0.065). For both males and females, the complication rates were lower in the rhBMP-2 group than in the

control group but it was only significantly lower in females (Relative Risk (RR) of 0.974 [CI 0.953–0.995,

p=0.015] in males and 0.976 [Cl 0.960–0.993, p=0.005] in females). The authors also report 90-day reoperation rates of 1.84% in the control group, which was significantly lower compared to 2.03% in the rhBMP-2 group (Relative Risk (RR) 1.108 (Cl 1.060–1.158, p<0.01). In both the control and rhBMP-2 groups, patients younger than 65 years were more likely to have a reoperation than patients older than 65 years (p < 0.001). Although this is a large study the difference in response (overall, age, and gender specific) for rhBMP-2 and non-rhBMP-2 patients cited by the authors has limited implication in a real world setting given the nearly 1 relative risk in all cases.

The outcomes that favoured rhBMP-2 compared to ICBG were mean operative time for patients, which was significantly less for patients treated with rhBMP-2 than that of patients who underwent ICBG harvest, and the number of patients requiring additional surgical treatment during 2 postoperative years, which was also significantly lower in the rhBMP-2 groups (Zhang et al., 2014).

Nearly 50% of the patients who underwent lumbar fusion with ICBG experienced donor site pain at 2 years follow up and the risk of complications at the ICBG donor site was 7% (Noshchenko et al., 2014).

Cost effectiveness:

The evidence of cost effectiveness is based on two studies, one systematic review of studies evaluating cost effectiveness of rhBMP-2 against ICBG (Hsu et al., 2014) and one cost utility analysis in 33 patients receiving posterior lumbar fusion using rhBMP-2 (Alvin et al., 2014).

The systematic review included 5 studies (Polly et al., 2003; Garrison et al., 2007; Alt et al., 2009; Carreon et al., 2009; AHRQ, 2010) that compared fusion with rhBMP-2 to fusion with ICBG in patients with degenerative disease of the lumbar spine. In all cases, 2 year time horizon was used and no discounting was performed. All relied on a single non inferiority randomized trial (Burkus et al., 2002) for clinical data that served as the pivotal trial for FDA approval of Medtronic Sofamor Danek Inc., (Memphis, TN) Infuse (rhBMP-2). Two studies (AHRQ, 2010; Garrison et al., 2007) relied solely on this RCT, one (Alt et al., 2009) also used data from 2 other nonrandomized trials of the same grafts inserted laparoscopically, and one (Polly et al., 2003) also used expert opinion. Two studies (AHRQ, 2010; Garrison et al., 2007) undertook cost-utility analyses (CUA) from a payer perspective. Both derived utility estimates from unpublished preoperative and 6-month SF-36 data from the trial.

There were conflicting conclusions reached depending on the type of data used, cost-measurement methods and study design. For example, the National Health Service study used cost of treatment and hospitalization data from the United Kingdom and concluded that rhBMP-2 was not cost-effective. rhBMP-2 versus ICBG was associated with £120,390 per QALY gained. No sensitivity analysis was performed.

Conversely, Alt et al. (2009) reported data including return-to-work parameters from 3 different European countries and concluded that the increased loss of productivity seen from the ICBG group resulted in a savings with use of rhBMP-2 per patient. Outcome measures used in the analysis included need for secondary surgery and return-to-work. Compared with ICBG, rhBMP-2 use resulted in savings ranging from £236 to £529 per patient as a result of decreased rates of secondary surgery and £4938 to £5450 savings from prevented lost productivity. The authors concluded that from a societal perspective, use of rhBMP-2 resulted in savings over time that offset the higher upfront cost of rhBMP-2 use compared with ICBG. All of the studies in the review had limitations including: lack of time horizon discounting, basis on a single RCT with a short time scale (2 years), lack of sensitivity analysis (Alt et al., 2009; Carreon et al., 2009) and no inclusion of indirect costs in all except Alt et al. (2009). All studies except AHRQ (2010) and Garrison et al. (2007) were linked to sponsoring from manufacturers of rhBMP-2. In another study, Alvin et al. (2014) demonstrated that the 1-year cost-utility ratio (Total Cost/ΔQALY) for the ICBG cohort was significantly lower (£94,177/QALY gained) than that of the rhBMP-2 cohort (£179,092/QALY gained) (P<0.01).

A cost effective analysis by Virk et al. (2012) suggested that while rhBMP-2 has better cost per QALY (£10,910/QALY) compared to ICBG (£14,008/QALY), the sensitivity analysis shows that rhBMP2 is not the most cost-effective option if the revision rate is significantly raised. This is significant considering that the findings from a recent population level study by Savage et al. (2015) showed that the 90 day reoperation rate in a group using rhBMP-2 for lumbar spinal fusion was significantly higher than group using non- rhBMP-2 methods (RR1.108, CI 1.060–1.158).

Based on the current evidence it can be concluded that there is no clear evidence that using rhBMP-2 is more cost effective than ICBG. If anything, the evidence suggests that the cost per QALY of rhBMP-2 is higher than ICBG but this is based on studies with low levels of evidence and study design, and industry sponsorship.

[Original figures provided in euros and US dollars were converted to the nearest full pound based on conversion rate on 17/11/2015 of £1 to 1.43 euro and £1 to \$1.52 and is provided as a guideline for comparison only]

This clinical evidence review also considered the following specific questions related to the clinical effectiveness, safety and cost effectiveness of bone morphogenetic protein-2 (rhBMP-2)

Question 1: Is the use of rhBMP-2 safe and effective (in terms of clinical and radiographical outcomes) when used in adults for revision spinal fusion surgery when autologous bone graft (ABG) has previously been used and failed to achieve union (pseudoarthrosis)?

Question 2: Is the use of rhBMP-2 safe and effective (in terms of clinical and radiographical outcomes) when used in adults for primary spinal fusion surgery where there is high risk of pseudoarthrosis compared with autologous bone graft (ABG) alone?

Response to question 1:

Evidence on the use of rhBMP-2 in revision spinal fusion surgery is available from one retrospective cohort study by Taghavi et al. (2010), however this considered posterior lumbar fusion only. The objective of this study was to determine the efficacy of rhBMP-2 or local bone, to either allograft combined with bone marrow aspirate (BMA) or autograft, in revision instrumented, posterolateral fusions (PLF). Indications for revision surgery included: symptomatic pseudoarthrosis (pain and/or instability) following a previous PLF for degenerative conditions of the lumbar spine, such as degenerative disc disease, stenosis, or spondylolisthesis. Sixty-two patients were divided into 3 groups: Group 1 (n = 24) received rhBMP-2, Group 2 (n = 18) received BMA/allograft, and Group 3 (n = 20) received autograft. The exact source of autograft bone for Group 3 was not clearly defined. All 3 cohorts received supplemental local bone. Static and dynamic radiographs were used to assess fusion and clinical outcome was determined through Visual Analogue Scale (VAS) scores. At 2 years follow up, there was no difference between group 1 and 3, a fusion rate of 100% was observed for both groups. Similarly, no difference in VAS score was observed between group 1 and group 3.

The ability to generalise the results is limited due to the retrospective nature of the study design and small sample size.

Dorward et al. (2013) evaluated cervical fusion rates with rhBMP-2 in 57 patients, this group included 48 patients (84.2%) who had undergone previous cervical surgery, and 42.1% who had a pre-existing non-union. Successful fusion was seen in 89.5% of patients. The neurologic symptoms were resolved postoperatively in 50 patients (87.7%) and both VAS and Neck Disability Index (NDI) scores improved significantly from baseline. The results were not provided in subgroups by previous surgery or non-union. The study is also limited by the lack of a comparator group, a lack of randomisation and small sample size.

Response to question 2:

There are a limited number of studies evaluating the risk of pseudoarthrosis when using rhBMP-2 in people with one or more risk factors.

A study by Lee et al. (2013) compared fusion rates for rhBMP-2 versus autograft in patients with fusion-related risk factors. Fusion related high risk factors were defined as i) old age (>65 years) ii) pseudoarthrosis with a T-score of less than -2.5 based on dual energy X-ray absorptiometry iii) those who had continuously smoked for at least 1 year before surgery (iv) postoperative, medical comorbidities, including those who were receiving treatment for 2 or more concurrent medical diseases such as diabetes mellitus, hypertension, and thyroid disease v) revision surgery including cases in which surgery was performed for pseudoarthrosis, or vi) multilevel fusion cases in which >2 levels were surgically treated. One hundred and ninety-five patients were divided into 4 groups depending on fusion material and the presence/absence of fusion-related risk factors for non-union; Group A was defined as rhBMP-2 used in the presence of high-risk factors (FRRF), group B was defined as rhBMP-2 used in the absence of FRRF, group C was defined as autograft used in the presence of FRRF.

Although time to fusion was faster in group A than in group C in all fusion-related risk factors (age, sex, revision, fusion level, smoking, DM, osteoporosis, and comorbidity), there was no statistically significant difference between groups A and C at 2 years follow up. Similarly, fusion rate was higher in group A than in group C in other fusion related risk factors, except revision surgery but there was no statistically significant difference between groups A and C in all fusion-related risk factors.

There was no significant difference in results for subjects who were over 65 years of age or for smokers.

3. Research questions

1. Is the use of rhBMP-2 safe and effective (in terms of clinical and radiographical outcomes) when used in adults for revision spinal fusion surgery when autologous bone graft (ABG) has previously been used and failed to achieve union (pseudoarthrosis)?

2. Is the use of rhBMP-2 safe and effective (in terms of clinical and radiographical outcomes) when used in adults for primary spinal fusion surgery where there is high risk of pseudoarthrosis compared with autologous bone graft (ABG) alone?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix 1

Level	Study of	design a	nd interve	ention		Outcomes					Reference			Other
Level of	Study	Study size	Intervention	Category	Primary	Primary Result	Secondary	Secondary	Study	Study	Reference	Complication	Benefits	Comments
evidence	design				Outcome		Outcome	Result	Endpoint	Endpoint Result		s noted	noted	
1+	Systemati c	Of the 5 studies, 3 studies are based on one RCT with 279 subject, one is based on 1 RCT and 2 prospectiv e studies and 6th is based on a RCT with 106 patients	BMP	Cost effectiveness	Cost per QALY, Incremental cost per QALY per year, reduces costs from societal perspective calculated as reduced need for secondary surgery, and average prevented lost productivity	Among the 5 studies that met the inclusion criteria to compare cost-effectiveness of rhBMP-2 versus ICBG, discordant conclusions were reached depending on the type of data used, cost-measurement methods, and study design. For example, the National Health Service study used cost of treatment and hospitalisation data from the United Kingdom and concluded that rhBMP-2 was not cost-effective. Conversely, Alt et al reported data including return-to-work parameters from 3 different European countries and concluded that the increased loss of productivity seen from the ICBG group resulted in a savings with use of BMP per patient. Finally, the AHRQStudy used Centers for Medicare & Medicaid Services cost data for initial and secondary interventions and concluded that thBMP-2 would be cost-effective compared with ICBG if there was no additional cost for the product; however, at a price of \$3000, there was no significant difference.	None	-			Hsu, Wellington K.; Hashimoto, Robin E.; Berven, Sigurd H.; Nassr, Ahmad. Biological subsitutes/extende rs for spinal arthrodesis: which agents are cost- effective?. Spine. 2014,		As in primary outcome measures	Population: Lumbar spine 1-level. DDD and disabiling symptoms for ≿ 6months. 42.5+ years. Comments: This systematic review of cost effectiveness was designed to evaluate: 1. Is there evidence to suggest that the use of rhBMP-2 for spinal arthrodesis is cost-effective compared with the use of iliac crest bone graft (ICBG)? 2. Is there evidence to suggest that the use of allograft or bone graft extenders (demineralised bone matrices, synthetic carriers, and allogeneic stem cell products) is cost-effective in spinal arthrodesis compared with the use of ICBG? 3. Are there differences in cost-effectiveness with the use of allograft bone versus polyetheretherketone cages with bone graft substitutes in anterior cervical discectomy and fusion (ACDF). There were 5 studies that met the inclusion criteria to compare cost-effectiveness of Q1 rhBMP-2 versus ICBG (AHRQ 2010; Alt et al., 2009; Carreon et al., 2009; Garrison et al., 2007; Polly et al., 2003). There were discordant conclusions reached depending on the type of data used, cost- measurement methods, and study design. For example, the National Health Service study used cost of treatment and hospitalisation data from the UK and concluded that rhBMP-2 was not cost-effective. Anterior lumbar interbody fusion with rhBMP-2 versus ICBG was associated with £120,390 per QALY gained, and thus is not likely to be cost effective, depending on the willingness to pay threshold. No sensitivity analysis was performed. Conversely, Alt et al. (2009) reported data including return-to-work parameters from 3 different European countries and concluded that the increased loss of productivity seen from the ICBG group resulted in a savings with use of BMP per patient. Outcome measures used in the analysis included need for secondary surgery and return-to-work. Costs included in the analysis were those of the initial treatment, secondary surgery, and rest resulted in savings from avoiding lost productivity accounted for 82% to 92% of the overall savings as eassociated with tPMD-2 to escrum

1		0 1 1	4400	5	01: : 1			0 5 5							
	1++	Systemati	1138	Bone	Clinical	Patient-centred	The pooled 2-year postoperative clinical outcomes were	Complications	-	-	-	Nosnchenko,	-	-	Population: Degenerative disk disease. Varying ages.
		С		Morphogene	effectiveness of	clinical	equivalent in BMP and ICBG groups, and exceeded minimum	requiring				Andriy; Hoffecker,			Comments: This is an independently conducted, well designed and presented meta-
				tic Protein	the intervention	evaluations	clinically important differences for Oswestry Disability Index. SF-	additional				Lilian: Lindley.			analysis of studies comparing rhBMP-2 with ICBG. The study has clear eligibility criteria
						boforo and 24	26 (physical scale) and numeric rating scale (back pain) ICBG	surgical				Emily M : Burgor			with inclusion and exclusion criteria, primary and secondary outcomes. The risk of higs
						before and 24	oo (physical scale), and numeric rating scale (back pain). IODO	Surgioui				Emily M., Darger,			with inclusion and exclusion of reliable uses deep using the 40 extension and exclusion and but the
						months after	was associated with increased pain and complications at the	treatment during				Evalina L.; Cain,			assessment and evaluation of validity was done using the 12 criteria recommended by the
						surgery,	donor site (P<0.01). The pooled average operative time was 21	the 24 months				Christopher M. J.;			Cochrane review group. Data extraction and assessment of clinical relevance was done
						including:	minutes less in BMP versus ICBG (P<0.001). The pooled rate	follow-up. (2)				Patel, Vikas V			by two reviewers independently. Robust statistical methods were used to assess
						Oswestry	of additional surgical treatment was 2 times less in the BMP	Non-union (fusion				Perioperative and			heterogeneity, clinical relevance was assessed using questions recommended by
						Disability Index	than in the ICBG groups (P=0.006). The pooled risk of non-	failure) at 24.				long-term clinical			Cochrane Back Review Group. A random effect model was used in the meta-analysis and
						(ODI) OF 00						iong term ennioar			obernane back review ordap. A random circle model was used in the meta analysis and
						(ODI), SF-36,	union at 24-month follow-up was 2 times less in the BMP than in	month follow-up.				outcomes for bone			runnel plots and statistics tests (Egger's and Begg's) were done to assess publication
						back and leg	the ICBG groups (P=0.037), however, this effect was likely	(3) Donor site				morphogenetic			bias. The pooled 2-year postoperative clinical outcomes were equivalent in the rhBMP-2
						pain numeric	biased.	complications. (4)				protein versus iliac			and ICBG groups, and exceeded minimum clinically important differences for ODI, SF-36
						or analog		Donor site pain at				crest bone graft for			(physical scale), and numeric rating scale (back pain). ICBG was associated with
						scales rate of		24-month follow-				lumbar fusion in			increased pain and complications at the donor site (P<0.01). The pooled average
						socios, rate or		24 110101110100				degenerative diek			apprentive time was 21 minutes less in rhDMD 2 versus ICBC (D -0.001). The pooled rotage
						patients		up.				degenerative disk			operative time was 21 minutes less in movie-2 versus ICBG (F<0.001). The pooled rate
						satisfied with		(5) Wound				disease: systematic			of additional surgical treatment was 2 times less in the rhBMP-2 than in the ICBG groups
						surgical		infection. (6)				review with meta-			(P=0.006). The pooled risk of non-union at 24-month follow-up was 2 times less in the
						treatment		Employment				analysis, J Spinal			rhBMP-2 than in the ICBG groups (P=0.037). Some of the limitations of this review, as
						outcome (2)		before and after				Disord Tech 2014			recognised by the authors, include: low quality of studies included (as evaluated using
						Daries estive		summers (7)				510010 10011 2011			On the second seco
						Perioperative		surgery. (7)							Cochrane review group quality assessment tool), lack of double blinding and the majority
						outcomes:		Bone/graft							of the trials were sponsored by the manufacturers.
						operative time		resorption. (8)							
						(min), blood		Ectopic or							
						loss (ml.)		heterotopic bone							
						loss (IIIL),		formation (0)							
						nospital stay		rormation. (9)							
						(day),		Retrograde							
						complications/		ejaculation. (10)							
						adverse events		Postoperative							
						(rate)		back/leg pain or							
						(iate).		backley pain of							
								radiculopathy.							
								(11)							
								Postoperative							
								cancer risk.							
								ourioor non.							
	0	RCT	140	C1-C2 fusion	Clinical	Operative	The fusion rate was 82.4% (56 of 68) in the rhBMP-2/ACS	None	-	-	-	Yan, Liang; Chang,	There were	As in primary	Population: C1-C2 fusion for age related cervical spine conditions. 60+ years.
				with iliac	effectiveness of	time.	group and 78.7% (52 of 66) in the ICBG group (P=.782). Mean					Zhen: He, Baorong:	more wound	outcome	Comments: This study is published as and RCT however no full text was available from
				crost bono	the intervention	octimated	fusion time was 11 days charter in the rhBMP 2/ACS group					Liu Tuonijona:	complication	moacuro	the publichers so it is difficult to commont on the generalizability of the results due to lack
				clest bolle		esumateu	rusion une was in days shorter in the motivit -2/ACG group					Liu, Tuanjiany,	complication	measure	the publishers so it is difficult to comment on the generalisability of the results due to lack
				graft (ICBG)		blood loss,	(81.8±29.4 days) than in the ICBG group (92.9±23.7 days)					Wang, Xiaodong;	s requiring		of info on study methodology and analysis. However, the results suggest that there was
						hospital length	(P=.034). There were more wound complications requiring					Guo, Hua; Hao,	treatment in		no significant difference in the fusion rate of C1 C2 vertebrae but the group using rhBMP-
						of stay, clinical	treatment in the rhBMP-2/ACS group (n=6; 8.8%) than in the					Dingjun. Efficacy of	the rhBMP-		2+ICBG had shorter healing time and higher rate of wound complication requiring
						results.	ICBG group (n=2: 3.0%), although this was not statistically					rhBMP-2 versus	2/ACS group		treatment.
						norionorativo	cignificant (P- 119)					iliac croct bono	(n=6: 9.9%)		
						penoperative	Signinoani (F=.110).					liac crest borie	(11=0, 0.076)		
						complications,						graft for posterior	than in the		
						fusion rate,						C1-C2 fusion in	ICBG group		
						fusion time.						patients older than	(n=2: 3.0%).		
						and rovision						60 voore	although this		
						and revision							aimougininis		
						rate.						Orthopedics. 2014	was not		
													statistically		
													significant		
						1		1					(P-118)		
						1							(1 =. 110).		
				1		1		1	1			1			
						1		1							
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1++	Systemati c	1852	rhBMP	Clinical effectiveness of the intervention	(1) solid fusion rate, (2) clinica outcomes, (3) complications, and (4) the reoperation rate.	BMPs group significantly increased fusion rate (RR: 1.13; 95% C1 1.05–1.23, P = 0.001), while there was no statistical difference in overall success of clinical outcomes (RR: 1.04; 95% C1 0.95–1.13, P = 0.38) and complications (RR: 0.06; 95% C1 0.85–1.09, p = 0.54). A significant reduction of the reoperation rate was found in BMPs group (RR: 0.57; 95% C1 0.42–0.77, p = 0.0002). Subgroup analysis of the fusion rate stratified by the two types of BMPs yielded different results. Compared with ICBG, the use of BMP-2 ratio increase solid fusion rate, by contrast, pooled BMP-7 studies do not have similar effects.	(1) the operation time and blood loss, and hospital stay, (2) patient satisfaction with the treatment, (3) work status and return to work rate.	BMPs group had a significantly lower operating time (MD- 0.32; 95% CI20.55, 20.08; P = 0.009), but no significant difference was found in the blood loss, the hospital stay, patient satisfaction, and work status.	-	-	Zhang, Haifei; Wang, Feng; Ding, Lin; Zhang, Zhiyu; Sun, Deri; Feng, Xinmin; An, Jiuli; Zhu, Yue. A meta analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous lifac crest bone graft. PLoS ONE. 2014	As in secondary outcome results	-	Population: Adult patients suffering from degenerative conditions of the lumbar spine requiring fusion; the main intervention was lumbar fusion. rhBMP-2 and rhBMP-7. Mean age of studies ranged from 40 - 73 yrs with majority of studies in the 40 - 50 years age range. Comments: This is an independently conducted, well designed and presented metaanalysis of studies comparing BMP with ICBG published between 2000-Nov 2013. The study has clear eligibility criteria with inclusion and exclusion criteria, primary and secondary outcomes. The risk of bias assessment and evaluation of validity was done using the 12 criteria recommended by the Corkrane review group. Data extraction and assessment of clinical relevance was done two reviewers independently. Robust statistical methods were used to assess heterogeneity, clinical relevance was assessed using questions recommended by Cochrane Back Review Group. A random effect model was used in the metaanalysis and Funnel plots and statistics tests (Egger's and Beggs's test were done to assess publication bias. Quasi-RCT and non-RCTs were excluded from the study and the quality of the overall evidence for each individual outcome was evaluated using GRADE system. The results of the metaanalysis showed that compared with ICBG. BMPs in lumbar fusion can increase the fusion rate, while reduce the reoperation rate and operating time. However, it doesn't increase the complication rate, the amount of blood loss and hospital stay. No significant difference was found in the overall success of clinical outcome of the two groups. However some limitation of this review as recognised by the authors including low quality of studies included as evaluated using Cochrane review group quality assessment tool, lack of double blinding and majority of the trails were sponsored by the manufacturers. Also as the search was restricted to reports of published RCTs only this could have resulted inclusion of studies with positive and statistically significant results only.
1+	RCT	197	Recombinar t human bone morphogene tic protein (rhBMP-2)	Clinical effectiveness of the intervention	Radiographical fusion rate and clinical outcome for surgical lumban arthrodesis	After 4 years of follow-up, radiographical fusion rates remained significantly higher in patients treated with rhBMP-2 (94%) than those who received autograft (99%) (P = 0.007). However 36- lem Short Form Health Survey, Oswestry Disability Index, and leg/back pain scores were comparable between the 2 groups. ICBG group experienced significantly more graft-site complications.		-	-	-	Hurlbert, R. John; Alexander, David; Bailey, Stewart; Mahood, James; Abraham, Ed; McBroom, Robert; Jodoin, Alain; Fisher, Charles. rhBMP-2 for posterolateral instrumented lumbar fusion: a multicenter prospective randomized controlled trial. Spine. 2013	-	-	Population: Degenerative disc disease with corresponding back and/ or leg pain necessitating instrumented fusion. Failure of conservative (nonsurgical) care for at least 6 months. Adults, 18+ years. Comments: A RCT comparing ICBG with rhBMP-2 with main primary outcome being radiological fusion rate. After 4 years of follow-up, radiographical fusion rates remained significantly higher in patients treated with rhBMP-2 (494) than those who received autograft (69%) (P = 0.007). However SF-36, ODI, and leg/back pain scores were comparable between the 2 groups. The ICBG group experienced significantly more graft- site complications. Main limitations of the study are: lack of clear methodology on randomisation, only mentions patients were randomised to either of the groups at the time of surgery, open label study, only the radiographers who interpreted the x-rays were blinded. Lack of blinding likely to create bias for patient reported outcomes including SF36, ODI. This study was also funded by the manufacturer- Medtronic.

4	Oursteam 1	Antonio	+ DMD0	Olisiaal	Euclide est	ALIE Madente strength wideness of an energy of 199	Mana	<u>г г</u>			E. Danamak			Description: A duit anti-standa with about a low boot and a low boot of the first o
1++	Systemati	Anterior	mBMP2	Clinical	Fusion rates,	ALIF: Moderate-strength evidence of no consistent differences	None	-	-	-	Fu, Rongwei;	-	-	Population: Adult patients with chronic low back pain and a lumbar disc degenerative
	с	Lunmbar		effectiveness of	Adverse	between rhBMP-2 and ICBG in overall success, fusion rates, or					Selph, Shelley;			condition. Mean age varied form 40- 57.6 years. Anterior Lumbar Interbody Fusion (ALIF),
		Interbody		the intervention	events	other effectiveness measures from 6 weeks through 24 months					McDonagh, Marian;			Posterior Lumbar body Fusion (PLF), Posterior Lumbar Interbody Fusion (PLIF) and
		fusion			including	after surgery. The rhBMP-2 group had 3 points higher than					Peterson, Kimberly;			cervical spine fusion.
		(ALIF) 465			retrograde	ICBG group for SF-36 score at 3, 6, 12, and 24 months but not					Tiwari, Arpita;			Comments: A large scale, independent meta-analysis based on individual participant data
		patients			ejaculation,	statistically different. At 24 months, fusion rates ranged from					Chou, Roger;			obtained from the manufacturer and published data conducted as part of The Yale
		from 5			urine retention	, 60% - 100%, and the average overall success rate was 61% for					Helfand, Mark.			University Open Data Access (YODA) Project. The paper included sound methodology
		RCTS.			subsidence,	the rhBMP-2 group and 53% for the ICBG group and was not					Effectiveness and			including: search strategy, inclusion criteria, stattical analysis for heterogeneity, bias and
		Posterior			ectopic bone	statistically different. Adverse events were common.					harms of			quality of studies and presenetaion of data as CI. Although the rhBMP-2 had higher rates
		Lumbar			formation,	Metaanalysis showed no significant differences between groups					recombinant			of fusion at 24 months for both ALIF and PLF, it was not statistically different from ICBG.
		Fusion			cancer and	for any specific adverse event, including lumbar radiculitis,					human bone			Similarly, there was no difference bewteen the two group for patient related factors
		722			death	although estimates were frequently imprecise, precluding strong					morphogenetic			measured using ODI and SF36 . The adverse events were common. Meta-analysis
		patients				conclusions. For retrograde ejaculation, subsidence (defined as					protein-2 in spine			showed no significant differences between groups for any specific adverse event,
		from 5				sinking or settling of the device into bone), and urogenital					fusion: a systematic			including lumbar radiculitis, although estimates were frequently imprecise, precluding
		RCTs,				problems, risk estimates favoured ICBG but the differences					review and meta-			strong conclusions. For retrograde ejaculation, subsidence (defined as sinking or settling
		PLIF-67				were not statistically significant. PLF: There was moderate-					analysis. Ann.			of the device into bone), and urogenital problems, risk estimates favoured ICBG but the
		from 1				strength evidence of no consistent difference between rhBMP-2					Intern, Med., 2013			differences were not statistically significant. The results of the study are generalisable and
		RCT				and ICBG in effectiveness outcomes through 24 months. The								few limitations of the meta-analysis, as noted by the authors, include lack of blinding for
		-				fusion rate at 24 months ranged from 70% to 90% in the ICBG								outcome assessment and ascertaintment of harms was poor in trials. All studies included
						group and 86% to 100% in the rhBMP-2 group; the rate of								had links to industry.
						overall success ranged from 40% to 60% in both groups. No								
						significant difference were observed between the rhBMP-2 and								
						ICBG groups in adverse events. But authors comment that								
						estimates were frequently imprecise precluding strong								
						conclusions. The only excention was that the rhBMP-2 group								
						had increased risk for back and leg pain through 4 weeks								
						although avants unrelated to fusion surrany could not be not								
						ruled out. Convised Spine Eusion: Read on small study (n. 32)								
						the MD 2 and ICRC did not differ in effectiveness and points								
						HBMP-2 and ICBG did hot differ in enectiveness end points.								
						mBiviP-2 was associated with a greater risk for adverse events								
						than ICBG at 24 months (45 adverse events in 18 patients vs.								
						13 adverse events in 15 patients; rate ratio, 2.88 [CI, 1.30 to								
						6.41J). Evidence from observational studies suggest that mBMP								
						2 was associated with significant increased risk for								
						complications (odds ratio, 1.43 [CI, 1.12 to 1.70]), dysphagia or								
						dysphonia (odds ratio, 1.63 [CI, 1.30 to 2.05]), and wound								
						complications (odds ratio, 1.67 [CI, 1.10 to 2.53]). In posterior								
						cervical spine fusion, there were no controlled trials of rhBMP-2								
						and 1 cohort study showed no difference in rates of major								
						complications.								
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1++	Systemati	1408	rhBMP2	Clinical	In addition	At 24 months, pain assessed by ODI scores were 3.5% lower	Return to work,	There was no	-	-	Simmonds, Mark		Population: Degenerative disc disease. Mean age of participants in trials 40 - 70 years.
	С			effectiveness of	fusion primary	(better) with rhBMP-2 than with ICBG (95% CI, 0.5% to 6.5%)	hospital stay,	difference in			C.; Brown, Jennifer		Anterior lumbar fusion, posterior lumbar fusion, anteror cervical fusion.
				the intervention	outcomes	and radiographic fusion was 12% higher (CI, 2% to 23%). At or	operating	duration of			V. E.: Heirs, Morag		Comments: This is another large scale, independent meta-analysis based on Individual
					were those	shortly after surgery, pain was more common with rhBMP-2	timeadverse	hospital stay			K Higgins Julian		Participant data obtained from manufacturer and published data conducted as part of The
					likely to be	(adda ratio 1.78 ICL 1.06 to 2.0El). Conser was more common	avento	(maan			D. T. Monnion		Vale University Organ Data Assaga (VODA) Braiget The paper included sound
					likely to be	(odds fallo, 1.76 [Cl, 1.06 to 2.95]). Cancer was more common	eveniis,	(mean			P. L., Marinion,		Tale University Open Data Access (TODA) Project. The paper included sound
					important to	after rhBMP-2 (relative risk, 1.98 [CI, 0.86 to 4.54]), but the		difference, -			Richard J.;		methodology, including: search strategy, inclusion criteria, statistical analysis for
					patients	small number of events precluded definite conclusions.A		0.15 days [CI, -			Rodgers, Mark A.;		heterogeneity, bias and quality of studies and presenetation of data as CI. The results of
					including The	subgroup analyses to investigate whether the effectiveness of		0.33 to 0.03			Stewart, Lesley A		the metanalysis demonstrated that at 24 months, rhBMP-2 increases fusion rates,
					Oswestry	rhBMP-2 varied among patients who had anterior lumbar fusion		days]) or that			Safety and		reduces pain by a clinically insignificant amount, and increases early postsurgical pain
					Dischility Index	or posterior lumbar fusion, found no ovidence of a difference in		shRMD 2			offectiveness of		compared with ICBC. Evidence of increased concertingidence is inconclusive. The results
					Disability index	or posterior lumbar rusion, round no evidence or a difference in		IIIDIVIF-2			enectiveness of		compared with ICBG. Evidence of increased cancer incoence is inconclusive. The results
					(ODI) and	the RRs for successful fusion (P=0.88) or any other outcome at		surgery			recombinant		of the study are generalisable and main limitations of the meta-analysis, as noted by the
					Neck Disability	24 months across surgery types.		increased the			human bone		authors, include lack of blinding for outcome assessment and ascertaintment of harms
					Index for			probability of			morphogenetic		was poor in trials. Observational studies included in the reveiw were diverse and at risk of
					cervical spinal			returning to			protein-2 for spinal		bias. Most studies included had links to industry.
					surgery			work or usual			fusion: a meta-		···· ,
					ourgory			a stinite a selies					
					measure lower			activity earlier			analysis or		
					back and neck			compared with			individual-		
					pain,			ICBG (RR at			participant data.		
					respectively,			24 months,			Ann. Intern. Med		
					on a scale			1.01 ICL 0.88			2013		
					from 0% (no			to 1 171) Lising					
					non 078 (no			to 1.17 j). Using					
					pain) to 100%			mBiviP-2					
					(extreme pain).			shortened					
					TheShort Form			operating					
					36 (SF-36)			times by 21					
					Physical			minutes (CL 15					
					Component			to 27 minutos)					
					Component Ourranse (DOC			to 27 minutes)					
					Summary(PCS			from an					
) assesses			average of 135					
					pain and			minutes.					
					physical								
					function on a								
					scale from 0%								
					(warat) to								
					(worst) to								
					100% (best).								
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 Normality in the second second			>	interventio	contained in	intervention	ejaculation	(3.4%) of the 207 patients who received the rhBMP-2 treatment	-				Dryer, Randall F.;		mentioned	for a for a single-level stand-alone ALIF. 19 - 70 years. Subgroups by surgical approach-
Improve Opened Test <				n vs 301	one of the 3			compared with 5 (1.7%) of the 301 patients who received the					Peloza, John H			retroperitoneal vs transperitoneal.
Image: second processing in processing of the second procesecond processing in processing of the second processi				comparat	different			autograft or lumbar disc treatment (p = 0.242, Fisher exact test).					Retrograde			Comments: This is a study reporting on the complication of retrograde ejaculation after
 Instant of the second se				or group)	types of			Retrograde ejaculation occurred at the highest rates in the					ejaculation			interbody surgery among groups treated with rhBMP-2, ICBG or lumbar arthroplasty
** Part P Control of the density of the					intradiscal			earliest clinical trial (Burkus et al 2002). Of the 146 men, 6					following single-			implant. Results from 5 RCTs are combined and presented as rates of complications and
*** Special Description Description <thdescription< th=""> <thdescription< th=""> <thdescript< td=""><td></td><td></td><td></td><td></td><td>implants 1.</td><td></td><td></td><td>(4.1%) developed RE postoperatively. In subsequent studies,</td><td></td><td></td><td></td><td></td><td>level anterior</td><td></td><td></td><td>difference between tested using Fischer exact test. Combining the data from the 5 trials,</td></thdescript<></thdescription<></thdescription<>					implants 1.			(4.1%) developed RE postoperatively. In subsequent studies,					level anterior			difference between tested using Fischer exact test. Combining the data from the 5 trials,
Image: Second					Threaded,			the rates of RE ranged from 0% to 2.1%. The difference in					lumbar surgery with			retrograde ejaculation (RE) was reported in 7 (3.4%) of the 207 patients who received the
Image: Second					tapered			surgical approaches was significant (p = 0.007, Fisher exact					or without			rhBMP-2 treatment compared with 5 (1.7%) of the 301 patients who received the
Image: state in the s					titanium			test). Cases of RE were higher in group who underwent					recombinant			autograft or lumbar disc treatment (p = 0.242, Fisher exact test). RE occurred at the
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1 Provide Light for the standard biology					(burkus			(7/445) patients who underwent a retroperitoneal spinal					morphogenetic			developed RE postoperatively. In subsequent studies, the rates of RE ranged from 0% to
11 Partner Factor Factor <td></td> <td></td> <td></td> <td></td> <td>2002); 2. Threaded</td> <td></td> <td></td> <td>exposure; There was no difference in the rate of RE based on</td> <td></td> <td></td> <td></td> <td></td> <td>protein-2 in 5</td> <td></td> <td></td> <td> Ine difference in surgical approaches was significant (p = 0.007, Fisher exact test). </td>					2002); 2. Threaded			exposure; There was no difference in the rate of RE based on					protein-2 in 5			 Ine difference in surgical approaches was significant (p = 0.007, Fisher exact test).
Image: Second					mieaded,			the fullibal level exposed ($p = 0.739$). Wullivariate analyses					controlled trials:			cases of RE were higher in group who underwent transpentorieal approach (5/56, 8.6%)
 Note: a single bits Note: a single bits<					allograft			were consistent with the considerions from Fighter exact tests.					clinical article .1			There was no difference in the rate of RE based on the lumbar level exposed ($n = 0.739$)
 ¹⁴ Symmet ¹⁴⁰ Symmet ¹⁴¹ Symmet ¹⁴¹ Symmet ¹⁴⁴ Symmet ¹⁴⁴ Symmet ¹⁴⁵ Symmet ¹⁴⁵ Symmet ¹⁴⁵ Symmet ¹⁴⁵ Symmet ¹⁴⁶ Symmet ¹⁴⁶ Symmet ¹⁴⁶ Symmet ¹⁴⁶ Symmet ¹⁴⁶ Symmet ¹⁴⁷ Symmet ¹⁴⁷ Symmet ¹⁴⁶ Symmet ¹⁴⁸ Symmet ¹⁴⁸ Symmet ¹⁴⁸ Symmet ¹⁴⁹ Symmet ¹⁴⁹ Symmet ¹⁴⁹ Symmet ¹⁴¹ Symmet ¹⁴¹					bone dowels								Neurosura Spine.			Multivariate analyses were consistent with the conclusions from Fisher exact tests. The
 We will be a set of basic methods for products by for a set of basic methods for a set of basic methods for products by for a set of basic me					(Burkus								2013			generalisability of the results is limited for number of reasons, including: studies selected
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 Press 2013. The particular statement of the p					Burkus											RCTs conducted by the manufacturer. The quality of studies is not evaluated and there is
 In Backd, Sylawing Carl, Samo L, Samo L,					2002) 3.											no detail on the patient selection or how the heterogeneity was analysed suggesting
Image: Second					Threaded,											possibility of bias. The author of the paper is the author of the 4 RCTs included in the
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1+ Normal Systemati 1342 MBMP2 Clinical Fusion failure. Compared with ICBS, the use of MBMP2 applicativity Non especifically - months probability of the disk dusion failure at all the intervention. Chone, Zhigunang Authors Space manual probability Population: Limbar fusion failure failure failure failure failure failure intervention in the 0.598 (c) = 0.427-0.75; 24 Population: The SF-36 Population: R = 0.52, 955 (c) = 0.427-0.408 and the rate of the failure at all the intervention in the 0.598 (c) = 0.427-0.408 and the rate of the failure and the singht probability of the failure																
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the intervention the Osevestry monthis p=0.0001, RR = 0.35, 95% (C I = 0.27-0.75; 24 monthis p=0.0003, RR = 0.35, 95% (C I = 0.27-0.46) and the physical component is unmary and secondary outcomes. The risk and highly varient with the operation (p = 0.001, RR = 0.35, 95% (C I = 0.37-0.72). There was no statistical difference in clinical summary. The improvement numeric rating on the Osevestry Disability index, attrough a favorable trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and provide trend in scores for leg pain. All objects and statistics trend in the direct object and provide trend in scores for leg pain. All objects and statistics trend in the direct object and provide trend in scores for leg pain. All objects and statistics trend in the relation of the leg pain. The scores for leg pain. All objects and statistics trend in the leg pain. The log provide trend in the leg pain. All objects and statistics trend in the relation of values per- son of the leg pain. All objects and statistics trend in the relation of the left score in on all objects and statistics trend in the relation of values person of the left score in on all objects and statistics trend in the relation of values person of the left score in on all objects and statistics trend in the relation of values person of the log pain. The left score is an object score in on all objects and statistics trend in the relation of the left score in on all objects and statistics trend in the relation of the re		c				effectiveness of	Reoperation,T	decreased the risk of fusion failure at all time intervals (6	mentioned in the				Ba, Gen; Shen,	mention	outcome	40 - 70 years. Instrumental PLF, PLIF, posterolateral interbody fusion (IF) and ALIF.
Disability Index months: p = 0.0003, RR = 0.033, BS % CI = 0.27-0.72; A4 The SF-36 Recombinant eiscuaton and others The SF-36 months: p = 0.0003, RR = 0.33; BS % CI = 0.27-0.72; A4 and others Nama bore are of reoperation (p = 0.0001, RR = 0.33; BS % CI = 0.07-0.72). Three was no statistical difference in clinical summary. The morphogenetic Nama bore are of the disals Nama bore morphogenetic Nama bore bore bore operation Nama bore are of autogenous liac Nama bore morphogenetic Nama bore bore bore operation Nama bore morphogenetic Nama bore bore bore bore operation Nama bore morphogenetic Nama bore bore bore bore bore operation Nama bore morphogenetic Nama bore bore bore bore bore bore bore bore						the intervention	he Oswestry	months: p<0.0001, RR = 0.55, 95 % CI = 0.42-0.72; 12	study				Tao; Fu, Qin.	Retrograde	measure	Comments: This is a independently conducted, meta-analysis of studies comparing
The SF-36 months: p-0.0001, Re 0.5, 95 (Cl = 0.21-0.48) and the pylysical pictor of reoperation (p = 0.0001, Re 0.5, 95 (Cl = 0.001-Re 0.							Disability Index	months: p = 0.0003, RR =0.53, 95 % CI = 0.37-0.75; 24					Recombinant	ejacuation		rhBMP-2 with ICBG published up to Feb 2013. The study has clear eligibility criteria with
physical rate of reoperation (p = 0.000, R = 0.52, 95 % Cl = morphogenetic, but details an ent component 0.37-0.72, There was no statistical difference in clinical morphogenetic, but details an ent scores for the hBMP-2 group was solut (p = 0.012, R = 0.73, 95 % Cl = morphogenetic, and could up a subscore or enter-analysis on adverse events was solution in the tobs assess between group and inter-analysis on adverse events was not performed. pack pain. Adverse point (-0.000, R = 0.48, 95 % Cl = 0.000, R = 0.37, 0.75, 24 months: p-0.0000, R = 0.37, 0.75, 24 months: p-0.0000, R = 0.31, 95 % Cl = 0.40 details assess between group analysis on reduces analysis on adverse events was not performed. normats, meta-analysis on adverse events was not performed. point in the mBMP-2 group was indicating there or in clinical improvement on the O.01, attracting in point in the majority of the trade indicating indindicating indicating indicating indicating indindicating indicati							The SF-36	months: p<0.00001, RR = 0.31, 95 % CI = 0.21-0.46) and the					human bone	and others		inclusion and exclusion criteria, but no primary and secondary outcomes. The risk of bias
comported summary. The umprovement on the Oswestry Disability Index, although a favorable trend in improvement on the Oswestry Disability Index, although a favorable trend in the MBM-P2 optop was sound ($p = 0.12, RR = 0.73, 95 \% Cl =$ the ABM-P2 optop was sound ($p = 0.12, RR = 0.73, 95 \% Cl =$ the ABM-P2 optop was significantly lower than that of the ICBG group (anterior subgroup $p = 0.02, RR = 0.73, 95 \% Cl =$ the ABM-P2 optop was significantly lower than that of the ICBG group (anterior subgroup $p = 0.002, RR = 0.63, 95 \% Cl =$ the randow meta-analysis on adverseprotein - 24 versus adverseCochrane review group and clinical relevance was assessed using questions was camered by Cochrane Back Review Group. Route statistical effect model was used in the meta-analysis on due to assess phticaruly lower than that of the JCBG group (anterior subgroup) $p = 0.002, RR = 0.63, 95 \% Cl = 40.27 - 212 months: p-to moths: p-0.0001, RR = 0.55, 95 \% Cl = 40.27 - 212 months: p-to moths: p-0.0001, RR = 0.55, 95 \% Cl = 40.27 - 212 months: p-to moths: p-0.0001, RR = 0.55, 95 \% Cl = 40.27 - 252, 95 \%$							physical	rate of reoperation (p = 0.0001, RR = 0.52, 95 % CI =					morphogenetic	but details		assessment and evaluation of validity was done using the 12 criteria recommended by the
summary. The improvement numeric rating 0 nHe Oswestry Disability Index, although a favorable trend in the nHBMP-2 group was tout (0 = 0.12, RF = 0.73, 95 % Cl = 0.40-1.081. The result of subgroups, the rate of reoperation in mumeric rating scores for leg pain. Adverse events. R = 0.45, 95 % Cl = 0.32-0.32, 85 % Cl = 0.42-0.72; 12 months: p 0.28-0.88; posterolaterial subgroups, the rate of reoperation in mBMP-2 group was solutificant on the CBG pain. Adverse events. R = 0.45, 95 % Cl = 0.32-0.72; 12 months: p 0.28-0.88; posterolaterial subgroups, p = 0.00, 28, 95 % Cl = 0.42-0.72; 12 months: p 0.28-0.88; posterolaterial subgroups, p = 0.00, 28, 95 % Cl = 0.32-0.72; 12 months: p 0.28-0.89; posterolaterial subgroups, p = 0.00, 28, 95 % Cl = 0.32-0.72; 12 months: p 0.28-0.89; posterolaterial subgroups, p = 0.00, 28, 95 % Cl = 0.32-0.73; 28 % Cl = 0.32-0.72; 12 months: p 0.28-0.89; posterolaterial subgroups, p = 0.00, 28, 95 % Cl = 0.32-0.72; 12 months: p 0.28-0.89; posterolaterial and provement on the ODI, although a formats, meta-analysis on adverse events was not performed.							component	0.37–0.72). There was no statistical difference in clinical					protein-2 versus	are not		Cochrane review group and clinical relevance was assessed using questions
Image: Interformed in the dSweetry Disability Index, atthough a favorable trend in scores for the dSW-2 group was found (p = 0.12, RR = 0.73, 95 % Cl = 0.49-1.08). The result of subgroup analysis on reoperation in the mRM-2 group was significantly decreased the ink of fusion failure numeric rating denomics result of subgroup analysis on reoperation in mBM-2 group was significantly decreased the ink of fusion failure ten randomized pain. Adverse eventsthe result of subgroup analysis on reoperation in mBM-2 group was significantly decreased the ink of fusion failure ten randomized different ten randomized difference in clinical improvements on the ODS, B5 % Cl = 0.26-0.88 (S Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed.the make filteration of the comparison of the compar							summary. The	improvement					autogenous iliac	mentioned,		recommended by Cochrane Back Review Group. Robust statistical methods were used
scores for the thBMP-2 group was found (p = 0.12, RR = 0.73, 95 % Cl = back pian. The past-108). The result of subgroups analysis on reoperation in meta-analysis of aut due to demonstrated that, in both subgroups, the rate of reoperation in mBMP-2 group was significantly lower than that of the ICBG pain. Adverse significantly correctly as significantly lower than that of the ICBG pain. Adverse significantly correctly as significantly correctly as significantly correctly as significantly decreased that, in both subgroups, the rate of reoperation in meta-analysis of aut at formats. Arch Orthop 0.26-0.89; posterolateral subgroup; p = 0.002, RR = 0.54, 95 % Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed. RR = 0.54, 95 % Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed. RR = 0.54, 95 % Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed. RR = 0.54, 95 % Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed. Reference in clinical improvement on the ODI, although a favorable tend in the ribBMP-2 group was seessment ougling of subgroup analyses exertis was not performed. Reference in clinical improvement on the ODI, although a favorable tend in the ribBMP-2 group was seessment ougling of subgroup analyses exerts was not performed. Reference in clinical improvement on the ODI, although a favorable tend in the ribBMP-2 group was seessment ougling of subgroup analyses exerts was not performed. Reference in clinical improvement on the ODI, although a favorable tend in the ribBMP-2 group was seessment ougling of subservice and the real of the period group quality assessment ougling of subservice and the real of the related for adverse events was not performed. Reference in the ribBMP-2 group was seessment ougling of subservice and the real of the related for adverse events was not performed. Reference in the rib							numeric rating	on the Oswestry Disability Index, although a favorable trend in	1				crest bone graft for	The analysis		to assess heterogeneity. A random effect model was used in the meta-analyis and funnel
back pain. The [0.49–1.08]. The result of subgroup, analysis on reoperation numeric rating demonstrated that, in both subgroups, the rate of reoperation in hBMP-2 group was significantly lower than that of the ICBG group (anterior subgroups, the -0.02, RR = 0.48, 95% Cl = 0.28; posterolateral subgroup: p = 0.02, RR = 0.48, 95% Cl = 0.28; 0.08; posterolateral subgroup: p = 0.002, RR = 0.54, 95% Cl = 0.37-0.75; 24 months; p=0.0001, RR = 0.31, 95% Cl = 0.21-0.46) and the rate of reoperation (p = 0.0001, RR = 0.31, 95% Cl = 0.21-0.46) and the rate of reoperation (p = 0.0001, RR = 0.32, 95% Cl = 0.37-0.75; 24 months; p=0.0001, RR = 0.53, 95% Cl = 0.37-0.75; 24 months; p=0.0001, RR = 0.53, 95% Cl = 0.37-0.75; 24 months; p=0.0001, RR = 0.54, 95% Cl = 0.37-0.75; 24 months; p=0.002, RR = 0.54, 95% Cl = 0.32-0.79). Due to different data formats, meta-analysis on adverse events was not performed. Frauma Surg. 2012							scores for	the rhBMP-2 group was found (p = 0.12, RR = 0.73, 95 % CI =					lumbar fusion: a	was carried		plots and statistics tests (Egger's and Begg's) were done to assess publication bias.
humero rating demonstrated that, in both subgroups, the rate of reoperation in gemonstrated that, in both subgroups, the rate of reoperation in sources for leg pain. Adverse pain. Adverse pain. Adverse pain. Adverse events. RP = 0.54, 95% Cl = 0.42, 0.72, 12 months; pc0.0001, RR = 0.53, 95% Cl = 0.42, 0.72, 12 months; pc0.0001, RR = 0.53, 95% Cl = 0.42, 0.72, 12 months; pc0.0001, RR = 0.53, 95% Cl = 0.42, 0.72, 12 months; pc0.0001, RR = 0.53, 95% Cl = 0.42, 0.72, 12 months; pc0.0001, RR = 0.54, 95% Cl = 0.27-0.75; 24 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.72; 2 months; pc0.0001, RR = 0.54, 95% Cl = 0.37-0.73; Distributing of the rhBMP-2 group was low to be different data formats, meta-analysis on adverse events was not performed. For most low to different data formats, meta-analysis on adverse events was not performed. For most low to different data formats, meta-analysis on adverse events was not performed. For most low group quality assessment tool, three of ten included studies included as evaluated using Cochrane review group quality of studies included studies included studies were rated to be with "high risk of bias", lack of double blinding and the majority of the trials were sponsored by manufacturers of BMP.							back pain. The	0.49–1.08). The result of subgroup analysis on reoperation					meta-analysis of	out due to		Compared with ICBG, the use of rhBMP-2 significantly decreased the risk of fusion failure
soores for leg mbMP-2 group was significantly lower than that of the IUBG controlled finals. Idata formats = 0.0003, RR = 0.53, 95 % Cl = 0.37-0.72, 4 months: p = 0.002, RR = 0.54, 95 % Cl = 0.37-0.72, 0.0001, RR = 0.54, 95 % Cl = 0.21-0.46) and the rate of responsible trend in the rbBMP-2 group was significantly lower than that of the IUBG up to the rate of responsible trend in the rbBMP-2 group was significantly lower than that of the IUBG up to the rate of responsible trend in the rbBMP-2 group was significantly lower than that of the IUBG up to the rate of responsible trend in the rbBMP-2 group was significantly lower than that of the IUBG up to the rate of responsible trend in the rbBMP-2 group was significantly lower than the IUBG up to the rate of responsible trend in the rbBMP-2 group was significantly as the rate of responsible trend in the rbBMP-2 group was significantly as the rate of responsible trend in the rbBMP-2 group was significantly as the rotat of the rotat o							numeric rating	demonstrated that, in both subgroups, the rate of reoperation in					ten randomized	differenr		at all time intervals (6 months: p<0.0001, RR = 0.55, 95 % CI = 0.42–0.72; 12 months: p
Pain. Adverse group (anternate of reoperation (p; p = 0.002, RR = 0.43, 95 % CI = 0.37–0.72). events. 0 = 0.002, RR = 0.54, 95 % CI = 0.000, RR = 0.02, BS % CI = 0.000, RS % CI = 0.000, RR = 0.02, BS % CI = 0.000, RR = 0.02, RR = 0.0							scores for leg	INBINE-2 group was significantly lower than that of the ICBG					controlled trials.	data formats		= 0.0003, RR =0.53, 95 % CI = 0.37-0.75; 24 months: p<0.00001, RR = 0.31, 95 % CI =
events. 0.26-0.95, yos 0.2 = 0.02, 49, 5% Cl = 0.36-0.79). Due to different data formats, meta-analysis on adverse events was not performed. frauma Surg. 2012 frauma Surg. 2012 Infere was no statistical improvement on the OUD, approximation of the Inference in clinication of the OUD, approximation of the Inference in clinication of the					1		pain. Adverse	group (anterior subgroup: p = 0.02, KK = 0.48, 95 % CI =	1				Arch Urthop			0.21-0.40) and the rate of reoperation (p = 0.0001, RR = 0.52, 95 % CI = 0.37-0.72).
Image: With a group with a							events.	0.20-0.69; posterolateral subgroup: p = 0.002, DD = 0.54, 05 % Cl = 0.26, 0.70). Due to different data					rauma Surg. 2012			I nere was no statistical difference in clinical improvement on the ODI, although a
101445. Inducation of this review include: low quality of studies included studies were rated to be with "high risk of blas", lack of double blinding and the majority of the trials were sponsored by manufacturers of BMP.								formate, mota analysis on advorce systems and participate								Tavorable trend in the mb/mP-2 group was round (p = 0.12, KK = 0.73, 95 % CI = 0.40, 1.09). Subgroup analyzes stratified by the time of surgical precedure violated similar
Performed. However, some limitation of this relative analysis of adverse events will be included as evaluated using Cochrane review group quality assessment tool, three of ten included as evaluated using Cochrane review group quality assessment tool, three of ten included studies were rated to be with "high risk of bias", lack of double blinding and the majority of the trials were sponsored by manufacturers of BMP.								normais, meta-analysis on adverse events was not performed.								u.es-1.00). Subgroup analyses strattieu by the type of surgical procedure yielded similar results. Due to different data formate, meta analysis on advarea events was not
as evaluated using Cochrane mutature for the matching and the studies included studies were rated to be with "high risk of blas", lack of double blinding and the majority of the trials were sponsored by manufacturers of BMP.							1		1							nesting of a uncerent used rormals, meta-analysis on adverse events was not
studies were sponsored by manufacturers of BMP.																as evaluated using Cochrane review group quality assessment tool, three of ten included
the trials were sponsored by manufacturers of BMP.							1		1							studies were rated to be with "high risk of bias". lack of double blinding and the majority of
							1		1							the trials were sponsored by manufacturers of BMP.
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2+	Systemati c	780	rhBMP-2	Clinical effectiveness of the intervention	Complications from rhBMP2 compared with ICBG	rhBMP-2 use in spine fusion ranging from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life- threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early back pain and leg pain adverse events; higher doess of rhBMP-2 were also associated with a greater apparent risk of new malignancy.	None	-	-	-	Carragee, Eugene J.; Hurwitz, Eric L.; Weiner, Bradley K A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011	As in primary outcome measure	As in primary outcome measure	Population: Patients with lumbar and cervical spondylosis. PLF, PLIF, ALIF and anterior cervical fusion. Comments: This is a systematic review of studies evaluating safety of rhBMP-2 compared with ICBG. This review has clear onbjectives, serach methods and statistical methods. However, the methodology doesn't include polling of data to estimate the effect size and regression methodology to doesn't include polling of data to estimate the effect size and previously reported, low levels of side effects of rhBMP-2, authors found that rhBMP-2 was associated with high levels of adverse effects ranging from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. The generalisation of study are limited in that most of the studies included in the review are retrospective case series with poor patient selection methods and lack of blinding in patient reported measures. However, findings from this study are significant as it highlighted the side effects with rhBMP-2
1+	Systemati c	184324 (28,815 experimen tal, 155,509 controls)	rhBMP-2	Safety of the intervention	General complications, heterotopic ossification (HO), retrograde ejaculation, cervical swelling, and cancer rates with the use of rhBMP-2 in lumbar and cervical spine fusion.	There was a significantly higher risk of general complications with hBMP-2 compared to iliac crest bone graft (ICBG) with an odds ratio (OR) of 1.78 (95 %CI 1.20–2.63), (p = 0.004). The odds ratio for HO was 5.57 (95 %CI 1.90–16.36), (p = 0.002), for retrograde ejaculation 3.31 (95 %CI 1.42–15.67), (p = 0.011), all significantly higher in the rBMP-2 group. The pooled odds ratio for new onset of tumor was 1.35 (95 %CI 0.93–1.96), which represents no statistically significant difference between the groups (p = 0.111).	None	-			Vavken, Julia; Mameghani, Alexander; Vavken, Patrick; Schaeren, Stefan. Complications and cancer rates in spine fusion with recombinant human bone morphogenetic protein-2 (rhBMP- 2). Eur Spine J. 2015	-		Population: Not specified. Mean age was 51.1 +/- 1.8 years. Comments: This is an independently conducted, well designed and presented meta- analysis of studies comparing complications of rh BMP-2 with ICBG using PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) and QUOROM (Quality Of Reporting Of Meta-analysis) statements. The study has clear eligibility criteria with inclusion and exclusion criteria, primary and secondary outcomes. Internal validity of each study was evaluated with modified Jadad scale and publication bias was assessed using funnel plot and Egger's weighted regression technique. There was a significantly higher risk of general complications with rhBMP-2 compared to lilac crest bone graft (ICBG) with an odds ratio (OR) of 1.78 (95 %CI 1.20–2.63), (p = 0.004). The OR for HO was 5.57 (95 %CI 1.90–16.36), (p = 0.002), for retorgrade ejaculation 3.31 (95 %CI 1.20–9.09), (p = 0.020), and for cervical swelling 4.72 (95 %CI 1.42–15.67), (p = 0.011), all significantly higher in the rhBMP-2 group. The pooled OR for new onset of tumour was 1.35 (95 %CI 0.19.9.1–1.6), which represents no statistically significant difference between the groups (p = 0.111). However, some limitations of this review, as recognised by the authors, include low quality of studies, lack of double blinding and the majority of trails were sponsored by the manufacturers.

2.	Cooo	22	de DMD 0	Cost	Destonarativa	1 year cast utility ratio (Total Cast/AOALX) for the control ashert	1 1000	No dotoilo			Ahrin Motthour Di			Deputation: Not appointed
2+	Case	33 potiente	olono or in	offectiveness	1 voor	1-year cost-utility ratio (Total Cost/2QALT) for the control conort	r-year	NU details	-	-	Alvin, Watthew D., Derekkehen	-	-	Commenter A small study of 75 patients in which 22 receiving the PMD 2 in addition to
	selles	patients	alone of in	enectiveness	1-year	was significantly lower (\$143,251/QAL Figained) than that of the	posioperative	available morn			Delakrishan,			Comments. A small study of 75 patients in which 35 received mBMP-2 in addition to
		receiving	addition to		cost/utility	rnBiviP-2 conort (\$272,414/QALY gained) (P<0.01). At 1-year	Health outcomes	the abstarct			Adeeb; Lubeiski,			either local bone autograft of ICBG (mBiviP-2 conort) and 42 patients receiving only local
		mBMP-2	either iocai		ratios and the	to the shows of the control group dominated the ICER compared to	assessed based				Daniel; Abdullan,			bone autograft of ICBG (control conort) for one of two-level dorsal lumbar fusion. Study is
		in addition	bone		incremental	the mBMP-2 group.	on Visual				Kalii G.; Whitmore,			presented with good methodolgy with description tools used in measuring health
		to either	autograft or		cost		Analogue Scale				Robert G.; Benzel,			outcomes and estimation of various costs. Health outcomes were assessed based on
		local bone	ICBG for for		effectiveness		(VAS), Pain				Edward C.; Mroz,			Visual Analogue Scale (VAS), Pain Disability Questionnaire (PDQ), Patient Health
		autograft	one or two-		ratio (ICER)		Disability				Thomas E Cost-			Questionnaire (PHQ-9), and EuroQol-5 Dimensions (EQ-5D) questionnaires. Direct
		or ICBG	level dorsal		to assess for		Questionnaire				utility Analysis of			medical costs were estimated using Medicare national payment amounts and indirect
		(rhBMP-2	lumbar		cost		(PDQ), Patient				One and Two-level			costs were based on patient missed work days and patient income. Postoperative 1-year
		cohort)	fusion		effectiveness		Health				Dorsal Lumbar			cost/utility ratios and the incremental cost effectiveness ratio (ICER) were calculated to
		and 42	includingpost		using a		Questionnaire				Fusions With and			assess for cost effectiveness using a threshold of \$100,000/QALY gained. The 1-year cost
		patients	erolateral		threshold of		(PHQ-9), and				Without			utility ratio (Total Cost/∆QALY) for the control cohort was significantly lower
		receiving	fusion (PLF),		\$100,000/QAL		EuroQol-5				Recombinant			(\$143,251/QALY gained) than that of the rhBMP-2 cohort (\$272,414/QALY gained)
		only local	posterior		Y gained		Dimensions (EQ-				Human Bone			(P<0.01). At 1-year follow-up, the control group dominated the ICER compared to the
		bone	lumbar				5D)				Morphogenic			rhBMP-2 group. By 2 years, the control cohort was considered cost effective
		autograft	interbody				questionnaires.				Protein-2 at 1-year			(\$71,625/QALY gained) compared to (\$136,207/QALY) f or the rhBMP-2 cohort. Main
		or ICBG	fusion				Direct medical				Follow-up. J Spinal			limitations of the study include: it was not a direct comparision of rhBMP-2 against ICBG
		(control	(PLIF), and				costs estimated				Disord Tech. 2014			and lack of randomisation in patient selection methods and lack of blinding, especially for
		cohort) for	transforamin				using. Medicare							the patient reported measures. It is not clear form the methods if there was time horizon
		one or two	al lumbar				national payment							discounting for estimation of cost effectiveness.
		level	interbody				amounts and							
		dorsal	fusion (TLIF				indirect costs							
		lumbar					based on patient							
		fusion					missed work							
							days and patient							
							income							
1			1											
1			1											
			1											

3	Case	57	rhBMP-2	Clinical	Fusion status	Postoperatively, 51 patients (89.5%)	The neurologic	The neurologic	-	-	Dorward, Ian G.:	-	-	Population: Common surgical indications were adjacent-level spondylosis following fusion
-	series	patients		effectiveness of	was	developed fusion, while 6 (10.5%) had radiographic evidence of	symptoms of	symptoms of			Buchowski, Jacob			(35 cases, 61.4%) and symptomatic pseudarthrosis (22 cases, 38.6%). Other indications
		(Forty-		the intervention	determined by	nseudarthrosis	Visual analog	50 natients			M · Stoker			included basilar invagination, postsurgical kyphosis, rheumatoid arthritis, and chronic
		eight			bony bridaina		scale (VAS) pain	(87.7%)			Geoffrey E.:			Ifracture non-union. Mean age 56.1 + 13.6 years.
		patients			on computed		and Neck	resolved			Zebala, Lukas P.			Comments: This is a retrospective study of 57 patients who underwent cervical fusion
		(84.2%)			tomography		Disability Index	nostoperatively			Posterior Cervical			using rbBMP-2 Forty-eight patients (84.2%) had undergone previous cervical surgery
		had			scans		(NDI)	and Visual			Fusion with			and 42 1% had a pre-existing non-union) There was no comparator group and the patient
		undergone			absence of		(analog scale			Recombinant			selection method is poorly described. The results show that 87% achieved fusion and
		previous			radiolucency			(VAS) pain			Human Bone			there was significant improvement in VAS and NDI score from baseline. The primary
		cervical			around			and Neck			Morphogenetic			outcomes are not anlaysed according to previous surgery although the majority of the
		surgery			instrumentation			Disability Index			Protein-2			nations had undergone a cervical fusion surgery. The generalisability of the results is
		and			and absence			(NDI) 26			Complications and			limited by lack of comparator, lack of blinding, and small sample size.
		42.1%			of motion on			scores			Fusion Rate at			,
		had a			lateral			improved			Minimum Two-Year			
		preexisting			flexion/extensio			significantly			Follow-Up. J Spinal			
		nonunion)			n radiographs			from baseline			Disord Tech 2013			
		nonanion,:			maalographio			VAS $(0 = n0)$			210010 10011 2010			
								pain. 10 =						
								maximum						
								pain) fell from						
								a mean of 6.8						
								± 1.8 to 3.9 ±						
								3.1 (P < 0.001)						
								and NDI						
								improved from						
								a mean of 50.6						
								± 20.6 to 36.7						
								± 19.3 (P =						
								0.002).						
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	1				1									
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														-
1-	Systemati	0	RhBMP-2	Cost	cost/QALY	Incremental cost-effective ratio for each graft option when	-	-	-	-	Virk, Sohrab;	-	As in primary	Population: Lumbar degenerative spondylolisthesis.
	с		(RhBMP),Ilia	effectiveness		compared with living with chronic back pain was \$21,308/QALY					Sandhu, Harvinder		outcome	Comments: This is a good quality study evaluating cost effectiveness of grafts used in
			c crest bone			for ICBG, \$16,595/QALY for RhBMP, \$21,204/QALY for LBG,					S.; Khan, Safdar		measure	lumbar surgery, including: rhBMP-2, ICBG, local bone alone (LBG), demineralised bone
			graft			\$21,287/QALY for DBM, and \$28,153/QALY for CCA. However					N Cost			matrix with local bone (DBM) and local bone with corticocancellous allograft chips (CCA).
			(ICBG),,local			the sensitivity analysis showed RhBMP was not the most cost-					effectiveness			Base comparison was chronic back pain and an incremental cost effectiveness ratio
			bone alone			effective option if the revision rate is significantly raised, and if					analysis of graft			(ICER) was calculated for each graft option. ICER is calculated as (cost fusion-cost
			(LBG),			the cost of treatment with RhBMP rises >\$42,250. In that case					options in spinal			chronic back pain)/(QALY fusion-QALY chronic back pain). Sensitivity analysis was
			demineralize			LBG becomes the likely cost-effective treatment.					fusion surgery			performed to stress the inputs within the Markov model. Specifically, the revision rates,
			d bone								using a Markov			costs associated with primary fusion surgery and QALY values for each graft option were
			matrix with								model. J Spinal			varied. One-way sensitivity analysis for each of these 3 variables was performed. Two-
			local bone								Disord Tech. 2012			way sensitivity analysis was also performed to evaluate those variables that seemed to
			(DBM), local											most affect the results of the model. All costs are appropriately adjusted as 2011 dollars.
			bone with											For rhBMP-2 and ICBG, the rates of fusion, revision rates, and complications are based
			corticocancel											on studies by Cahill et al. (2011). Dimar et al. (2009). Vaccaro et al. (2007). Result show
			lous allograft											that cost-effective ratio when compared with living with chronic back pain was
			chips (CCA)											\$16,595/OALY for rhBMP-2- the most cost-effective graft option. However the sensitivity
														analysis shows that rhBMP-2 is not the most cost-effective option if the revision rate is
														significantly raised. If the cost of treatment with rhBMP-2 rises >\$42,250, then LBG
														becomes the likely cost effective treatment. This is significant considering the findings
														from a recent population level study by Savage et al. (2015) which showed that the 90
														day complications rate in group using rhBMP-2 for lumbar spinal fusion was significantly
														higher than group using non-BMP methods (RR1.108 (CI 1.060–1.158). Limitations of this
														study include the lack of long-term follow up of revision rates and the number of natients
														involved in evaluating OALY data points was often small
														involved in evaluating tener data points was often sinali.
				1			1					1		

		N	1.01400	1 e · · ·	D ()		1							
U	Systemati	Not	mBMP2	clinical	Bone fusion	Anterior lumbar fusions: rhBMP2 likely associated with an	none	-	-	-	vvaiker, Brett;	-	as in primary	Population: Spinal fusion including lumbar and cervical. High risk groups- cancer,
	С	mentioned		effectiveness of	and clinical	increased rate of radiographic arthrodesis when compared with					Koerner, John;		outcome	smokers, osteomyelitis.
	1	1		the intervention	outcome	ICBG. However, this does not necessarily translate to an					Sankarayanaryana			Comments: This is an overview of studies evaluating rhBMP-2. The study doesn't include:
	1	1			measures as	improvement in clinical outcomes. There are potential					n, Sriram: Radcliff			a search strategy, patient selection, evaluation of study guality or statistical methods to
				1	measured	complications that are specific to rhBMP-2 utilization including					Kris, A consensus			pool data. Hense generalisability of this study is limited.
						estechnic and retrograde size ulation, rhBMD 2 may also he					statement			poor data. Therase generalisability of this study is infliced.
					using ODI,	osteolysis and retrograde ejaculation. mBiviP-2 may also be					statement			
					back pain and	associated with lumbar plexopathy when utilized in the					regarding the			
					leg pain scores	transpsoas lumbar fusion cases.					utilization of BMP in			
						Single level posterior lumbar fusions: rhBMP-2 may improve the					spine surgery. Curr			
						rates of radiographic arthrodesis in posterior lumbar fusion					Rev Musculoskelet			
						procedures, particularly in patients at high-risk for					Med. 2014			
						nseudarthrosis such as smokers but is based one study by								
						Clearman at al. BhBMn2 anapitia complications include								
						Glassman et al. Kribivipz specific complications include								
						increased early back and leg pain, ectopic bone formation and								
						radiculitis.								
						Multiple level posterior lumbar fusions: There are very limited								
						studies which examine only multilevel posterior degenerative								
						lumbar fusions. The existing data provides evidence that rate of								
						complications rbBMP-2 is similar to ICBG								
						Conviced functional There are relatively few high quality studies								
						Cervical fusions. There are relatively lew high quality studies								
						assessing the risks and benefits of mBMP-2 utilisation in								
						anterior cervical spine fusion surgery. The use of rhBMP-2 in								
						posterior cervical fusions is likely safer than in anterior								
						approaches. Anterior cervical fusion is associated with higher								
						rate of complications including dysphagia, dysphonia and wound								
						infection								
1				1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
	1	1		1	1									
1	1		1	1	1	1							1	

1+	Systemati	496	rhBMP2 or	Clinical	radiological	Of the 496 patients with clinical and radiographic data at 1 and	Clinical outcomes	Patients with	-	-	Noshchenko.	None	as in primary	Population: Patients with lumbar arthrodesis, using rhBMP-2 or ICBG.
	c	pateients	ICBG	effectiveness of	fusion	2 year follow-ups were identified. Of these, 5.5% [95%CI: 3.7:	(Oswestry	fusion had			Andriv: Lindley.	mentioned/in	outcome	Comments: This is a good quality meta-analysis of RCTs comparing ICBG and rhBMP-2
	-	with eithet		the intervention		8 31 had radiographic nonunion which did not require	Disability Index	better			Emily M : Burger	cluded		to enaluate relation between radiological hone fusion, which is used as primary outcome
		rhBMP2				reoperation	(ODI): Numeric	improvements			Evalina L.: Cain.			measure, and clinical outcomes. The results show that patients who had radiological
		or ICBG					Rating Scales	in ODI			Christopher M. J.:			fusion had significantly better patient outcomes, including clinical outcomes (Oswestry
							(NRS) for back	(P<0.001) and			Patel, Vikas V.			Disability Index (ODI): Numeric Rating Scales (NRS) for back and leg pain). However, the
							and leg pain	NRS back pain			What is the Clinical			abstact doesnt present the results by ICBG and rhBMP-2. The study is limited in that
								scores			Relevance of			patients in the RCTS were not blinded, so role bias cannot be ruled out. Authors also note
								(P<0.001). The			Radiographic			that the predictive values of fusion for clinical outcomes were poor, with low specificity and
								overall			Nonunion after			low negative predictive values and need for direct evaluation of patient related outcomes
								percentage of			Single-level			in future studies.
								fused patients			Lumbar Interbody			
								with ODI and			Arthrodesis in			
								NRS back pain			Degenerative Disc			
								scores that			Disease? A Meta-			
								exceeded the			Analysis of the			
								criteria for			YODA Project			
								minimal			Database. Spine.			
								clinically			2015			
								important						
								differences						
								(MCID) was						
								also						
								significantly						
								higher than						
								that of patients						
								with nonunion						
								(ODI, OR =						
								2.7, P = 0.019;						
								NRS back						
								pain, OR = 3.5,						
								P = 0.033).						
								However, the						
								predictive						
								values of						
								rusion for						
								clinical						
								outcomes						
								were poor,						
								with low						
								specificity and						
								predictive						
								values						
								values.						
1														
1														

3	Case	1997-	rbBMP2 for	Clinical	Oswestry	The fusion rates for BMP group were 93.5% and 71.9% for the	None	-	I-	-	Kim Han lo	-	As in primary	Population: Ambulators who were candidates for long fusions (thoracic as the upper level)
-	series	2006	long fusions	effectiveness of	Disability Index	ICBG group. The rate pseudarthrosis was 6.4% (2/31) in the					Buchowski, Jacob		outcome	to the sacrum. Adults.
			to the	the intervention	and 3 domains	BMP and 28.1% (9/32) in the ICBG group (P = 0.04). Oswestry					M.: Zebala, Lukas		measure	Comments: A retrospective case series of 63 patients treated for long fusion to sacrum
			sacrum		of the Scoliosis	Disability Indexes were similar between groups. However, the					P.: Dickson.			using rhBMP-2 or ICBG. The rhBMP-2 group had higher rate of radiological fusion but
					Research	BMP group demonstrated superior sum composite Scoliosis					Douglas D.;			ODI scores were simialr across both groups, suggesting that radiological fusion didn't
					Society score .	Research Society scores in pain, self-image and function					Koester, Linda;			translate into better patient outcomes. The authors conclude that patients receiving higher
					BMP dose	domains (P = 0.02). The concentration and dosage of					Bridwell, Keith H			dose of rhBMP-2 had better success but there is lack of infomation on baseline
						recombinant human bone morphogenetic protein 2 (rhBMP-2)					RhBMP-2 is			characteristics of high dose and also the clinical reasons for high dose. Overall, the
						used seems to have an effect on the rate of fusion and					superior to iliac			generalisability of study results is limited due to patient selection, lack of bliniding and lack
						pseudarthrosis rate because no patient receiving more than 5					crest bone graft for			of robust statistical methods in estimating differences in outcomes between the groups.
						mg per level had apparent or detected pseudarthroses (n =					long fusions to the			
						20/20).					sacrum in adult			
											spinal deformity: 4-			
											to 14-year follow-			
											up. Spine. 2013			
2-	Case	148	rhBMP2 for	Clinical	Radiologically	At 2 years postoperatively, solid fusion was demonstrated in all	none	-	-	-	Glassman, Steven	-	-	Population: Lumbar Degenerative disc disease . Adults. Smokers.
	series		single-level	effectiveness of	estimated	55 nonsmokers in the rhBMP-2 group (100%). Successful					D.; Dimar, John R.;			Comments: A retrospective study comapring outcome of lumbar fusion using rhBMP-2 in
			lumbar	the intervention	Solid fusion	tusion was seen in 20 of 21 smokers in the rhBMP-2 group					Burkus, Kenneth;			patients with smoking and non-smokers. At 2 years postoperatively, solid fusion was
			fusion.		and clinical	(95.2%). Fusion was achieved in 48 of 51 nonsmokers in the					Hardacker, James			demonstrated in all 55 non-smokers in the mBMP-2 group (100%). Successful fusion was
					outcome	iliac crest bone graft (ICBG) group (94.1%), but only 16 of 21					W.; Pryor, Philip			seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51
					measures	smokers (76.2%) in the ICBG group.					W.; Boden, Scott			nonsmokers in the iliac crest bone graft (ICBG) group (94.1%), but only 16 of 21 smokers
					including						D.; Carreon, Lean			(76.2%) in the ICBG group. The generalisability of study is limited due to retrospective
					Oswestry						Y The efficacy of			patient selection methods , with no randomisation and lack of explanation for excluding
1			1		Disability					1	mbiviP-2 for			patients who had similar surgery but were excluded from the study.
1			1		muex, SF-36,					1	posterolateral			
			1		back, and leg					1	ameliar rusion in			
1			1		pain scores					1	smokers. Spine.			
			1							1	2007			
										1				

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2+	Case	Sixty-two	rhBMP-2 on 0)	Radiological	Patients in rh-BMP-2 and autogenous bone graft group	Complicationrate	8% (2/24) of rh	-	-	Taghavi CE1, Lee	8% (2/24) of	As in primary	Population: Indications for revision surgery included symptomatic pseudarthrosis (pain
	series	patients.	an		bone fusion	achieved a 100% fusion rate for both single- and multilevel		BMP2, 22% of			KB. Keorochana G.	rh BMP2.	outcome	and/or instability) following a previous PLF for degenerative conditions of the lumbar
			absorbable		and clinical	rovision PLE. In RMAA group the fusion rate for single level		BAAA (4/19)			Trong ST Voo III	22% of	roculte	spino, such as degenerative disc discase, stangels, or spendylelisthesis, Group 1
			absorbabic			revision PLE was 4000((7/7) and the multilavel funite rete of		D/00((4,10)			Ware IO Date		results	spine, such as adjenterative dise disease, steriosis, or spinovicinitesis. Oroup 1
			collagen		outcomes. For	revision PLF was 100% (7/7) and the multilevel rusion rate or		and 10%			wang JC Bone	BAAA (4/18)		contained 24 patients (13 single- [group 1A] and 11 multilevel [group 1B]) who underwent
			sponge.		the radiologic	64% (7/11). There was a significant decrease between		(2/20) of			Morphogenetic	and 10%		Instrumented revision PLF using rhBMP-2 on an absorbable collagen sponge. Group 2
					assessment of	preoperative and 2-year postoperative VAS scores in all groups		autograft			Protein-2 and Bone	(2/20) of		included 18 patients (7 single- [group 2A] and 11 multilevel [group 2B]) with procedures
					fusion rate, 3	(P 0.001), but no significant difference among groups at all time		groups			Marrow Aspirate	autograft		using bone marrow aspirates in conjunction with allograft (BMAA). Group 3 consisted of
					criteria were	noints		required			With Allograft as	arouns		20 patients (10 single- [group 3A] and 10 multilevel [group 3B]) with procedures using
					usod: tho	pointoi		additional			Altornativos to	roquirod		autograft
					useu. ine			adultional			Alternatives to	required		
					presence or			surgical			Autograf tin	additional		Comments: This is a small restrospective case reveiw of 62 consecutive patients who
					trabeculated			intervention			Instrumented	surgical		underwent instrumented revision posterolateral spine fusion between January 2002 and
					bone between			and four			Revision	intervention		December 2006. Patients were treated with either rhBMP-2 on an absorbable collagen
					transverse			patients (20%)			Posterolateral	and four		sponge (n-24). Bone marrow aspirates used in conjunction with allograft(BMAA) (n=18) or
					nrocesses no			in autograft			Lumbar Spinal	nationts		autograft (n=20). The exact source of autograft hone for Group 3 was not clearly defined
					implant			aroup			Eurion Opinal	(200()) in		All 2 schorte reseived supplemental level hans, statis and dynamic radiographs were
					impiant			group			Fusion . Spine.	(20%) In		All 3 conorts received supplemental local bone, static and dynamic radiographs were
					loosening, and			complained of			2010	autograft		used to assess fusion and were reviewed by 3 blinded independent reviewers with a
					less			persistent				group		diagnosis of non-union based on either surgical exploration if revision performed or
					than 2° of			donor-site pain				complained		radiographic findings. Clinical outcome was determined through VAS scores. The
					movement on			at 2-vear				of persistent		baseline characteristics of the three groups were similar in demography and risk factors
					lateral flavion			follow up				deper eite		The regulate about that have furgion rate in the RMD 2 and outpareft uses 100% for both
					lateral nexion			TOIIOw-up				donor-site		The results show that bolie fusion rate in highwer-2 and autograft was 100% for both
					and extension							pain at 2-		single and multi-level fusion. The BAAA had lower fusion rate for multi-level fusion but
					films. Clinical							year follow-		100% for single level fusion. There was no difference betwen groups for clinical
					outcomes							up		outcomes. Higher proportion of patients in BAAA had a revision surgery and (20% in
					were assessed							-		autograft group complained of persistent donor-site pain at 2-year follow-up.
					using a VAS (0									
					no pain 10									
					no pain, 10									
					worst possible									
					pain) for back									
					and leg pain									
					before surgery									
					and at 6-week									
					6- 12- and									
					0-, 12-, and									
					24-month									
					follow-up									
1	1	1	1											
		1												
		1												
		1												
1	1	1												
1	1	1	1											
1	1	1				1	1	1				1		

2+	Case series	One hundred hundred ninety-five patients were divided into 4 groups depending on fusion material and the presence/ absence of fusion- related risk factors for nonunions;	rhBMP2	clinical effectiveness	Fusion rate and rate of fusion	The time to fusion was significantly faster in group B than in group D in patients with no history of smoking (P<0.05), The time to complete fusion was also significantly faster in group B than in group D in patients undergroup (P<0.05), single-level surgery (P<0.05), no diabetes mellitus (P<0.01), no smoking history (P<0.05), no diabetes mellitus (P<0.01), and no significant comorbidity (P<0.01), and no significant fuer were no significant differences between groups B and D. Although initial fusion mass and time to solid fusion was faster in group C than in group C. there were no significant differences between groups B and D. Although nitial fusion mass and time to solid fusion rates were higher in group C than in group C. There were no significant differences between groups A and C. In addition, fusion rates were higher in group C than in group C than in group C. There were no significant differences between groups A and C. In addition, fusion rates were higher in group C than in group A, looking at all factors except revision surgery, but the differences were not statistically significant.	None	-	-	Kwang-Bok Lee, MD, PhD, Tw Jared S. Johnson, MD,* Kyung-Jin Song, MD,w Cyrus E. Taghavi, BS,* and Jeffrey C. Wang, MD*. Use of Autogenous Bone Graft Compared With RhBMP in High-risk Patients A Comparison of Fusion Rates and Time to Fusion. J Spinal Disord Tech V. 2013	None included	As in primary outcome measure	Population: Degenerative lumbar spine diseases. Adults. Group A defined as rhBMP-2 used in the presence of high-risk factors (FRRF), group B was defined as the MP-2 used in the absence of FRRF, group C was defined as autograft used in the presence of FRRF, and group D was defined as autograft used in the presence of FRRF, and group D was defined as autograft used in the presence of FRRF, and group D was defined as autograft used in the presence of FRRF, and group D was defined as autograft used in the presence of FRRF, and group C in all fusion-related risk factors (age, sex, revision, fusion level, smoking, DM, osteoporosis, and comorbidity), there was no statistically significant difference between groups A and C. Similarly, fusion rate was higher in group A than in group C in other fusion related risk factors, except revision surgery but there was no statistically significant difference between groups A and C in all fusion-related risk factors. The generalisability of the study is limited due to retrospective patient selection methods, with no randomisation and lack of explanation of patiants who had simialr surgery but were excluded from the study.
2-	Case series	127	rhBMP-2 and allograft	clinical effectiveness	Fusion rate and rate of fusion, clinical outcome, VAS, perioperative complications and revision rate	At the end of 24 month follow up period the fusion rate and fusion time were similar in groups A and C; however, these were lower than that observed in group B. Clinical outcomes were similar amongst the groups, there were no significant differences in VAS and perioperative complication rate between groups A and C. Similarly there was also no difference in fusion rate between the group A and group C when analysed by gender, comorbidity, osteoporosis, previous surgery for fusion, and smoking	None	-		Kwang-Bok Lee, Cyrus E. Taghavi, Margaret S. Hsu, Kyung-Jin Song, Jeong Hyun Yoo. Gun Keorochana, Stephanie S. Ngo, Jeffrey C. Wang . The efficacy of rhBMP-2 versus autograft for posterolateral lumbar spine fusion in elderly patients. Eur Spine J. 2010	-	As in primary outcome measure	Population: Degenerative lumbar spine diseases. Adults. Subjects in group A (n = 34) consisted of patients 65 + years who received rhBMP-2 and allograft. Group B (n = 52) was composed of patients under 65 years of age with rhBMP-2 and allograft. Subjects in group C (n = 41) were 65 + years with autograft use. Comments: A retrospective study comparing rhBMP-2 with allograft and autograft in older patients. At the end of 24 month follow up period the fusion rate and fusion time were similar in groups A and C; however, these were lower than that observed in group B. Clinical outcomes were similar amongst the groups, there were no significant differences in VAS and perioperative complication rate between groups A and C. Similarly, there was also no difference in fusion rate between the group A and group C when analysed by gender, comorbidity, osteoporosis, previous surgery for fusion and smoking. The generalisability of the study is limited due to retrospective patient selection methods , with no randomisation and lack of explanation of patiants who had similar surgery but were excluded from the study.

2	Detropped	460772	DMD for	Clinical	Complications	The everall complication rate in the BMB group was 19 39/	Nene				looon W. Source	Ao in primon (Deputation: Detients who undepute tumber fusion either using RMD or non RMD; all
2-	Retrospec	460773	BIVIP TOF	Clinical	Complications	The overall complication rate in the BiviP group was 18.2%	None	-	-	-	Jason w. Savage,	As in primary	As in primary	Population: Patients who underwent lumbar rusion either using BiviP or non BiviP; all
	tive		spinal fusion	effectiveness of	were	compared with 18.7% in the control group. The RR of BMP use					MD ,1 MICK P.	outcome	outcome	ages; subgroups by age and sex.
	Cohort			the intervention	categorized	compared with no BMP use was 0.976 (CI 0.963–0.989) (p <					Kelly, MD ,2 Scott	measure	measure	Comments: This is an industry sponsored retrospective case series comparing
					into 1 of 10	0.001). Age: In both treatment groups, patients older than 65					A. Ellison, MB A,3			complication rates in patients undergoing lumbar fusion using BMP vs non BMP. The
					groups:	years had a significantly higher rate of postoperative					and Paul A.			objective and defintion of primary outcimes are well defined. Although patient selection
					respiratory;	complications than the younger patients (p < 0.001) . In patients					Anderson, MD 2. A			method for patient using BMP is defined there is lack of clarity in patient selection
					peripheral	younger than 65 years, the RR of developing a complication					population-based			methods of patients using non BMP. Also there is information on patients by different
					vascular; CNS;	with the use of BMP was 1.042 (CI 1.017-1.067), whereas in					review of bone			types of lumber surgery ie. anterior, lateral or posterior. The results show that the
					hematoma;	the patients ≥ 65 years old, the opposite was true (RR 0.950 [CI					morphogenetic			complication rates were significantly lower in BMP group. Authors also report complication
					accidental cut.	0.935-0.0651. Effect of Sex: For both males and females, the					protein: associated			in <65 vrs age group was higher in BMP group than non -BMP group but opposite was
					puncture or	complication rates were lower in the BMP group than in the					complication and			true in >65 vr age group. Also complication was significantly lower in the BMP group for
					hemorrhage	control group. The RRs of BMP use compared with no BMP					reoperation rates			females but not for males ($n < 0.001$). However for the reoperations rates: the overall 90-
					during the	use were 0.974 (CL0.953, 0.995) in males and 0.976 (CL					after lumbar coinal			day reaparation rates were 1 84% in the control group and 2 02% in the BMP group. The
					auning the	0.000, 0.002) in females. The DD was significantly lower in the					fueion Neuropura			BD of responsible was 1 109 (CI 1 060, 1 159) indicating a significantly lower rate in the
					procedure,	0.900-0.993) in remaines. The RR was significantly lower in the					Tusion. Neurosurg			RR of reoperation was 1.100 (Cr 1.000–1.150), indicating a significantly lower rate in the
					complications	Biving group for remaines but not for males (p < 0.001). Chanson					FUCUS . 2015			control group. The results of the study are generalisable in the context of large sample
					of the	Comorbidity Index: Patients with 1 or more complications had a								size nowever as the study lacks into by types of lumbar surgery and also by types of non
					operative	higher CCI than patients in all subgroups who had no								BMP it is not possible to conclude the safety of BMP by type of surgery. Also the data for
					wound,	complications. In addition, patients who underwent spinal fusion								the study patients is based on industry database the completeness of which is unknown
					including	without BMP had a higher CCI than the patients in all subgroups								and also patient selection methods are insufficent to make a recommendation.
					infection;	who received BMP, except for female patients without a								
					other; CSF	complication. Reoperations Rates: The overall 90-day								
					leak; deep veir	reoperation rates were 1.84% in the control group and 2.03% in								
					thrombosis;	the BMP group . The RR of reoperation was 1.108 (CI								
					and	1.060-1.158), which was significant and indicates a lower rate								
					mechanical	in the control group. In both the control and BMP groups,								
					complication of	patients younger than 65 years were more likely to have a								
					an implant or	reoperation than patients older than 65 years ($p < 0.001$).								
					graft In	······································								
					addition we									
					determined the									
					average									
					Charlson									
					Comorbidity									
					Comorbidity									
					Index (CCI) for									
					patients									
					without									
					complications									
					and for									
					patients with 1									
					or more									
					complications.									
			1											
			1											
			1											

Appendix Two

Literature search terms

Assumptions / limits applied to	o search:
Original search terms:	Meta-analyses Systematic reviews Randomised controlled trials Prospective non-randomised clinical studies or other clinical studies Health economics studies
Updated search terms - Population	Anterior lumbar interbody fusion* Lumbar fusion* Spine fusion* ALIF Trans-foraminal lumbar interbody fusion* Transforaminal lumbar interbody fusion* Posterior Lumbar Interbody Fusion* Cervical fusion* TLIF PLIF Thoracic fusion* An additional search for the intervention, comparator and following population terms only is as follows: Pseudarthrosis Non-union* Non-union* Non union* Non union* Revised Ununited fracture* Fail*
Updated search terms - Intervention	Bone morphogenetic protein* Bone morphogenetic protein-2 Inductos Infuse Dibotermin alfa BMP-2 rhBMP-2 rBMP rhBMP

	lliac graff*
Updated search terms -	Autogenous gran
Comparator	
	liac bone
	lliac crest
Updated search terms -	Not applicable
Outcome	
	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria.
	1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review
	available)
	2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high
	quality clinical trials available)
	>>>> If studies included reaches 30, inclusion stops here
	3.All relevant case control and cohort studies, that qualify after exclusion criteria
	>>>> Il studies included reaches 30, inclusion stops nere
	4. All relevant non analytical studies (case series/ reports etc.) that quality after exclusion criteria
	Specific inclusion criteria
Inclusion criteria	epidemic articles were included per suggestion of the evidence reviewer:
	Globernan Steven D. Dimar John R. Burkus Kenneth: Hardacker James W. Prvor Philip W. Boden Scott D. Carreon Leah V. The efficacy of rhBMP-2 for
	nostarolataral lumbar filsion in smokers. Snine 2007
	2 Taghavi CEL Lee KB, Keorochana G, Tzeng ST, Yoo, H, Wang IC, Bone Mornhogenetic Protein-2 and Bone Marrow Aspirate With Allograft as Alternatives to
	2. raginari De I, Lee RD, Reologiana G, Tzeng GT, Too GT, Wang GC. Done working ender Friender and Done Mariow Aspirate With Anogran as Alternatives to Autograf in Instrumented Pavision Destorealistical Limber Spinal Europa. Spina 2010
	Autogra un instrumente Aversion Fosterolateral Lumbar Spinari usion - Spinar 2010
	S. Rwalig-bok Lee, MD, FHD, W Jaleu S. Johnson, MD, Kyuig-Jin Jong, MD, Cytus L. Laghavi, DS, and Jenney C. Walig, MD. Use of Autogenous Bone Gran
	Compared with Known Fillinghrisk Fatterits A Comparison of Lesion Kates and time to Lesion. Sophial Disourted 1, 2015
	4. Kwang-bok Lee, Cyrus E. Fraghavi, Margaret S. Hsti, Kyung-Jin Song, Jeong Hyun Yoo. Gun Keorochana, Stephanie S. Ngo, Jenrey C. Wang . The endady of mbMP-
	2 versus autograf for posteroratera rumbar spine rusion in eldeny patients. Eur Spine J. 2010
	5. Jason W. Savage, MD, 1 Mick P. Kelly, MD, 2 Scott A. Ellison, MB A,3 and Paul A. Anderson, MD 2. A population-based review of bone morphogenetic protein:
	associated complication and reoperation rates
	after lumbar spinal fusion. Neurosurg Focus . 2015
	General exclusion criteria
	Studies with the following characteristics will be excluded:
	1. Does not answer a PICO research question
	2. Comparator differs from the PICO
	3 No relevant outcomes
Exclusion criteria	π . Inducion of automotion for only one surgeon/dector or only one clinical site (where studies with > one surgeon/dector or one clinical site axist)
	S. Indivision of outcomes for only one surgeon/voctor of only one clinical site (where surgeon/voctor of one clinical site exist)
	\mathbf{U} . Manalive / non-systematic reviews (relevant relevant studies to be included)
	Specific exclusion criteria
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