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**Peer Review File**
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## ROUND 1

### Reviewer A

Comment 1: Line 141: change "amines" to "molecules"
Reply 1: we have modified our text as advised (line 141)".
Changes in the text: This refers to bioactive molecules

Comment 2: Line 439 check accuracy of fusion rates. As written appears that BMP has lower fusion rates
Reply 2: we have modified our text as advised (see line 439)

Changes in the text: fusion rates (assessed by CT) with Attrax (80%) than with rhBMP-2 (96%) at 24

### Reviewer B

Comment 1: First, total dose per level is a convenient was to describe dose, but physiologically, it is the rhBMP-2 concentration in space (mg/cc) within the carrier that determines if it is in the therapeutic window or at higher risk for local side effects (swelling, inflammation, bone resorption). In addition, rhBMP-2 concentrations of 1.5 mg/cc were optimized initially for endplate sparing cages, not heavy decortication and access to vertebral cancellous bone marrow. So the osteoclastic resorption is most commonly seen when those higher concentrations are exposed to cancellous bone and marrow, rather than in posterolateral fusions.
Reply 1: The FDA (www.accessdata.fda.gov) state the concentration of rhBMP-2 is 1.5 mg/ml. Hence lines 173-174 in our text are not changed. We agree with Reviewer B that higher concentrations of rhBMP-2 in the interbody space lead to osteoclastic resorption as already discussed in lines 250-258.

Changes in the text: None needed.

Comment 2: The authors suggest that 3+ levels for PLF are the value point for rhBMP-2. Our published studies have shown addition of rhBMP-2 can increase the fusion rate in 1 or 2 level PLF from 75% with iliac crest to over 95%, and can improve the success of local bone graft to a 98% fusion rate as determined by CT scans in 1 or 2 level PLF. Similarly, the value proposition in TLIF which has a higher fusion rate regardless of bone substitutes is less compelling.

Reply 2: We agree that RhBMP-2 increases fusion rates in 1-2 level lumbar fusion hence have changed (i) line 524 to "fusion at all levels for degenerative disease"; (ii)

line 560 to “lumbar fusion irrespective of the number of levels”; and (iii) line 887 Table 2 Recommendations: for all levels of lumbar fusion.
Changes in the text: (i) fusion at all levels for degenerative disease
(ii) lumbar fusion irrespective of the number of levels for
(iii) In Table 2: Lumbar fusion for degenerative disease +++

Comment 3: There were several studies that suggest PRP actually inhibited bone healing and may decrease the effects of local BMPs, which were not explicitly mentioned.
Reply 3: we have added to line 376 a reference supporting that suggest PRP actually inhibited bone healing.
Changes in the text: Line 376: However, a recent systematic review on overlapping meta-analyses found PRP was associated with lower spinal fusion rates (add Muthu et al 2022).

Comment 4: Recent studies have demonstrated the addition of "stem cells" to demineralized bone matrix carriers have not shown any substantial improvement in healing above the DBM carrier alone.
Reply 4: we have added in line 417 a reference regarding stem cells with DBM.
Changes in the text: Line 417:The addition of stem cells to DBMs have not shown any substantial improvement in fusion rates above DBMs alone (add Shepard et al 2021).

**Reviewer C**

Comment 1: Results Page 5 line 151. Autograft has been shown to have osteoinductive, conductive as well as osteogenic characteristics though in varying strengths. Authors mention autograft is not osteoinductive per se. It's suggested authors include appropriate references and discuss the relevant evidence regarding this.
Reply 1: we have corrected our text as advised (see lines 149-152)

Changes in the text: Autograft provides all of these factors and can be harvested from local bone at the site of surgery or from the iliac crest, rib, fibula, or elsewhere. ~~it is not osteoinductive per se~~. Similarly, demineralized bone matrix (DBM) and exogenous rhBMP-2, are also osteoinductive.

Comment 2: Strength and validity of results obtained from randomized controlled trials is higher than retrospective studies. Furthermore, studies with higher sample size are better powered to detect the differences than lower patient population studies. Narrative review lacks the statistical comparison. The conclusions should be interpreted carefully. Additionally, reporting bias was a potential concern in earlier studies of rh-BMP2 funded by industry. Limitations of the review should be included in the manuscript.
Reply 2: we have modified our text as advised (see line 565).
Changes in the text: We acknowledge the limitations of this narrative review basing the conclusion on the studies and literature included in the analysis. Secondly, these studies

may have an inherent bias on behalf of the authors, as they are describing their experience or option of a range of studies that could skew the conclusion towards a particular view or opinion. Additionally, reporting bias was a potential concern in earlier studies of rhBMP-2 funded by industry leading to the YODA reviews.

Comment 3: Page 17 line 508. Patient preferences between autograft versus substitutes- The concept for autograft as a gold standard for spinal fusion is questioned. First, the study based on which this conclusion is made is a retrospective study with a small sample size based on non-validated survey questions. As is inherently the limitation of a retrospective study there was a significant potential for recall bias in this study- patients are more likely to remember recent experience than the procedure they underwent several years ago. Furthermore, the imaging method to assess fusion was not standardized for all patients. Clinical results after ACDF are based on adequacy of decompression and less likely dependent on the graft material used. Thus patients prefer option that is "less morbid" however to dismiss autograft as a gold standard based on a single study is a bold conclusion.
Reply 3: we have modified our text as advised (see lines 501-510).

Changes in the text: A single-centre retrospective study of 574 patients treated with ACDF surgery over a 9-year period included a small sample size of 22 patients who initially underwent ACDF surgery with an autograft (ICBG) and then subsequently underwent ACDF with a bone graft substitute. Of these 22 patients, 21 (95%) reported preferring the procedure with a graft substitute, and 91% (20/22) reported that the ICBG incision was more painful than the neck incision. Based on these results, the authors of this study questioned the traditional recommendation that autograft is the gold standard for ACDF (93). Alternative “less morbid” bone graft substitutes compared to autograft are now available.

**Reviewer D**

Comment 1: Title
- Consider changing "Bone morphogenetic protein" to "Recombinant human bone morphogenetic protein-2" as this more precisely describes the nature of the review.
Reply 1: Title changed as advised

Changes in the text: Recombinant human bone morphogenetic protein-2 in spine surgery: recommendations for use and alternative bone substitutes — a narrative review

Comment 2: Methods
- Consider removing the first paragraph or combining with the final paragraph of the introduction. Stating the objective and explaining what the review will discuss does not fit here.
Reply 2 we have deleted the first paragraph as advised (see lines 89-94).

Changes in the text: ~~The main objective of this review is to discuss the literature on the safety and~~

~~90 complications associated with the use of rhBMP-2 in spine surgery, especially in~~
~~91 situations when it is used "off-label", without an LT-cage. This narrative review will~~
~~92 discuss the physiology of bone fusion in spine surgery, formulations and indications~~
~~93 of rhBMP-2, evidence on cancer risk with rhBMP-2, quality of the available evidence,~~
~~94 alternatives to rhBMP-2, and studies regarding patient preferences.~~

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Comment 3: Line 98: Consider mentioning that the inclusion criteria included lumbar and cervical spinal conditions before listing the operative approaches.
Reply 3: we have modified our text as advised (see line 97).
Changes in the text: included patients who underwent treatment of cervical and lumbar degenerative disc disease,

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Comment 4: Line 100: Delete period highlighted in black
Reply 4: we have deleted the period the as advised (see line 100).

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Changes in the text:(rhBMP-7) were not included. Inclusion was not restricted by operative approach;

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Comment 5: Results
- Line 134: Consider adding a citation.
Reply 5: Thank you but most experienced surgeons know this.
Changes in the text: no citation needed.

Comment 6: Line 155: Consider adding a citation.
Reply 6: citation number 16 added (see line 155)

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Changes in the text: potential prolongation of the hospital length of stay (16). Infection, fracture, haematoma,

Comment 7: Lines 230-234: These lines don't refer rhBMP-2 "dose" but rather their use or not. These lines do not really add value to this section - consider removing.
Reply 7: we have deleted lines 230-234 as advised including references 37 and 38.

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Changes in the text: ~~The accurate recording of rhBMP type and dosage~~
~~231 in these studies contrasts with two large US Medicare studies: one reported that~~
~~232 "…the overwhelming majority of procedures use rhBMP-2" (according to ICD-9-CM~~
~~233 code for rhBMP) (37), whereas the other provided no information regarding rhBMP~~
~~234 dosage (38).~~

Comment 8: Line 238: Citation 41 is a superscript rather than parentheses (as the other citations are).
Reply 8: Citation 41 needs to be in parentheses please.

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Changes in the text: because of bone resorption (5%)(41). 238 ~~41~~ May et al. reported that rhBMP-2 at

Comment 9: Line 376: Add p-value.
Reply 9: we have added p=0.002 to line 376

Changes in the text: 376 with autograft alone (94% versus 74%, p= 0.002) (65).

Comment 10: Line 447: Change PFL to PLF.
Reply 10: we have changed PFL to PLF

Changes in the text: 447 (78). In a rabbit model of PLF evaluating another β-TCP/HA blended ceramic

Comment 11: Discussion
- Line 524 & 561: The authors should be more specific with their recommendation for rhBMP for pseudoarthrosis. Does this apply to pseudoarthrosis at every level, lumbar only, lumbar and cervical, any level except anterior cervical (as is mentioned in the "conclusions"), etc?
- Similarly, are these recommendations used in the authors' practice? If so, have any studies been performed with these recommendations?
Reply 11: we have amended the text from line 523-525 and line 561 to recommend rhBMP-2 for pseudoarthrosis at posterior cervical and anterior/posterior lumbar. We have added reference Walker et al 2014 to line 522.

Changes in the text: Line 523: Thus, we recommend the use of rhBMP-2 for four indications: (i) ASD surgery, (ii) lumbar fusions at all levels for degenerative disease, (ii) revision surgery for posterior cervical and anterior/posterior lumbar pseudoarthrosis, and (iv) surgery in patients with low-yield or poor-quality harvested autograft.
Line 561: revision surgery for pseudoarthrosis (posterior cervical, anterior/posterior lumbar)

Comment 12: Table 1
- What is the difference between the "Date of search" and "Timeframe" rows? It seems more appropriate to have a single date (when the search was conducted) listed for "date of search" and the included timeframe (Jan 1996-Jan 2022) under "timeframe".
Most of this information is written in the methods section and is a bit redundant. Consider adjusting the table or including other variables to differentiate (eg, number of search results, number excluded, number included, etc.).
Reply 12: we have amended the Date of Search and Timeframe in Table 1 as advised. We have amended line 116 as advised. The Methods section has been shortened with deletion of lines 89 – 94.
Changes in the text: Date of Search: January 2022
Timeframe: January 1996 to January 2022

Comment 13: There is no use of p-values or confidence intervals to demonstrate significant results (often the percentages are listed and it was undetermined whether the results were significant or not).
Reply 13: Only significant results with percentages are listed to aid the reader. Non-significant results are not listed or commented in the manuscript. Important p values have been added in Line 376.

Changes in the text: Line 376: with autograft alone (94% versus 74%, p= 0.002)

**Reviewer E**

Comment 1: Your "Recommendations" do not naturally arise from your excellent review. Your first and third recommendations are unfounded and may be your opinion but are not substantiated by anything in your literature review. i would recommend that both of those be removed as they may be quoted in future malpractice litigation against spine surgeons, and frankly, have no place in a review article. The review itself is excellent, thorough, educational, and the second recommendation logically proceeds from the review article.

Reply 1: Thank you but we consider that the *first* recommendation about obtaining informed consent about rhBMP-2 being a potent biologic with informed patient consent about the benefits versus risks and available bone substitutes to be valid. The *third* recommendation about appropriate indications, dose, avoidance of excessive use and cost of bone substitutes are equally valid.

Changes in the text: None needed.

**Reviewer F**

Comment 1: Excellent discussion of bone morphogenic protein in spinal fusion surgery. No major flaws or issues. Contributes to existing literature.

Reply 1: Thank you.

Changes in the text: None.

**ROUND 2**

**Review Comments:**

*Comment 1*: It is suggested that autograft has all three bone healing properties, including osteoinduction. In fact, mineralized autograft is NOT osteoinductive at all and this has been well demonstrated in animals. Adding that revision as suggested by the reviewer would insert an innacurate statement.

*Reply 1*: Thank you for this correction. We have reviewed the text and changed it back to the document submitted originally. Please see changes from lines 149-152.

*Changes in text*: Lines 149-152: Although autograft provides some of these factors and can be harvested from local bone at the site of surgery or from the iliac crest, rib, fibula,

or elsewhere, it is not osteoinductive per se. This is in contrast to demineralized bone matrix (DBM) and exogenous rhBMP-2, which are osteoinductive.

*Comment 2*: Otherwise, I would still suggest the authors insert language about the concentration of rhBMP-2 (mg/mL) and the site of use (e.g. paraspinal, interbody without endplate decortication, interbody with endplate decortication) would be important in determining the liklihood of local side effects and osteoclast activation.

*Reply 2*: Thank you for your expert suggestion. We believe lines 224-248 discuss the importance of concentration and likely side effects when using rhBMP-2. We also note, lines 563-565 state that we recommend "*Regulatory oversight of the type, volume, and dose of bone graft substitute (both per level and per procedure) to ensure appropriate indications, prevent excessive usage, and thereby enhance cost containment*."

*Changes in text*: We note no changes to text. The sections have been highlighted in blue.

*Lines 224-248*: Dosage of rhBMP-2: In a study published in 2015, dosages of rhBMP-2 used off-label in various types of spinal fusion were reported over a 10-year follow-up period in 527 patients. The mean Infuse dose per level was 8.4 mg for PLIF, 3.6 mg for ALIF, 4.2 mg for LLIF, and 8.4 mg for PLF (36), with a total mean dose per level of 6.2 mg. This was lower than the mean Infuse dose per level of 11.2 mg used during long fusions to the sacrum for ASD at Saint Louis, MO, USA (28). ~~The accurate recording of rhBMP type and dosage in these studies contrasts with two large US Medicare studies: one reported that "…the overwhelming majority of procedures use rhBMP-2" (according to ICD-9-CM code for rhBMP) (37), whereas the other provided no information regarding rhBMP dosage (38).~~

Dose specification is important, as high doses of rhBMP-2 have been correlated with increased rates of deep infection (2.4%), arrhythmias (2.4%), and pseudarthrosis because of bone resorption (5%)(41). 238 ~~41~~ May et al. reported that rhBMP-2 at supraphysiologic levels provides no beneficial effects in patients undergoing spine fusion (39). Data describing more contemporary use of rhBMP-2 have shown that smaller doses of rhBMP-2 are now being used in spine fusion surgery to optimize fusion rates and minimize the risk of complications. Mannion et al. reported a 12-month interbody fusion rate (according to CT) of 97.2% after PLIF/TLIF using low244 dose rhBMP-2 of only 1.4 mg per level (40). A systematic review and meta-analysis of 2,729 patients between 2011 and 2019 reported an overall fusion rate of 94%, with rhBMP-2 doses ranging from 1.3 to 12 mg per level. Thus, lower doses of rhBMP-2 are now being used in spinal fusion surgery, with fusion rates remaining high and similar to those of previous studies using higher doses (40, 41).

*Lines 563-565*: 3. Regulatory oversight of the type, volume, and dose of bone graft substitute (both per level and per procedure) to ensure appropriate indications, prevent excessive usage, and thereby enhance cost containment.