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Subject: Draft Health Technology Assessment: BMP for Spinal Fusion

To Whom it May Concern:

On behalf of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), we would like to thank the Washington State Health Care Authority for the opportunity to comment on the draft Health Technology Assessment (HTA) regarding the use of recombinant human Bone Morphogenetic Protein (rhBMP2 and rhBMP7). We appreciate the efforts of your team in developing a very thorough review of the published literature reporting on the use of BMP as an adjunct to spinal fusion.

We believe rhBMPs are a comparably safe and effective bone graft alternative appropriate in patients with medical indications as determined by their treating surgeon. FDA approval of the on-label indications of rhBMP noted equivalent or superior fusion rates, shorter operative times, and decreased bone graft donor site complications. Our assessment of the literature would indicate that rhBMPs are appropriate bone graft options for single level anterior (ALIF) and posterior (PLIF) lumbar interbody fusion, and can also be considered an appropriate bone graft substitute in single-level posterolateral lumbar fusion.

The HTA approaches assessment of BMPs through addressing 5 “Key Questions.” For clarity, our comments will parallel the approach of the HTA authors.

Key Question 1: Expected Treatment Outcomes and Validated Instruments

The Washington HTA identified three outcomes measures most commonly used in the literature: Short Form 36 (SF-36), Oswestry Disability Index (ODI) and Visual Analogue Pain Scale (VAS). Of these, only the SF-36 has been evaluated for validity in spinal fusion patients. There is a paucity of validated outcome measures of minimal clinically important difference for spinal fusion patients to compare rhBMP to autograft and allograft.

The metrics used in the assessment of patients undergoing lumbar fusions have been used for decades and are well accepted. In development of the National Neurosurgery Quality and Outcomes Database (N2QOD) by the AANS, outcome measures were chosen to develop a collaborative reporting mechanism to assess the extent lumbar spinal surgery improves pain, disability, and quality of life, while adjusting for bias and influential confounders, including variances in co-morbidity, surgical approach, cultural factors, region, structure and process of health services. Furthermore, risk-adjusted benchmarks of surgical

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morbidity and effectiveness, which define spine surgical quality, are being developed as well. In the N2QOD model, VAS, ODI, Euro-Qol 5D (EQ-5D), and the NASS Patient Satisfaction Index (PSI) were considered to provide an optimal foundation for future study design.

Key Question 2: Evidence of Efficacy and Effectiveness of BMP

The HTA reviews the level of evidence in the available literature concerning the efficacy and effectiveness of rhBMP-2 and rhBMP-7 for on-label and off-label uses in the lumbar and cervical spine. The authors conclude that no evidence was found to support the use of rhBMP-7 for posterolateral lumbar spine fusion or cervical fusion given the absence of literature on those topics. They have identified varying levels of evidence to support both the efficacy and effectiveness for the use of on-label and off-label rhBMP-2 in the lumbar and cervical spine as well as off-label use of rhBMP-7 in the lumbar spine.

As noted in the report, there are large systemic reviews assessing the use of rhBMP in lumbar fusions. These reports echo the conclusions of our societies, finding that rhBMP is an effective tool to facilitate lumbar fusion in single level procedures and may be considered an effective substitute to autograft or allograft. It should also be taken into consideration that many of the initial BMP studies were powered to demonstrate non-inferiority. Through this early experience, spine surgeons have gained greater proficiency in use of rhBMPs and have begun to modify their clinical use. It is our expectation that the level of evidence supporting use of biologics in spinal fusion will continue to rise as our experience using these agents matures.

Key Question 3: Safety of On- or Off-Label Use of rhBMP

We agree with the Washington HTA's review that reported adverse events related to BMP use are either low or very low in incidence. The largest reported series of BMP use comes from the Scoliosis Research Society Database analyzing complications in over 55,000 patients undergoing fusion surgery. Out of this patient population, over 11,900 patients received BMP. With the exception of anterior cervical surgery, overall complication rates were not significantly different between patients receiving BMP and those not receiving BMP (8.4% vs. 8.5%; $P = 0.5$). A concern is also with heterotopic bone formation, such as with off-labeled use in posterior lumbar interbody fusions. The study by Haid et al did identify an increased heterotopic bone graft formation (71% versus 12%), but did not find this clinically relevant in their patients (a).

However, in anterior cervical fusions where BMP was used, overall complications were more common (5.8% vs. 2.4%; $P < 0.001$). Multivariate analysis for anterior cervical spinal fusion also verified the increased complication rate, even after adjusting for the effects of patient age and revision surgery status. In regards to a reported increase in death rates in anterior cervical surgery with use of rhBMP, this was not identified to be statistically significant. However, since the reporting of such severe adverse events, rhBMP has been used in conjunction with steroids in this context to reduce excess inflammation during the peri-operative period (b).

Any potential adverse effect of BMP use should be weighed against those of autograft and allograft. Iliac crest bone grafting and harvest has a well -known morbidity with patient complaints of pain related to the harvesting of iliac crest bone, which may be permanent. With the exception of anterior cervical spine fusion, the present literature does not support that complication rates in patients undergoing spine fusion with BMP (on label or off label) are significantly higher than those patients undergoing autograft harvest. Beyond random anecdotal case reports and editorial opinions, there is no clear literature that provides a causal relationship between BMP use and increased risk of complications, except in the aforementioned cervical cases.

Key Question 4: Evidence of Differential Efficacy or Safety for Spinal Fusion

The Washington HTA reports that there is "no strong evidence of the differential effectiveness of spinal fusion using rhBMP-2 or rhBMP-7 versus ICBG or alternative bone graft substitutes in any subpopulation". Specific subpopulations included in this Key Question had been in the exclusion criteria of many studies, as characteristics such as tobacco use and multi-level or complex spinal fusions are known potential risk factors for failure of fusion. Recombinant human BMP-2 and rhBMP-7 clinical efficacy studies have generally excluded subjects with these characteristics.

However, as noted in Glassman et al, smokers undergoing posterolateral lumbar fusion had a 95.2% fusion rate in the rhBMP group compared to only a 76.2% fusion rate with autogenous bone (c). Additional studies of lesser quality such as by Slosar have denoted the potential of rhBMP-2 as a graft extender in higher risk patients, such as smokers, with rhBMP-2 having a 0% nonunion rate per level compared to a 22.2% nonunion rate per level for smokers who did not receive rhBMP-2 (d).

The benefit of enhancing fusion for patients with complex underlying conditions extends to those undergoing multilevel revision and spinal deformity surgery. Obtaining autogenous iliac crest bone graft may be limited in patients requiring multilevel revision or deformity surgery secondary to either previously harvested ilium or the need to secure iliac fixation. The lack of Level I evidence to support the use of BMP for specific subpopulations does not discount its potential benefit.

Key Question 5: Cost Implications and Cost-Effectiveness of On- or Off-Label Use

Acknowledging the associated costs of BMP as a product (including merchandise, processing and handling of implant) are greater than that of autograft, there have been a number of variables cited for the cost effective use of rhBMP such as shorter operating room time, shorter hospital stay, fewer revision surgery needs, more rapid mobilization of postoperatively, and, at least anecdotally, faster return to work.

Glassman et al. published two studies in 2008 documenting the cost-effectiveness of BMP in spinal surgery in comparison to iliac crest bone autograft). In patients over 60 years of age, there were more complications and additional treatments in the autograft group compared to those who received BMP. Overall costs of admission (first and second admissions, both and individually) were nearly the same between autograft and BMP. In a second study, the authors concluded that the hospital carries the cost burden for using BMP in lumbar fusions, but cost savings include decreased payment for in-patient rehabilitation and improved hospital reimbursement by decreasing the length of stay, physician costs, and outpatient services in the first three months following surgery (the standard global period). The cost for the first admission was greater for BMP versus autograft ICBG, but all other costs were greater for the autograft ICBG group versus the BMP group: physician costs, postoperative inpatient rehabilitation, and total combined costs (e).

In a cost analysis of lumbar fusion in Germany, France and England, overall cost-savings offset the upfront price for BMP. Savings were mainly achieved by reduced productivity-loss due to faster return-to-work time for patients treated with BMP in anterior lumbar fusion. Improved patient clinical outcomes combined with better health economic outcomes for the society support BMP as a valuable alternative compared to autograft (f).

Further study is appropriate to assess the effectiveness, both in clinical and cost parameters, of BMP in other spinal disorders, including long segment fusions, subtypes of fusions, and specific subpopulations of patients with poor bone quality and/or advanced age. As the candidacy for surgical intervention widens, peri-operative factors available to optimize and to improve healing will doubtlessly be valued.

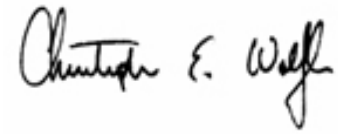
Conclusion

We appreciate the opportunity to review the draft Washington HTA. Thank you for considering our comments. We recognize that rhBMP is a costly technology and is not appropriate for the majority of spinal fusion procedures.

After review of the current literature, the AANS and CNS believe rhBMP remains a viable alternative to autograft and allograft for clinically appropriate cases, as chosen by treating surgeons. The full potential of rhBMP as an adjunct to spinal fusion cannot be determined by the current literature. It is almost certain that there are a number of patients for whom rhBMP will maximize the potential for a successful clinical outcome and restoration of an acceptable quality of life.

Again, thank you for this opportunity to comment and we look forward to seeing your final position pertaining to the use of recombinant human Bone Morphogenetic Protein (rhBMP2 and rhBMP7). If you have any questions, please feel free to contact John Ratliff (John.Ratliff@jefferson.edu) or Joseph Cheng, MD (joseph.cheng@vanderbilt.edu), Committee for Payor and Policy Responses, or Cathy Hill, Senior Manager, Regulatory Affair AANS/CNS (chill@neurosurgery.org).

Sincerely,



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