INTRODUCTION: Bone morphogenetic protein (BMP) is currently approved by the FDA for anterior lumbar interbody fusion (ALIF) with an interbody cage, treating open tibial shaft fractures, and for sinus or localized alveolar ridge augmentations in the U.S. It has also been approved under a Humanitarian Device Exemption (HDE) for revision posterolateral spine fusion and treating recalcitrant long bone nonunions. However, BMP has also been used off-label for posterolateral spine fusion (PSF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), cervical fusion, and acute long bone fractures. The purpose of this study was to evaluate the prevalence of on-label and off-label use of BMP in the United States using a nationally representative administrative database.

METHODS: We characterized the prevalence of BMP usage in the U.S. using the Nationwide Inpatient Sample from October 1, 2002 to December 31, 2007. NIS is a stratified, statistically valid survey of hospitals conducted by the Federal Healthcare Cost and Utilization Project. In 2007, the NIS had a sample size of approximately 8 million records from 1,044 hospitals in 40 states, which represent approximately 20% of all discharges from community hospitals in the U.S., regardless of payment source. Sampling weights are produced to provide the national estimates. Because of the large size of the database, the Nationwide Inpatient Sample is particularly well suited for epidemiological studies related to specific procedures or diseases in the national population.

The prevalence of BMP use during inpatient procedures (ICD-9-CM code 85.42) was calculated for population subgroups as a function of age, gender, race, census region, primary payer, hospital size, and hospital type. The BMP code was only effective since October 2002; hence, this study only considered NIS data from that period forth.

RESULTS: A nationwide estimate of 340,251 inpatient procedures with BMP usage were identified from the NIS between October 2002 and December 2007. Between 2003 and 2007, the number of procedures involving BMP increased 4.3-fold from 23,900 to 103,194. Spine fusion accounted for the vast majority (92.8%) of principal procedures with BMP. The remaining applications included long bone fracture fixation, ankle fusion, and vertebral fracture repair. The predominant use of BMP was in PLIF/TLIF, with 155,362 principal procedures that accounted for 45.7% of BMP-related procedures (Figure 1). The remaining principal procedures with BMP included 56,525 ALIF (16.6%), 46,230 cervical fusions (13.6%), 16,341 PSF (4.8%), and 13,216 thoracolumbar fusions (3.9%). 19.3% of ALIF with BMP principal procedures did not involve the utilization of BMP (off-label use), and BMP was also used in a substantial number of revision fusion procedures comprising of 13,493 revision PLIF/TLIF (4.0%), 3,360 revision ALIF (1.0%), 3,343 revision cervical fusions (1.0%), 2,057 revision thoracolumbar fusions (0.6%), and 949 revision PSF (0.3%).

The rate of BMP use, particularly for spine fusion, has also increased steadily since 2002. With the exception of ALIF, BMP was utilized in less than 5% of fusion procedures in Q4, 2002, but up to 4.2% (of PSF) in 2007 (Figure 2). BMP was implanted in 14.3% of ALIF procedures in Q4, 2002, which increased steeply to 48.2% in 2004 and steadily to 54.0% in 2007. The majority of BMP was used in female (55.6%) and white (87.3%) patients, as well as in patients aged 45-64 years (<45 y.o.: 20.0%; 45-64 y.o.: 53.1%; ≥65 y.o.: 26.9%). Private insurance was the primary payer for 52.3% of the procedures, compared with 28.3% by Medicare, 4.4% by Medicaid, and 15.0% by other sources. The South region accounted for 40.3% of BMP procedures, in contrast to 25.9% in the Midwest, 21.3% in the West, and 12.5% in the Northeast. Urban non-teaching and large hospitals performed 53.0% (urban teaching: 42.9%, rural: 4.1%) and 69.6% (medium: 20.7%; small: 9.7%) of these procedures.

DISCUSSION: According to a nationally representative database, BMP was used most often in procedures other than ALIF for which it was FDA-approved. While the off-label uses of BMP in PSF and TLIF have demonstrated good short-term clinical outcomes [1, 2], some concerns have been raised regarding the rare occurrence of potential neurologic compromise associated with ectopic bone formation [3] and the development of osteolytic defects within the vertebral body [4,5] following BMP use in PLIF or TLIF. The use of BMP in the anterior cervical spine has also been associated with higher than usual rates of soft-tissue swelling, dysphagia, and respiratory complications [6,7], which led to the issuance of a Public Health Notification by the FDA. Despite increased awareness, since 2006, of adverse effects associated with BMP use for certain applications [4-7] and the FDA’s public warning, the relative use of BMP did not decline in the most recent year of NIS data. With uncertainty regarding the risks of using BMP in certain off-label applications, further research will be needed to better define the appropriate indications for use of BMP. It is unclear if the utilization of BMP will change substantially as more evidence regarding the safety, efficacy, and cost-effectiveness of BMP becomes available. In the future, longitudinal administrative databases, such as Medicare, provide a mechanism to evaluate the comparative effectiveness of BMP for off-label use in PSF/PLIF/TLIF and cervical spine fusion in the U.S.