Appendix 1 Table F. Off-Label Comparative Study Surgery and Perioperative Outcomes

Investigator (yr, country, ref #) Surgical Site	Study design	Comparisons No. pts (BMP dose)	Patient diagnosis	Surgical intervention	Mean OR time (hr)	Mean estimated blood loss (mL)	Mean hospital LOS (days)	Perioperative complications (n)	Second surgeries (n)	Comment
Boden et al., 2002 USA (84) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP2/CRM plus Texas Scottish Rite Hospital (TSRH) Spinal System (TSRHSS) n=11	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 ICBG	rhBMP2/CRM /TSRHSS 3.7±0.3	rhBMP2/CRM /TSRHSS 577±113	rhBMP2/CRM /TSRHSS 3.3±0.1	rhBMP2/CRM /TSRHSS 2 (1 transient leg pain, 1 epidural hematoma)	rhBMP2/CRM /TSRHSS 2 (1 decompression 1 level above index to relieve leg pain, 1 decompression 3 levels above index to relieve stenosis)	No significant intergroup differences other than mean OR time
		(40 mg/pt) rhBMP2/CRM alone n=11			rhBMP2/CRM alone 2.0±0.2	rhBMP2/CRM alone 333±121	rhBMP2/CRM alone 4.0±0.9	rhBMP2/CRM alone 2 (1 persistent leg pain, 1 superficial hematoma)	rhBMP2/CRM alone 1 (anterior lumbar interbody fusion to relieve low back and leg pain)	
		(40 mg/pt) ICBG plus TSRHSS n=5			ICBG/TSRHSS 3.1±0.4 (p=0.002 rhBMP2/CRM	ICBG/TSRHSS 430±82	ICBG/TSRHSS 4.4±0.5	ICBG/TSRHSS 0	ICBG/TSRHSS 0	

					alone vs other 2 groups)					
Burkus et al., 2005 USA (85) **Lumbar Spine** Note: includes all pts from Burkus et al., 2002, rec# 11510; same pts as Burkus et al., 2006, rec# 6640	Multicenter, nonblinded RCT	rhBMP2 n=79 (8-12 mg/pt)	single-level lumbar lumbar DDD	primary single-level anterior lumbar fusion with a pair of threaded allograft cortical bone dowels (CBD) plus rhBMP2 or ICBG	rhBMP2 1.4	rhBMP2 87	rhBMP2 2.9	NR	rhBMP2 2 (2 supplemental fixations)	Perioperative outcomes were significantly better in the rhBMP2 group than the ICBG group
		ICBG N=52			ICBG 1.9 (p < 0.001)	ICBG 185 (p < 0.001)	ICBG 3.3 (p=0.20)		ICBG 8 (8 supplemental fixations)	
Dimar et al., 2009 USA (86) **Lumbar Spine** Note: contains pts in Glassman et al., 2007, rec# 4040; Dimar et al., 2006 rec# 5480; Glassman et al., 2005, rec# 8040	Multicenter nonblinded RCT	rhBMP2/CRM n=239 (40 mg/pt)	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG	rhBMP2/CRM 2.5±0.09	rhBMP2/CRM 343±265	rhBMP2/CRM 4.1±2.3	rhBMP2/CRM technical difficulty (1)	rhBMP2/CRM 20 (4 revisions, 10 nonelective removal of graft, 6 supplemental fixation)	No surgical reintervention was related to recurrent stenosis or inadequate decompression
								(2) dural injury		
								cardiovascular (13)		
								malpositioned implant (1)		
								other (1)		

								vertebral fracture (3)		
		ICBG n=224			ICBG 2.9±1.0 (p < 0.001)	ICBG 449±302 (p < 0.001)	ICBG 4.0±1.9	ICBG technical difficulty (0)	ICBG 36 (4 revisions, 23 nonelective removals, 9 supplemental fixations) (p=0.015 for total number of surgeries)	
								cardiovascular (0)		
								dural injury (18)		
								malpositioned implant (0)		
								other (0)		
								vertebral fracture (3)		
Glassman et al., 2007 USA (99) **Lumbar Spine**	Retrospective with historical control group	rhBMP2 n=91 (12 mg/pt)	single- and multi-level lumbar DDD, degenerative scoliosis, postdiscectomy instability, spinal stenosis, adjacent level degeneration	single- or multi-level primary or revision instrumented posterolateral lumbar fusion	rhBMP2 3.2 (1.5-6)	rhBMP2 542 (100-3,600)	NR	NR	rhBMP2 5 of 48 (10) 1-level primary fusions	No significant differences noted
		ICBG n=35			ICBG NR	ICBG NR			ICBG NR	
Glassman et al., 2008 USA	Multicenter nonblinded RCT	rhBMP2/ACS n=50 (dose not	single- or multi-level lumbar DDD	single- or multi-level primary	rhBMP2 4.1±0.6	rhBMP2 670±487	NR	rhBMP2 8 (16) (1 cardiac, 1	rhBMP2 4 (8) (1 wound	Bone graft filler/extender used in 100%

(87) **Lumbar Spine**		reported)		instrumented posterolateral lumbar fusion plus rhBMP2 or ICBG				wound infection, 1 line-related sepsis, 2 GI, 1 UTI, 1 shingles, 1 broken toe))	infection, 1 adjacent level fracture, 1 nonunion, 1 adjacent level degeneration)	rhBMP2 and 67% ICBG cases, available local bone used in all cases
								Overall complications rhBMP2 8		
		ICBG n=52			ICBG 4.5±1.0 (p=0.024)	ICBG 675±456		ICBG 12 (23) (7 cardiac, 4 wound infection, 3 back or leg pain requiring readmission or epidural steroids, 3 GI, 1 UTI, 1 neurologic deficit)	ICBG 11 (2 wound infection, 1 pedicle screw reposition, 5 nonunions, 1 late screw removal, 1 pain pump insertion, 1 adjacent level degeneration)	
								Overall complications ICBG 20 (p=0.014)		
Haid et al., 2004 USA (88) **Lumbar Spine**	Multicenter, nonblinded RCT	rhBMP2 n=34 (4.2-8.4)	single-level lumbar DDD	single-level primary posterior lumbar interbody fusion (PLIF)	rhBMP2 2.6	rhBMP2 323	rhBMP2 3.4	rhBMP2 3 (3 dural tears)	rhBMP2 6 (3 failures, 3 fusion at different level)	No significant differences between pt groups

		ICBG N=33		interbody fusion cages plus rhBMP2 or ICBG	ICBG 3.0	ICBG 373	ICBG 5.2 (p=0.065)	ICBG 3 (1 DVT, 2 dural tears)	ICBG 6 (3 failures, 3 fusions at different level)	
Johnsson et al., 2002 Sweden (92) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=10 (7 mg/pt) ICBG n=10	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	NR	NR	NR	None reported	rhBMP7 2 ICBG 1	No perioperative results reported
Kanayama et al., 2006 Japan, Cleveland (93) **Lumbar Spine**	Multicenter nonblinded RCT	rhBMP7 n=9 (7 mg/pt) AGB/CRM n=10	single-level lumbar DDD	single-level primary instrumented posterolateral lumbar fusion with rhBMP7 or AGB/CRM	NR	NR	NR	NR	NR	No perioperative results reported
Mummaneni et al., 2004 USA (100) **Lumbar Spine**	Retrospective single-center cohort study	rhBMP2/AGB n=25 (8.4 mg/pt) ICBG N=19	single- or multi-level lumbar DDD	single- or multi-level primary transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages with rhBMP2 plus AGB or ICBG alone	NR	NR	NR	NR	NR	
Pradhan et al., 2006 USA (101)	Prospective consecutive patient single-center	rhBMP2 n=9 (dose NR)	single-level lumbar DDD	single-level primary anterior lumbar	NR	NR	NR	NR	rhBMP2 3 (3 instrumented	Salvage posterior fusions performed

Lumbar Spine	cohort study			interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or ICBG					posterior salvage fusions)	secondary to subsequent pseudarthrosis and intractable symptoms
		ICBG n=27							ICBG 7 (7 instrumented posterior salvage fusions)	
Singh et al., 2006 USA (102) **Lumbar Spine**	Prospective single-center case-matched cohort study	rhBMP2/ICBG n=39 (12-36 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented posterolateral lumbar fusion with rhBMP2 plus ICBG or ICBG alone	NR	NR	NR	rhBMP2/ICBG 2 (dural tear)	rhBMP7 1 (lumbar decompression above index level)	
		ICBG N=11						ICBG None reported	ICBG None	
Slosar et al., 2007 USA (103) **Lumbar Spine**	Prospective consecutive patient single-center cohort study	rhBMP2 n=45 (3-9 mg/pt)	single- or multi-level lumbar DDD	single- or multi-level primary instrumented anterior lumbar interbody fusion (ALIF) with femoral ring allograft (FRA) plus rhBMP2 or allograft bone chips (ALG)	NR	NR	NR	rhBMP2 2 (1 wound infection, 1 dural tear))	rhBMP2 0	Salvage posterior fusions performed secondary to subsequent pseudarthrosis
		ALG N=30						ALG 1 (wound dehiscence	ALG 4 (salvage posterolateral fusion)	
Vaccaro et al., 2008 USA (94)	Multicenter nonblinded RCT	rhBMP7 n=207 (7 mg/pt)	single-level lumbar DDD	single-level primary uninstrumented	rhBMP7 2.4	rhBMP7 309	NSD but data not provided (p=0.529)	Proportion with treatment-related SAE	rhBMP7 21	Significantly shorter OR time and less blood loss on

Lumbar Spine				posterolateral lumbar fusion with rhBMP7 or ICBG				rhBMP7 20%		average in rhBMP7 pts compared to ICBG
		ICBG n=86			ICBG 2.7 (p=0.006)	ICBG 471 (p=0.00004)		ICBG 26%	ICBG 11 (p=0.242)	
Vaccaro et al., 2008 USA (95) **Lumbar Spine** Note: Long-term F/U study that includes all pts from Vaccaro et al., 2004, (184), and Vaccaro et al., 2005, (185)	Multicenter, nonblinded RCT	rhBMP7 n=24 (7 mg/pt) ICBG n=12	single-level lumbar DDD	single-level primary uninstrumented posterolateral lumbar fusion with rhBMP7 or ICBG	rhBMP7 2.3±0.7 (0.8-3.7) ICBG 2.6±0.5) (1.9-3.6) (Data from Vaccaro et al., 2005, rec# 7310)	NR	rhBMP7 3.9±1.7 (2-10) ICBG 4.3±2.0 (3-9) (Data from Vaccaro et al., 2005, rec# 7310)	rhBMP7 89 total (includes 16 procedural, 40 referable to musculoskeletal and connective tissue, 6 infections) ICBG 51 total (includes 14 procedural, 21 referable to musculoskeletal and connective tissue, 1 infection)	rhBMP7 2 (2 revision decompression)	No significant differences between pt groups
Baskin et al., 2003 USA (89) **Cervical Spine**	Multicenter, nonblinded RCT	rhBMP2/ALG n=18 (0.6-1.2 mg/pt)	single- or two-level cervical DDD	single- or two-level primary instrumented ACDF with rhBMP2/ALG or ICBG/ALG	rhBMP2/ALG 1.8	rhBMP2/ALG 91	rhBMP2/ALG 1.4	None reported	rhBMP2/ALG 1 (unrelated to index procedure, but required removal of anterior cervical plate)	No significant intergroup differences reported
		ICBG/ALG n=15			ICBG/ALG 1.8	ICBG/ALG 123	ICBG/ALG 1.1			

Butterman et al., 2008 (104) **Cervical Spine**	Prospective nonrandomized cohorts of consecutive patients	rhBMP2/CRA n=30 (0.9-3.7 mg/pt)	single- or multiple-level cervical DDD	single- or multi-level primary instrumented or uninstrumented ACDF with rhBMP2/CRA or ICBG	rhBMP2/CRA 1.9±0.4	rhBMP2/CRA 65±51	rhBMP2/CRA 1.3±0.5	Cervical swelling rhBMP2/CRA 15 (50%) Re-admit rhBMP2/CRA 3 (10%) MD evaluation rhBMP2/CRA 7 (23%) Phone call (RN) rhBMP2/CRA 10 (33%)	rhBMP2/CRA 1 (adjacent level ACDF with decompression due to disc herniation)	Cervical swelling caused dysphagia that was more severe in rhBMP2/CRA group than ICBG group, at 4 days after surgery and persisting for 21 days
		ICBG n=36			ICBG 1.9±0.4	ICBG 65±84	ICBG 1.2±0.4	Cervical swelling ICBG 5 (14%) ($p < 0.01$) Re-admit ICBG 0 MD evaluation ICBG 3 (8%) Phone call (RN) ICBG 4 (11%)	ICBG 1 (pseudarthrosis repair)	
Crawford et al., 2009 USA (105) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2/BGE n=41 (4.2-12 mg/pt)	single- or multi-level posterior cervical stenosis, ACDF	single- or multi-level instrumented posterior cervical spinal fusion	rhBMP2/BGE 2.8±1.0	rhBMP2/BGE 275±224	rhBMP2/BGE 4.2±2.6	Wound complications rhBMP2/BGE 6 (15%) Prolonged drainage	NR	No significant differences reported between groups

			nonunion, or unstable spondylosis	with rhBMP2/BGE or ICBG				rhBMP2 2 (5%)		
								Presumed deep infection rhBMP2/BGE 4 (10%)		
								Medical rhBMP2/BGE 0		
		ICBG n=36			ICBG 2.7±0.9	ICBG 337±317	ICBG 3.5±1.2	Wound complications ICBG 1 (3%)		
								Prolonged drainage ICBG 1 (3%)		
								Presumed deep infection ICBG 0		
								Medical ICBG 3 (8%)		
Smucker et al., 2006 (106) **Cervical Spine**	Retrospective case-control	rhBMP2/CRA n=69 (dose NR)	NR	single- or multi-level instrumented ACDF with rhBMP2/CRA or CRA alone	NR	NR	NR	Cervical swelling (total) rhBMP2/CRA 19 (28%)	NR	Bivariate unadjusted logistic regression model showed significant association between cervical swelling and rhBMP2 ($p < 0.0001$), C4-C5 level

										surgery (p=0.003), age ≥ 50 years (p=0.003), surgery at ≥ 3 levels (p=0.007), combined sugery (p=0.04)
								Swelling Complications :Discharge delay rhBMP2/CRA 9 (13%)		Adjustment for demographic differences showed only rhBMP2 use was significantly associated with cervical swelling (OR 10.1, 95% CI 3.4, 29.7, p < 0.0001)
								Readmission for medical management rhBMP2/CRA 2 (3%)		Timing and presentation of cervical swelling in rhBMP2 recipients was reported distinct from that typically seen after ACDF, usually about 4 days after
								ER or ENT consult rhBMP2/CRA 5 (7%)		
								Incision and drainage of site rhBMP2/CRA		

								3 (4%)		surgery and qualitatively different
								Reintubation, PEG, Tracheostomy, delayed extubation rhBMP2/CRA 4 (6%)		
								Severe dysphagia rhBMP2/CRA 5 (7%)		
		CRA n=165						Cervical swelling (total) CRA 6 (4%) ($p < 0.0001$)		
								Swelling Complications :Discharge delay CRA 5 (3%)		
								Readmission for medical management CRA 0		
								ER or ENT consult CRA		

								1 (1%) Incision and drainage of site CRA 0 Reintubation, PEG, Tracheostomy, delayed extubation CRA 4 (2%) Severe dysphagia CRA 2 (1%)		
Vaidya et al., 2007 (107) **Cervical Spine**	Retrospective cohort of consecutive patients	rhBMP2 n=22 (1-3 mg/pt) ALG/DBM n=24	single- or multiple-level cervical DDD with radiculopathy or myelopathy	single- or multi-level primary instrumented ACDF with interbody fusion cages rhBMP2 on ACS or ALG/DBM	NR	NR	rhBMP2 2.9 (1-9) ALG/DBM 2.3 (1-6)	Dysphagia IPO, 0.5, 1.5, 24 mos rhBMP2 17, 17, 13, 4 Hoarseness rhBMP2 20 (60%) Cervical swelling ALG/DBM 24 (100%) Dysphagia IPO, 0.5, 1.5, 24 mos ALG/DBM 10, 7, 4, 4 Hoarseness	rhBMP2 2 (1 for swelling, 1 below index level)) ALG/DBM 1 (non-union)	Cervical swelling was significantly greater in the rhBMP2 group compared to the ALG/DBM group for 6 weeks postsurgery

								ALG/DBM 11 (62%)		
Boraiah et al., 2009 USA (108) **Open Tibial Fractures**	Retrospective case series	rhBMP2 (1) n=17 (12 mg/pt)	Complex tibial plateau fractures	Surgery for Acute traumatic tibial plateau fractures	NR	NR	NR	Development of HO BMP group 10 (59%)	4 patients in BMP group had ectopic bone removed. No other surgeries reported	
		(2) n=23 no BMP						No BMP 1 (4%)		
Jones et al., 2006 USA (90) **Open Tibial Fractures**	Multicenter prospective RCT	rhBMP2 (1) n=15 (12 mg/pt with allograft bone chips	Diaphyseal tibial fracture with cortical defects	Reconstruction of diaphyseal tibial fractures with cortical defect	BMP 150min ± 82.7	BMP 117 ±100.3	NR	Soft tissue swelling BMP 12 (80%)	2 per group	
								Epidermal erythema BMP 5(33%)		
								Infection BMP 3(20%)		
								Screw breakage BMP 0		
								Hererotopic ossification BMP 1(7%)		
								Anti-bodies to BMP-2 BMP 0		
								Antibodies to type I bovine collagen BMP 0		
		(2) n=15 autogenous bone graft			No BMP 169min ±49.3 Note: This is duration of anesthesia	No BMP 353 ± 284.4		Soft tissue swelling No BMP 9(60%)		
								Epidermal erythema		

								No BMP 0 Infection No BMP 1(7%) Screw breakage No BMP 2(13%) Hererotopic ossification No BMP 0 Acute pain at iliac crest donor site No BMP 14(93%) Pustules or drainage at donor site No BMP 3(20%) Antibodies to type I bovine collagen Non BMP 1(7%)		
Ristiniemi et al., 2007 Finland (110) **Open Tibial Fractures** (same pts as rec#4560)	Retrospective cohort of matched patients	Rh-BMP7 N=20 Matched Zone 43 fracture	Distal tibial fracture (OTA zone 43) treated with external fixation	Distal tibial fracture (OTA zone 43) treated with external fixation by BMP7 and graft	NR	NR	NR	Infection One pin track 6 Three pin track 1 Calcification in the wound 1 Infection One pin track 4	rhBMP7 n=2 Matched n=7	

		(OREF) N=20						Three pin track 0 Calcification in the wound 0		
Bilic et al., 2006 Croatia, Netherlands (96) **Miscella-neous Off-Label Uses**	Single-center, unblinded RCT	rhBMP7/AGB n=6 (3.5 mg/pt) rhBMP7/ALG n=6 (3.5 mg/pt) ICBG n=6	symptomatic proximal pole scaphoid nonunion	revision of nonunion	rhBMP7/AGB 2.3 rhBMP7/ALG 1.6 ICBG 2.3	NR	NR	NR	NR	Patients who were treated with rhBMP7/ALG lost estimated 50 mL less blood than those in the other two groups
Dickinson et al., 2008 USA (91) **Miscella-neous Off-Label Uses**	Single-center RCT	rhBMP2/ACS n=9 (dose not given) ICBG n=12	unilateral cleft lip-palate with an alveolar cleft defect	repair of unilateral cleft lip-palate with an alveolar cleft defect	NR	NR	rhBMP2/ACS 0.4±0.4 ICBG 1.8±0.8	NR	NR	
Ekrol et al., 2008 UK (97) **Miscella-neous Off-Label Uses**	Prospective randomized cohort	RhBMP2 Non bridging external fixation N=4 Bone graft Non bridging external fixation	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation)	Osteotomy of the distal radius for symptomatic malunion (with and without external fixation) with RhBMP-7 and autologous bone graft	NR	NR	NR	RhBMP2 Non bridging external fixation: N=2 pts. Developed extensive osteolysis, 1 pt dorsal defect Bone graft Non bridging external fixation: n= 1	RhBMP2 Non bridging external fixation: n=1 Bone graft internal fixation w/ pi-plate	

		N=6						pt had recurrence of deformity	N=7 for plate removal	
		RhBMP-7 internal fixation w/ pi-plate N=10						RhBMP-7 internal fixation w/ pi-plate N=5 pts had dorsal defect, 2 pts had non-union, 1 rupture of extensor pollicis longus	RhBMP-7 internal fixation w/ pi-plate N=3 for plate removal	
		Bone graft internal fixation w/ pi-plate N=10						Bone graft internal fixation w/ pi-plate N=5 donor site hematoma, 1 pt rupture all extensor tendons on the dorsum of wrist	Bone graft internal fixation w/ pi-plate N = 0	
Geesink et al., 1999 Netherlands (98) **Miscella-neous Off-Label Uses**	Prospective double-blind randomized study	Untreated N=6	High tibial osteotomy	High tibial osteotomy with three osteoinductiv e materials	NR	NR	NR	Wound Complications :	NR	
		DMB N=6						OP-1 n=1 (16.6%) hematoma on lateral side of leg, spontaneousl y resolved		
		Collagen						Collagen n=1		

		type I N=6 OP-1 (2.5mg) with Collagen type I N=6						(16.6%) oozing fibular wound (no intervention)		
Karrholm et al., 2006 UK (111) **Miscella-neous Off-Label Uses**	Single-center case-control	Cups rhBMP7/ALG (1 g/pt) n=10 Cups: ALG n=10 Stems rhBMP7/ALG (1 g/pt) n=11 Stems: ALG n=30	required revision of total hip arthroplasty	impaction grafting for revision of hip arthroplasty	NR	NR	NR	NR	Cups rhBMP7/ALG 2 Cups ALG 0 Stems rhBMP7/ALG 2 Stems ALG 1	
Maeda et al., 2009 USA, Japan (109) **Miscella-neous Off-Label Uses**	Cohort study with nonconcurrent control group	rhBMP2/BGE n=23 (64-320 mg/pt) ICBG n=32	spinal deformity	primary instrumented posterior spinal fusion from thoracic spine to the sacrum or ilium, or anterior fusion between same locations using interbody fusion cage	NR	NR	NR	rhBMP2/BGE 1 (acute tubular necrosis)	rhBMP2/BGE 1 (4) ICBG 6 (19)	All patients who underwent second surgeries had a fusion site pseudarthrosis