A. Summary of Safety and Probable Benefit

A. General Information

Device Generic Name:	Osteogenic Protein 1
Device Trade Name:	OP-1 Putty
Applicant's Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Humanitarian Device Exemption (HDE) Number:	H020008
Date of Humanitarian Use Device Designation:	September 5, 2002, January 30, 2003 (revised)
Date of Panel Recommendation:	The HDE was not taken to the Orthopedic and Restorative Devices Panel for review.
Date of Notice of Approval to Applicant:	APR - 7 2004

B. Indications for Use

OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

C. Contraindications

- OP-1 Putty should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen.
- OP-1 Putty should not be applied at or near the vicinity of a resected tumor or in patients with a history of malignancy.
- OP-1 Putty should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).

- OP-1 Putty should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

D. Warnings and Precautions

See Warnings and Precautions in the final labeling (Package Insert).

E. Device Description

OP-1 Putty consists of the recombinant human Osteogenic Protein (rhOP-1), Type 1 Bovine Bone Collagen Matrix (collagen matrix) and the Putty Additive carboxymethyl cellulose sodium (CMC). OP-1 Putty is intended to be reconstituted with sterile saline (0.9%) solution.

OP-1 Putty is provided as two components:

- A large vial containing one gram sterile dry powder consisting of bone collagen and OP-1.
- A small vial containing the Putty Additive (230 mg) consisting of a sterile dry powder comprised of carboxymethyl cellulose (CMC).

Storage: 2 to 8 °C
Shelf-life: 18 months when stored at recommended temperature.

F. Alternative Practices and Procedures

The following are possible alternatives for compromised patients requiring revision of a failed posterolateral (intertransverse) lumbar fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion:

- Allograft bone – A revision spinal fusion could be performed using bone from a donor. These types of procedures do not have the risks associated with them that autograft does. These risks include, but are not limited to new or increased pain, fracture of the donor site bone because of larger bone loss or injury to the nerves or blood vessels in the donor site area because of scar tissue from the previous surgery. Because allograft bone is from a donor, there is the risk of disease transmission.

- Bone graft substitutes – These are man-made materials that provide a guide for the formation of new bone. These devices do not have the risks associated with autograft or allograft.

- Bone Growth Stimulators - Devices that apply energy to site of the previous fusion in an attempt to promote bone formation.

- No surgical treatment – Some patients may choose to forego a second attempt at spinal fusion, in favor of pain management and non-surgical treatments.

G. Marketing History

OP-1 Putty has not been marketed prior to this HDE. OP-1 Putty contains OP-1 Implant, which is approved for commercial use in the United States (H010002), Canada, Australia and the European Union for certain long bone indications.

H. Potential Adverse Effects of the Device on Health

The following table was compiled from multi-center pilot and pivotal studies of OP-1 Putty in patients with degenerative spondylolisthesis requiring primary fusion of the affected spinal level. Although this indication differs from the indication approved in this HDE, these data were used to support relative safety. This table contains all of the events for the two groups that were reported to the studies as of October 17, 2003.

Summary of Adverse Events for All Patients in the Pilot and Pivotal Posterolateral Spinal Fusion Studies[1]

Body System	OP-1 (n=228)	Autograft (n=98)
Abnormal lab values	6 (3%)	8 (8%)
Blood and lymphatic system disorders	8 (4%)	14 (14%)
Cardiac disorders	9 (4%)	1 (1%)
Gastrointestinal disorders	30 (13%)	10 (10%)
General disorders and administration site condition	36 (16%)	18 (18%)
Infections and infestations	18 (8%)	8 (8%)
Injury, poisoning and procedural complications	44 (19%)	23 (24%)
Metabolism and nutrition disorders	6 (3%)	1 (1%)
Musculoskeletal and connective tissue disorders - other	50 (22%)	23 (24%)
Musculoskeletal and connective tissue disorders - joint inflammation	24 (11%)	6 (6%)
Musculoskeletal and connective tissue disorders - pseudarthrosis	12 (5%)	3 (3%)
Nervous system disorders - other	26 (11%)	10 (10%)
Nervous system disorders - TIA	4 (2%)	0 (0%)
Psychiatric system disorders	10 (4%)	3 (3%)
Renal and urinary disorders	13 (6%)	9 (9%)
Respiratory, thoracic and mediastinal disorders	15 (7%)	4 (4%)
Skin and subcutaneous tissue disorders - other	8 (4%)	1 (1%)
Skin and subcutaneous tissue disorders – wound infection	15 (7%)	2 (2%)
Vascular Disorders	17 (8%)	10 (10%)

[1]Other events seen in 1% or less of the investigational population include: ear and labyrinth disorders; eye disorders; immune system disorders; neoplasms (benign, malignant or unspecified); reproductive system and breast disorders; social circumstances; and surgical and medical procedures.

From the worldwide experience with OP-1 (Implant and Putty), 7 patients reported the occurrence of cancer. Six of the seven events reported were non-osseous cancers occurring in elderly patients. A seventh event of recurring chondrosarcoma was reported in a patient with a history of chondrosarcoma.

Recurrence and disease progression were considered consistent with population data associated with this type of cancer. The incidence of cancer in patients treated with OP-1 is less than 1% and is within the range of cancer occurrence in the general populations of the U.S. and Australia (the countries in which most patients were treated).

As with all therapeutic proteins, there is a potential for immune responses to be generated against components of the OP-1 Putty. In the degenerative spondylolisthesis pilot study, antibodies to OP-1 were measured at pretreatment and 6 weeks and 6 months post treatment. Antibodies were detected in 23 out of 24 (96%) patients treated with OP-1 Putty. No antibodies were detected in patients treated with autograft. Neutralizing antibodies were detected in 7/24 (29%) patients treated with OP-1 Putty. For six out of the seven patients, neutralizing activity was detected at 6 weeks post treatment, but not at 6 months post treatment. For the seventh patient, neutralizing activity was detected only at 6 months post treatment. The clinical significance of these antibodies is not known. The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to OP-1 Putty with the incidence of antibodies to other products may be misleading.

I. Summary of Preclinical Studies

Safety and Biocompatibility Testing

Safety and biocompatibility studies were conducted in accordance with ISO 10993 and the Tripartite Guidance. Testing performed to evaluate the safety and biocompatibility of OP-1 Putty and its components include: sensitization, cytoxicity, hemocompatibility, genotoxicity, system toxicity, developmental toxicity, biodistribution pharmacokinetics, and systemic pharmacokinetics. The majority of the testing performed was with OP-1 Implant, the active component of OP-1 Putty. As deemed necessary, additional safety and biodistribution testing has been performed for the putty additive and OP-1 Putty as a final product.

The following tables represent Non-Clinical Safety and Biocompatibility Testing for rhOP-1 protein, OP-1 Implant, Putty Additive and OP-1 Putty. The results of these tests support the safety of OP-1 Putty and its components for human use.

Table 2. Safety and Biocompatibility Testing - rhOP-1 Protein

Test	Study	Result
Systemic Toxicity	Acute Intravenous Toxicity in Rats	Negative
	Acute Intravenous Toxicity Test in Mice	Negative
	Comparative 4-Week Toxicity Study in Cynomologus Monkeys	Paravascular fibrosis and subintimal vasculopathy occurred at the injection sites in the saphenous veins; related to intravenous administration of OP-1 and not considered relevant to intraosseous implantation.

Test	Study	Result
Biodistribution & Pharmacokinetics	Pharmacokinetics and distribution in the rat following single intravenous administration	Elimination of OP-1 from serum was rapid. Results suggest uptake of OP-1 from blood by liver. Results suggest OP-1 is not distributed into tissues. Uptake into thyroid considered associated with free ^{125}I.
	Pharmacokinetics following single intravenous administration to male Cynomologus monkeys	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed in deep compartments in the tissues.
Biodistribution & Pharmacokinetics cont'd.	Pharmacokinetics following single intravenous administration to male rats.	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed in deep compartments in the tissues.
Safety Pharmacology	Effects of OP-1 in the Irwin Test in rats	Negative
	Cardiovascular effects of OP-1 in Conscious, Telemetered Rats	Transient observations of increased blood pressure, bradycardia, tachycardia, and slight increase in body temperature to excess dose of intravenously administered OP-1 not considered cause for concern regarding intended use of intraosseous implantation.
Reproductive and Developmental Toxicity	The placental transfer of ^{125}I-OP-1 in the rat following single intravenous administration	Placental transfer of ^{125}OP-1 to rat fetal tissue was <1% dose.
	A range-finding developmental toxicity study in rats via intravenous injection	Negative
	A study for the effects of OP-1 administered intravenously on embryo-fetal development in rats	No observable effect level determined at 0.4 mg/kg/day
	A study for the effects of OP-1 administered intravenously on embryo-fetal development in rabbits	No observable effect level determined at 0.4 mg/kg/day

Table 3. Safety and Biocompatibility Testing - OP-1 Implant

Test	Study	Result
Cytotoxicity	L929 Agar Overlay Test for Cytotoxicity In Vitro	Negative
	CHO Mammalian Cell cytotoxicity assay on test article OP-1	Invalid: Test system incompatible with OP-1 Implant. Results inconsistent with known biocompatibility with CHO cells.
Sensitization	Sensitizing potential in the guinea-pig: Epicutaneous Maximization Test (EMT)	Negative
	Dermal Sensitization study of OP-1 Implant in Guinea-Pigs (Buehler's Technique Modified)	Negative
	Developing collagen-induced (Type II) arthritis (CIA) model in mice	Negative
Hemocompatibility	Assessment of the Hemolytic Property of a Test Article: Direct Contact and Saline Extract Tests	Negative
Genotoxicity	Ames/Salmonella-E.coli reverse mutation assay	Negative
	Chromosomal aberrations assay with CHO cell culture in vitro: OP-1 Implant	Negative
System Toxicity	A study to determine the acute toxicity of the test device (osteogenic device) following subcutaneous implantation in laboratory rats	No adverse toxic affects observed
	Twenty-eight (28) day intravenous toxicity study in rats administered test article OP-1.	Negative
	OP-1 Device: 13 week toxicity study in rats with subcutaneous implantation	No adverse toxic affects observed
	A Study to Determine Localized Inflammatory Response to the Test Device (OP-1) and the Vehicle (Collagen Matrix) Following Subcutaneous Implantation in Long Evans Rats	No adverse toxic affects observed

Test	Study	Result
	104 week carcinogenicity study in rats with subcutaneous implantation with 52 week toxicity study	Tumors were found at the site of implantation in OP-1 treated animals. These results are believed to be consistent with the solid state carcinogenesis phenomenon observed when objects are implanted in rats.
	Healing of Segmental Defects in Dogs – Healing Time Course	No adverse toxic effects observed
	Healing of Segmental Defects in Dogs – Long-term Implantation	No adverse toxic effects observed. Presence of anti-OP-1 and anti-collagen antibodies did not correlate with clinical observations. No evidence of neoplastic or pre-neoplastic abnormalities long term (18 months).
	The Safety of OP-1 for Lumbar Fusion with Decompression – a Canine Study	Negative: No abnormal or prolonged neurological deficits or pathological damage observed.
	A Study Evaluating the Effects of the Osteogenic protein device on the neurological tissue in a canine laminectomy and poster-lateral spinal fusion model.	Negative: No evidence of toxicity to the canine central nervous system.
Biodistribution & Pharmacokinetics	A biodistribution study of a ^{125}I-labelled test device (^{125}I Osteogenic Protein-bovine collagen matrix) following subcutaneous implantation in laboratory rats	No significant quantity of OP-1 is detected systemically. OP-1 eliminated from implantation site by 21 days.
	^{125}I-OP-1 Implant – The disposition of radioactivity in rabbits following repair of a tibia bone defect	No significant quantity of OP-1 is detected systemically.

Table 4. Safety and Biocompatibility Testing - Putty Additive

Test	Study	Result
Cytotoxicity	L929 Agar Overlay Test for Cytotoxicity In Vitro	Grade I (USP XXIII) slight reactivity
Hemocompatibility	Assessment of the Hemolytic Property of a Test Article: Direct Contact and Saline Extract Tests	Negative

Table 5. Safety and Biocompatibility Testing - OP-1 Putty

Test	Study	Result
Sensitization	Sensitizing potential in the guinea-pig: Epicutaneous Maximization Test (EMT)	Negative
System Toxicity	OP-1 + CMC osteogenic device-14 day implant study in the rat	No adverse toxic effects observed
	Histologic compatibility of using carboxymethyl cellulose as an additive to OP-1 Device	No adverse toxic effects observed
	The Safety of OP-1 for Lumbar Fusion with Decompression – a Canine Study	Negative: No abnormal or prolonged neurological deficits or pathological damage to spinal cord observed.
	A Study Evaluating the Effects of the Osteogenic protein device on the neurological tissue in a canine laminectomy and posterolateral spinal fusion model.	Negative: No evidence of toxicity to the canine central nervous system.
Biodistribution & Pharmacokinetics	^{125}I-OP-1 Putty – The disposition of radioactivity in rabbits following repair of a tibia bone defect	No significant quantity of OP-1 is detected systemically
Genotoxicity	Ames/Salmonella-E.coli reverse mutation assay on OP-1 Implant/CMC	Negative

Performance Testing

Utility of OP-1 Putty for use in posterolateral lumbar spinal fusion was demonstrated through several animal studies including models in dogs, rabbits and sheep. These

studies showed that OP-1 stimulated new bone formation. Studies in rabbits demonstrated a superior ability of OP-1 Putty to promote fusion compared to repeat autograft in revision of pseudarthrosis caused by nicotine.[1,3] This study supported the use of OP-1 Putty in the proposed indication.

Additional animal studies were also performed for other indications in additional models. The studies provided in Table 6 demonstrated the viability of OP-1 Putty as an acceptable alternative to autograft.

Table 6. Bioactivity of OP-1 Implant and OP-1 Putty in Posterolateral Lumbar Fusion

Study	Test Model	Test Article	Result
Test reports			
Osteogenic protein-1 (rhOP-1) Putty versus autograft for posterolateral spinal arthrodesis. An in vivo time-course study using a canine model.	Dog	OP-1 Putty	OP-1 Putty as an adjunct or as a stand alone therapy showed increased fusion and biomechanical strength compared to autograft alone.
A Study Evaluating the Effects of the Osteogenic protein device on the neurological tissue in a canine laminectomy and poster-lateral spinal fusion model	Dog	OP-1 Putty and OP-1 Implant	OP-1 Putty is equivalent to OP-1 Implant in production of new bone growth at fusion site and superior to autograft alone.
A Pilot Study Evaluating the Safety and Efficacy of the OP-1 Implant for Lumbar Posterolateral Spinal Fusion. An *In Vivo* Sheep Model.	Sheep	OP-1 Implant	Safe with no complications to spinal cord and nerves. Evidence of efficacy in this model.
A Pilot Study Evaluating the Safety and Efficacy of OP-1 Implant for Lumbar Posterolateral Spinal Fusion.	Sheep	OP-1 Implant	Safe, as efficacious as autograft in this model. A viable alternative to autograft.
Literature			
[1] Grauer, JN, et al. "Development of a New Zealand White Rabbit Model of Pseudarthrosis Repair and Evaluation of the potential Role of OP-1 to Overcome Pseudarthrosis." Accepted for publication in *Spine*.	Rabbit	OP-1 Putty	OP-1 Putty demonstrated superior ability to promote fusion following nicotine induced pseudarthrosis compared to autograft.
[2] Grauer JN, et al. "Evaluation of OP-1 as a Graft Substitute for Intertransverse Process Lumbar Fusion." *Spine*, 2001; 26 (2): 127-133.	Rabbit	OP-1 Putty	OP-1 Putty reliably induced solid intertransverse fusion at 5 weeks in rabbits. Results show superiority to autograft.
[3] Patel TC, et al. "Osteogenic Protein-1 Overcomes the Inhibitory Effect of Nicotine on Posterolateral Lumbar Fusion," *Spine*, 2001; 26 (15): 1656-1661.	Rabbit	OP-1 Putty	OP-1 Putty reliably induced solid fusion by 5 weeks in rabbits exposed to nicotine. Results show superiority to autograft.
[4] Jenis LG, et al. "The effect of osteogenic protein-1 in instrumented and noninstrumented posterolateral fusion in rabbits," *The Spine Journal*, 2002; 2: 173-178.	Rabbit	OP-1 Putty	OP-1 Putty reliably induced solid intertransverse fusion at 3 and 12 weeks in rabbits. Results show superiority to autograft.
[5] Cook SD, et al. "*In Vivo* Evaluation of Recombinant Human Osteogenic protein-1 (rhOP-1) Implants as a Bone Graft Substitute for Spinal Fusion," *Spine*, 1994;19:1655-1663.	Dog	OP-1 Implant	Rapid healing with OP-1 Implant compared to autograft. OP-1 Implant is a viable alternative to autograft.

J. Summary of Clinical Information

Pilot Study of OP-1 Putty in the Posterolateral Spine

A multicenter, prospective, randomized, controlled study was conducted in the United States. Forty-eight patients with symptomatic single level degenerative lumbar spondylolisthesis and spinal stenosis underwent decompression and bilateral treatment with OP-1 Putty alone, OP-1 Putty/autograft combination or autograft alone, in a 2:1:1 ratio. The study investigated the use of OP-1 Putty in primary fusion patients. Although this study evaluated the use of OP-1 Putty in primary posterolateral spinal fusions, the basis for using these data to support the probable benefit of using OP-1 Putty for revision posterolateral spinal fusion surgery is described in Section K below.

Blinding: Because of the requisite donor site surgery associated with the control group, it was not possible to blind patients and physicians to treatment type. However, blinding was used for the independent review of all study radiology. Two radiologists were blinded to patient identification, clinical history both prior to and since treatment, and site identification.

Patient Population: Patients were randomized at a 2:1:1 ratio, OP-1 Putty, OP-1 Putty/autograft, and autograft, respectively. Each patient in the OP-1 Putty and OP-1 Putty/autograft groups received 2 units of product (1 unit per side). The study included 5 investigational sites, with a total of 48 skeletally mature patients under the age of 81 with a diagnosis of single level degenerative lumbar spondylolisthesis (grade I/II) with spinal stenosis.

Baseline Demographics: Examination of the demographics suggest a comparable patient dataset between treatment groups for most of the demographic parameters. The average age for all treated patients was 65. Height and weight were comparable between treatment groups at approximately 65 inches and between 175 and 200 pounds. Patients were treated predominantly at the L4-L5 level, as well as the L3-L4 level.

Demographic differences existed in the ratio of females to males in each group, as well as the presence of coexisting medical conditions. The percentage of female patients was 54%, 58% and 75% for the OP-1 Putty alone, autograft and OP-1 Putty/autograft groups, respectively. Seven of the OP-1 Putty alone patients reported a medical history of compromising factors including osteoporosis, diabetes, arthritis and multiple joint disease.

Study Endpoints: Effectiveness was based on clinical and radiographic endpoints. Clinical success was defined as improvement of at least 20% on the Oswestry Disability Index compared to pre-op scores, and no revisions, removals or supplemental fixations intended to promote fusion. Radiographic success was defined as lack of motion of flexion/extension radiographs, *i.e.* not more than 5° angulation or 2 mm translation, and evidence of bridging trabecular bone, as

determined by independent radiological evaluation. Overall success was defined as the percentage of patients with both clinical and radiographic success as a function of the total number of patients in the group.

Safety was based on the rate and type of adverse events (device-related or not), donor site pain and post-op neurological status compared to pre-op.

Success Rates: Only those effectiveness data which pertain to OP-1 Putty alone and autograft alone treatment groups are presented here. Analyses have been performed on all available 3, 6, 9, 12 and 24 month data to determine efficacy.

Success rates [% (n)]

		3 months	6 months	9 months	12 months	24 months
clinical success	**OP-1 Putty**	88% (21/24)	91% (21/23)	87% (20/23)	86% (18/21)	94% (17/18)
	autograft alone	67% (8/12)	67% (8/12)	67% (6/9)	73% (8/11)	60% (6/10)
radiographic success	**OP-1 Putty**	46% (11/24)	63% (15/24)	57% (12/21)	74% (14/19)	65% (11/17)
	autograft alone	64% (7/11)	55% (6/11)	63% (5/8)	60% (6/10)	40% (4/10)
overall success	**OP-1 Putty**	42% (10/24)	58% (14/24)	48% (10/21)	58% (11/19)	63% (10/16)
	autograft alone	36% (4/11)	36% (4/11)	38% (3/8)	40% (4/10)	30% (3/10)

Safety Analyses:
Refer to the adverse event table in Section H for a description of the type and rates of events that were observed.

Heterotopic Bone Formation: Heterotopic bone was observed in 4 patients (3 OP-1 Putty, 1 autograft) by one or both of the independent radiologists. For all patients, the observation was made by 3 months, with continued observation at 6 months. In at least one case (OP-1 Putty), the heterotopic bone may represent exuberant bone formation. In no case was the heterotopic bone identified clinically as an adverse event.

Pivotal Study of OP-1 Putty in the Posterolateral Spine
A multicenter, prospective, randomized, controlled study following the same protocol as the pilot study described above is ongoing in the United States. An analyses of these data is not yet available.

K. Risk / Probable Benefit Analysis

The results of the preclinical studies in animals demonstrate that OP-1 Putty is osteoinductive and:

- is capable of inducing solid fusion in the posterolateral spine following primary treatment or revision of nicotine induced pseudarthrosis.
- induces bone formation in a variety of animal species
- generates bone that is mechanically and histologically normal

Based on a pilot clinical study, OP-1 Putty has demonstrated probable benefit as an alternative to autograft in patients who required a primary uninstrumented fusion for the treatment of degenerative spondylolisthesis. While these data cannot be directly extrapolated to the expected performance of OP-1 Putty in revision posterolateral spinal fusions in the compromised population, there is reason to believe that OP-1 Putty could have a probable benefit in this population.

When revision of a failed fusion is required, most patients are limited to either living with pain and altered function or repeating the original procedure with additional autologous bone, which may result in depletion of the bone stock and further risk to the patient. Allograft bone and bone graft substitutes are not considered feasible alternatives to autograft in revision surgery due to their lack of osteogenic potential. For certain patients, *e.g.*. those with implanted leads, bone growth stimulators would not be considered as feasible options. OP-1 Putty has the potential to eliminate the risks and complications associated with these treatment alternatives while providing a feasible and beneficial alternative treatment.

The preclinical and clinical data suggest that it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits or currently available alternative treatments.

L. Panel Recommendation

This HDE was not reviewed by the Orthopaedic and Restorative Devices Advisory Committee. However, the review of this HDE was done collaboratively between scientists in the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research.

M. CDRH Decision

CDRH has determined that, based on the data submitted in this HDE application, the OP-1 Putty will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on APR – 7 2004

N. Approval Specifications

Directions for use: See the physician's labeling.

Hazards to Health from Use of the Device: See Indications, Contraindication, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

O. References

[1] Grauer, JN, AR Vaccaro, M Kato, BK Kwon, JM Beiner, T Patel, AS Hilibrand, K Chiba, TJ Albert. "Development of a New Zealand White Rabbit Model of Pseudarthrosis Repair and Evaluation of the potential Role of OP-1 to Overcome Pseudarthrosis," Manuscript was accepted September 2003 for publication in *Spine*.

[2] Grauer JN, Patel TC, Erulkar JS, Troiani NW, Panjabi MM, Friedlaender GE. "Evaluation of OP-1 as a Graft Substitute for Intertransverse Process Lumbar Fusion," *Spine*, 2001; 26 (2): 127-133.

[3] Patel TC, Erulkar JS, Grauer JN, Troiano NW, Panjabi MM, Friedlaender GE. "Osteogenic Protein-1 Overcomes the Inhibitory Effect of Nicotine on Posterolateral Lumbar Fusion," *Spine*, 2001; 26 (15): 1656-1661.

[4] Jenis LG, Wheeler D, Parazin SJ, Connolly RJ. "The effect of osteogenic protein-1 in instrumented and noninstrumented posterolateral fusion in rabbits," *The Spine Journal*. 2002; 2: 173-178.

[5] Cook SD, Dalton JE, Tan EH, Whitecloud TS, and Rueger DC. "*In Vivo* Evaluation of Recombinant Human Osteogenic protein-1 (rhOP-1) Implants as a Bone Graft Substitute for Spinal Fusion," *Spine*, 1994;19:1655-1663.

[6] An HS, Simpson JM, Glover JM, Stephany J. "Comparison Between Allograft Plus Demineralized Bone Matrix Versus Autograft in Anterior Cervical Fusion," *Spine*, 1995;20(20): 2211-2216.

[7] SF-36 Physical & Mental Health Summary Scales: A User's Manual. Health Assessment Lab, New England Medical Center, Boston MA, December 1994.

[8] Govender, PV, YR Rampersaud, L Rickards, MG Fehlings. "Use of osteogenic protein-1 in spinal fusion: literature review and preliminary results in a prospective series of high-risk cases." *Neurosurg. Focus*, 13, 2002 December, pp. 1-6.