Lumbar Fusion with 3D-Printed Porous Titanium Interbody Cages – A Single-Blinded Randomized Controlled Trial Evaluating Nexxt Matrixx™ Versus PEEK Cages

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TITLE: Lumbar Fusion with 3D-Printed Porous Titanium Interbody Cages – A Single-Blinded Randomized Controlled Trial Evaluating Nexxt Matrixx™ Versus PEEK Cages

Protocol Number:
Date:

The signatures of the investigator and representative of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this Clinical Trial will be conducted according to Good Clinical Practices and to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality.

It is agreed that the protocol contains all necessary information required to conduct the Clinical Trial as outlined in the protocol.

It is agreed that all participants in this study will provide written informed consent and/or a HIPAA Authorization and agree to the Clinical Trial procedures as approved by the Institutional Review Board, as applicable.

SPONSOR:

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PRINCIPAL INVESTIGATOR:

_____
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1 INVESTIGATIONAL PLAN

1.1 Purpose

The purpose of this randomized controlled trial is to assess and compare radiographic and clinical outcomes in patients who are to undergo combined interbody/posterolateral lumbar fusion procedures, supplemented with pedicle screw instrumentation, using one of the following interbody cages; the Nexxt Spine Nexxt Matrixx™ 3D-printed titanium cage or the Honour™ poly-ether-ether-ketone cage.

2 INTRODUCTION

2.1 Background

In 2012, over 727,000 spinal fusion and non-fusion procedures were performed in the US (Millennium Research Group (MRG), 2013). This included treatment for various conditions such as DDD, spinal stenosis, spondylosis, spondylolisthesis, spinal deformities, tumors, and traumatic spinal injuries. Over time, intervertebral discs wear down and lose water and then disc height. The degeneration of these discs can impact the spine in several ways, including spinal canal stenosis, spondylolisthesis, and osteophyte and bony growth formation. These changes can impinge on the spinal cord and nerve roots, causing chronic pain. Consequently, as the older population in the US expands, demand for treatments that address back and extremity pain will rise accordingly. The correlation between age and the incidence of DDD has been well-documented; for example, one study concluded that there was a direct relationship between age and the macroscopic grade of degeneration caused by DDD (Quint and Wilke, 2008). Increasing rates of obesity in the US will also likely contribute to growth in spinal fusion and non-fusion volumes because obesity represents a risk factor for DDD (Hangai M, et al., 2008).

The premise behind fusion surgery for lower back pain (LBP) and leg pain is that a degenerated and mobile lumbar segment acts as a pain generator. Consequently, if motion is prohibited through a fusion, it is expected that the patient will experience improvement in both pain and disability, which will increase their ability to function. Currently, there is no way to be certain which structure or structures actually are causing the pain, but the main interest has been focused on the facet joints, discs, or a combination of both (Fritzell P et al., 2002).

Lumbar spine fusion rates can vary according to the surgical technique. Although many studies on spinal fusion have been conducted and reported, the heterogeneity of the study designs and data handling make it difficult to identify

which approach yields the highest fusion rate. Traditional posterolateral inter transverse process fusion (PLF) still remains a good procedure with acceptable fusion rates for most degenerative conditions. For solid fusion, PLF can be combined with interbody fusion (IF) to circumferentially stabilize the relevant segment, even though it is unclear whether this improves the rate of fusion (Lee et al, 2011).

A bone graft or bone graft substitute is required to produce the fusion and can be implanted on its own, in the posterolateral gutters, or contained with an interbody device using either a posterior or anterior approach. Spinal fusion procedures are the largest source of bone graft product use. The current gold standard is autograft bone, wherein tissue is harvested from the patient, usually from the iliac crest or locally, and is then placed over the fusion surfaces. Autograft is the gold standard because it possesses all of the characteristics necessary for new bone growth—namely, osteoconductivity, osteogenicity, and osteoinductivity. Osteoconductivity refers to the situation in which the graft supports the attachment of new osteoblasts and osteoprogenitor cells, providing an interconnected structure through which new cells can migrate and new vessels can form. Osteogenicity refers to the situation when the osteoblasts that are at the site of new bone formation are able to produce minerals to calcify the collagen matrix that forms the substrate for new bone. Osteoinductivity refers to the ability of a graft to induce nondifferentiated stem cells or osteoprogenitor cells to differentiate into osteoblasts (Laurencin C. et al., 2006).

The mechanical and structural properties of an interbody device are used to support osteogenesis across the interbody space and contribute to the success of a spinal fusion procedure. One of the most popular synthetic implant materials is poly-ether-ether-ketone (PEEK). PEEK is used as a spacer between vertebrae while providing surfaces allowing for bone formation. While macroscale properties such as implant shape contribute to the growth of a fusion mass, microscale properties such as implant topography likely play a much larger role through facilitating osteoblastic differentiation, osteoid synthesis, and mineralization.

Recent studies have shown that PEEK does not integrate well with the surrounding bone and instead may form a fibrous connective interface (Kurtz and Devine, 2007; Anjarwalla et al., 2006). Recently, the relative failure of osseo-integration observed with PEEK implants has been demonstrated to be associated with the reduced ability of cells on the implant surface to generate an environment rich in angiogenic factors. In contrast, implants fabricated from titanium result in good bone-to-implant contact and are osseo-integrated into the surrounding bone. Osteoblasts

on rough titanium substrates have been shown to produce angiogenic factors including significantly higher VEGF-A and FGF-2 levels on smooth and rough titanium alloys than on PEEK, an effect significantly more robust on rough titanium alloy (Olivares-Navarrete et al., 2013).

2.2 Device Description

Subjects enrolled in this study will have either the Nexxt Spine Nexxt Matrixx™ 3D-printed titanium cage or the Honour™ PEEK cage implanted at each level of 1 or 2-level lumbar arthrodesis procedures. All constructs will be supplemented with a pedicle screw system (Depuy Synthes Expedium) cleared for lumbar spinal fusion.

Nexxt Matrixx™ interbody fusion cages are manufactured with detailed specifications utilizing modern 3-D printing technology to replicate the cellular structure of cancellous bone. 3-D printing technology allows for the creation of a complex lattice geometry that cannot be created by traditional orthopedic manufacturing processes. First, a uniform 3-D architecture with a consistent 70% porosity provides an optimal biomechanical and biological environment for promotion of osseous tissue regeneration throughout implant walls. Second, an interconnected array of 300-700µm pores creates ideal an environment for natural influx of proteins, hormones, growth factors and mesenchymal stem cells to promote osteoinduction.

In a review article by Karageorgiou and colleagues (2005), a noted minimum pore size of 100 µm was reported to be more conducive to bone ingrowth than pore sizes less than 75 µm. However, the authors recommended pore sizes greater than 300 µm as other studies have shown a better osteogenic response. In a transcortical rabbit study, titanium alloy (Ti6Al4V) implants with 100, 200, and 300 µm pores were compared; the larger pore sizes resulted in a higher percentage of bone within the pores and a higher percentage of that bone to be lamellar (Götz HE et al., 2004). Another study used a 3D-printed Ti6Al4V scaffold implanted over the transverse process of goats to study the effects of pore size and porosity on osseointegration (Li JP et al., 2007). Five groups of implants having a pore size and porosity ranging from 160µm/39% to 680µm/68% were evaluated. While the small sample size prevented an evaluation of statistical significance, data trends led to the conclusion that the larger pores and porosity allow for greater amounts of newly formed bone. Taken together, these studies support the varied porosity selection of 300-700µm pore size of the Nexxt Matrixx™ System implants.

An additional parameter evaluated is the surface finish (Götz HE et al., 2004). One set of the 200µm implants were surface-blasted using an aluminum oxide such that a roughness average (Ra) of 7.25µm resulted. The effect of this roughness was an increase in the bone-implant contact overall on the surface and within the pores. However, a later study (Nakada H. et al, 2007) compared osseointegration when alumina and a multiphase calcium phosphate (MCD) were used as the blast media. Blasted Ti6Al4V cylinders were implanted into rabbit tibiae and were then evaluated two and four weeks after implantation. The histologic results showed the MCD to illicit a greater volume of new bone formation. The MCD used in this study is the same as the calcium phosphate blast media used in the manufacture of the Nexxt Matrixx™ System implants.

The Nexxt Matrixx™ System implants have a roughened surface with a Ra measurement ranging from 5.0 to 11.8 that is attained via a calcium phosphate surface-blasting process. As stated above, this surface was selected specifically due to its capacity for osseointegration.

3 TRIAL DESIGN

3.1 Design

The randomized controlled trial will prospectively evaluate the safety and efficacy of the Nexxt Matrixx™ System titanium implant supplemented with a pedicle screw system as compared to a representative PEEK cage currently used in routine fashion for lumbar interbody fusion procedures. This study will capture clinical and radiographic outcomes on patients up to 2 years post operatively. Both cages will be used in conjunction with milled local autograft bone generated as part of the spinal fusion procedure (no iliac crest autograft will be utilized).

This single centered study will enroll up to 70 subjects (n = 35 per group), with subjects followed for a minimum of 12 months post-surgery. All subjects enrolled in the study will be recruited from a pool of subjects eligible for combined interbody/posterolateral lumbar fusion surgery. The inclusion/exclusion criteria are listed below.

3.2 Inclusion Criteria

Subjects will be considered for inclusion in this trial if they satisfy the following criteria.

1. Subject is scheduled to undergo combined interbody and posterolateral spinal fusion surgery using either the Nexxt Matrixx™ 3D-printed titanium cage or Honour™ PEEK cage in conjunction with local autograft bone, and supplementation with a pedicle screw system.
2. Subject must be over the age of 18 years old.
3. Subject has been unresponsive to conservative care for a minimum of 6 months.
4. The subject must in the investigator's opinion, be psychosocially, mentally, and physically able to fully comply with this protocol including the required follow-up visits, the filling out of required forms, and have the ability to understand and give written informed consent.

3.3 Exclusion Criteria

Subjects will be excluded from this trial if they satisfy any of the following criteria:

1. Subjects with previous lumbar arthrodesis surgery.
2. Subjects requiring additional bone grafting materials other than local autograft bone.
3. Subject has inadequate tissue coverage over the operative site.
4. Subject has an open wound local to the operative area, or rapid joint disease, bone absorption, or osteoporosis.
5. Subject has a condition requiring medications that may interfere with bone or soft tissue healing (i.e., oral or parenteral glucocorticoids, immunosuppressives, methotrexate, etc.).
6. Subject has an active local or systemic infection.
7. Subject has a metal sensitivity/foreign body sensitivity.
8. Subject is morbidly obese, defined as a body mass index (BMI) greater than 40.
9. Subject has any medical condition or extenuating circumstance that, in the opinion of the investigator, would preclude participation in the study.
10. Subject is currently involved in another investigational drug or device study that could confound study data.
11. Subject has a history (present or past) of substance abuse (recreational drugs, prescription drugs or alcohol) that in the investigator's opinion may interfere with protocol assessments and/or with the subject's ability to complete the protocol required follow-up.
12. Subjects who are pregnant or plan to become pregnant in the next 12 months or who are lactating.

13. Subject is involved in or planning to engage in litigation or receiving Worker's Compensation related to neck or back pain.
14. Subject is a prisoner.

4 STUDY PROCEDURE

4.1 Screening Assessments

4.1.1 Informed Consent

Subjects will be provided with an informed consent and will be given ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study specific procedures, that are not part of the investigator's standard of care begin. A copy of the informed consent will be given to the subject. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

All subjects who have agreed to participate in this study, have signed the informed consent and who meet the inclusion/exclusion criteria will be considered enrolled and assigned a subject ID number. Once a Subject ID number has been issued, it cannot be reassigned or used for another subject.

4.1.2 Medical History and Demographic Data

Within 60 days prior to the surgery date, the following information will be collected:

- Demographic data
- Medical history, including a complete history of spinal disorder(s) (non-operative or operative treatments performed)
- Physical examination (including height, weight)
- X-Rays
- Current pain medications and other drug therapies.
- Neurological status - All subjects' neurological status will be assessed and recorded as intact or not intact, based upon the investigator's motor, sensory and reflex evaluations.

4.1.3 Pregnancy Screening

A pregnancy test will be performed and negative results shall be kept on file for all female subjects unless infertile or post-menopausal to ensure subjects are not enrolled into the study who are pregnant.

4.1.4 Clinical Assessments

Subject study data will be collected preoperatively, intra-operatively and postoperatively at 3, 6, 12, and when available 24 months. The following data will be recorded on the Case Report Forms (CRFs) and in addition, electronic data entry will be employed via an Internet connection when possible using the Research Electronic Data Capture (REDCap) program.

Oswestry Disability Index version 2.1a (ODI v2.1a): Pre-operatively the subject will complete the Oswestry Disability Index for a baseline low back pain and function assessment. The questionnaire is a combined pain and function index which will be used to assess the subject's back pain and how that pain affects the subject's ability to manage in everyday life. The questionnaire is divided into ten sections designed to assess limitations of various activities of daily living. Each section contains six statements and each statement describes a greater degree of difficulty in that activity than the preceding statement. The subject marks the one statement in each section, which describes his/her limitations most accurately. Each section is scored on a 0-5 scale, 5 representing the greatest disability. The scores for all sections are added together, giving a possible score of 50. The total is doubled and expressed as a percentage. If a subject marks two statements, the highest scoring statement is recorded as a true indication of his disability. If a section is not completed because it is inapplicable, the final score is adjusted to obtain a percentage.

Back and Radicular Leg Pain: Preoperatively all subjects will assess their back and/or radicular leg pain in one or both legs using a visual analog scale (VAS) from 0 - 10 with 10 being considered most painful.

4.2 Randomization

All subjects will be randomized in the trial to receive either the Nexxt Spine Nexxt Matrixx™ 3D-printed titanium cage or the Honour™ PEEK cage supplemented with a pedicle screw system and milled local autograft bone. Subject randomization will be stratified according to smoking status. Subjects will be blinded to their group status for the duration of the study assessments and procedures (12 months post-operatively).

4.3 Perioperative and Postoperative Management

Surgeons will perform combined interbody and posterolateral lumbar fusion utilizing either Nexxt Matrixx™ or PEEK cages supplemented with a pedicle screw system cleared for fusion and milled local autograft bone (per customary protocol).

Data will be collected during and immediately after the surgery according to the parameters described by the Nexxt Matrixx™ IF/PLF CRFs. This includes: diagnosis, duration of surgery, blood loss, OR time, length of hospital stay, instrumentation used, type of procedure, and surgical level(s). In addition, all intra-operative complications (e.g. excessive blood loss, hematoma, vascular injury, etc.) will be reported and recorded as a complication on the CRF.

Intra-operative (after hardware installation is completed) or immediate post-operative x-rays will be obtained. Postoperative care will follow the standard of care at each institution for subjects who undergo fusion procedures.

Postoperative care is extremely important. The subject should be warned that noncompliance with postoperative instructions could lead to breakage of the pedicle screw system and/or possible migration requiring revision surgery to remove the pedicle screw system.

4.4 Schedule of Events

	Screening/ Enrollment (-60 days of procedure)	Procedure	3 months (± 7 days)	6 months (± 14 days)	12 months (± 30 days)	24 months (± 60 days)
Informed consent	X					
Medical History	X					
Demographics	X					
Concomitant medications review	X	X	X	X	X	X**
Randomization		X				
Oswestry Disability Index v2.1a	X		X	X	X	X**
Visual Analog Scale (VAS) back and leg	X		X	X	X	X**
Radiographic X-rays (AP/ Lateral with Flexion and Extension)	X		X	X	X	X**
CT Scan				X*		
AE/ SAE review	X	X	X	X	X	X**

*A CT scan post-op is standard of care in clinical practice to document fusion. The CT scan will be done at 6 months post-op rather than the usual 12 months. Cost will be covered by study sponsor. **Optional time point (when available).

4.5 Follow-Up Assessments

Subjects will be asked to return postoperatively at 3 months (± 1 week), 6 months (± 2 weeks), and 12 months (± 1 month) for a clinical and radiographic exam. An additional visit at 24 months may be scheduled at the request of either the physician or the subject. The following data will be recorded on the Case Report

Forms (CRFs) and in addition, electronic data entry will be employed via an Internet connection when possible using REDCap.

Clinical assessment: The investigator will carry out a clinical examination at the 3, 6, 12, and when available, 24-month visits to assess:

- subject compliance with postoperative care instructions,
- ability to return to work and normal activity, and
- any procedure related or device related adverse events since discharge from the hospital
- review of medication usage
- progress towards fusion consolidation
- Neurological status - All subjects' neurological status will be assessed and recorded as intact or not intact, based upon the investigator's motor, sensory and reflex evaluations.

Subject self-assessment (Patient completed forms):

- Each subject will be asked to complete a follow-up Oswestry Disability Index (ODI) form and a Back and Leg Pain VAS form at each follow-up visit.

Radiographic assessment: Each subject will undergo AP, lateral and flexion/extension radiographs at the 3, 6, 12, and when available, 24-month visits as well as a CT scan at 6 months to assess:

- integrity of the device and graft, with observation for events such as rod, hook, screw and/or spacer (if applicable) migration or subsidence, hardware fracture, and progress towards fusion consolidation

Findings from any additional imaging studies deemed necessary by the investigator will be recorded and reported with study results.

4.6 Independent Radiographic Assessment

An independent radiographic analysis will be performed to evaluate all images and assess subjects' radiographic status. The independent radiographer will receive deidentified disks and will not have access to any personally identifiable information. The following quantitative and qualitative assessments will be performed.

Fusion Determination

Fusion will be assessed by an independent radiographer when data collection is complete. X-rays at each visit and a lumbar CT at 6 months will be evaluated for fusion determination. Interbody fusion will be graded by the method of Brantigan and Steffee as modified to describe the Fraser definition of locked pseudoarthrosis (BSF scale) (Santos et al., 2003). The grading system is as follows:

- BSF-1: Radiographical pseudarthrosis
- BSF-2: Radiogaphical locked pseudarthrosis
- BSF-3: Radiographical fusion

Radiographic Success: Radiographic success is defined by radiographical fusion (BSF-3) presenting bone bridges within at least half of the fusion area with at least the density originally achieved at surgery.

Radiographic Failure: Radiographic failure is defined by radiographical pseudarthrosis (BSF-1 or -2)

X-rays will be uploaded into the REDCap as a JPEG image at each subject visit.

4.7 Success Criteria

4.7.1 Primary Measure of Effectiveness

A subject will be considered a success if fusion is a Grade BSF-3 at 6 months. The primary outcome measure of effectiveness will be determined by the fusion rate at 6 months post-operatively in subjects implanted with either titanium cage as compared to the PEEK cage.

4.7.2 Secondary Measure of Effectiveness

Secondary measures of effectiveness will be determined by evidence and timing of fusion observed in X-rays post-operatively (3, 6, 12, and when available, 24 months).

4.8 Subject Withdrawal

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment.

Other Conditions for Withdrawal:

Any subject who develops a severe concurrent medical illness during the trial should be withdrawn. This type of illness is defined as any illness that would hinder the subject's ability to return for scheduled follow-up appointments. Such a withdrawal will not be counted for the purposes of determining success or failure.

5 COMPLICATIONS

In addition to the standard operating procedures for reporting complications per hospital/physician protocol, all clinical events, including both observed or volunteered problems, complaints, symptoms, physical signs or disease which either occur during the study, having been absent at baseline, or, if present at baseline, appear to worsen during the clinical outcomes collection study are to be recorded as complications in the subject's medical record and on the appropriate case report form.

Complications reported in the literature as most commonly associated with interbody and posterolateral lumbar fusion procedures include, but are not limited to, infection, nerve damage, blood clots, blood loss, and bowel and bladder problems, along with complications associated with anesthesia. A potential risk inherent to spinal fusion is failure of the vertebral bone and graft to properly fuse, a condition that may require additional surgery.

5.1 Definitions

A complication is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, performance, or any indication of the failure of a medical product to meet a user or customer's expectations. The complication may be the possible failure of a device or tissue product, labeling, or packaging to meet any of its specifications after it is released for distribution.

6 STATISTICAL ANALYSIS PLAN

Statistical analyses will be performed as deemed appropriate to evaluate fusion outcomes across the groups.

An interim analysis may be performed once, at minimum, half of the subject accrual is met. In the case early findings show a statistical difference between the two studied cages, enrollment will cease as investigators are unlikely to maintain clinical equipoise to continue to randomize patients. Similarly, if the interim

analysis suggests it is unlikely the study will achieve statistical significance, the investigators may choose to close the trial early for futility. Currently enrolled subjects will be followed throughout the remainder of the study, up to 12 months post-surgery.

7 REFERENCES

Anjarwalla NK, Morcom RK, Fraser RD. Supplementary stabilization with anterior lumbar intervertebral fusion--a radiologic review. Spine (Phila Pa 1976) 2006;31(11):1281–7.16688045.

Fernyhough JC, Schimandle JJ, Weigel MC, et al. Chronic donor site pain complicating bone graft harvesting from the posterior iliac crest for spinal fusion. *Spine* 1992;17:1474–80.

Fritzell P, Hägg O, Wessberg P, Nordwall A; Swedish Lumbar Spine Study Group. Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomized study from the Swedish lumbar spine study group. Spine (Phila Pa 1976). 2002 Jun 1;27(11):1131-41.

Götz HE, Müller M, et al. Effect of surface finish on the osseointegration of laser-treated titanium alloy implants. *Biomaterials.* 25:4057, 2004.

Hangai M, et al. Factors associated with lumbar intervertebral disc degeneration in the elderly. *Spine*.2008;8:732–740.

Karageorgiou V, Kaplan D. Porosity of 3-D biomaterial scaffolds and osteogenesis. *Biomaterials.* 26:5474, 2005.

Kurtz SM, Devine JN. PEEK biomaterials in trauma, orthopedic, and spinal implants. Biomaterials. 2007;28(32):4845–69.17686513.

Laurencin C, Khan Y, El-Amin SF. Bone graft substitutes. Expert Rev Med Devices. 2006 Jan;3(1):49-57. Review.

Laurie SW, Kaban LB, Mulliken JB, et al. Donor-site morbidity after harvesting rib and iliac bone. *Plast Reconstr Surg* 1984;73:933–8.

Lee CS, Hwang CJ, Lee DH, Kim YT, Lee HS. Fusion rates of instrumented lumbar spinal arthrodesis according to surgical approach: a systematic review of randomized trials. Clin Orthop Surg. 2011 Mar;3(1):39-47. doi: 10.4055/cios.2011.3.1.39. Epub 2011 Feb 15. Review.

Li JP, Habibovic P, et al.: Bone ingrowth in porous titanium implants produced by 3D fiber deposition. *Biomaterials*. 28:2810, 2007.

Millennium Research Group (MRG) US Markets for Spinal Implants 2013

Nakada H, Sakae T, et. al.: Early tissue response to modified implant surfaces using back scattered imaging. *Implant Dentistry*. 16(3):281, 2007.

Nemoto, O., Asazuma, T., Yato, Y. et al. Comparison of fusion rates following transforaminal lumbar interbody fusion using polyetheretherketone cages or titanium cages with transpedicular instrumentation. Eur Spine J (2014) 23: 2150. doi:10.1007/s00586-014-3466-9

Olivares-Navarrete, R., Hyzy, S. L., Gittens, R. A., Schneider, J. M., Haithcock, D. A., Ullrich, P. F., Boyan, B. D. (2013). Rough titanium alloys regulate osteoblast production of angiogenic factors. Spine Journal, 13(11), 1563–1570.

Quint U, Wilke HJ. Grading of degenerative disk disease and functional impairment: imaging versus patho-anatomical findings. *European Spine Journal*. 2008;17(12):1705–1713.

Santos ER, Goss DG, Morcom RK, Fraser RD. Radiologic assessment of interbody fusion using carbon fiber cages. *Spine.* 2003;28: 997–1001.

Summers BN, Eisenstein SM. Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br* 1989;71:677–80.

Younger EM, Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma* 1989;3:192–5.

APPENDIX 1

Case Report Forms (CRFs)