

ORTHOPEDIC AND REHABILITATION DEVICES PANEL
Gaithersburg, Maryland
September 8, 2005

PMA P040033 – Birmingham Hip Resurfacing (BHR) System

Device Description

The Birmingham Hip Resurfacing (BHR) prosthesis is a metal-on-metal hip resurfacing prosthesis. It consists of two components: a cast cobalt-chrome (ASTM F75-01) stemmed femoral head resurfacing component and a cast cobalt-chrome (ASTM F75-01) hemispherical acetabular component. The bearing surfaces between femoral head and the acetabular components are metal on metal. It is a resurfacing prosthesis because only the surface of the femoral head is removed to attach a femoral head resurfacing component. The stemmed femoral head resurfacing component is designed for cemented fixation and the hemispherical acetabular cup is designed for cementless fixation. The acetabular cup has an integrally cast beaded outer surface coated with hydroxyapatite. Acetabular cups configured for dysplasia indications (i.e., dysplasia cups and bridging cups) are also available for those patients with superolateral acetabular defects. These cups have two superolateral locking screw holes for additional fixation. Instrumentation sets are provided as standard; several additional instruments are available as options.

Applicant Name and Address:

Smith & Nephew Orthopaedics
1450 Brooks Road
Memphis, Tennessee 38116

Reason for the Panel Meeting:

The PMA device is a first of a kind in the United States (i.e., total hip system with a resurfacing femoral component and metal-on-metal articulating surfaces). The PMA is supported by clinical data essentially from one source: the surgical experience of Dr. Derek J.W. McMinn, FRCS, who performed his surgeries at the Birmingham Nuffield Hospital, Edgbaston, Birmingham, United Kingdom. The PMA includes safety and effectiveness data from an uncontrolled, consecutive case series of all 2,385 procedures implanted with the Birmingham Hip Resurfacing (BHR) device by Dr. McMinn from July 1997 through May 2004. The objective of this PMA is to demonstrate the safety and effectiveness of the Birmingham Hip Resurfacing (BHR) System. The safety assessments included data on revisions, adverse events, deaths and a metal ion literature review. The effectiveness assessments included survivorship, radiographic, pain and function data as evaluated by the Oswestry-modified Harris Hip (OSHIP) Score, and patient satisfaction data. FDA requests expert clinical opinion regarding the safety and effectiveness data collection methods, the applicability of the foreign data from a single investigator and United Kingdom practice of medicine to the target United States population and practice of medicine, and the study results with respect to the device's safety and effectiveness.

Executive Summary

Introduction

This is an Executive Summary for the Smith & Nephew Orthopaedics Birmingham Hip Resurfacing (BHR) System (P040033). The device has been reviewed by the Orthopedic Devices Branch of the Division of General, Restorative, and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

The Executive Summary contains an identification of the applicant and manufacturer, indications for use and contraindications, and FDA's summary review memo of the device description, preclinical, clinical information, Oswestry-modified Harris Hip (OSHIP) Questionnaire, and statistical summary. The memo contains the following sections:

<u>Information</u>	<u>Page Number</u>
Applicant/Manufacturer Information	2
Indications for Use/Contraindications	3
Device Description	4
Preclinical Information	10
Clinical Information	18
Oswestry-modified Harris Hip (OSHIP) Questionnaire	63
Statistical Information	65

Applicant/Manufacturer Information

Applicant name and address:

Smith & Nephew Orthopaedics
1450 Brooks Road
Memphis, Tennessee 38116

Manufacturing sites/addresses:

Smith & Nephew Bromsgrove
Saxon Business Park
Hanbury Road
Stoke Prior
Bromsgrove, Worcestershire
B60 4AD United Kingdom

Indications for Use

The Birmingham Hip Resurfacing (BHR) System is a single use device intended for hybrid fixation: cemented femoral head component and cementless acetabular component. The BHR system is intended for use in patients requiring primary hip resurfacing arthroplasty due to:

- Non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/DDH, or
- Inflammatory arthritis such as rheumatoid arthritis.

BHR System hip resurfacing arthroplasty is intended for joint replacement in patients who are at risk of requiring future, ipsilateral hip joint revision. While it is impossible to predict if a patient will require more than one joint replacement, several factors are known to increase risk of revision surgery including age less than 55 years at index surgery and/or high physical activity level postoperative.

Contraindications

Contraindications for use of the Birmingham Hip Resurfacing (BHR) System include:

- Patients with infection or sepsis,
- Patients who are skeletally immature,
- Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery,
- Patients with bone stock inadequate to support the device including:
 - Patients with severe osteopenia should not receive a BHR procedure. Patients with a family history of severe osteoporosis or severe osteopenia.
 - Patients with osteonecrosis or avascular necrosis (AVN) with >50% involvement of the femoral head (regardless of FICAT Grade) should not receive a BHR.
 - Patients with multiple cysts of the femoral head (>1cm) should not receive a BHR.
- Females of child-bearing age due to unknown effect on the fetus of metal ion release.
- Patients with known moderate to severe renal insufficiency.

Executive Summary: Device Description

The Birmingham Hip Resurfacing (BHR) prosthesis is a metal-on-metal hip resurfacing prosthesis. It consists of two components: a cast cobalt-chrome (ASTM F75-01) stemmed femoral head resurfacing component and a cast cobalt-chrome (ASTM F75-01) hemispherical acetabular component. The bearing surfaces between femoral head and the acetabular components are metal on metal. It is a resurfacing prosthesis because only the surface of the femoral head is removed to attach a femoral head resurfacing component. The stemmed femoral head resurfacing component is designed for cemented fixation and the hemispherical acetabular cup is designed for cementless fixation. The acetabular cup has an integrally cast beaded outer surface coated with hydroxyapatite. Acetabular cups configured for dysplasia indications (i.e., dysplasia cups and bridging cups) are also available for those patients with superolateral acetabular defects. These cups have two superolateral locking screw holes for additional fixation. Instrumentation sets are provided as standard; several additional instruments are available as options.

The metal-on-metal hip resurfacing components are produced from high carbon (25-35 weight % carbon) cobalt chrome material, conforming to ASTM F75-01 and ISO 5832-4. The components are produced from as-cast cobalt chrome molybdenum (CoCrMo) alloy superfinished (or highly polished) to a surface roughness greater than 0.05 micrometers Ra, which meets with ISO standard for conventional total hip replacement (THR). The roundness of the femoral component is within 2 micrometers.

The sponsor provided engineering drawings of these components in Amendment 11 (response to item 26). The sponsor mentioned modular femoral components and McMinn Hybrid implants in various places in the PMA but these components are **NOT** part of this PMA submission.

The following components are included in the system:

- Resurfacing Femoral Head;
- Acetabular Cup: Standard, Dysplasia, and Bridging; and
- Dysplasia/Bridging Cup Screws.

Each of these components is described below.

Resurfacing Femoral Head:

The Resurfacing Femoral Head is supplied in a range of six sizes, identified by the external diameters: 38mm, 42mm, 46mm, 50mm, 54mm, and 58mm. The femoral head has a central stem that varies proportionally with the external diameter. Stable fixation is achieved with the use of bone cement. There are 6 equally spaced internal recesses to provide anti-rotational locking for the cement mantle.

Acetabular Cups:

The hemispherical Acetabular Cups are designed for cementless interference fit into the

acetabulum. The Acetabular Cups are configured for standard (standard cups) and dysplasia (dysplasia and bridging cups) indications. Each acetabular component is characterized by a cast-in beaded surface such that the beads are integral with the substrate material. The beaded surface is coated with a nominal 75 +/- 20 micrometer layer of HA for uncemented fixation. (See below for additional information on the beaded (POROCAST) and HA coatings).

Standard Acetabular Cup:

There is a range of 12 sizes for the standard acetabular components (two for each femoral head size to address the condition of occasional head/cup mismatch) identified by the external diameters: 44mm, 46mm, 48mm, 50mm, 52mm, 54mm, 56mm, 58mm, 60mm, 62mm, 64mm, or 66mm. Thus a 38mm head can be used with a 44mm or 46mm cup, a 42mm head with a 48mm or 50mm cup, etc.

Head Outer Diameter/Standard Acetabular Inner and Outer Diameters:

Head OD	Standard Cup ID	Standard Cup OD
38mm	38mm	44mm or 46mm
42mm	42mm	48mm or 50mm
46mm	46mm	52mm or 54mm
50mm	50mm	56mm or 58mm
54mm	54mm	60mm or 62mm
58mm	58mm	64mm or 66mm

Dysplasia Cup:

For those patients with a deficiency in the superolateral aspect of the acetabulum, an alternative cup is available. The Dysplasia Cup is designed with screw holes that accommodate the Dysplasia Cup Screws. There is a range of six sizes for the Dysplasia Cup identified by external diameter: 46mm, 50mm, 54mm, 58mm, 62mm, and 66mm.

The sponsor provided the following table of compatibility between the femoral resurfacing head and dysplasia cup:

Head Outer Diameter/Dysplasia Acetabular Inner and Outer Diameters:

Head OD	Dysplasia Cup ID	Dysplasia Cup OD
38mm	38mm	46mm
42mm	42mm	50mm
46mm	46mm	54mm
50mm	50mm	58mm
54mm	54mm	62mm
58mm	58mm	66mm

Bridging Cup:

A Bridging Cup is designed with a thicker wall section than the Dysplasia Cup to allow for mismatch between femoral head size and surgically prepared acetabulum. The Bridging Cup is also designed with screw holes that accommodate the Dysplasia Cup Screws. The Bridging Cup is available in 5 sizes as identified by external diameter: 50mm, 54mm, 58mm, 62mm, and

66mm. The sponsor provided the following table of compatibility between the femoral resurfacing head and bridging cup:

Head Outer Diameter/Bridging Acetabular Inner and Outer Diameters:

Head OD	Bridging Cup ID	Bridging Cup OD
38mm	38mm	50mm
42mm	42mm	54mm
46mm	46mm	58mm
50mm	50mm	62mm
54mm	54mm	66mm

Dysplasia/Bridging Cup Screws:

The Dysplasia/Bridging Cup Screws are threaded through a threaded lug on the superolateral aspect of either the Dysplasia or Bridging Cup and lock in situ. The screws also lock into the posterior cortical Bone of the ilium. Screws are made from CoCrMo alloy and are available in sizes ranging from 24mm to 88mm in 2mm increments.

Clearances between Femoral Head and Acetabular Cup Components:

The sponsor provided the following table of clearances between the femoral head and acetabular cup:

BHR Head OD/Cup ID (mm)	ΔD	Range of Clearances (includes tolerances)
38mm	██████ μm	██████ μm
42mm	██████ μm	██████ μm
46mm	██████ μm	██████ μm
50mm	██████ μm	██████ μm
54mm	██████ μm	██████ μm
58mm	██████ μm	██████ μm

Beaded Coating on the Acetabular Shell:

The beaded coating is a cast CoCr beaded coating (POROCAST) that is further coated with hydroxyapatite (HA). The HA coating is performed by Plasma Biotol Limited, North Derbyshire, UK.

The sponsor stated that the POROCAST CoCr beaded surface is a single layer of spherical beads on the outer hemispherical surface of the acetabular cup. The spherical beads are produced as part of the acetabular cup component casting process. The beads are free standing and project from the external hemispherical surface. The bead density is █████ beads/cm². The sponsor stated that they are not intended to be in contact with each other but there is acceptance of some beads becoming attached to each other. The sponsor stated that because the beads are cast during the “parent component” casting manufacturing process, there is no machining or special preparation of the surface prior to fixing the beads.

Elemental composition:

- Chromium: Cr = [REDACTED]%
- Molybdenum: Mo = [REDACTED]%
- Nickel: Ni = [REDACTED] max
- Iron: Fe = [REDACTED] max
- Carbon: C = [REDACTED] max
- Manganese: Mn = [REDACTED] max
- Silicon: Si = [REDACTED] max
- Cobalt: Co = [REDACTED]

Microstructure:

Provided in response to item 42 of Amendment 11.

Metallographic Images:

Provided in response to item 42 of Amendment 11. Based on the microstructure, there is no interconnecting subsurface porosity.

Surface Thickness:

Technical report (TM-05-14). In this report, the sponsor calculated the total thickness of the fixation surface. The sponsor reported that the average total thickness of the beaded surface with HA coating was [REDACTED] micrometers. The CoCr beaded coating was an average of [REDACTED] micrometers (n=32 measurements) and the HA coating was an average [REDACTED] micrometers (n=32 measurements);

Pore Diameter and & Porosity:

Technical report (TM-05-11). In this report, the sponsor measured pore size and % porosity of the POROCAST surface with and without the HA coating. The sponsor evaluated 3 cup sizes (44, 56, and 66mm cups) for this study. The sponsor characterized the percent porosity (volume percent of void) and pore size (mean void intercept length) as defined in ASTM F1854 (n=14 fields). The sponsor reported that the average pore size (mean void intercept length) was [REDACTED] micrometers and the average % porosity (volume percent of void) was [REDACTED] for the POROCAST surface with HA coating. The sponsor then compared these results to the results previously reported for the POROCAST surface without HA coating (n=17 fields evaluated). The sponsor reported that the average pore size (mean void intercept length) was [REDACTED] micrometers and the average % porosity (volume percent of void) was [REDACTED] for the POROCAST surface without HA coating. Based on the microstructure, there is no interconnecting subsurface porosity.

Bead Neck size:

Average was [REDACTED] micrometers (Range: [REDACTED] micrometers)

Static Shear Strength of Beaded Surface:

[REDACTED] MPa ([REDACTED] psi) (range: [REDACTED] MPa) (ASTM F1044, n=6) – sponsor stated that all failures were debonding epoxy and no beads failed during testing.

Shear Fatigue Strength of Beaded Surface:

[REDACTED] MPa ([REDACTED] psi) (ASTM F1044, n=23, 10Hz, 10million cycles) – sponsor stated that all

failures were debonding epoxy and no beads failed during testing.

Static Tensile Strength of Beaded Surface:

██████ MPa (██████ psi) (range: ██████ MPa) (ASTM F1044, n=12) – sponsor stated that all failures were debonding epoxy and no beads failed during testing. The sponsor noted batch variation in testing results but all exceeded the 20MPa strength value cited in FDA’s guidance document for porous coated devices.

Substrate Yield:

██████ MPa

Substrate UTS:

██████ MPa

Substrate % Elongation:

██████

Abrasion Testing of Coating:

The sponsor stated that because the surface texture is cast with the substrate and not sintered, it is integral with the substrate. In addition, there is only one layer. Therefore, the sponsor concluded that the abrasion resistance should be equivalent to the currently available CoCr porous beaded coatings.

HA Coating:

In Amendment 11 (response to item 41), the sponsor provided a letter of authorization from Plasma Biotol Limited, the hydroxyapatite coating facility for the BHR, to access the master file for information regarding the HAP coating (MAF 1333). In addition, the sponsor provided a test report OR-05-54 for information regarding environmental stability.

Environmental Stability:

- The sponsor provided Test Report OR-05-54 Environmental Stability of HA Coating on the Fixation Surface of the BHR Acetabular Cup in Attachment 41.2 to address the solubility of CAPTAL 30. The sponsor reported the average Solubility product (Ksp) of the plasma sprayed HA to be ██████ (Ksp = [Ca]⁵ x [PO4]³ x [OH]). The sponsor reported that the pH of the HA solution ranged from ██████ over a period of 7 days;
- The sponsor provided Test Report OR-05-54 Environmental Stability of HA Coating on the Fixation Surface of the BHR Acetabular Cup in Attachment 41.2 to address the dissolution rate of CAPTAL 30. The sponsor reported the dissolution rate of the plasma sprayed HA powder to be ██████ mg/day;

HA Coating Thickness:

- Technical report (TM-05-12) in Attachment 8 of Amendment 12. The sponsor stated that the HA coating vendor (Plasma Biotol, North Derbyshire, UK) specifies the HA coating thickness to be ██████ micrometers. The sponsor clarified that this specification is for flat coupons that are used to set up the plasma spray parameters. The sponsor then discussed that the apparent discrepancy between the HA coating thickness used in the specification (██████ micrometers) and that measured on the actual

component [REDACTED] micrometers) can be attributed to the component geometry and the measurement technique used.

Static Shear and Tensile Strength of HA Coating:

- The sponsor provided static shear and tensile testing (OR-05-88) in Attachment 9 of Amendment 12. The testing was performed on samples that had been HA coated by Plasma Biotral Limited, UK to cast cobalt chrome coupons with a 19mm diameter for evaluation according to ASTM F1044. The specimens were loaded to failure and the maximum load was recorded. The sponsor reported that the average shear strength for the HA coated coupons (n=6) was [REDACTED] MPa (S.D.= [REDACTED] MPa). The average tensile strength for the HA coated coupons (n= [REDACTED]) was [REDACTED] MPa (S.D.= [REDACTED] MPa). The sponsor stated that all failures were a result of debonding HA from the surface of the coupon;

Chemical and Crystallographic Analysis:

- The sponsor referenced the master file (MAF1333) for chemical and crystallographic analysis including XRD and IR of CAPITAL 30. The sponsor provided IR spectra of the HA powder and coating materials in the MAF 1333;

Additional HA coating information:

- Particle size range of CAPITAL 30 powder: [REDACTED]
[REDACTED] m
- Acceptable Ca/P ratio is [REDACTED]
- Surface area of device that is coated ranges from [REDACTED] mm² (on the 44mm cup) to [REDACTED] mm² (on the 66mm cup).
- SEM was provided in Appendix C of original PMA.
- Chemical analysis was provided on p.100 of original PMA.
- Heavy metals: Pb, Cd, As, Hg less than [REDACTED] ppm;
- % HA: Greater than [REDACTED]% by XRD;
- % relative crystallinity: Greater than [REDACTED]% (typically [REDACTED]%)
- Other phosphate phases: [REDACTED]%

Executive Summary: Pre-Clinical Information

The sponsor provided pre-clinical testing information on the following topics:

- Biocompatibility
- “Forensic Evaluation of Long-Term Survived Ring and McKee-Farrar Arthroplasty Devices”
- Wear
- Surface Topography
- Friction
- Kinematics
- Femoral Stem Fatigue Strength:
- Evaluation of polar and equatorial roundness before and after HAP coating
- Evaluation of equatorial roundness after simulated implantation
- Evaluation of the strength of the dysplasia/bridging cup screws
- Evaluation of the strength of the dysplasia/bridging cup lugs
- Evaluation of the static strength of the femoral component stem
- Explant Analysis
- Sterilization/ Shelf Life

Biocompatibility:

The sponsor claimed conformance to ASTM F75 and ISO 5832 for the CoCrMo and ISO 13779-1, -2, and -4 (draft) for the hydroxyapatite coating. The sponsor concluded that additional biocompatibility testing is not required.

“Forensic Evaluation of Long-Term Survived Ring and McKee-Farrar Arthroplasty Devices”

The sponsor stated that at the Sheffield Hallam Univ. Materials Research Institute, these scientists carried out a forensic evaluation of long-term survived Ring and McKee-Farrar arthroplasty devices, in some cases devices that had been implanted for over 30 years. Note that the Ring and McKee-Farrar devices were first generation metal/metal total hip replacement devices. The researchers used optical microscopy, SEM, TEM and chemical analysis of these devices. This information was used to develop the design requirements for the BHR device. This is why the sponsor settled on high carbon (above 25% carbon), produced in an as-cast condition to achieve a microstructure with coarse primary carbide throughout the matrix. The sponsor cited a paper by J. Metcalf and TJ Band “Metal on Metal Bearing Project” (Unpublished, Spring 1997) to support these statements. The sponsor then stated that these observations were confirmed following a similar study of a larger population of first generation devices. The sponsor cited a paper by J. Metcalf and TJ Band “Examination of Femoral Hip Metal on Metal Bearing Surfaces Project” (Unpublished, Autumn 2000) to support these statements. The sponsor provided a copy of these literature articles in Amendment 11 in response to item 34.

A paper that was provided in Tab 1 of Appendix C titled, “A tribological study of cobalt chromium molybdenum alloys used in metal-on-metal resurfacing hip arthroplasty” evaluated a

series of CoCrMo alloy sample coupons with different combinations of thermal treatments including solution heat treatment, hot isostatic pressing or sintering. The sponsor performed metallographic studies to determine the volume fraction of carbide present and also performed a micro-abrasion test to conclude that the carbide volume fraction is critical to the development of a low wear rate system. Those alloys with the highest carbide volume fraction produced the lowest wear rates in the micro-abrasion test. Finally, mechanical properties, including hardness, were not generally affected by the carbide volume fraction of the thermal and thermo-pressure treated samples.

Additional evaluation of the wear of this material by the sponsor led them to believe that this material has less wear than heat treated (HT), HIPped (hot isostatically pressed), and HIP and HT materials. The sponsor provided a graphical comparison of these materials and wear results on p.87 of the original PMA. The sponsor correlated the wear performance with the microstructure (i.e., phase proportions of carbide volume fractions). The sponsor provided a paper by McMinn and co-workers in Tab 7 of Appendix C of the original PMA to support these statements titled, "Hip Resurfacing: How Metal on Metal Articulations Have Come Full Circle."

Wear:

The sponsor provided a wear test report by Durham University, Centre for Biomedical Engineering. Wear testing was performed using 6 devices (5 active stations and 1 dynamically loaded control station) in a Durham Mark 1 hip joint simulator. Wear testing was performed for 5 million cycles. The sponsor originally tested for 3 million cycles and provided this information in the original PMA submission. In response to FDA's letter, the sponsor resumed testing for a total of 5 million cycles. All prostheses were 50mm in diameter (see sponsor's rationale for testing the 50mm head/cup couple below). The diametral clearances of the head/cup couples were in the range of [REDACTED] micrometers (see sponsor's rationale for testing head/cup couples with this range of diametral clearance below).

The sponsor also performed an analysis of frictional torque and an evaluation of surface topography throughout the wear study. The results of this testing is presented below.

The heads and cups were tested in anatomical position, 33° orientation of the acetabular cup to the horizontal. The motion and loading parameters chosen for the wear test were a Paul curve with a maximum load of [REDACTED] and a minimum load of [REDACTED] N. The components were placed in [REDACTED] mL of lubricant (bovine serum, total protein content of [REDACTED] mg/mL diluted to 25% and filtered through a [REDACTED] micrometer filter, [REDACTED]% sodium azide and [REDACTED] mM EDTA), at a temperature of [REDACTED] C. The control only experienced dynamic loading with no tangential motion.

The heads and cups were cleaned and weighed before the tests began and then at intervals of 0.5 million cycles until 3 million cycles. At a later date, this test was resumed according to the same protocol and followed to 5 million cycles. Gravimetric changes were converted to a volumetric loss using the density of the metal of 0.0085g/mm³. The sponsor reported that one component

produced much higher wear than the other 4 components tested. The sponsor attributed the difference to a potential different amplitude characteristic or the variation in materials or clearances.

The sponsor reported that initially (in the first million cycles) the head/cup couples produced a higher wear rate (\bullet mm³/million cycles) than subsequent cycles. Over the whole 5 million cycles, the average wear rate was \bullet mm³/million cycles (total wear of the head and cup). Once the initial wear had taken place, the wear rate was \bullet mm³/million cycles (from 1.5-3million cycles). The average wear rate over the final 2 million cycles was \bullet mm³/million cycles (3-5million cycles). The sponsor compared these results to other resurfacing and total m/m hip systems. The wear testing in conjunction with the clinical data and metal ion evaluations provided characterization of the wear performance of the device.

Rationale for Selecting the 50mm Head/Cup Couple for Wear Testing:

In Amendment 11 (in response to item 36), to provide a justification for testing the 50mm components as the “worst-case”, the sponsor provided equations regarding wear and fluid film-thickness. The sponsor stated that if K, the wear factor, and L, the load were constant, the worst-case (for greatest wear) would be the largest head diameter because it has the greatest sliding distance. However, the sponsor also stated that larger heads increase the chance of fluid-film lubrication because of several factors including a higher entraining velocity; therefore, this would decrease K for a larger head (K would be larger for a smaller head). This would make the smaller head the worst-case with respect to the wear factor K and the effect of fluid-film lubrication on K. So, the sponsor stated that the selection of a single head size to test is difficult because it is a function of which lubrication mode is present. The sponsor provided some calculations for fluid film thickness with assumptions for synovial fluid viscosity, equivalent elastic modulus, fluid entraining velocity and relative radius of curvature based upon clearance for the 38mm, 50mm and 58mm heads/cups. The sponsor’s calculations demonstrated that the theoretical predictions for fluid film thickness favored the largest head sizes. Although the predictions were for full-fluid-film lubrication for the 50mm size, there was metal-to-metal contact and wear for the 50mm couple. The sponsor stated that since the 50mm couple would have a greater sliding distance than the 38mm couple, this would produce more wear. The sponsor concluded by stating that the wear rates would be similar at all diametral sizes because of the two competing factors, K (wear factor) and x (sliding distance) though smaller clearances would be better (less wear) than larger ones for the clearances identified.

Rationale for Selecting Diametral Clearance of \bullet micrometers for the Head/Cup Couple in the Wear Testing:

In Amendment 12 (in response to item 7), the sponsor stated that the clearance for the 50mm head/cup proposed for marketing ranged from \bullet micrometers. The sponsor provided a Technical Memo (TM-05-16) in Attachment 7.1 of Amendment 12 to discuss the BHR clearances and the components used in the wear testing. The sponsor stated that the fluid film thickness (and wear) is relatively insensitive to the typical range of diametral clearances seen in 50mm diameter couples (i.e., “typical range” = \bullet micrometers; sponsor’s specification

for the range of diametral clearances for their 50mm diameter couple= \blacksquare micrometers). The sponsor provided a Figure of fluid film thickness and diametrical clearance that showed that the theoretical minimum fluid film thickness ranged from approximately \blacksquare micrometers for a \blacksquare micrometer clearance to approximately \blacksquare micrometers for a \blacksquare micrometers clearance between the head and cup. The sponsor determined that this difference in clearance has a minimal effect on fluid film thickness. The sponsor also stated that testing wear couples of lower clearance values are representative of the worst-case to evaluate the potential for joint seizure. Therefore, the components selected for the wear testing were representative of the lower clearance values for the 50mm diameter couple.

Surface Topography:

The sponsor stated that surface topography was measured at the start of the wear test and every 0.5million cycles throughout the wear test up to 3 million cycles on the Zygo NewView 100 non-contacting 3-D profilometer. 10 measurements were taken on the polar region of the contact area of each component and 5 on the periphery (heads only). The sponsor stated that the peripheral regions of the contact area of the cup could not be measured as the lens of the Zygo would not fit into the cup. Roundness measurements were also taken.

The sponsor reported that initially (as supplied) the peak-to-valley heights (PV) for the femoral heads averaged \blacksquare micrometers with a positive skewness, indicating that the majority of the height ranges were above the mean line and thus were peaks. The RMS values were $S_a=0.023$ micrometers and $S_q=\blacksquare$ micrometers. The cups had the following measurements: $PV=0.421$ micrometer, $S_a=\blacksquare$ micrometers, and $S_q=\blacksquare$ micrometers. At the end of the test, the PV values had generally increased for the heads. For the cups, some PV values increased and some decreased. The positively skewed distribution for heads was generally negative, indicating that most variations from the mean plane were in the form of scratches while the peaks had been smoothed. The cups were less consistent; although the skewness decreased for all the cups they remained slightly positive. The sponsor stated that the surface with less peaks would be an advantage to fluid-film generation.

Regarding roundness and linear wear rates, the sponsor reported that the average total (head and cup) linear wear at 0.5 million cycles was \blacksquare micrometers/million cycles. At 2.5-3 million cycles, it was \blacksquare micrometers/million cycles.

Friction:

The sponsor stated that on one of the head/cup couples friction tests were carried out before, during and after wear testing. A modified Paul curve was used to provide a dynamic loading cycle with a maximum load of 2000N and a minimum load of 100N. The femoral head was in an inverted position but with a relative position between the head and cup the same as the wear simulator. As flexion-extension motion took place \blacksquare deg. with a period of \blacksquare sec), the friction generated within the prosthesis was measured throughout the cycle. Tests were performed using 5 viscosities of lubricant ranging from \blacksquare s. The lubricant was different ratios of calf

serum and carboxymethyl cellulose (CMC) with a serum concentration of [REDACTED], sodium azide and EDTA were added for consistency. The sponsor reported decreasing friction over the course of the test. Frictional torque ranged from [REDACTED] Nm pre-test, to [REDACTED] Nm after 3 million cycles, to [REDACTED] Nm after 5 million cycles. Frictional torque appeared to be a bit higher for lower lubricant viscosities but this was not consistent for all components tested.

Kinematics:

In Amendment 11 (in response to item 40), the sponsor provided an analysis of ROM according to Annex A of ISO 21535: 2002. ISO 21535 was meant for diaphyseal anchored types of hip implants; therefore, the test procedure was modified because the femoral implant component is attached to the proximal femoral head directly and not to an intramedullary stem. The sponsor stated that the ROM of the resurfacing head will be restricted by impingement between the femoral neck and the rim of the acetabular cup (neglecting the presence of ligaments and the capsule). To simulate the femoral neck, a cylindrical plastic component with the IDE of the femoral head (51mm) was placed on the stem of the femoral head. The ROM is limited by the contact between the cylindrical "femoral neck" and the rim of the acetabular cup. The sponsor measured flexion-extension, abduction-adduction, and rotation. The sponsor stated that the 38mm head has the largest angular displacement and the 58mm head has the smallest angular displacement. Therefore, the 58mm head has the smallest ROM and this size was selected to perform the ROM testing. Note that this is different than for a total hip replacement (not resurfacing) where the larger the head the greater the ROM. The 58mm head can be used with either the 64 or 66mm diameter cups because they have identical articulating surface contact areas. The worst case was determined to be the 66mm cup. The test result for flexion-extension was an average of [REDACTED] deg., for abduction-adduction was [REDACTED] deg., and for rotation was [REDACTED] deg. These values were reported to be higher than the ISO minimum values of 80 deg. for flexion-extension, [REDACTED] deg. for abduction-adduction, and 90 deg. for rotation per ISO 21535.

Femoral Stem Fatigue Strength:

In Amendment 11 (in response to item 37), the sponsor performed cantilever fatigue testing of the femoral stem and reported that no deformation or cracking of the post following 5 million cycles of loading at [REDACTED] lbf (this load produced a stress of [REDACTED] ksi [REDACTED] MPa) at the base of the stem). The sponsor provided technical report OR-05-32 that contains a summary of testing. The sponsor tested five (n=5) 58mm heads. The sponsor stated that they used the largest heads to represent the "worst-case". The sponsor stated that all of the stems have the same diameter at the base but the stem length increases as the diameter of the head increases. So, since the load is applied near the tip of the stem, this would produce the largest moment arm. The sponsor applied the load 2.5" from the base of the stem. The sponsor applied a load of [REDACTED] lbf for 5 million cycles at 10Hz. This produced a stress of [REDACTED] ksi. The sponsor reported that all five stems passed without deformation or cracking and that the femoral head should have sufficient strength to survive expected clinical use.

Evaluation of polar and equatorial roundness before and after HAP coating

The sponsor measured polar and equatorial roundness before and after HAP coating in test reports FD98-03 and FD97-03. Based on their findings, the sponsor's recommendation is to inspect 10% (minimum of 1 cup) of the cups per batch for cups under 60mm and 50% for cups 60mm in diameter and greater (i.e., 60, 62, 64, and 66mm). The sponsor also recommended that polar roundness is unaffected by HA coating.

Evaluation of equatorial roundness after simulated implantation

The sponsor provided test report FI97-15 in Tab 9 of Appendix C of the original PMA in which the equatorial roundness of the cup was evaluated after finishing, after insertion of cables and impaction into balsa wood. The equatorial roundness was [REDACTED] micrometers after finishing, [REDACTED] micrometers after insertion of cables, and [REDACTED] micrometers after impaction. The sponsor concluded that impaction of the cup into balsa wood appeared to have no detrimental effect on the equatorial roundness.

Evaluation of the strength of the dysplasia/bridging cup screws

In Amendment 11 (in response to item 38), the sponsor provided technical report OR-05-09 in which the sponsor provided testing on the longest screws. The sponsor determined the static strength of the screws (88mm). The sponsor reported that the average failure load for the 88mm BHR dysplasia fixation screws was [REDACTED] bf [REDACTED] N (n=5). The sponsor chose the longest screws to represent the worst-case as they maximize the load offset. The failure mode was plastic deformation near the flange. The sponsor stated that the testing set-up represented an extreme case where there is little to no bone support in the acetabulum and all load is transmitted to the very end of the screw. The sponsor stated that in the clinical case, the load would likely be applied over the length of the screw. Also, the fit of the shell in the acetabulum should provide additional support and reduce the loading on the screws.

Evaluation of the strength of the dysplasia/bridging cup lugs

In Amendment 11 (in response to item 38), the sponsor provided technical report OR-05-09 in which the sponsor provided testing on the lugs proposed for the subject device. The sponsor determined the static strength of the threaded flanges for the Bridging Cup (50mm). The average failure load for the bridging cup flange (50mm) was [REDACTED] bf [REDACTED] N (n=5). The sponsor stated that the bridging cup flange design and dimensions are identical to the dysplasia cup. Furthermore, the flange dimensions are unchanged on each available cup size; therefore, the "worst-case" is considered represented by the cup size selected. The sponsor stated that the fracture load was in excess of [REDACTED] times body weight and exceeds the load that would be expected to be seen in vivo. The sponsor concluded that the screws and flanges should be able to withstand the predicted in vivo loads.

Evaluation of the static strength of the femoral component stem

In the original PMA submission, the sponsor provided test report FI977 in Tab 9 of Appendix C in which the strength of the femoral component head/stem (42mm).

A femoral stem was mounted in a fixture and a load was applied to the femoral head to deflect/fracture the stem. The sponsor stated that the loads exceeded the maximum value for the Instron (██████ N) before the stem fractured. However, the stems clearly yielded. The sponsor stated that the stem exhibited elastic material behavior to load levels in excess of those the component would experience in vivo due to normal daily activities (i.e., ██████ N as opposed to ██████ N).

In Amendment 11 (in response to item 38), the sponsor provided technical report OR-05-09 in which the sponsor provided additional testing on the femoral component. The sponsor provided technical report OR-05-10 to determine the static strength of the stem of the BHR resurfacing femoral head. The sponsor determined the average yield point during testing of the static strength of the BHR femoral stem to be ██████ N (██████ lbf) (n=5). Since the stem size is a function of head size, the sponsor chose the smallest head (size 38mm) to test as it has the smallest stem. The stem was gripped and the load was applied to the femoral head until the stem began to yield. The sponsor stated that the stem yielded near the point where the chuck was used to grip the stem. The sponsor stated that this load is significantly higher than expected in vivo loads.

Explant Analysis:

The sponsor provided three reports in Appendix C of the original PMA submission titled “Wear Retrieval Analysis of Birmingham Resurfacing,” “Finsbury Test Report “FI98001,” and “Hip Resurfacing: How Metal on Metal Articulations Have Come Full Circle.”

In the first abstract, the wear characteristics of the BHR device were investigated using 3 pairs of BHR bearings that were explanted from patients at 6-18mo post-implant. The sponsor stated that these patients were known to be active for at least 6 months after receiving the device. The sponsor used an instrument with a resolution of 0.01 micrometers and stated that no measurable wear was detected as compared to their manufactured form.

In the Finsbury Test Report, FI98001, an explant analysis of one BHR device was performed to evaluate roundness and surface finish. The device was retrieved following femoral neck fracture. The device was in place for 4 months (Aug-Dec. 1997). Results showed that the BHR head diameter was unchanged. Roundness was changed slightly equatorial from 0.██████ μm to ██████ μm and polar from ██████ μm to ██████ μm. Cup roundness was raised on the equatorial from 0.██████ μm to ██████ μm. The report stated that the head showed approximately ██████% as slightly dulled “worn” but the authors reported that there was no undue damage or abnormalities. Surface finish changes were not significant. The authors concluded that little change had taken place since implantation.

In the third explant analysis in the paper titled “Hip Resurfacing: How Metal on Metal Articulations Have Come Full Circle,” the authors report that 4 pairs of McMinn 1996 Hybrid resurfacing implants where metallosis and osteolysis were observed at revision were analyzed. (Please note that the author stated that although these devices are all “McMinn” Dr. McMinn used single heat-treated, double heat-treated and as-cast CoCrMo alloy materials as the bearing materials in hip resurfacing components. Dr. McMinn has had high bearing wear, metallosis, and osteolysis with some components inserted during 1996). Wear was measured on a roundness measurement device by multiple traces which first established the original shape and then the exact amount of wear on the articulating surfaces of the cup and head. Also, the metal microstructure of the articular surfaces was identified using SEM and optical microscopy. The presence of carbide in the metal of each component was graded on a scale from 0 to 40 where 0 is no carbide in the metal and 40 is the normal carbide presence in high carbon as-cast chrome cobalt. The results showed that the highest wear rates occurred when the metal is most carbide depleted and the lowest wear rates occur in less carbide depleted components. Please note that the McMinn Hybrid implants are not part of the PMA submission.

STERILIZATION/ SHELF LIFE:

- The subject device is sterilized by gamma irradiation – Cobalt 60 source; and
- Shelf life testing for sterile package integrity to 5 years.

Executive Summary: Clinical Information

INTRODUCTION:

The PMA device is a first of a kind in the United States (i.e., total hip system with a resurfacing femoral component and metal-on-metal articulating surfaces). The PMA is supported by clinical data essentially from one source: the surgical experience of Dr. Derek J.W. McMinn, FRCS, who performed his surgeries at the Birmingham Nuffield Hospital, Edgbaston, Birmingham, United Kingdom. The PMA includes safety and effectiveness data from an uncontrolled, consecutive case series of all 2,385 procedures implanted with the Birmingham Hip Resurfacing (BHR) device by Dr. McMinn from July 1997 through May 2004. FDA requests expert clinical opinion regarding the safety and effectiveness data collection methods, the applicability of the foreign data from a single investigator and United Kingdom practice of medicine to the target United States population and practice of medicine, and the study results with respect to the device's safety and effectiveness.

STUDY OBJECTIVES AND ASSESSMENTS:

The objective of this PMA is to demonstrate the safety and effectiveness of the Birmingham Hip Resurfacing (BHR) System. The safety assessments included data on revisions, adverse events, deaths and a metal ion literature review. The primary effectiveness assessments included survivorship and radiographic data. The secondary effectiveness assessments included pain and function data as evaluated by the Oswestry-modified Harris Hip (OSHIP) Score, and patient satisfaction data.

PATIENT SELECTION METHODS AND INDICATIONS FOR USE:

Generally, prospective clinical investigations pre-define the study population with specific inclusion and exclusion criteria. This theoretically allows the study results to be generalized to that diagnostic group. In case series studies, it is more difficult to generalize the results to a defined population because the patients were not enrolled for pre-defined conditions. This is the case for the clinical data provided in this PMA submission. The clinical data were derived from the surgical experience of a single surgeon who used the Birmingham Resurfacing Hip System. The sponsor did not identify the set of diagnostic indications for the device, but instead provided a list of the diagnoses for the patients implanted with the device.

Because these patients were not investigated under an investigational protocol with pre-defined inclusion and exclusion criteria, it may be important to determine the diagnoses of all of the patients who were evaluated by Dr. McMinn during this same time period but did not receive the Birmingham Resurfacing Hip device and either had no surgery or had surgery with a conventional total hip replacement or other device. However, a complete review of these patients was not presented in the PMA. With this information, it might have been possible to retrospectively determine what criteria, if any, were used to select candidates for the Birmingham Resurfacing Hip device. However, to retrospectively develop the indications for use and physician labeling, the sponsor provided a list of the factors that contributed to Dr. McMinn's decision to perform a total hip replacement (THR) in certain patients rather than a hip resurfacing procedure (BHR). These factors included:

- **Advanced age:** Patients of advanced age, especially those with low activity levels, were typically candidates for THR rather than BHR. Only 8.1% of the 2,385 cases included in the Overall McMinn cohort were >65 years of age. In these cases, BHR was selected despite advanced age if the patients had high activity levels, and had good bone stock of the femoral head.
- **Low activity level:** Patients with a low activity level were considered at lowered risk for future revision, and therefore good candidates for THR. Low activity level was characterized by no participation in sports activities, no heavy work required by job, a sedentary/retired lifestyle, or comorbidities that precluded a high activity level, such as severe arthritis in other joints or severe heart disease.
- **Poor bone stock:** Patient with poor bone stock were selected for THR rather than BHR because they were considered at risk for femoral neck fracture or femoral head collapse with a hip resurfacing procedure. Poor bone stock was characterized as severe osteopenia of the femoral head or femoral neck (determined by risk factors, medical history and/or diagnostic imaging), extensive AVN (>50% of femoral head, regardless of FICAT Grade), or the presence of multiple cysts.

The sponsor stated that Dr. McMinn's collection of a patient's pre-operative history, physical, and diagnostic work-up was commonly sufficient to screen candidates for BHR versus THR, and that only in rare instances would the planned surgical procedure be

revised intraoperative. The sponsor stated that although Dr. McMinn rarely changed his preoperative plan based on intraoperative findings, all patients were consented for a hip arthroplasty, and informed about the probable type of prosthesis they would receive. As with any surgical procedure, patients were also informed that based on the intraoperative findings, there could be changes to the planned procedure. The patients were thus consented for both a BHR and THR procedure.

Based upon the patient population studied, the factors outline above, and an analysis of the BHR revisions in the Overall McMinn Cohort (i.e., femoral neck fracture, femoral head collapse, dislocation, AVN, and infection), the sponsor proposed the following indications for use and contraindications for the device:

Indications for Use

The Birmingham Hip Resurfacing (BHR) System is a single use device intended for hybrid fixation: cemented femoral head component and cementless acetabular component. The BHR system is intended for use in patients requiring primary hip resurfacing arthroplasty due to:

- Non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/DDH, or
- Inflammatory arthritis such as rheumatoid arthritis.

BHR System hip resurfacing arthroplasty is intended for joint replacement in patients who are at risk of requiring future, ipsilateral hip joint revision. While it is impossible to predict if a patient will require more than one joint replacement, several factors are known to increase risk of revision surgery including age less than 55 years at index surgery and/or high physical activity level postoperative.

Contraindications

Contraindications for use of the Birmingham Hip Resurfacing (BHR) System include:

- Patients with infection or sepsis,
- Patients who are skeletally immature,
- Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery,
- Patients with bone stock inadequate to support the device including:
 - Patients with severe osteopenia should not receive a BHR procedure. Patients with a family history of severe osteoporosis or severe osteopenia.
 - Patients with osteonecrosis or avascular necrosis (AVN) with >50% involvement of the femoral head (regardless of FICAT Grade) should not receive a BHR.
 - Patients with multiple cysts of the femoral head (>1cm) should not receive a BHR.
- Females of child-bearing age due to unknown effect on the fetus of metal ion release.
- Patients with known moderate to severe renal insufficiency.

In addition to the factors described above, the sponsor also considered the review of 50 BHR femoral neck fractures reported by Shimmin and Back¹ in their development of the labeling. In this publication, the authors reported a review of 3497 BHR cases performed in Australia by 89 surgeons. There were 50 femoral neck fractures in the series (1.46%) which the authors attributed to osteoporosis, notching of the superior femoral neck, varus placement of the device by more than 5°, and technical difficulties including poor exposure due to obesity, change in intra-operative alignment, and poor impaction of the femoral component. Based on these findings, the sponsor added the following warnings and precautions to the labeling:

Warnings

- Avoid notching the femoral neck, as this may lead to femoral neck fracture.
- Avoid placing the femoral component in varus. Varus placement of the femoral component has been associated with femoral neck fracture.

Precautions

- Improper selection, placement, positioning, and fixation of the implant component may result in early implant failure.

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING DEVICE LABELING

Question #6:

Do the patient selection methods and data presented on the BHR device support the proposed labeling indication?

Please comment on any other aspects of the product labeling, such as:

- **Contraindications**
- **Warnings**
- **Precautions**
- **Potential Adverse Effects on Health**

¹ Shimmin AJ, Back D. Femoral neck fractures following Birmingham hip resurfacing: A national review of 50 cases. J Bone Joint Surg [Br] 87-B:463-4, 2005.

DESCRIPTION OF COHORTS AND DATA COLLECTED

The 2,385 procedures implanted with the Birmingham Hip Resurfacing (BHR) device by Dr. McMinn from July 1997 through May 2004 were divided into the following three main cohorts:

- **X-ray cohort:** First 124 BHR cases performed by McMinn from July 1997 through December 1997.
- **Oswestry cohort:** Next 1502 BHR cases performed by McMinn from January 1998 through March 2002.
- **McMinn cohort:** Next 759 BHR cases performed by McMinn from April 2002 through May 2004.

The following table outlines the dates of implantation, number of procedures, and types of safety and effectiveness data collected for these 3 cohorts:

			Types of Safety and Effectiveness Data Collected						
			Safety Data Collected			Effectiveness Data Collected			
Cohort	Dates of Implantation	Number of Procedures	Adverse Events	Revisions	Deaths	Survivorship	Radiographic	Pain and Function (OSHIP)	Patient Satisfaction
X-ray	7/97-12/97	124	X	X	X	X	X	X**	X
Oswestry	1/98-3/02	1502	X	X	X	X		X**	X
McMinn	4/02-5/04*	759*	X	X	X	X		***	

- Note: An X in the table indicates that this data was collected for the respective cohort
- * The sponsor stated that there were 5 cases in the McMinn cohort whose implantations were performed prior to 4/02. These cases should have been part of the Oswestry cohort, but for unknown reasons were not. Therefore, unlike the majority of the McMinn cohort, some of these 5 cases have longer term follow-up.
 - ** See note in Table of Combined Cohorts below regarding the number of procedures contributing to the pain and function (OSHIP) effectiveness data.
 - *** The pain and function data for the procedures in the McMinn cohort were collected using the Oxford Hip Score evaluation method (and not the OSHIP Score). The sponsor explained that because the 759 procedures in the McMinn Cohort were not tracked by the Oswestry Outcome Center but by the National Health Services (NHS) Center, the sponsor did not have access to the Oxford hip score data.

As noted in the Table above (with the large bolded “X”), only 124 procedures in the X-ray cohort contributed to the assessment of radiographic effectiveness in the PMA. Radiographic evaluations were not provided for the 1502 procedures in the Oswestry cohort or the 759 procedures in the McMinn cohort.

Where there were common data elements collected in the 3 cohorts outlined above, the sponsor pooled this information into the following two combined cohorts:

- **X-ray/Oswestry/McMinn combined cohort or Overall McMinn cohort:** Note that for the rest of this Executive Clinical Summary, this cohort will be referred to as the **Overall McMinn cohort**.
- **X-ray/Oswestry combined cohort**

The following table outlines the dates of implantation, number of procedures, and types of safety and effectiveness data collected for these 2 combined cohorts:

Cohort	Dates of Implantation	Number of Procedures	Types of Safety and Effectiveness Data Collected						
			Safety Data Collected			Effectiveness Data Collected			
			Adverse Events	Revisions	Deaths	Survivorship	Radiographic	Pain and Function (OSHIP)	Patient Satisfaction
Overall McMinn Cohort	7/97-5/04	2,385	X	X	X	X			
X-ray/Oswestry Combined	7/97-3/02	1,626	X	X	X	X		X**	X

Note: An X in the table indicates that this data was collected for the respective cohort

** Only 1,111 unilateral procedures in the X-ray/Oswestry combined cohort contributed to the assessment of pain and function effectiveness data, as evaluated by the Oswestry-modified Harris Hip (OSHIP) Score.

As noted in the Table above (with large bolded “X”s), the 2,385 procedures in the Overall McMinn cohort contributed to the assessment of safety including adverse events, revisions, and deaths. The 1,626 procedures in the X-ray/Oswestry combined cohort contributed to the assessment of survivorship. Also, as noted in the Table above, only 1,111 unilateral procedures in the X-ray/Oswestry combined cohort contributed to the assessment of pain and function effectiveness data, as evaluated by the Oswestry-modified Harris Hip (OSHIP) Score. See discussion below regarding unilateral and bilateral involvement when evaluating pain and function. Finally, 1,626 procedures in the X-ray/Oswestry Combined cohort contributed to the patient satisfaction effectiveness in the PMA.

Additional Data Sources:

The main data sources were presented above but the sponsor also included additional, less complete data on 3,374 BHR cases performed by 140 surgeons worldwide (other than Dr. McMinn). The follow-up for these cases was also contracted to the Oswestry Outcomes Centre and includes primarily the same parameters as the follow up for the X-ray/Oswestry combined cohort (adverse events, revisions, deaths, pain and function (OSHIP) scores, and patient satisfaction. The Oswestry Outcomes Centre, therefore, collected data on a total of 5000 BHR cases. These 5000 cases are referred to as the **Oswestry Worldwide Cohort**. The Oswestry Worldwide Cohort consists of 1) the 1626 Dr. McMinn cases of the X-ray/Oswestry cohort, and 2) an additional 3,374 non-McMinn (“all other”) cases. The Oswestry Outcomes Centre has provided Smith & Nephew access to all available data for the BHR cases from its database. Although the sponsor considers the data from the 3,374 “all other” cohort to be of some value, Smith & Nephew has no ability to independently verify any of the data provided to the Oswestry Outcomes Centre by sites other than the McMinn Center, and has no ability to request additional follow-up or clarifications of any kind from non-McMinn patients or physicians. For these reasons, the analysis on the Oswestry Outcomes Centre worldwide database has some limitations, and is not considered a primary data source for this PMA.

DATA COLLECTION METHODS

Safety Data Collection Methods

The safety data including adverse events, revisions, and deaths were collected by:

- The Oswestry Outcomes Center using an annual, patient-completed, mail-in questionnaire (deaths were identified while attempting to perform scheduled follow-up);
- The McMinn Center by recording the findings of post-operative patient visits to the McMinn Center in patient records; and
- Recording information provided to Dr. McMinn by primary care physicians.

Dr. McMinn's follow-up was described as follows:

- Dr. McMinn performed regular evaluations (history, physical examination, radiographs to assess implant status, and any necessary laboratory work) in the preoperative and postoperative time periods according to standard practice, although the timepoints and evaluations were not according to a standard protocol.
- All revision surgeries were performed by Dr. McMinn (except in one known case). Therefore, the revision status was directly known to Dr. McMinn.
- There were no pre-defined follow-up time windows, standardized clinical evaluations, adverse event report forms, or standardized radiographic evaluations.

In addition, the Oswestry Outcome Center (OOC) provided the following information regarding follow-up procedures:

- The Oswestry Outcomes Center collected data on revisions and adverse events using an annual, patient-completed, mail-in questionnaire.
- With the exception of 8 cases classified by OOC as “no consent” (subjects who withdrew or did not agree to participate in the study), all other cases are not considered lost-to-follow-up by OOC since they continue to make attempts to contact patients.
- Of the 180 cases missing their last theoretical expected mail-in questionnaire follow-up, 84 are missing at least 2 yearly evaluations, while 96 are only missing their last evaluation. These cases represent only 11.1% (180/1626) of the cases in the Oswestry/X-Ray Combined Cohort
- The steps taken at the OOC to regain contact if a patient does not respond to a request for information, are as follows:
 - Send reminder letters;
 - Use e-mail with request for data;
 - Contact consultant surgeon by letter for patient’s current contact details;
 - Use the National Strategic Tracing Service database to determine patient whereabouts;
 - Contact surgeon and/or patient by telephone;
 - Attempt trace using online (Internet) census information;
 - If none of these produce results, an annual request for an update on progress is sent to the patient’s last known address by Royal Mail and e-

mail until the tenth anniversary of the operation. Patients are not classified as lost-to-follow-up until all avenues have been exhausted.

The sponsor states that they performed a 100% audit of all 2,385 procedures in the Overall McMinn Cohort, and therefore believe that all reported adverse event information have been captured.

In addition to the safety data collection methods outlined above, the sponsor provided a metal ion literature analysis. Included in the sponsor's analysis was an unpublished report by Daniel J, Ziaee H, and McMinn D, entitled, "Metal ion studies in patients treated with the Birmingham Hip Resurfacing, a comparable FDA-approved device and historic metal-metal total hip replacements." The authors conducted 4 metal ion studies in patients who received BHR, Metasul metal-metal total hip replacements, and other (historic) metal-metal total hip replacements. The four studies included:

1. A short-term longitudinal study of urinary Co and Cr levels in patients with the BHR and the Metasul metal-metal total hip replacement.
2. A long-term cross-sectional study of urinary Co and Cr levels in patients with the BHR and the Metasul metal-metal total hip replacement.
3. A longitudinal study of whole blood Co and Cr levels in patients with the BHR.
4. A cross-sectional study of whole blood Co and Cr levels in patients with the BHR and metal-metal total hip replacements.

In addition, the sponsor provided a summary of 18 literature references pertaining to the medium and long-term safety of cobalt and chromium ion exposure in the subject device (BHR), metal-on-metal total hip replacements, and metal-on-polyethylene total hip replacements. These literature references are summarized below in the Executive Clinical Data Summary – Summary of Safety Data.

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE SAFETY DATA COLLECTION METHODS

Question #1:

Please discuss the evaluation methods used to collect safety data (i.e., data on revisions, adverse events, deaths, metal ion literature analysis) and whether or not these methods are reliable to assess the safety of the device.

Effectiveness Data Collection Methods

Primary Effectiveness Data Collection Methods

Survivorship Data Collection Method:

The primary effectiveness measurement was the X-Ray/Oswestry combined cohort survivorship study that included 1626 procedures performed from 7/97 through 3/02 at the Birmingham Nuffield Hospital. These procedures were a minimum of 2 years post-op. Of the 1626 procedures, data are available for 546 of the 601 BHR procedures eligible for 5 year follow up (90.8%). The data for the survivorship study was collected using the same methods presented above for the safety data collection methods.

Radiographic Data Collection Method:

The PMA contained the results of an independent radiographic review of the X-Ray Cohort, the first 124 procedures performed in the series from 7/97 through 12/97. Radiographic evaluations were not provided for the 1502 procedures in the Oswestry Cohort or the 759 procedures in the McMinn Cohort.

Radiographs were taken on 108 of the 118 procedures expected at 5 years postoperatively (91.5%). Six (6) procedures were not expected at 5 years postoperatively because one patient with bilateral hip implants died from a motor neuron disease unrelated to the BHR procedure; and 4 of the 124 BHR procedures (3.2%) have undergone revision: 3 cases were revised for infection, and 1 case required revision because of a femoral neck fracture. Therefore, 118 procedures (124 hips - 2 hips due to death - 4 revisions = 118 procedures) were eligible for 5 year radiographic evaluation of the BHR. Ten other cases were missing due to lost to follow-up or incomplete film records. Therefore, one hundred and eight (108) of the 118 hips surviving to 5 years had 5 year radiographs available for independent review (91.5%). (Note: The sponsor reported that an additional bilateral patient died 7 years post-op due to stroke but had 5 year x-rays taken).

There were immediate post-operative films on 89 of the 108 procedures with 5-year radiographs but the sponsor stated that these films were low quality portable films and unusable for the purposes of precise postoperative measurement comparisons. Therefore, baseline films for the purposes of comparisons were made in each of the 108 cases in the postoperative time period (usually within 3 months, but 8 of the 108 procedures had baseline evaluations performed at time points ranging from 110-860 days).

The radiographs were interpreted by Dr. Nick Evans (Royal Orthopaedic Hospital, Birmingham, UK). The sponsor states that a prospective protocol was used to assess the radiographs. The 5-year AP and lateral view radiographs were compared with the baseline radiographs for the following:

- Medial-lateral migration (reference point = Kohler's line)
- Acetabular orientation (tilt angle)

- Femoral and acetabular radiolucencies (femoral: Amstutz defined 1-3 zones; acetabular: DeLee and Charnley defined I-III zones), each graded on a 0-9 scale. Radiolucency is defined as a lucent area parallel to and in close proximity to the prosthesis/bone interface encompassing at least 50% of the zone and at least 1mm in width.
- Heterotopic ossification (HO) (Brooker classification, I-IV)
- Other radiographic findings, including bone resorption, acetabular protrusion, cysts, buttressing, and other abnormalities.

A radiographic success was defined as having all of the following:

- Absence of radiolucencies or a radiolucency in any one or two zones (a score of 0-6);
- Component migration ≤ 2 mm; and
- Change in acetabular angle $< 5^\circ$

A radiographic failure is defined as the following:

- Presence of incomplete or complete radiolucencies or a radiolucency in all zones (a score of 7 or 8);
- A migration of the component > 2 mm; or
- A change in acetabular orientation of $\geq 5^\circ$

The individual success criterion was the absence of radiographic findings that suggest revision is necessary.

Secondary Effectiveness Data Collection Methods

Oswestry-Modified Harris Hip (OSHIP) Score Data Collection Method

The clinical data used to support this PMA were collected by the Oswestry Outcomes Center using an annual, patient-completed, mail-in questionnaire. The responses to the pain, function, and movement questions in the questionnaire were used to generate the Oswestry-modified Harris Hip (OSHIP) Score.

The OSHIP questionnaire allows patient assessments without direct physician or examiner evaluation. No other sources of pain and function information were used to support this PMA.

Data entry for the OSHIP outcomes data used to support this PMA was performed by the trained employees of the Oswestry Outcomes Center. The Center's standard operating procedures for data input and clarification for the patient-administered OSHIP questionnaires were as follows:

- Trained employees carefully reviewed all questionnaires and identified any unclear, incomplete, or ambiguous items by highlighting them. Available information was recorded in the database, and any missing/unclear/conflicting information was recorded as "missing data" (indicated by an asterisk).
- The questionnaires with missing data were returned to the patients with specific instructions on how to complete or clarify any suspect data fields. The preferred

method of follow-up for missing data was by mail; however, secondary methods of follow-up included e-mail and telephone.

- Upon receipt of missing data, the trained employees verified that the highlighted data fields had been completed/clarified, and the data was entered into the database.
- All reasonable attempts to collect the data via mail, e-mail, or telephone were made. If all reasonable efforts at data collection failed, the score for any missing item was assumed to be the lowest possible (typically zero), unless otherwise indicated.

The sponsor stated that in an unpublished paper titled, “A Self-completed Tool for Evaluation of Hip Function: The Oswestry Hip Score,” D. Barnes and co-workers reported that the OSHIP was developed by Professor James Richardson FRCS (Orth), Professor of Orthopaedics at the Institute of Orthopaedics, Robert Jones and Agnes Hunt Orthopaedics and District Hospital—NHS Trust in Oswestry, Shropshire, England. According to Barnes’ paper, creation of the OSHIP began with the following premises:

- Long-term evaluation following hip replacement is essential and follow-up must be regular.
- Large-samples are necessary.
- Long-term and large-sample follow-up is difficult to obtain when using a score that requires surgeon- or radiologist-assessment.
- Physician-administered surveys are susceptible to bias (which may inflate the final scores) and may not truly represent the patients’ own feelings.
- Existing patient-completed scores lack accurate measurements of range of movement.
- Questionnaires need to be simple and relatively short to make long-term and large-scale collection of data more efficient.

Building on these premises, Professor Richardson developed the OSHIP by combining elements of both the Harris and Merle d’Aubigne scores. The OSHIP produces an overall index score similar to that of the Harris score between 0 (worst) and 100 (best). Both the OSHIP and Harris Hip Score (HHS) are made up of the three domains of pain, function, and hip movement, with function being further divided into gait (walking, limp, and distance), and activity (stairs, sitting and transport).

The main difference between the OSHIP questionnaire and the HHS is that the OSHIP allows patient assessments without direct physician or examiner evaluation. In addition, the OSHIP questionnaire does not include the three HHS questions regarding physician assessment of Range of Motion (5 pts.), Absence of Deformity (4 pts.), and the patient’s ability to put on socks/tie shoes (4 pts.) but substitutes a “movement” question (13 pts.) that is intended for the patient to estimate their ability to flex their hip.

The sponsor provided references to justify the use of the OSHIP in lieu of the HHS and the validity of self-administered questionnaires.

While Ragab² reported a lack of correlation between patient self-assessment of pain/function and physician assessment of pain/function ($r=0.467$, $p<0.01$), several others have reported the opposite—a very close correlation between patient self-assessment and physician assessment.

Research by Mahomed et al.³ demonstrated that patients are able to accurately respond to HHS questions regarding pain and function with little difficulty, and that there is excellent correlation between the overall HHS pain/function scores reported by patients and the overall HHS pain/function scores reported by physicians (Pearson correlation coefficient= 0.99 , $p<0.0001$). In this study, Mahomed also reported that the κ statistic, which is a measure of the reproducibility between repeated assessments of the same categorical variable, ranged between 0.79 and 1.00 ($p<0.0001$) for each item of the HHS and, according to the paper, “indicated excellent reproducibility.” Note that both Ragab and Mahomed’s studies did not include patient or physician evaluations of range of motion or deformity, these questions were eliminated from both the patient and physician assessments. Furthermore, McGrory et al.⁴ found that a brief follow-up phone call (similar to the OOC follow-up procedure discussed above) was effective in capturing missing data and clarifying multiple or contradictory responses from mailed patient self-assessment questionnaires.

Barnes et al. have evaluated the reliability and validity of the Oswestry Hip Score as documented in the research paper, “A Self-completed Tool for Evaluation of Hip Function: The Oswestry Hip Score.” In Mr. Barnes’ study, a group of 61 patients completed the Oswestry Hip Score (OSHIP). They were then sent a second copy of the OSHIP to be completed two weeks later and returned by mail. The results of these two sets of surveys were compared to look for reproducibility. When comparing the OSHIP responses from the first self-administration to the results of the second self-administration two weeks later, the total intra-class correlation coefficients was 0.93 with intra-class correlation coefficients for the individual items and domains ranging from 0.67 to 0.92 .

Mr. Barnes’ study also included a separate group of 28 consecutive patients who were given both a patient-administered OSHIP and a physiotherapist-administered Harris Hip Score. The correlation between the patients’ overall self-administered OSHIP scores and physiotherapist-administered overall HHS scores was 0.91 ($p<0.0001$). Correlation between the individual corresponding domains of the Oswestry Hip Score and Harris Hip Score ranged from 0.60 and 0.89 . The strongest correlation was between the domains of ‘stairs’ and ‘walking/support’ (0.89) and the lowest for the domains of ‘limp’ (0.60). FDA requested additional correlations be provided that were not included

² Ragab A.A. *Validity of self-assessment outcome questionnaires: patient-physician discrepancy in outcome interpretation*, Biomed Sci Instrum (2003); 39: pp.579-84

³ Mahomed NN, Arndt DC, McGrory BJ, Harris WH. *The Harris Hip Score: Comparison of patient self-report with surgeon assessment*. J Arthroplasty 16(5):575-80, 2001.

⁴ McGrory BJ, Shinar AA, Freiberg AA, Harris WH. *Enhancement of the value of hip questionnaires by telephone follow-up evaluation*. J Arthroplasty 12(3), 1997.

in Mr. Barnes' study. Correlation between the OSHIP "movement" domain and the HHS "shoes & socks," "deformity," and "range of motion" domains were requested and performed by the sponsor. The correlation between OSHIP "movement" and HHS "shoes and socks," and HHS "range of motion," was 0.40 and 0.21, respectively. The sponsor stated that the correlation between OSHIP "movement" and HHS "deformity" was not included and not useful because all 28 subjects scored the maximum of 4 points on the HHS scale (score is either 0 or 4). FDA performed additional correlations between OSHIP "movement" domain and the sum of the scores for the HHS "range of motion," "shoes and socks," and "deformity." The correlation between these items was calculated because the OSHIP "movement" domain is the substitute for the HHS "range of motion," "shoes and socks," and "deformity" domains. The correlation was calculated to be 0.40. In addition, FDA performed a linear regression analysis to predict HHS total score from OSHIP total score for the 28 subjects. The linear regression analysis is summarized in the Executive Statistical Summary and the calculated R^2 is approximately 0.83, which measures the proportion of total variation about the mean explained by the linear regression model (Fitted HHS = $9.6 + (0.9276 \times \text{OSHIP})$). FDA believes that due to an unclear randomization scheme and questionable masking procedure used to select these 28 sample patients, it is not easy to generalize the above correlations to the general target patient population. Clinical judgement is needed.

Like the Barnes study, Ragab⁵ also reported a relative lack of correlation between patient assessment of limp and physician assessment of limp which he believed was due to the physician's tendency not to report limps that occurred only after long walks or during weather change, while patients were likely to report such limps. However, unlike the Barnes study in which the OSHIP and HHS item regarding "pain" had a correlation of 0.83, Ragab found that when the patients reported significant pain (i.e., pain scores less than 30), they were often attributing the pain to their hips when the pain, in most cases, was not truly hip related. The author reported that the physician was better able to distinguish "true" hip pain from pain coming from other sources (e.g., secondary to trochanteric bursitis, lumbar spondylosis, arthrosis of the contralateral hip).

An additional finding by McGrory and co-workers⁶ was that questions about whether patients could cut their toenails and put on socks/shoes correlated significantly with postoperative weighted HHS range of motion calculation ($P = 0.0002$, $r = 0.569$, $R^2 = 0.323$ for cutting toe nails and $P = 0.0006$, $r = 0.529$, $R^2 = 0.280$ for putting on socks and shoes). The authors concluded that responses to these two questions could therefore be used to estimate the weighted HHS range of motion. In addition, Johnston and Smidt⁷ reported that there is a distinct relationship between hip flexion and shoe tying. In a motion study of 135 post-total-hip-replacement cases, they found that

⁵ Ragab A.A. *Validity of self-assessment outcome questionnaires: patient-physician discrepancy in outcome interpretation*, Biomed Sci Instrum (2003); 39: pp.579-84.

⁶ Johnson RC, Smidt GL. Hip motion measurements for selected activities of daily living. Clin Orthop 72:205-216, 1970.

⁷ McGrory BJ, Freiberg A, Shinar AA, Harris WH. Correlation of measured range of motion following tota hip arthroplasty and responses to a questionnaire. J Arthroplasty 11(5):565-71, 1996.

patients with $\geq 120^\circ$ of flexion could tie their shoes. They found that the majority of patients with 90-100° of flexion could tie their shoes with difficulty. They found that the majority of patient with $<90^\circ$ of flexion could not tie the shoes.

A review of the raw data from the Barnes' study, as described above, of 28 patients given both a patient-administered OSHIP and a physiotherapist-administered Harris Hip Score also revealed the following:

- The average OSHIP score for the 28 subjects was 62.25, while the average HHS score was 67.36.
- The OSHIP results indicated that 9 of 28 (32%) subjects achieved an overall score of 80 or better, while the HHS results indicated that 12 of 28 (43%) of subjects achieved an overall score of 80 or better.
- The OSHIP results indicated that 14 of 28 (50%) subjects scored <70 , while the HHS results indicated that 12 of 28 (43%) subjects scored <70 .
- There were 14 pairs of data where the OSHIP and HHS scores differed by more than 5 points. Of the 14, the HHS score was higher in 12 cases (85.7%) while the OSHIP was higher in only 2 cases (14.3%).

In the final comment from the study by D. Barnes and co-workers, the authors stated that the Oswestry Hip Score is not intended to replace clinical examinations at the critical phases following hip surgery (i.e., 1-year, 5-years, and 10-years). However, it can be a useful tool along with X-rays to replace unnecessary yearly follow-up following hip surgery.

The sponsor used the referenced studies by Mahomed, McGrory, and Barnes to justify the use of patient self-administered questionnaires to adequately report pain and function data. Furthermore, the sponsor asserted that the close correlation of the overall OSHIP and HHS scores reported by Barnes, and the tendency of the OSHIP scores to be somewhat lower relative to the HHS scores, suggests that the OSHIP is a very close, although *conservative*, estimate of the HHS.

Patient Satisfaction Data Collection Method

Patient satisfaction data was also collected using the annual, patient-completed, mail-in questionnaire. For the purpose of the BHR study, an additional question about patient satisfaction was appended to the end of the OSHIP assessment questionnaire. Patient satisfaction data was collected by presenting the patient with the following question:

Satisfaction

- I am extremely pleased with the operation.
- I am pleased with the operation.
- I am no different than before the operation.
- I am worse than before the operation.
- I am much worse and would not recommend the operation.

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE EFFECTIVENESS DATA COLLECTION METHODS

Question #2:

Please discuss the evaluation methods used to collect effectiveness data (i.e., data on survivorship, OSHIP score, radiographic, and patient satisfaction) and whether or not these methods are reliable to assess the effectiveness of the device.

CONTROLS:

The sponsor conducted a literature search to find published studies of ceramic-on-ceramic total hip replacements to provide a comparison for the BHR clinical study data. The sponsor utilized the PaperChase internet service and found 400 citations. The abstracts were reviewed and excluded if the article was not in English; was conducted prior to 1990; was a review article; was a small case series with <25 patients; had a highly select patient population; had no specific device identification available; did not use the Harris Hip Score; and did not have a 2-year minimum follow-up. Only two literature articles met these criteria:

D'Antonio J., et al.: New experience with alumina-on-alumina ceramic bearings for total hip arthroplasty. J. Arthroplasty, 17(4): , 2002.

This clinical dataset is the same group of 514 procedures that are included in the Howmedica Osteonics ABC System and Trident System PMA (P000013) that used a CoCr alloy femoral stem and a porous-coated Ti alloy acetabular shell with Alumina Bearing Couple (ABC) and the hydroxyapatite-coated titanium shell.

Garino JP: Modern ceramic-on-ceramic total hip systems in the United States: Early results. Clin. Orthop., 379: , 2000.

This clinical dataset is the same group of 333 procedures presented in Wright Medical's Ceramic Transcend Articulation System PMA (P030027).

PATIENT DEMOGRAPHICS

Demographics for X-Ray, Oswestry, McMinn, and Overall McMinn cohorts

Patients in the Overall McMinn cohort were 70.6% men and 29.4% women, ages 13-86 years (average 53.1 years). The primary diagnosis was osteoarthritis in 75.0%, dysplasia in 15.8%, avascular necrosis in 4.1%, inflammatory arthritis in 2.4%, and “other” in 2.7%.

Procedure Demographics				
	X-Ray Cohort	Oswestry Cohort	McMinn Cohort	Overall McMinn
Hips	124	1502	759	2385
Men	81 (65.3%)	1082 (72.0%)	520 (68.5%)	1683 (70.6%)
Women	43 (34.7%)	420 (28.0%)	239 (31.5%)	702 (29.4%)
Age (range)	52.8 (27.8-75.3)	53.0 (13.4-86.5)	53.3 (21.6-79.5)	53.1 (13.4-86.5)
Age ≤65 years	111 (89.5%)	1388 (92.4%)	692 (91.2%)	2191 (91.9%)
Dx: OA	92 (74.2%)	1171 (78.0%)	526 (69.3%)	1789 (75.0%)
Dx: DDH	22 (17.7%)	197 (13.1%)	158 (20.8%)	377 (15.8%)
Dx: AVN	7 (5.6%)	59 (3.9%)	31 (4.1%)	97 (4.1%)
Dx: Inflammatory	2 (1.6%)	39 (2.6%)	16 (2.1%)	57 (2.4%)
Dx. Other	1 (0.8%)	36 (2.4%)	28 (3.7%)	65 (2.7%)

Demographics for X-Ray/Oswestry combined cohort

Patients in the survivorship study (X-ray/Oswestry combined cohort) ranged in age from 13.4 to 86.5 years (mean 53 years); 72% of the patients are male, and 28% are female. Of the 1,626 BHR procedures in this cohort, 1,499 (92%) were performed in patients ≤ 65 years old, and 127 (8%) were performed in patients > 65 years old.

Diagnostic Indications for Unilateral and Bilateral procedures in X-Ray/Oswestry combined cohort

One thousand one hundred and eleven (1,111) of the X-ray/Oswestry combined cohort cases (68%) were unilateral procedures and 515 (32%) were bilateral procedures. The indication for the majority of cases was osteoarthritis. The table below provides the breakdown of unilateral and bilateral cases by indication.

Diagnostic Indication for BHR

Diagnosis	Unilateral	Bilateral	TOTAL
Osteoarthritis	849 (76.4%)	414 (80.4%)	1263 (77.7%)
Dysplasia	160 (14.4%)	59 (11.5%)	219 (13.5%)
Avascular necrosis	52 (4.7%)	14 (2.7%)	66 (4.1%)
Inflammatory arthritis	18 (1.6%)	23 (4.5%)	41 (2.4%)
Other	32 (2.9%)	5 (1.0%)	37 (2.3%)
TOTAL	1111 (68%)	515 (32%)	1626

The sponsor explained that some of the patients with bilateral hip replacements were included in different groups depending on when the second hip procedure was performed.

Hip Procedures								
Cohort	Patients	Hips	Unilateral	Bilateral	Contralateral Single Hip Cohort*			Singles
					X-Ray	Oswestry	McMinn	
X-Ray	113	124	83	11	-	11	8	19
Oswestry	1301	1502	1028	201	11	-	61	72
McMinn	683	759	542	74	8	61	-	69

* Patients with bilateral hip replacements with the contralateral hip not included in the first hip replacement's evaluation cohort.

Demographics: Literature Control

The study published by D'Antonio *et al.* reported findings from a multicenter study conducted at 22 investigational sites; the study published by Garino was conducted at 11 investigational sites.

Demographics

Author	Patients	Procedures	Age (Average)	Bilateral Procedures
D'Antonio J <i>et al</i>	458	514: • 349 ceramic • 165 control	53	19
Garino JP	333 (f=132, m=201)	333	52	0

D'Antonio *et al.* reported the indication for THR as osteoarthritis in 399/514 procedures (77.6%) and avascular necrosis in 82/514 procedures (16%); Garino did not provide a breakdown of indication for THR.

Indication for Arthroplasty

Diagnosis	D'Antonio	Garino
OSTEOARTHRITIS	399	
TRAUMATIC OSTEOARTHRITIS / DJD	21	
AVASCULAR NECROSIS	82	
OTHER / NOT REPORTED	12	333
TOTAL	514	333

DESCRIPTION OF DEVICE IMPLANTATIONS

The sponsor provided the following information on the femoral head sizes and acetabular cup styles and sizes implanted in the 2385 procedures in the Overall McMinn cohort.

Surgical Data: Implant Sizes All Patients						
Acetabular Cup	Femoral Resurfacing Component/Head					
	38mm	42mm	46mm	50mm	54mm	58mm
44mm	2 (0.1%)					
46mm	5 (0.2%) 4 ^D (0.2)					
48mm		119 (5.0%)				
50mm		67 (2.8%) 39 ^D (1.6)				
52mm			342 (14.3%)			
54mm			154 (6.5%) 1 ^C (0.0) 50 ^D (2.1)			
56mm				683 (28.6%)		
58mm			3 ^B (0.1%)	167 (7.0%) 28 ^D (1.2)		
60mm					460 (19.3%)	
62mm				1 ^B (0.0)	137 (5.7%) 38 ^D (1.6)	
64mm						51 (2.1%)
66mm					1 ^B (0.0)	22 (0.9%) 10 ^D (0.4)

- B Bridging cups
- C Custom cups
- D Dysplastic cups

Stratification of Results by Hybrid/Cement/Uncemented:

The sponsor states that there was only one case (of the 1,626 cases in the X-ray/Oswestry combined cohort) in which the femoral component was not cemented (a customized implant to accommodate broken metal that remained in the femoral head from a previous event). Therefore, the number of non-hybrid implants (cemented femoral resurfacing component/uncemented acetabular cup) was negligible.

PATIENT ACCOUNTING

The follow-up rates for the Combined X-Ray / Oswestry Cohort, upon which the effectiveness analyses were performed, at the 1-year, 2-year, 3-year, 4-year, and 5-year postoperative evaluation time points were 76.6%, 77.3%, 88.1%, 88.6%, and 90.8%, respectively. There were 546 procedures (hips) evaluated at 5 years in this cohort.

Patient Accounting						
Based on the number procedures (Table 1.1)						
	Baseline	1 years	2 years	3 years	4 years	5 years
Accounting for Survivorship (% Revision Free)						
Cohort		# Patients observed at beginning of each study year (# revisions, # censored) ¹				
X-Ray	-	124 (1, 0)	123 (0,0)	123 (1,0)	122 (0,0)	122 (0,20) ⁶
Oswestry	-	1502 (9,63)	1430 (5,49)	1376 (4,256)	1116 (1,321)	794 (1,392)
McMinn	-	759 (3,290)	466 (0,379)	87 (0,84)	3 (0,0) ⁷	3 (0,0) ⁷
X-Ray Cohort						
Expected ¹	124	123	123	122	122	118
Evaluated ²	82	101	51	122	119	112
F/U % ²	66.1%	82.1%	41.4%	100.0%	97.5%	94.9% ³
Evaluated ⁴	124	-	-	-	-	108
F/U % ⁴	100%	-	-	-	-	91.5%
Oswestry Cohort						
Expected ¹	1502	1493	1484	1227	885	482
Evaluated ²	1229	1137	1192	1067	773	434
F/U % ²	81.8%	76.2%	80.3%	87.0%	87.3%	90.0%
X-ray / Oswestry Combined Cohort						
Theoretical ¹	1626	1626	1626	1385	1045	647
Deaths (procedures)	0	2	7	16	18	26
Revisions (cumulative)	0	10	15	20	21	23
Expected ¹	1626	1616	1607	1349	1007	601
Evaluated ²	1311	1238	1243	1189	892	546
F/U % ²	80.6%	76.6%	77.3%	88.1%	88.6%	90.8%
F/U +base ⁵	1311	1067/1304	1050/1294	944/1046	660/726	368/397
+base %		82%	81%	90%	91%	93%
F/U -base ⁵	315	171/312	193/313	245/303	232/281	178/204
-base %		55%	62%	81%	83%	87%

¹ Note that for the Survivorship data the "year 1" data is starting from day 1 and the "year 2" data is starting from day 366, etc. but for the OSHIP scores, the "year 1" data was collected between day 366-730, the "year 2" data was collected between day 731-1095, etc.

² Evaluated by OSHIP score

³ OSHIP score was available for one hip that was revised shortly after the 5-year follow-up interval, OSHIP data available on 112/119 (94.1%) of hips surviving to 5 years

⁴ Evaluated by X-Ray

⁵ The follow-up of those who had baseline OSHIP scores (+base) and those without baseline OSHIP scores (-base).

⁶ Note that there were 2 revisions in the x-ray cohort at >5 years

⁷ The sponsor stated that there were 5 cases in the McMinn cohort whose implantations were performed prior to 4/02. These cases should have been part of the Oswestry cohort, but for unknown reasons were not. Therefore, unlike the majority of the McMinn cohort, some of these 5 cases have longer term follow-up.

For the unilateral patients in the X-Ray / Oswestry combined cohort, the follow-up rates at the 1-year, 2-year, 3-year, 4-year, and 5-year postoperative evaluation time points were 75.7%, 76.6%, 88.2%, 88.4%, and 91.1%, respectively.

Patient Accounting						
Summary of the Oswestry and X-Ray Cohorts - Unilateral						
Based on Available OSHIP Data (Table 16.1)						
	Baseline	1 years	2 years	3 years	4 years	5+ years
Theoretical	1111	1103	1100	927	687	395
OSHIP data	892	835	842	818	607	360
%	80.3	75.7	76.6	88.2	88.4	91.1

Patient Accounting: Literature Control

Author	Mean follow-up (range)	Number of hips (patients) included
D'Antonio	35.2 mo (24 to 48 mo) for ceramic on ceramic. 33.6 mo (24 to 48 mo) for control (metal on polyethylene)	319 ceramic-on-ceramic THR procedures (318 patients) <ul style="list-style-type: none"> • 335 hips (307 pts) at 24 mos • 243 hips (227 pts) at 36 mos • 72 hips (71 pts) at 48 mos 165 control THR procedures (161 patients), <ul style="list-style-type: none"> • 149 hips (147 pts) at 24 mos • 111 hips (111 pts) at 36 mos • 26 hips (26 pts) at 48 mos
Garino	Range 18-36 months	"100% follow up for all 333 procedures"

SAFETY DATA

Safety: Revisions

The sponsor provided the cumulative revisions data per cohort in Table 8.5.

There were 27 procedures that required revision. In A12, Attachment 5 (File 4.1.4.1.2 on the Panel CD) the sponsor provided narratives of all patients that had a revision. There were 10 revisions due to a femoral neck fracture, 6 for femoral head collapse, 1 for dislocation, 2 for AVN (1 lead to femoral head collapse and 1 lead to a femoral neck fracture), and 8 for infections (2 lead to head collapse, 1 lead to a femoral neck fracture). Altogether, there were 12 femoral neck fractures that required revisions. Factors that may have contributed to the femoral neck fractures include age-related osteopenia (2 patients), poor preoperative bone quality as evidenced by cysts in the femoral head and acetabulum (1 case), SLE (1 case), severe RA (1 case), infection that lead to bone death (1 case), femoral head cysts (1 case), and malpositioned component (1 case).

The 9 cases with femoral head collapse (6 primary femoral head collapses, 2 collapses due to infection and 1 due to AVN). Factors that may have contributed to the femoral head collapse include infection (2 cases), AVN (1 case), femoral head cysts and soft bone (3 cases), and osteopenia (1 case).

Revisions Table 8.5						
	X-Ray Cohort N=124					
	Postop	1 year	2 years	3 years	4 years	5+ years
Number of procedures	124	124	123	123	122	122
Revisions	-	1	0	1	0	2
	Oswestry Cohort N=1502					
Number of procedures	1502	1502	1430	1376	1116	794
Revisions	-	9	5	4	1	1
	McMinn Cohort N=759					
Number of procedures	759	759	466	87	3	3
Revisions	-	3	0	0	0	0
	X-Ray + Oswestry Combined Cohort N=1626					
Number of procedures	1626	1626	1553	1499	1238	916
Revisions	-	10	5	5	1	3
	Overall McMinn Cohort N=2385					
Number of procedures	2385	2385	2019	1586	1241	919
Revisions	-	13	5	5	1	3

Safety: Revisions Comparison with Literature Controls

The sponsor provided a comparison of the revision rates between the BHR study cohorts and the two literature control groups. The revision rate for the primary efficacy cohort was 1.4% at 5 years compared to 1.2%, 5.2%, and 1.2%, respectively, for the D'Antonio ceramic-ceramic, D'Antonio metal-poly, and Garino literature control groups.

Revision Rate Comparisons								
	Cohort					Control Data		
	X-Ray	Oswestry	X-Ray/ Oswestry Combined	McMinn	Overall McMinn	D'Antonio C/C	D'Antonio M/P	Garino
N	124	1502	1626	759	2385	338	151	333
Revised	4	20	24	3	27	4	8	4
Rate %	3.2	1.3	1.4	0.3	1.1	1.2	5.2	1.2
f/u years	5	4	4-5	1	3	3	3	1-3

Safety: Adverse Events

The sponsor provided detailed time course distributions of adverse event type in Table 21.1. The Overall McMinn Cohort contains the X-Ray, Oswestry, and McMinn cohorts, and can be considered the safety cohort for this study. Also, presented below, is a table with the total number of adverse events in the Overall McMinn Cohort stratified by adverse event type and compared with Literature Controls.

Adverse Events Overall McMinn Cohort Table 21.1						
Adverse Event	Overall McMinn Cohort N=2385					
	Postop	1 year	2 years	3 years	4 years	5+ years
Number of procedures	2385	2157	1667	1378	1018	620
Procedures with AE (%)	1126 (46.2)	847 (39.3)	155 (9.3)	64 (4.6)	34 (3.3)	53 (8.5)
AVN femoral head/neck	31 (1.3%)	2 (<0.1%)	1 (<0.1%)	0	0	1 (0.2%)
Femoral head collapse	7 (0.3%)	3 (0.1%)	3 (0.2%)	1 (<0.1%)	0	1 (0.2%)
Component migration/loosening	1 (<0.1%)	7 (0.3%)	8 (0.5%)	2 (0.1%)	0	1 (0.2%)
Femoral neck fracture	0	10 (0.5%)	0	2 (0.1%)	0	1 (0.2%)
Impingement	2 (<0.1%)	1 (<0.1%)	0	0	0	0
Infection	0	7 (0.3%)	3 (0.2%)	1 (<0.1%)	1 (<0.1%)	2 (0.3%)
Dislocation	0	5 (0.2%)	0	2 (0.1%)	0	2 (0.3%)
Cardiac event	15 (0.6%)	1 (<0.1%)	0	1 (<0.1%)	0	0
Hg drop	179 (7.5%)	2 (<0.1%)	0	0	0	0
Heterotopic Ossification	0	33 (1.5%)	19 (1.1%)	3 (0.2%)	1 (<0.1%)	3 (0.5%)
Hypotension	33 (1.4%)	4 (0.2%)	0	0	0	0
Limp	0	203 (9.4%)	4 (0.2%)	2 (0.1%)	0	1 (0.2%)
Event at implant site (clicking, etc.)	0	51 (2.4%)	14 (0.8%)	9 (0.7%)	1 (<0.1%)	3 (0.5%)
Reaction at incision site	8 (0.3%)	62 (2.9%)	1 (<0.1%)	1 (<0.1%)	0	2 (0.3%)
Other (see description below)	171 (7.2%)	121 (5.6%)	19 (1.1%)	7 (0.5%)	7 (0.7%)	5 (0.8%)
Thromboembolic event	3 (0.1%)	3 (0.1%)	0	0	0	0
Pain	26 (1.1%)	223 (10.3%)	76 (4.6%)	22 (1.6%)	20 (2.0%)	29 (4.7%)
Deep Vein Thrombosis	5 (0.2%)	1 (<0.1%)	2 (0.1%)	0	0	0
Infection	28 (1.2%)	13 (0.6%)	0	0	0	0
Pneumonia	2 (<0.1%)	0	0	0	0	0
Fever	171 (7.2%)	1 (<0.1%)	1 (<0.1%)	0	0	0
X-ray report comment	0	23 (1.1%)	12 (0.7%)	7 (0.5%)	3 (0.3%)	7 (1.1%)
Stiffness, weakness, flexion deformity, restricted ROM	0	184 (8.5%)	11 (0.7%)	9 (0.7%)	3 (0.3%)	3 (0.5%)
Urinary	234 (9.8%)	1 (<0.1%)	0	0	0	0
Wound exudate	588 (24.7%)	1 (<0.1%)	0	0	0	0

Safety: Adverse Events Overall McMinn Cohort and Comparison with Literature Controls

The rate of wound exudates differs significantly between the two literature control groups and the Overall McMinn Cohort, 3.4% and 1.4% versus 25%. The sponsor states that this is probably due to a difference in the definition or reporting requirements. There does not appear to be a correlation between wound exudates and superficial or deep infections. AVN of the femoral head (1%), femoral head collapse (<1%), and femoral neck fracture (<1%), which are not possible in conventional total hip replacements, occurred at low rates. The rates of a fall in hemoglobin levels (8%) and limp (9%) were noted but of questionable significance. The “other” adverse events in the Overall McMinn Cohort included non-device and non-procedure related adverse events, such as dizzy spells, rashes, illnesses, ankle fracture, prostate cancer, or other pre-existing medical conditions.

Comparison of Adverse Events Overall McMinn Cohort (Table 20.1) vs. Controls					
Adverse Event	Overall McMinn Cohort Totals	Garino Control	D'Antonio Control N=319		
			ABC with porous	ABC with HA	Control
Number of procedures	2385	333	166	172	151
Procedures with AE (%)	1669 (70%)				
Total AEs	2912				
AVN femoral head/neck	35 (1%)				
Femoral head collapse	15 (<1%)				
Component migration/loosening	21 (<1%)				
Femoral neck fracture	13 (<1%)				
Impingement	3 (<1%)				
Infection	15 (<1%)	1 (<1%)			
Dislocation	8 (<1%)	3 (1%)	2.3%	3.4%	4.2%
Radiological AE	-				
Femoral calcar fracture		3 (1%)			
Acet liner misplaced		2 (1%)			
Liner chipped insertion		3 (1%)	2.9%	2.3%	-
Acetabular migration		1 (<1%)			
Shell malposition		1 (<1%)			
Bursitis		1 (<1%)			
Cardiac event	21 (<1%)				
Femoral fracture			2.4%	1.2%	1.2%
Hg drop	182 (8%)				
Heterotopic Ossification	56 (2%)		2.9%	3.4%	6.1%
Hypotension	37 (2%)				
Limp	211 (9%)		2%	4%	3%
Event at implant site (clicking, etc.)	75 (3%)				
Reaction at incision site	74 (3%)				
Other (see above description)	328 (14%)				
Thromboembolic event	7 (<1%)	1 (<1%)			

Pain	367 (15%)	2 (<1%)	9%	8%	7%
Deep Vein Thrombosis	8 (<1%)				
Infection	41 (2%)	1 (<1%)			
Pneumonia	2 (<1%)				
Fever	177 (7%)				
X-ray report comment	53 (2%)				
Stiffness	206 (9%)				
Urinary	235 (10%)				
Wound exudate	589 (25%)		3.4%	1.4%	
Not applicable (pre-existing condition)	3 (<1%)				
Foot-drop		1 (<1%)			
Vertebral fracture		1 (<1%)			
Other local complication		8 (2.5%)			

Safety: Adverse Event Reporting

The sponsor states that it has performed a 100% audit of all 2,385 procedures in the Overall McMinn Cohort, and therefore believes that all reported adverse event information has been captured.

The sponsor provided the following explanations/definitions:

- Device-related** Events that are possibly or probably related to the device.
- Hip/Procedure-related** Events that occur due to problems with the hip anatomy or the surgical process.

The sponsor provided the following explanations for the following specific AE categories:

- **AVN:**
 - Hip/Procedure-related: If AVN was present in the hip (a diagnostic indication for use) or identified during the surgery.
- **Infection of the index hip:**
 - Device-related: If the infection occurred than 30 days after surgery (“late infection”).
 - Hip/Procedure-related: If the infection occurred within 30 days after surgery. Wound ooze infections that resolve with antibiotics.
- **Dislocation/Prosthesis Dislocation:**
 - Device-related: If the hip prosthesis dislocates.
 - Hip/Procedure-related: If the dislocation was due to an accident (e.g., patient fall).
- **Migration / Loosening:**
 - Device-related: If the component migrates or loosens.

Safety: Adverse Events - Discussion of Infections

The infections were categorized as hip/procedure-related or device-related based on the time of occurrence. The sponsor states that there were 41 infections associated with the index hip resurfacing procedure within 30 days of surgery and were thus categorized as hip/procedure-related. All of these events were wound exudates or wound infections that resolved with antibiotics. There were 15 infections that occurred more than 30 days of surgery and were thus categorized as device-related. Of these 15 infections, 6 required revisions and 9 “resolved with antibiotics.” There were two patients who were revised for other indications (component migration and femoral neck fracture) who were found to be infected.

The 41 “hip/procedure-related” infections and the 9 “device-related” infections that resolved with antibiotics others probably should be categorized as wound problems or superficial wound infections. Infections that involve the prosthesis will not typically be successively treated with antibiotics alone. Therefore, it is unlikely these are actually device infections. Therefore, these should be categorized in the hip/procedure-related category, probably as wound problems or superficial infections.

Safety: Deaths

There were 20 patient deaths (26 procedures) in the Overall McMinn Cohort. The sponsor stated that in no case was a death related to the BHR procedure. In A12, Attachment 5 (File 4.1.5.2 on the Panel CD) the sponsor provided narratives of all patients that died. The causes were reported to be: 2 stroke, 4 cancer, 1 motor neuron disease, 1 oesophageal cancer and pneumonia, 1 myocardial infarction, 1 suicide, 1 ruptured aorta, 1 carcinoma prostate with metastases, 1 unconfirmed – either diving accident or myocardial infarction, 7 unreported.

Safety: Metal Ion Literature Analysis

The sponsor provided literature references to address concerns for metal ion release.

- The sponsor provided an unpublished report by **Daniel J, Ziaee H, and McMinn D, entitled, “Metal ion studies in patients treated with the Birmingham Hip Resurfacing, a comparable FDA-approved device and historic metal-metal total hip replacements”** (A11, Attachment 35.1; File 4.1.5.15 on the Panel CD).

The authors conducted 4 metal ion studies in patients who received BHR, Metasul metal-metal total hip replacements, and other (historic) metal-metal total hip replacements:

1. A short-term longitudinal study of urinary Co and Cr levels in patients with the BHR and the Metasul metal-metal total hip replacement.

12-hour urine collections were obtained preoperatively and postoperatively at 5 days, 2 months, 6 months, 1 year and 2 years for 26 consecutive patients who underwent BHR. The inclusion criteria were unilateral end-stage arthritis; 50mm and 54mm femoral heads; no other implanted metallic devices; and no renal failure. A

comparison group of 28 Metasul metal-metal total hip replacement patients operated on 1-3 years previously were studied. The metal ion analyses were performed using a High Resolution Inductively Coupled Plasma Mass Spectrometer (HRICPMS). The mean urinary Co output was 0.4µg/day, 4.0µg/day, 9.0µg/day, 19.2µg/day, 13.4µg/day, and 12.3µg/day for the preoperative, 5-day, 2-month, 6-month, 1-year and 2-year postoperative time points, respectively. The sponsor compared these values with the mean of 11.6µg/day in the 28 Metasul metal-metal total hip replacement patients at 1-3 years. The mean urinary Cr output was 1.6µg/day, 2.1µg/day, 4.0µg/day, 7.3µg/day, 5.3µg/day, and 5.3µg/day for the preoperative, 5-day, 2-month, 6-month, 1-year and 2-year postoperative time points, respectively. The sponsor compared these values with the mean of 3.7µg/day in the 28 Metasul metal-metal total hip replacement patients at 1-3 years.

2. A long-term cross-sectional study of urinary Co and Cr levels in patients with the BHR and the Metasul metal-metal total hip replacement.

12-hour urine collections were obtained from 58 patients who 5 years previously underwent BHR and 23 patients who received a Metasul metal-metal total hip replacement. At 5 years, the mean urinary Co output was 13.3µg/day for the BHR patients and 14.2µg/day for the Metasul patients. At the same time period, the mean urinary Cr output was 6.4µg/day for the BHR patients and 4.1µg/day for the Metasul patients

3. A longitudinal study of whole blood Co and Cr levels in patients with the BHR.

Whole blood samples were obtained preoperatively and 1 year postoperatively for 26 consecutive patients who underwent BHR (the same patients as the longitudinal study described above). In addition, the 58 patients who underwent BHR 5 years previously were also studied. The whole blood Co levels were 0.2µg/l, 1.3µg/l, and 1.8mg/l at the preoperative and 1-year time points and the 5-year study patients, respectively. The whole blood Cr levels were 0.3µg/l, 2.4µg/l, and 1.6mg/l at the preoperative and 1-year time points and the 5-year study patients, respectively.

4. A cross-sectional study of whole blood Co and Cr levels in patients with the BHR and metal-metal total hip replacements.

Whole blood samples were obtained 1 year postoperatively for 16 BHR patients who were described as “high quality sportspersons,” i.e., very physically active. Whole blood samples from 20 patients who underwent Metasul metal-metal total hip replacements 1 year previously and 16 patients who had “historic” metal-metal total hip replacements (Ring and McKee Farrar) were also studied. The mean whole blood Co levels were 2.7µg/l in the sportspersons BHR group, 2.1µg/l in the historic metal-metal THR group, and mean whole blood Cr levels were 5.8 µg/l in the sportspersons BHR group and 3.4µg/l in the historic metal-metal THR group.

The authors compared the measured 1-year and 5-year BHR and 1-year Metasul whole blood Cr levels (2.4µg/l, 1.7µg/l and 1.6µg/l) with the 17µg/l “safe limit” as proposed by the EKA (Expositionaquivalente für Krebserzeugende Arbeitsstoffe). The authors also compared the measured 6-month, 1-year and 2-year mean urinary output of Cr for the BHR patients (4.07µg/g creatinine, 4.24 µg/g creatinine, and 4.89µg/g creatinine) with the 300µg/g creatinine Biological Exposure Index for Cr as recommended by the ACGIH (American Conference of Government Industrial Hygienists).

The daily urinary output of metal ions in patients with BHR implants at 5 years is lower than that of patients with Metasul metal-metal total hip replacements. The whole blood levels of cobalt and chromium are higher postoperatively than preoperatively, but there does not appear to be an increase in the levels over time. In addition, the whole blood levels of cobalt and chromium in very active individuals in the early postoperative period was not different than in usual patients. Based on a comparison of the measure Co and Cr levels with the recommended safe reference levels (EKA and BEI), the metal ion levels in patients with BHRs were in the safe range.

The sponsor cited a long-term study of the cancer rates in 579 patients with historic metal-metal total hip replacements over a maximum period of 30 years. There was no increase in either all-site cancer or site-specific cancer rates (Visuri T, Pukkala E. Does metal-on-metal hip prosthesis have influence on cancer? A long-term follow-up study. Eds. Reiker C, Oberholzer S, Wyss U. World Tribology Forum in Arthroplasty (pub), Hans Huber Bern, Toronto, Seattle: pp.181-188, 2001.

- The sponsor provided a summary of the literature pertaining to the medium and long-term safety of cobalt and chromium ion exposure, and included copies of the 18 references.

Jacobs JJ, et al.: Cobalt and chromium concentrations in patients with metal on metal total hip replacements. Clin. Orthop., 329 (supplement): S256-S263, 1996. Abstract.

The authors measured the serum and urine concentrations of Co and Cr in 8 patients implanted with the McKee-Farrar metal-metal total hip replacements at greater than 20 years. There was a 9-fold elevation in serum Cr, 35-fold increase in urinary Cr, 3-fold increase in serum Co. In 6 patients with metal-metal surface replacements, there was a 3-fold increase in serum Cr, 4-fold increase in urinary Cr, and a 4-fold increase in serum Co at less than 2 years.

Jacobs JJ, et al.: Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J. Bone Joint Surg., 80(10): 1447-1458, 1998. Abstract.

The authors measured the serum and urine concentrations of Ti, Al, Co, and Cr in patients with metal-poly total hip replacements. At 36 months, patients had as much as a 3-fold increase in serum Ti levels.

Schaffer AW, et al.: Increased blood cobalt and chromium after total hip replacement. J. Toxicol. Clin. Toxicol., 37(7): 839-844, 1999. Abstract.

The authors found that there were significant postoperative elevations in urine Co and Cr and blood Co levels in all 76 patients, and in 29 patients the levels exceeded the EKA threshold limits for safe blood and urine Co levels.

Savarino, et al.: Ion release in stable hip arthroplasties using metal-on-metal articulating surfaces: a comparison between short- and long-term results. J. Biomed. Res., 66A(3): 450-456, 2003. Abstract.

The authors found that the serum Co and Cr levels were increased at 24 months and at 52 months. Delaunay CP found that there was no correlation between systemic Co concentrations and age, gender or patient activity. Ladon D found an increased incidence of chromosome translocations and aneuploidy in patients with both metal-metal and metal-poly total hip replacements.

Masse A, et al.: Ion release and chromosomal damage from total hip prostheses with metal-on-metal articulation. J. Biomed. Mater. Res. B. Appl. Biomater., 67(2): 750-757, 2003. Abstract.

The authors measured the Co, Cr, Ni and Mb levels in blood and urine after Metasul total hip replacements. The levels increased 2-fold (blood Co), 10-fold (urine Co), 1.5-fold (blood Cr), 3-fold (urine Cr) at 6 months. There were no changes in the frequency of markers of chromosomal damage in the peripheral lymphocytes at any observation time points.

Visuri T, et al.: Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. Clin. Orthop., 329 Supplement: S280-S289, 1996. Abstract.

The authors state that the risk of total cancer in patients with a metal-metal McKee-Farrar hip replacement is 1.23-fold compared to metal-poly hip replacements at 15.7 years.

Visuri T, Pukkala E. Does metal-on-metal hip prosthesis have influence on cancer? A long-term follow-up study. Eds. Reiker C, Oberholzer S, Wyss U. World Tribology Forum in Arthroplasty (pub), Hans Huber Bern, Toronto, Seattle: pp.181-188, 2001.

The authors surveyed 579 patients who received a McKee-Farrar metal-metal hip replacement and had long-term follow-up (average 16.8 years). The annual incidence of all-site cancers was the same as expected. There was an excess of cancers with unknown primary site in women, a borderline excess of colon cancer after 15 years,

higher number of leukemias, but a decreased number of urinary tract cancers. No bone or connective tissue sarcomas were observed. Other forms of cancer were the same as in the general population.

MacDonald SJ, et al.: Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clin. Orthop., 406: 282-296, 2003. Abstract.

Erythrocyte and urine metal ion levels were measured in 23 metal-metal and 18 metal-poly total hip replacement patients. 41% of the metal-metal patients had increasing metal ion levels at the latest follow-up. Patients with metal-metal THR had a 7.9-fold increase in erythrocyte Co, 2.3-fold increase in erythrocyte Cr, 35.1-fold increase in urinary Co, and a 17.4-fold increase in urinary Cr.

Maezawa K, et al.: Cobalt and chromium concentrations in patients with metal-on-metal and other cementless total hip arthroplasty. Arch. Orthop. Trauma Surg., 122(5): 283-287, 2002. Abstract.

The serum and urine concentrations of Co and Cr in 32 patients with metal-metal total hip replacements were measured and compared with 43 patients with metal-poly total hip replacements. The serum and urine Co concentrations were not detectable in any patients. The serum and urine Cr concentrations were elevated in 37.5% and 90.6% of metal-metal patients.

Witzlieb, WC, et al.: Histopathological findings and metal ion concentrations in MetaSul and Birmingham Hip Resurfacing metal on metal bearings. U Hanisch, V Neumeister & WC Witzler, University of Dresden, Germany.

The authors presented the results of 163 Birmingham Resurfacing Hip cases, including histopathology of 9 cases (5 BHR and 4 MetaSul) and serum Co and Cr concentrations in 67 BHR and 32 Metasul patients (average 6 and 14 months, respectively). There were wear particles in only 2 of the 5 BHR cases. There was regular but not high amounts of metal debris in the Metasul patients. There were no inflammatory changes, foreign body reactions or metallic debris in the BHR capsular tissue. Both devices produced detectable serum Co and Cr levels by 1 month postoperatively, but these levels did not change over the course of the 44 months follow-up time. There were no significant differences in the serum ion levels between the BHR and Metasul patients.

McMinn, D: Biological aspects of hip resurfacing. (no citation).

The author did not present new data.

Clarke MT, et al.: Levels of metal ions after small- and large-diameter metal-on-metal hip arthroplasty. J. Bone Joint Surg., 85B(6): 913-917, 2003.

The serum levels of Co and Cr were measured in 22 patients with metal-metal resurfacing and 22 patients with metal-metal total hip replacements. At 16 months, the median serum levels of Co and Cr were 38nmol/l and 53nmol/l, respectively, for the resurfacing patients and 22nmol/l and 19nmol/l, respectively, for the total hip patients.

Brodner W, et al.: Serum cobalt levels after metal-on-metal total hip arthroplasty. J. Bone Joint Surg., 85A(11): 2168-2173, 2003. Abstract.

The authors reported on the results of 50 Metasul metal-metal and 50 ceramic-poly total hip replacements. At 1 year, the median concentration of whole blood cobalt was 1.0µg/l and 0.7µg/l at 5 years in the metal-metal group, and undetectable in the ceramic-poly group.

Migaud H., et al.: Cementless metal-on-metal hip arthroplasty in patients less than 50 years of age. J. Arthroplasty, 19(8) Supplement 3: 23-28, 2004.

The authors reported on the results of 39 metal-metal total hip replacements. At a minimum of 5 years, the median concentration of whole blood cobalt was 0.62µg/l (range 0.2-4.7µg/l). Three women delivered healthy babies.

Delaunay, CP: Metal-on-metal bearings in cementless primary total hip arthroplasty. J. Arthroplasty, 19(8) Supplement 3: 35-40, 2004.

The authors measured the whole blood concentrations of cobalt in 99 patients who had Metasul metal-metal total hip arthroplasties out to 9 years. There were 76 patients with elevated postoperative Co levels (60 were in the laboratory "normal" range) and 23 patients that had unchanged levels.

Ladon D, et al.: Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. J. Arthroplasty, 19(8) Supplement 3: 78-83, 2004.

The authors found that there is a significant increase in the chromosome translocations and aneuploidy in lymphocytes at 6 months, 12 months and 24 months in patients with metal-on-metal hip arthroplasties who have elevated cobalt and chromium levels.

Jacobs, J, et al.: Can metal levels be used to monitor metal-on-metal hip arthroplasties? J. Arthroplasty, 19(8) Supplement 3: 59-65, 2004.

This is a review of the current practices of performing tests for metal ion concentrations in blood, serum, and urine in patients who have metal-on-metal hip replacements. The authors conclude that these tests are valuable research tools, but are not useful clinically to monitor patients for metal-related toxicity.

MacDonald SJ: Can a safe level for metal ions in patients with metal-on-metal total hip arthroplasties be determined? J. Arthroplasty, 19(8) Supplement 3: 71-77, 2004.

This paper is a review of previously reported studies of cobalt levels in total hip replacement patients and a discussion about the safety standards for metal ions. The author concludes that in order to determine whether there is a causal relationship between metal-on-metal bearings and any potential risk will require a significant number of patients.

These publications demonstrate that serum and urinary metal ion concentrations in patients with total hip replacement in general, and metal-metal implants in particular, increase in the postoperative period. However, there does not appear to be any conclusive evidence that elevated cobalt and chromium levels have any detrimental effects in total hip arthroplasty patients.

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE SAFETY DATA

Question #4:

Based on the safety data in 2,385 patients in the Overall McMinn Cohort (i.e., data on revisions, adverse events, deaths) and the analysis of the metal ion literature, please discuss whether or not you believe that the data contained in this PMA provide reasonable assurance of safety?

EFFECTIVENESS DATA

Primary Effectiveness: Survivorship

The survivorship estimates were based on the number of patients with no revision. The sponsor provided survivorship analyses for various cohorts and demographic subgroups calculated according to Peto's adjustment method as follows:

% Survivorship Analyses (no revision)					
Tables 8.5, 9.5, 10.5, 11.5, 12.5, 13.5, and 14.5					
Population	1 year	2 years	3 years	4 years	5 years
X-ray Cohort	99.2	99.2	98.4	98.4	98.4
Oswestry Cohort	99.4	99.0	98.7	98.6	98.4
X-ray/Oswestry Combined Cohort	99.4	99.0	98.7	98.6	98.4
McMinn Cohort	99.6	99.6	99.6	99.6	99.6
Overall McMinn Cohort	99.4	99.1	98.8	98.7	98.5
Male ¹	99.4	99.2	98.9	98.9	98.6
Female	99.4	99.0	98.5	98.2	98.2
Age ≤65 years ¹	99.5	99.2	98.8	98.7	98.5
Age >65 years	99.0	99.0	99.0	99.0	99.0
Dx: AVN ¹	98.9	98.9	96.7	96.7	92.1
Dx: Dysplasia	99.4	99.4	98.9	98.1	98.1
Dx: OA	99.5	99.1	98.8	98.8	98.8
Dx: Inflammatory	98.1	98.1	98.1	98.1	98.1
Dx: Other	100.0	100.0	100.0	100.0	100.0
Unilateral ¹	99.4	99.1	98.8	98.6	98.4
Bilateral	99.6	99.2	98.8	98.8	98.8
Baseline OSHIP ≤63	99.0	98.7	98.7	98.7	98.7
Baseline OSHIP >63	99.8	99.3	98.7	98.3	98.3
Baseline OSHIP missing	99.5	99.5	98.8	98.8	98.3
BMI ≤26	99.7	99.3	99.0	98.8	98.8
BMI >26	99.1	98.9	98.7	98.7	98.3
BMI missing	99.4	99.1	98.1	98.1	98.1

¹ For the Overall (2,385) patients

The only marginally statistically significant difference in 5-year survival probability was between the patients with Osteoarthritis (98.8%) and Avascular Necrosis (92.1%) as their primary diagnostic indication.

There were 37 cases (of the 1626 cases) with a diagnosis of "Other." There were no revisions in this group, and thus the survivorship at 5 years is 100%. The sponsor did not provide a separate analysis for this group and does not seek approval for indications other than OA, IA, AVN and DDH.

Primary Effectiveness: Radiographic Data

The PMA contained the results of an independent radiographic review of the X-Ray Cohort, the first 124 procedures performed in the series from 7/97 through 12/97. Radiographic evaluations were not provided for the 1502 procedures in the Oswestry Cohort or the 759 procedures in the McMinn Cohort.

Radiographs were taken on 108 of the 118 procedures expected at 5 years postoperatively (91.5%). Six (6) procedures were not expected at 5 years postoperatively because one patient with bilateral hip implants died from a motor neuron disease unrelated to the BHR procedure; and 4 of the 124 BHR procedures (3.2%) have undergone revision: 3 cases were revised for infection, and 1 case required revision because of a femoral neck fracture. Therefore, 118 procedures (124 hips - 2 hips due to death - 4 revisions = 118 procedures) were eligible for 5 year radiographic evaluation of the BHR. Ten other cases were missing due to lost to follow-up or incomplete film records. Therefore, one hundred and eight (108) of the 118 hips surviving to 5 years had 5 year radiographs available for independent review (91.5%). (Note: The sponsor reported that an additional bilateral patient died 7 years post-op due to stroke but had 5 year x-rays taken).

There were immediate post-operative films on 89 of the 108 procedures with 5-year radiographs but the sponsor stated that these films were low quality portable films and unusable for the purposes of precise postoperative measurement comparisons. Therefore, baseline films for the purposes of comparisons were made in each of the 108 cases in the postoperative time period (usually within 3 months, but 8 of the 108 procedures had baseline evaluations performed at time points ranging from 110-860 days).

Primary Effectiveness Radiographic Study: 5-Year Radiographic Assessments

The radiographs were assessed for radiolucencies, bone resorption, heterotopic bone, acetabular angle, medial-lateral migration, and other observations to determine whether a revision surgery was necessary.

Femoral radiolucencies: Radiolucencies were graded 0-9 (Amstutz). There were femoral radiolucencies found in 4 cases (4.1%)—1 each with grades 9 (migration), 5 (zone 2-3), 2 (zone 1) and 1 (zone 2). The patient with a grade 9 femoral radiolucency and was classified as a radiographic failure.

Acetabular radiolucency: Radiolucencies were graded 0-9 (DeLee and Charnley). There were 2 hips with acetabular radiolucencies, both with grade 8 (zones I-III, complete) findings. One hip had preoperative acetabular cysts that progressed over time, and the other had a preoperative dysplastic acetabulum and developed protrusio. Both were classified as radiographic failures. Three patients had insignificant radiolucencies (grade 1 in two hips and grade 2 in one hip).

Heterotopic bone: There were 21 hips that had Brooker I and 5 hips with Brooker II heterotopic ossification (HO). Only 2 hips had “clinically significant HO,” (i.e., Brooker III or IV). Both had Brooker III HO. Thus, 28 of the 108 procedures evaluated (28.9%) had any heterotopic bone at 5 years and 2.1% had

significant HO. None of the cases with heterotopic bone were determined to require a revision.

Acetabular angle: There was only 1 case that had a change in the acetabular angle $>5^\circ$. This patient also had the grade 8 acetabular radiolucency (see above). No cases had a change in acetabular angle that was determined to be an indication for a revision.

Medial / Lateral Migration: There were no procedures with a change in medial/lateral acetabular cup position, and no cases with a change in acetabular position that was determined to be an indication for a revision.

Additional observations: Bone resorption at the femoral neck was found in 3 cases. In no case was the resorption associated with any other notable radiographic findings. Bone cysts were found in 2 patients: one, described above, and the other had 3cm cysts associated with a grade 1 acetabular radiolucency. No other significant signs were noted.

The sponsor determined that 3 of the 108 (2.8%) patients for whom radiographs were available were radiographic failures at 5 years.

Radiographic Findings	
Number of procedures (%)	
Findings	Number (%)
Femoral radiolucencies	
Failure: Grade 9	1 (0.9)
Other: Grade 1	1 (0.9)
Other: Grade 2	1 (0.9)
Other: Grade 5	1 (0.9)
Acetabular radiolucencies	
Failure: Grade 8 ¹	2 (1.8)
Other: Grade 1	2 (1.8)
Other: Grade 2	1 (0.9)
Change in orientation/migration	
5° change in orientation ¹	1 (0.9)
Heterotopic ossification	
Brooker IV	0 (0.0)
Brooker III	2 (1.8)
Brooker II	5 (4.6)
Brooker I	21 (19.4)
Other	
Bone resorption, femoral neck	3 (2.8)
Femoral or acetabular cyst	2 (1.8)

¹ Occurred in the same patient

Primary Effectiveness Radiographic Study: Comparison to Literature Control

The radiographic results were compared with the literature control groups.

Radiographic Findings X-Ray Cohort vs. Literature Control Question 21(g)					
Radiographic Finding	Overall McMinn Cohort	Garino Control*	D'Antonio Control		
			ABC with porous (n=162)	ABC with HA (n=169)	Control M/PE (n=149)
Femoral RL zone 1	1 (0.9%)	-	4 (2.5%)	4 (2.4%)	6 (4.0%)
Femoral RL zone 2	1 (0.9%)	-			
Femoral RL zone 2 & 3	1 (0.9%)	-			
Femoral RL zone 7	0	-	2 (1.2%)	1 (0.6%)	0
Stem subsidence	0	-	0	1 ¹ (0.6%)	0
Unstable stem	1 (0.9%)	-	0	1 ¹ (0.6%)	0
Cup RL Zone I	2 (1.8%)	-	10 (6.2%)	1 (0.6%)	10 (6.7%)
Cup RL Zone II	1 (0.9%)	-	3 (1.9%)	0	7 (4.7%)
Cup RL Zone III	0	-	25 (15.4%)	0	35 (23.5%)
Cup RL all 3 zones	2 (1.8%)	-	0	0	0
Cup migration	1 (0.9%)	-	0	0	1 ² (0.7%)
Cup unstable		-	1 (0.6%)	0	1 ² (0.7%)

* No radiographic data.

¹ Same femoral component

² Same acetabular component

Secondary Effectiveness: Pain and Function - Oswestry Modified Harris Hip (OSHIP) Score—Unilateral Procedures Only

FDA believes that it is impossible to assess the pain and function of each hip separately in patients with bilateral hip involvement using the Harris Hip Score or the Oswestry-modified Harris Hip Score (OSHIP), because it is impossible to distinguish the contributions of each hip on functional assessments such as walking or support, walking distance, stair-climbing, sitting, and transportation. Therefore, FDA believes only the unilateral patients can be used in the analysis of pain and function. See below in this section for additional discussion regarding unilateral and bilateral assessments of pain and function.

The mean OSHIP Scores (unilateral procedures only) improved from a baseline mean of 60.1 to 94.8 at 5 years. For the group of patients who had high baseline OSHIP scores (≥ 80), the mean OSHIP scores improved from 84.5 to 99.3. The group of patients who had low baseline OSHIP scores (< 80), the mean OSHIP scores also improved from 59.4 to 95.6. At postoperative years 2, 3, 4 and 5, the percentage of cases with good or excellent OSHIP scores was 96.9%, 95.8%, 95.2%, and 92.8%, respectively.

Oswestry-Modified Harris Hip Score (OSHIP) X-Ray / Oswestry Combined Cohort—Unilateral only (Table 16.1)						
	Baseline	1 years	2 years	3 years	4 years	5 years
Theoretically Due	1111	1103	1100	927	687	395
OHSIP assessments	892	835	842	818	607	360
OSHIP mean	60.1	96.6	96.8	96.2	95.9	94.8
AVN OSHIP mean	49.4	91.3	93.6	96.2	94.3	97.4
N, AVN	43	35	38	32	23	14
Dysplasia OSHIP mean	57.7	96.2	96.7	95.2	94.7	90.6
N, Dysplasia	131	123	117	117	81	44
OA OSHIP mean	61.5	97.0	97.0	96.5	96.2	95.3
N, OA	678	642	652	632	484	287
IA OSHIP mean	48.5	95.5	94.9	93.2	91.6	89.3
N, IA	15	11	11	15	10	8
Other OSHIP mean	62.9	96.5	98.3	96.6	98.8	98.4
N, Other	25	24	24	22	9	7
OSHIP mean for procedures with baseline ≥ 80	84.5	96.1	97.8	97.3	99.6	99.3
N, for baseline ≥ 80	25	22	22	18	8	3
OSHIP mean for procedures with baseline < 80	59.4	96.9	96.9	96.6	96.4	95.6
N, for baseline < 80	867	693	686	635	440	240
OSHIP mean for procedures with baseline OSHIP	60.1	96.9	96.9	96.6	96.5	95.6
N, with baseline OSHIP	892	715	708	653	448	243
OSHIP mean for procedures without baseline OSHIP	-	94.8	96.2	94.8	94.1	92.9
N, without baseline OSHIP	-	120	134	165	159	117
Improved ≥ 10 (%)	-	703 (84.2)	697 (82.8)	645 (78.9)	445 (73.3)	239 (66.4)
Maintained (%)	-	130 (15.6)	142 (16.9)	173 (21.1)	161 (26.5)	121 (33.6)
Deteriorated ≥ 10 (%)	-	2 (0.2)	3 (0.4)	0	1 (0.2)	0
OSHIP Excel ≥ 90 (%)	2 (0.2)	757 (90.7)	775 (92.0)	722 (88.3)	529 (87.1)	307 (85.3)
OSHIP Good 80-89 (%)	23 (2.6)	56 (6.7)	41 (4.9)	61 (7.5)	49 (8.1)	27 (7.5)
OSHIP Fair 70-79 (%)	175 (19.6)	12 (1.4)	14 (1.7)	20 (2.4)	16 (2.6)	12 (3.3)
OSHIP Poor 60-69 (%)	349 (39.1)	3 (0.4)	5 (0.6)	9 (1.1)	8 (1.3)	8 (2.2)
OSHIP V Poor < 60 (%)	343 (38.5)	7 (0.8)	7 (0.8)	6 (0.7)	5 (0.8)	6 (1.7)

For the data in the table above regarding the number of procedures who improved ≥ 10 pts., maintained, or deteriorated ≥ 10 pts., the sponsor explained that those patients with no baseline scores were counted as “maintained.” The table below contains an analysis of the number of procedures who improved ≥ 10 pts., maintained, or deteriorated ≥ 10

pts., when the patients without baseline scores are removed from this analysis and just counted as missing.

OSHIP Improvement Oswestry and X-Ray Cohorts						
	Change	1 year	2 years	3 years	4 years	5+ years
Unilateral	Improve ≥ 10	703 (98.3)	697 (98.4)	645 (98.8)	445 (99.3)	239 (98.4)
	Same < 10	10 (1.4)	8 (1.1)	8 (1.2)	2 (0.4)	4 (1.6)
	Worse ≥ 10	2 (0.3)	3 (0.4)	0 (0.0)	1 (0.2)	(0.0)
	N	715	708	653	448	243
	Missing	388	392	274	239	152

Secondary Effectiveness: Pain and Function (OSHIP) - Unilateral and Bilateral Assessments

FDA believes that it is impossible to assess the pain and function of each hip separately in patients with bilateral hip involvement using the Harris Hip Score or the Oswestry-modified Harris Hip Score (OSHIP), because it is impossible to distinguish the contributions of each hip on functional assessments such as walking or support, walking distance, stair-climbing, sitting, and transportation. Therefore, FDA believes only the unilateral patients can be used in the analysis of pain and function. However, FDA believes that because revisions can be adequately assessed in bilateral patients (revision assessments aren't based on a clinical assessment instrument), the survivorship estimates, as presented above, can include bilateral patients.

The following table illustrates how the status of the contralateral hip for patients with bilateral hip involvement affects the clinical assessment of pain and function.

Evaluation of Resurfacing Hip Arthroplasty Patients with Bilateral vs. Unilateral Involvement	
Hip Involvement	Hip Assessments
1. Unilateral hip involvement and the contralateral hip functions normally.	The well-functioning contralateral hip will not negatively affect the evaluation of the ipsilateral hip function.
2. Bilateral hip involvement and the hips are equally involved. No contralateral THA is anticipated.	The poorly functioning contralateral hip will negatively affect the ipsilateral function scores, but if stable will allow assessment of the ipsilateral hip in relative terms. That is, if the contralateral hip status does not change, the ipsilateral hip may be accurately assessed for improvement. However, if the contralateral hip is worsening or improving, the ipsilateral hip assessments are inaccurate.
3. Bilateral hip involvement and the contralateral hip is better than the ipsilateral hip.	The well-functioning contralateral hip will not negatively affect the evaluation of the ipsilateral hip function if the contralateral hip status does not change.
4. Bilateral hip involvement. The contralateral hip had a previous THA that is functioning well.	The well-functioning contralateral hip will not affect the evaluation of the ipsilateral hip function. ¹
5. Bilateral hip involvement. The contralateral hip had a previous THA that is functioning poorly.	The poorly functioning contralateral hip will negatively affect the ipsilateral function scores, but if stable will allow assessment of the ipsilateral hip in relative terms. That is, if the contralateral hip status does not change, the ipsilateral hip may be

	accurately assessed for improvement. However, if the contralateral hip is worsening or improving, the ipsilateral hip assessments are inaccurate.
6. Bilateral hip involvement. The contralateral hip had a previous THA recently.	The assessments will be inaccurate because the contralateral hip function will negatively affect the Harris Hip Scores for the ipsilateral hip, and the contralateral hip function is changing.
7. Bilateral hip involvement. The contralateral hip requires a THA. The contralateral THA will be done in the near future.	The ipsilateral hip assessments will be inaccurate because the contralateral hip function will affect the Harris Hip Scores.
8. Bilateral hip involvement. The contralateral hip requires a THA. The contralateral THA will be done simultaneously with the ipsilateral hip.	The ipsilateral hip assessments will be inaccurate because the contralateral hip function will affect the Harris Hip Scores.

Secondary Effectiveness: Pain and Function - Comparison to Literature Control

In the literature controls, the authors used Harris Hip Score, not OSHIP, to collect pain and function effectiveness data. D'Antonio *et al.* reported Harris Hip Scores at 2 - 4 year follow up (mean 3 year) for the ceramic-on-ceramic hip procedures as follows:

- ABC System 1 (porous): 95.4 mean score (n=166)
- ABC System 2 (HA): 96.6 mean score (n= 172)

Garino reported an average increase in Harris Hip Score from 44 pre-operatively to a mean of 97 at follow up.

Secondary Effectiveness: Patient Satisfaction

The patient satisfaction question is not a standard component of the OSHIP assessment but was an additional question asked for this study in the annual, patient-completed, mail-in questionnaire. Table 16.1 summarizes the results as follows. At 5 years, 99.5% of the procedures in the X-Ray/Oswestry combined cohort were pleased or very pleased with the operation. In A12, the sponsor revised Table 33.1 to include only unilateral procedures from the X-Ray/Oswestry combined cohort. At 5 years, 99.2% of these procedures were pleased or very pleased with the operation.

Patient Satisfaction X-Ray/Oswestry Combined Cohort (Table 16.1, 33.1)						
X-Ray/Oswestry Combined Cohort N=1626						
	Base	1 year	2 years	3 years	4 years	5+ years
N	1626	1616	1607	1349	1007	601
Pleased	-	75 (6.1%)	62 (5.0%)	80 (6.7%)	50 (5.6%)	31 (5.7%)
Very please	-	1109 (89.6%)	1177 (94.7%)	1100 (92.7%)	839 (94.1%)	512 (93.8%)
X-Ray/Oswestry Combined Cohort - Unilateral Procedures Only						
# All Unilateral	1111	1103	1100	927	687	395
Assessments	892	835	842	818	607	360
Please/Very Pleased (VP)	-	800 (95.8%)	839 (99.6%)	813 (99.4%)	604 (99.5%)	357 (99.2%)
N, AVN	43	35	38	32	23	14
AVN Please/VP	-	35 (100.0%)	38 (100.0%)	32 (100.0%)	23 (100.0%)	14 (100.0%)

N, Dysplasia	131	123	117	117	81	44
Dysplasia Please/VP	-	119 (96.8%)	117 (100.0%)	115 (98.3%)	80 (98.7%)	43 (97.7%)
N, OA	678	642	652	632	484	287
OA Please/VP	-	613 (95.5%)	649 (99.6%)	630 (99.7%)	482 (99.6%)	285 (99.3%)
N, IA	15	11	11	15	10	8
IA Please/VP	-	11 (100.0%)	11 (100.0%)	15 (100.0%)	10 (100.0%)	8 (100.0%)
N, Other	25	24	24	22	9	7
Other Please/VP	-	22 (91.7%)	24 (100.0%)	21 (95.5%)	9 (100.0%)	7 (100.0%)

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE EFFECTIVENESS DATA

Question #5:

Based on the:

- **5-year survivorship analysis of the 1,626 procedures in the X-ray/Oswestry combined cohort;**
- **5-year radiographic data of the 124 procedures in the X-Ray cohort;**
- **5-year pain and function (OSHIP) data of the 1,111 unilateral procedures in the X-Ray/ Oswestry combined cohort; and**
- **5-year patient satisfaction analysis of the 1,626 procedures in the X-Ray/Oswestry combined cohort;**

Please discuss whether or not you believe that the data contained in this PMA provide reasonable assurance of effectiveness?

APPLICABILITY OF THE FOREIGN DATA FROM A SINGLE INVESTIGATOR AND UNITED KINGDOM PRACTICE OF MEDICINE TO THE TARGET UNITED STATES POPULATION AND PRACTICE OF MEDICINE

Comparison of the United States and United Kingdom Patient Populations

The clinical data were derived from a foreign clinical study conducted by Dr. McMinn at the Birmingham Nuffield Hospital in the United Kingdom. There are no racial or ethnic origin data for the patients in the clinical study. However, the sponsor reasons that the racial and ethnic distributions in the U.S. and U.K. populations are similar and that although the percentage of the population of African-descent is higher in the U.S. than the U.K., the target U.S. population should have a significantly higher percentage of Caucasian patients. The sponsor stated that neither literature control group data demonstrated that their surgical patient populations reflected the ethnic distribution of the general U.S. population.

Comparison of the Ethnic / Racial Distributions		
	U.S.	U.K.
White	75.1%	92.1%
Black	12.3%	2.0%
Asian	3.6%	4.0%
Native American	0.9%	-
Pacific Islander	0.1%	-
Chinese	-	0.4%
Other race	5.5%	0.4%
Mixed race	2.4%	1.2%

The following table includes a description of the gender, age, and diagnostic indications for the Overall McMinn Cohort and two multi-center studies used to support recently-approved hip arthroplasty devices:

Patient Demographics and Diagnostic Indication Comparisons			
	Overall BHR Metal/Metal Resurfacing Hip System	Wright Medical Ceramic/Ceramic Transcend Total Hip Replacement*	Howmedica Osteonics Ceramic/Ceramic Total Hip Replacement**
Hips	2385		
Men	70.6% (1683)	62%	65%
Women	29.4% (702)	38%	35%
Age (range)	53.1 (13.4-86.5)	51.4	53
Age ≤65 years	91.9% (2191)	-	-
Dx: OA	75% (1789)	72.2%	78%
Dx: DDH	15.8% (377)	4.4%	-
Dx: AVN	4.1% (97)	19.7%	16%
Dx: Inflammatory	2.4% (57)	-	-
Dx. Other	2.7% (65)	-	2%
Dx: Post-Traumatic Arthritis	-	3.8%	4%

* Data presented by sponsor from Summary of Safety and Effectiveness for Wright Medical Technology's Transcend Hip: P010001, February 3, 2003.

** Data presented by sponsor taken from D'Antonio, J., Capello, W., Manley, et al., "New experience with alumina-on-alumina ceramic bearings for total hip arthroplasty," J. Arthroplasty 17(4): 390-97, 2002.

The sponsor's justification for the applicability of the foreign data to the US patient population is based on its large sample size, as well as the comparable demographics and diagnostic indications to the multi-center control group studies.

Description of Dr. McMinn's Practice of Medicine

The sponsor specifies that all of the surgeries on the 2,385 cases in this PMA were performed by Dr. McMinn (with assistance from other surgeons) at the Birmingham Nuffield Hospital (except for 6 cases that were performed by Dr. McMinn at the Little Aston Hospital, Birmingham, U.K.). The sponsor stated that the practice of medicine, specifically the orthopedic practice of medicine, utilized by Dr. McMinn is the same as the standard of orthopedic practice in the U.S. The sponsor described Dr. McMinn's standard peri-operative regimen, as follows:

- Laminar air flow operating rooms with body exhaust suits
- Posterior surgical approach
- Standard surgical technique (described in the Surgical Technique Manual)
- Antibiotic prophylaxis intraoperatively and for 24 hours postoperatively (1.5g Cefuroxime)
- DVT prophylaxis using a single-dose (800 IU) intravenous heparin intraoperatively and compression stockings and low-dose aspirin postoperatively for 6 weeks
- Intraoperative venting of the femoral shaft to prevent fat/marrow emboli
- Early ambulation: full weight-bearing with a walker on postoperative day #1, progressing to crutches and canes
- Hospital discharge at postoperative day #6
- After 6 weeks postoperatively, begin range of motion exercises
- Recommended activities include swimming, pool exercise, non-impact or low-impact exercise at a gym; and, avoidance of high impact exercises during the first postoperative year

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE APPLICABILITY OF THE FOREIGN DATA FROM A SINGLE INVESTIGATOR AND UNITED KINGDOM PRACTICE OF MEDICINE TO THE TARGET UNITED STATES POPULATION AND PRACTICE OF MEDICINE

Question #3:

Please discuss whether or not the foreign data from a single investigator and UK practice of medicine is applicable to the target US population and practice of medicine.

ADDITIONAL DATA SOURCES

The main data sources were presented above but the sponsor also included additional, less complete data on 3,374 BHR cases performed by 140 surgeons worldwide (other than Dr. McMinn). This is called the **Worldwide/Other Cohort**.

Demographic information for the Worldwide/Other Cohort was provided in Table 28, including gender, age, diagnosis, BMI, baseline OSHIP scores. The study cohort demography was similar in the Worldwide/Other Cohort and the X-Ray/Oswestry combined cohort, with the mean age of 53.0 years in the X-Ray/Oswestry combined cohort and 52.5 years in the Worldwide/Other Cohort. The diagnostic indications were somewhat different between cohorts: OA (78% X-Ray/Oswestry combined cohort vs. 90.8% Worldwide/Other Cohort).

The sponsor provided a comparison of the revisions and survivorship estimates for the X-ray/Oswestry combined cohort versus the Worldwide/Other Cohort in Table 30.1. The primary reason for revision in the Worldwide/Other Cohort was a fracture in 34 cases

(1.0%), loosening in 26 cases (0.8%), infection in 7 cases, AVN in 5 cases, dislocation in 5 cases, miscellaneous device failures in 5 cases, pain in 3 cases, and unknown in 3 cases.

Revisions						
Table 30.1						
X-Ray/Oswestry Combined Cohort						
N=1626						
	Postop	1 year	2 years	3 years	4 years	5+ years
Number of procedures	1626	1626	1553	1499	1238	916
Revisions	-	10	5	5	1	3
Survivorship estimates	-	99.4	99.0	98.7	98.6	98.4
Worldwide/Other Cohort						
N=3374						
Number of procedures	3374	3374	3051	2888	2493	1417
Revisions	-	35	15	14	7	5
Survivorship estimates	-	98.7	98.0	97.5	97.0	96.3

The Worldwide/Other Cohort patients had slightly lower OSHIP scores at all time points.

OSHIP						
Worldwide/Other Cohort						
Attachment 33						
	Baseline	1 years	2 years	3 years	4 years	5 years
Worldwide OSHIP assessments	395	2356	2492	2364	1379	505
Worldwide Mean OSHIP	56.95	91.67	92.47	92.45	91.86	89.77

POST-APPROVAL STUDY

The FDA advised the sponsor that the PMA may be subject to conditions of approval including a post-approval study to evaluate the long-term safety and effectiveness of the device. In response to FDA's advisory, the sponsor included a post-approval study protocol.

The proposed post-approval study is a prospective, non-randomized, longitudinal, unblinded, multicenter trial to evaluate the long-term safety and effectiveness of the device. The sponsor proposes to enroll 150 patients at up to 15 investigational sites who meet the inclusion and exclusion criteria and sign the informed consent. Patients will be clinically and radiographically evaluated preoperatively, intraoperatively, and postoperatively at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. Continued long-term follow-up assessments will be performed using a self-administered, mail-in patient questionnaire from 6 years to 10 years. Explanted device components will be analyzed according to an explant protocol. Clinical and radiographic success and failure criteria were defined.

PLEASE BE ADVISED THAT YOU WILL BE ASKED TO DISCUSS THE FOLLOWING PANEL QUESTION REGARDING THE POST-APPROVAL STUDY

Question #7

A reasonable assurance of safety and effectiveness as defined in questions #4 and #5 above must be demonstrated for device approval. If you believe the data in the PMA demonstrate a reasonable assurance of safety and effectiveness but think there are remaining specific questions regarding this device that should be addressed in a post-approval study, please identify those questions.

		Hip Assessment Instruments	
Measurement	Oswestry-Modified Harris Hip Score (OSHIP)	Harris Hip Score (HHS)	
Pain	Pain (left and right)	Pain	
	44 No pain	44 None	
	40 Mild pain but normal activity	40 Slight	
	30 Mild pain when walking but disappears on resting	30 Mild pain	
	29 Tolerable	20 Moderate pain	
20 Severe restricting all activity	10 Marked pain		
10 My pain is severe at night	0 Totally disabled		
0 My pain is intense and permanent			
Function: Limp	Limp	Limp	
11 No limp	11 None		
8 Slight limp	8 Slight		
5 Moderate limp	5 Moderate		
0 Severe limp or unable to walk	0 Severe limp or unable to walk		
Function: Support	Walking	Support	
11 My walking is unrestricted	11 None		
8 No stick, slight limp	7 Cane, long walks		
7 Stick for long walks, slight limp	5 Cane, full-time		
5 One stick full time	3 Crutch		
2 Two sticks used full-time	2 Two canes		
1 Two crutches / frame full-time	0 Two crutches/walker		
0 Unable to walk	0 Unable to walk		
Function: Walking distance	Distance	Distance Walked	
11 I am able to walk unlimited distance	11 Unlimited		
8 I am able to walk more than a mile	8 6 blocks		
5 I am able to walk up to ½ mile	5 2-3 blocks		
2 I am able to walk indoors only	2 Indoors only		
0 Bed to chair	0 Bed to chair		
Function: Stairs	Stairs/Steps	Stairs	
4 I can climb stairs/steps normally	4 Normally		
2 I can climb stairs/steps using the banister	2 Normally with banister		
1 I can climb stairs/steps one foot at a time / any method	1 Any method		
0 I cannot climb stairs/steps	0 Not able		

Function: Shoes/Socks	NONE	Socks/Tie Shoes 4 With ease 2 With difficulty 0 Unable
Function: Sitting	Sitting 5 I can sit in any chair for about an hour 3 I can sit in a high chair for about ½ hour 0 I am unable to sit for 15 minutes	Sitting 5 Any chair, 1 hour 3 High chair for about ½ hour 0 Unable to sit for 15 minutes
Function: Transportation	Transport 1 I am able to get in and out of a car without pain 0 I am able to get in and out of a car with pain 0 I cannot get into a car	Public Transportation 1 Able to enter a car 0 Not able
Deformity	NONE	Deformity <30° flexion <10° adduction <10° IR Absence 4 points Presence 0
Range of Motion	NONE	ROM Flexion Abduction ER IR Adduction 5 points NONE
Movement	Movement (left and right) 13 I can bend to touch my toes/cut toenails with ease 12 I can bend to touch my toes/cut toenails with difficulty 8 I am able to touch the top of my ankle 7 I can put my shoes and socks on with ease 6 I can put my shoes and socks on with difficulty 4 I have trouble reaching down my shin 0 I am unable to bend my hip at all	

Reference: _____
 Name: _____
 Operation: _____
 Side: _____
 Score Type: _____

OSWESTRY HIPSCOREFORM
Post-operative Questionnaire



This questionnaire is designed to assess how your hip is functioning at present and also how it affects your ability to manage in everyday life. This allows us to monitor the health of your hip(s) and the success of the operation. The information you give will be stored on a database and may be used for research and presented in future reports/published articles from which you will not be personally identifiable.

Please tick the **ONE** statement per category that describes your situation today most accurately.

PAIN (Please complete the score for **both** hips)

	RIGHT	LEFT	
44	↑	↑	I have no pain.
40	↑	↑	I have mild pain but normal activity.
30	↑	↑	I have mild pain when walking but disappears on resting.
29	↑	↑	My pain is tolerable
20	↑	↑	My pain is severe restricting all activity.
10	↑	↑	My pain is severe at night.
0	↑	↑	My pain is intense and permanent.

WALKING (Here the score applies to both hips)

11	↑	My walking is unrestricted.
8	↑	No stick, slight limp.
7	↑	Stick for long walks, slight limp.
5	↑	One stick full time.
2	↑	Two sticks used full-time.
1	↑	Two crutches / frame full-time.
0	↑	Unable to walk.

LIMP (Here the score applies to both hips)

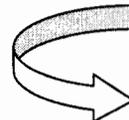
11	↑	No limp.
8	↑	Slight limp.
5	↑	Moderate limp.
0	↑	Severe limp or unable to walk.

DISTANCE (Here the score applies to both hips)

11	↑	I am able to walk unlimited distance.
8	↑	I am able to walk more than a mile.
5	↑	I am able to walk up to ½ a mile.
2	↑	I am able to walk indoors only.
0	↑	Bed to chair.

STAIRS/STEPS (Here the score applies to both hips)

4	↑	I can climb stairs/steps normally.
2	↑	I can climb stairs/steps using the banister.
1	↑	I climb stairs/steps one foot at a time / any method.
0	↑	I cannot climb stairs/steps.



Please turn over
and complete page 2



SITTING (Here the score applies to both hips)

- 5 | | I can sit in any chair for about an hour.
- 3 | | I can sit in a high chair for about ½ an hour.
- 0 | | I am unable to sit for 15 minutes.

TRANSPORT (Here the score applies to both hips)

- 1 | | I am able to get in and out of a car without pain.
- 0 | | I am able to get in and out of a car with pain.
- 0 | | I cannot get in to a car.

MOVEMENT (Please complete both the right and left side)

- | | RIGHT | LEFT | |
|----|-------|------|--|
| 13 | | | I can bend to touch my toes/cut toenails with ease. |
| 12 | | | I can bend to touch my toes /cut toenails with difficulty. |
| 8 | | | I am able to touch the top of my foot/ankle. |
| 7 | | | I can put my shoes and socks on with ease. |
| 6 | | | I can put my shoes and socks on with difficulty. |
| 4 | | | I have trouble reaching down my shin. |
| 0 | | | I am unable to bend my hip at all. |

Have you had any problems since your hip was replaced such as:-

- Blood clots, infection, etc? Yes No
- A dislocation or revision operation? Yes No } If yes, please describe these below:

SATISFACTION

- 4 | | I am extremely pleased with the operation.
- 3 | | I am pleased with the operation.
- 2 | | I am no different than before the operation.
- 1 | | I am worse than before the operation.
- 0 | | I am much worse and would not recommend the operation.

Would like to be kept informed about fundraising projects: Yes No

Occupation and/or daily activity:

Telephone: Email address:

If you do not wish us to contact you by email or telephone then please tick here

Information collected by the Outcome Centre is registered under the Data Protection Act 1998. By completing and signing this questionnaire the information you have given us will be stored and used for Orthopaedic Research.

DATE FORM COMPLETED:

SIGNATURE:

Reference: _____ Name _____
Score Form V2

Executive Summary: Statistical Information

Revision

There were a total of 27 revisions (2 beyond 5-year follow-up for X-Ray cohort due to infections), as follows:

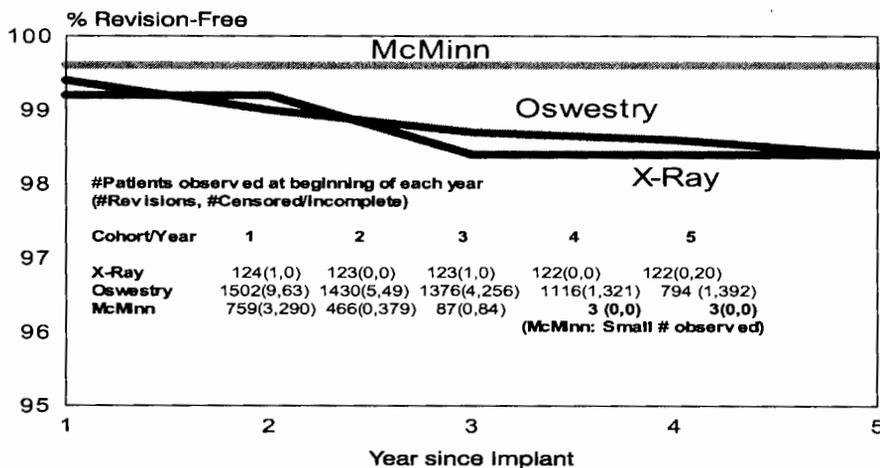
Table 1 Number and reason of revisions by study cohort (All hips)

Cohort	Infection	Femoral neck fracture	Collapse femoral head	Avascular Necrosis (AVN)	Dislocation	Mean in days (SD)
X-Ray	3/124 * (2.4%)	1/124 (0.8%)	0/124	0/124	0/124	1252 (848)
Oswestry	5/1502 (0.3%)	7/1502 (0.47%)	6/1502 (0.4%)	2/1502 (0.13%)	0/1502	495 (466)
McMinn	0/759	2/759 (0.26%)	0/759	0/759	1/759 (0.13%)	58.3 (72.6)
Total	8/2385 (0.3%)	10/2385 (0.4%)	6/2385 (0.25%)	2/2385 (0.08%)	1/2385 (0.04%)	
Mean (in years)	3.12	0.2	2.2	0.67	(1 day)	

(* Two revisions due to infections beyond 5-year follow-up)

There were no statistically significant differences in cumulative 5-year survival (revision-free) probabilities among three study cohorts. The following Figure 1 summarizes these cumulative survival probabilities (All hips):

Figure 1. Cumulative % Revision-Free, BHR



Due to small number of revisions (total 25, \leq 5-year follow-up) from large numbers in three study cohorts (total of 2385 hips), there were no statistically significant differences for all pairwise comparisons in 5-year survival (revision-free) probabilities among three cohorts, either by log-rank test, Wilcoxon test, or Cox proportional hazard (PH) regression analysis. Both the Cox PH regression model and the log-rank test require that the two survival probability curves be parallel or nearly parallel (no significant cohort by time crossover).

The above three statistical significance tests were also applied to several clinically important patient covariates, which include age (≤ 65 , >65), gender (M, F), reason for resurfacing (AVN, OA, IA, dysplasia, and others; reference group = OA), baseline OSHIP score (yes, no), hips (unilateral, bilateral). The only marginally statistically significant difference in 5-year survival probability is for AVN versus OA comparison (Table 2):

Table 2 % Revision-free, AVN versus OA, All hips and all cohorts

Group	<u>Follow-Up Year</u>				
	1	2	3	4	5 (95% CI)
OA	99.5	99.1	98.8	98.8	98.8 (98.3,99.4)
AVN	98.9	98.9	96.7	96.7	92.1 (82.2,100)

The p-values to compare these two % revision-free curves for OA versus AVN comparison are 0.0415 (Log-rank) and 0.2282 (Wilcoxon). Due to non-parallelism of these two survival curves, careful clinical interpretation is needed. Both log-rank and Wilcoxon test that the two revision-free curves are equal, and the Cox PH model tests that the ratio of the two hazards (probability of revision) is unity. The log-rank test assigns *equal weight* to *all* follow-up times and the Wilcoxon test assigns *more weight* to the *earlier* follow-up times where more patients are at risk of revision. The log-rank test has optimum statistical power if the parallelism assumption for the two revision-free curves is valid. The Cox PH model is not appropriate here due to obvious non-parallelism of the two curves in Table 2. The percentages of revisions (Table 11.1, 4/29/2005 submission) are 3.1% (3/97) for AVN (note: 2 revisions from individual patient revision listing, see blue tag after Attachment 5, 7/8/05, Part 1), 1.1% for dysplasia (4/377), 0.95% (17/1789) for OA, 1.7% (1/57) for Inflammatory arthritis (IA), and 0% for others (0/65), with a combined 1% (25/2385) revisions over all diagnostic groups, during 5-year follow-up.

Oswestry-Modified Harris Hip Score (OSHIP)

As agreed by FDA and the sponsor, only unilateral hips OSHIP data should be analyzed clinically/statistically. The following Table 3 summarizes the OSHIP outcome by follow-up year:

Table 3. Mean OSHIP scores by follow-up year, all *available* data, *X-Ray and Oswestry* cohorts combined, *Unilateral* hips only (from Table 16.1, 7/19/2005 submission)

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
# Hips (N)	1111	1103	1100	927	687	395
# Hips observed (n)	892	835	842	818	607	360
n/N (%)	80.3	75.7	76.5	88.2	88.3	91.1
Mean	60.1	96.6	96.8	96.2	95.9	94.8
SD*	13.1	6.75	7.3	7.4	8.0	9.7
SE**	0.44	0.23	0.25	0.26	0.32	0.51
95% CI	(59, 61)	(96, 97)	(96.3, 97.3)	(95.7, 96.9)	(95.2, 96.6)	(93.8, 95.8)

*SD = Standard deviation; **SE = Standard error of sample mean = SD/\sqrt{n} ; CI = confidence interval of true OSHIP mean

Clinical decision is needed to evaluate the adequacy of observed proportions of OSHIP scores (range: 75.7% in Year 1 to 91.1 % in Year 5). Due to non-randomization, one-group (BHR only) registry data, if we assume that missing OSHIP data behave similarly to the observed OSHIP data, then, no missing data imputation would be required. The 95% confidence intervals for true mean OSHIP scores are tight primarily due to large observed sample sizes.

The percentages of *combined* categorized outcomes [excellent (90-100) and good (80-89)] OSHIP scores are summarized in the following Table 4:

Table 4. Percentages (%) of combined (Excellent + Good) OSHIP scores, by follow-up year, *Unilateral* hips only, X-Ray and Oswestry cohorts combined, *All available* data (from Table 16.1, 7/19/2005 submission)

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Percentage (%)	2.8 % (25/892)	97.4% (813/835)	96.9% (816/842)	95.7% (783/818)	95.2% (578/607)	92.8% (334/360)

Likewise, as we did for the mean OSHIP scores in Table 3, we assume that the missing OSHIP data behave similarly to the observed data in Table 4.

The percentages of combined general pain (Intense + Very Severe + Severe) OSHIP scores are summarized in the following Table 5:

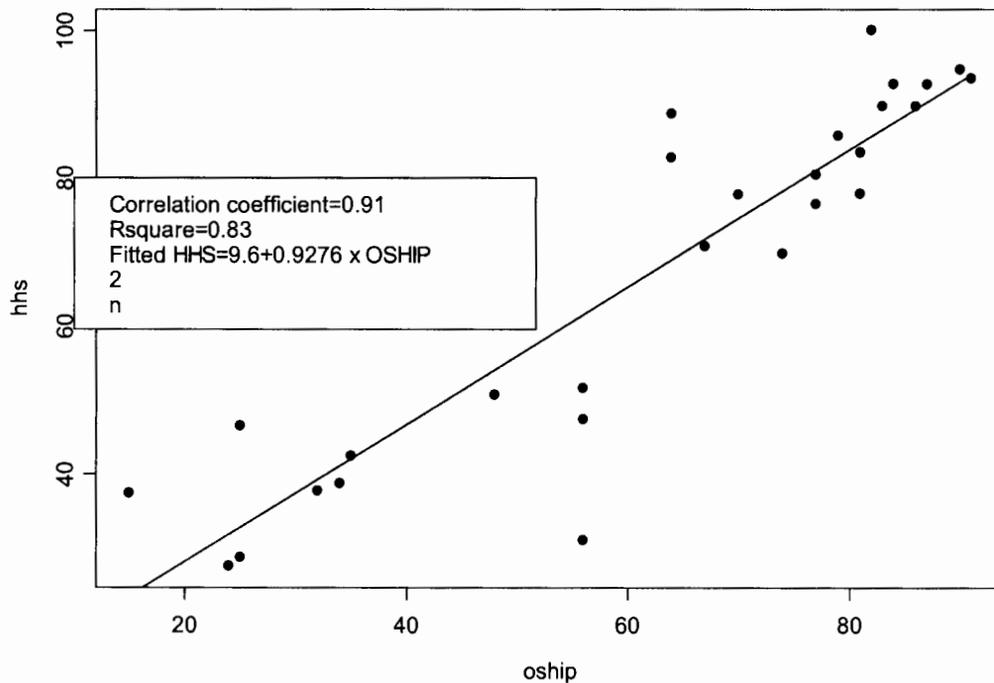
Table 5. Percentages (%) of combined pain (Intense + Very Severe + Severe) OSHIP scores, by follow-up year, *Unilateral* hips only, X-Ray and Oswestry cohorts combined, *All available* data (from Table 16.1, 7/19/2005 submission)

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Percentage (%)	26.3% (235/892)	0.2% (2/835)	0.6% (5/842)	0.5% (4/818)	0.3% (2/607)	0.55% (2/360)

Correlation between OSHIP and Harris Hip Scoring System (HHS)

Sponsor's correlation results were based on 28 consecutive patients (not randomly selected) who had both the self-administered OSHIP assessment and the physiotherapist-administered HHS, for various study parameters (pain, walking, distance, stairs, and others). Both Pearson and Spearman's rank correlations were calculated between these 28 pairs of OSHIP/HHS data. The ranges of calculated correlation coefficients were wide (e.g., 0.21 between HHS ROM and the OSHIP movement, possibly due to transforming the scales to 0.90 for OSHIP walking and HSS support). Due to different measurement scales of OSHIP and HHS systems, it is not easy to determine statistically how to predict HSS from OSHIP scores or vice versa. Clinical/scientific judgment is needed. Correlation alone is a necessary, but not a sufficient, condition to predict HHS from OSHIP or vice versa. FDA also prepared the linear regression analysis to predict HHS total score from OSHIP total score as shown in Figure 2. In Figure 2, the calculated R-square is approximately 0.83, which measures the proportion of total variation about the mean explained by the linear regression model. The Pearson correlation coefficient is 0.91 (square root of R-square 0.83) between total OSHIP score and total HHS score.

Figure 2: linear regression



The following Table 6 summarizes several estimated correlations and 95% confidence intervals (CI) between OSHIP and HHS (see Table IV. FDA’s Question number 22, 4/29/2005 submission)

Table 6 Estimated correlations between HHS and OSHIP scores, by selected study parameters, from 28 patients (see Barnes et. al. paper, 4/29/2005 submission)

HHS	OSHIP	Correlation (95% CI)
Pain	Pain	0.83 (0.66, 0.92)
Limp	Limp	0.60 (0.29, 0.80)
Support	Walk	0.89 (0.77, 0.95)
Distance	Distance	0.76 (0.54, 0.88)
Stairs	Stairs	0.89 (0.77, 0.95)
Sitting	Sitting	0.71 (0.45, 0.85)
Public Transport	Transport	0.68 (0.41, 0.84)
Function	Function	0.88 (0.75, 0.94)
Shoes and Socks	Movement	0.40 (0.03, 0.67)
Range of Motion	Movement	0.21 (-0.18, 0.54)
Range of motion + Socks +Deformity	Movement	0.40 (0.03, 0.67)
Total	Total	0.91 (0.81, 0.96)

Due to unclear randomization scheme and questionable masking procedure used to select these 28 sample patients, it is not easy to generalize the above correlations to the general target patient population. Clinical judgment is needed. The correlation results are quite comparable between Pearson correlation (bivariate normal) and Spearman non-parametric correlation.

Complications:

The following Table 7 summarizes various complications by study cohorts:

Table 7 Specific types of complications by combined cohort (X-Ray, Oswestry, and McMinn) and follow-up year (from Table 21.1, Volume III, 4/29/2005 submission), All hips

Type	Post-operative	Year					Total (X-Ray + Oswestry + McMinn)
		1	2	3	4	5	
N (# Hips)	2385	2157	1667	1378	1018	620	
AVN femoral head	31	2	1	0	0	1	35 (2 + 24 +9)
Collapse femoral head	7	3	3	1	0	1	15 (2 + 13 + 0)
Migration/Loosening	1	7	8	2	0	1	19 *
Fracture femur neck	0	10	0	2	0	1	13 (1+ 10 + 2)
Late infections	0	7	3	1	1	2	14**

* 21 (2 + 18 +1) in Table 20.1; ** 15 (4+11+0) in Table 20.1, 4/29/2005 submission