SUMMARY OF SAFETY AND EFFECTIVENESS DATA

PREMARKET APPROVAL APPLICATION P040033
SMITH & NEPHEW BHR
BIRMINGHAM HIP RESURFACING SYSTEM

Sponsor: **Smith & Nephew Orthopaedics**
1450 Brooks Road
Memphis, Tennessee 38116
Telephone 800-821-5700

Contact: **Marcos Velez-Duran,**
V.P ., Regulatory, Clinical, Quality - Trauma

Alternate Contact: **M Squared Associates, Inc.**
719 A Street NE
Washington, DC 20002
Telephone: 202-546-1262
Marie Marlow or Russ Pagano, Ph.D.

Last Updated: **August 5, 2005.**

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1.0 GENERAL INFORMATION

Device Generic Name:	Total hip resurfacing prosthesis, metal-on-metal
Device Trade Name:	Birmingham Hip Resurfacing (BHR) System
Applicant Name:	Smith & Nephew Orthopaedics
Applicant Address:	1450 Brooks Road
	Memphis, Tennessee 38116
Applicant Telephone:	1-800-821-5700
Applicant Fax:	1-901-398-5146
Contact:	Marcos Velez-Duran
	V.P ., Regulatory, Clinical, Quality - Trauma
Manufacturing Facility:	Smith & Nephew Orthopaedics Ltd.
	Saxon Business Park
	Hanbury Road
	Stoke Prior
	Bromsgrove, Worcestershire
	B60 4AD United Kingdom
Telephone:	+44 1527 573 100
Contact:	Tim Band, Technical Director
Alternate Contact:	M Squared Associates, Inc.
	719 A Street, NE
	Washington, DC 20002
Telephone:	202-546-1262
Contact Name:	Marie Marlow or Russ Pagano, PhD
PMA Number:	P040033
Date of Notice of Approval to Applicant:	To be determined by FDA

2.0 INDICATION 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.

3.0 DEVICE DESCRIPTION

The Birmingham Hip Resurfacing (BHR) prosthesis is a metal-on-metal bearing produced from high carbon cobalt chrome material, conforming to the specifications described in ASTM F75-01 and ISO 5832 Part 4. The components are produced from as-cast cobalt chrome molybdenum (CoCrMo) alloy.

3.1. 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 central stem is parametric and 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 antirotational locking for the cement mantle.

3.2. Acetabular Cups

The hemispherical Acetabular Cups are designed for cementless interference fit into the acetabulum. The Acetabular Cups are configured in standard, dysplasia, and bridging designs. Each acetabular component is characterized by a cast-in porous surface such that the beads are integral with the substrate metal. The beaded surface is coated with HA to enhance implant fixation

Standard Acetabular Cup HAP: There is a range of twelve 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 66 mm. Thus a 38mm head can be used with a 44mm or 46mm cup, a 42mm head with a 48mm or 50mm cup etc.

Dysplasia Cup HAP: 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.

Bridging Cup HAP: 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 five sizes as identified by external diameter: 50mm, 54mm, 58mm, 62 mm and 66mm.

Dysplasia Cup Screws: The Dysplasia 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 available in sizes ranging from 24mm to 88mm, in 2mm increments.

4.0 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

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.

Warnings in the use of the BHR System include:

- Do NOT use any component of the BHR system with another manufacturer's implant components, because designs and tolerances may be incompatible. Smith & Nephew accepts no responsibility for BHR system components that have been used with another manufacturer's system components.
- Do NOT use BHR system components (which are cobalt chrome) with any stainless steel components, since corrosion can occur between two dissimilar metals.
- Do NOT allow hydroxyapatite-coated surfaces to contact any substance other than the device packaging, clean gloves, or the patient's tissue.
- Previous hip surgery such as osteotomy, core decompression, hemiresurfacing, or internal fixation may increase the risk of early failure.
- 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.
- Do NOT re-use an implant. All implants are intended for single-use only.

Precautions in the use of the BHR System include:

- Use the recommended instruments and the recommended surgical technique.
- Excessive physical activity levels, excessive patient weight, and trauma to the joint replacement may cause early failure of the implant.
- Loosening of components may increase production of wear particles and accelerate damage to the bone, making successful revision surgery more difficult.
- Improper selection, placement, positioning, and fixation of the implant components may result in early implant failure.
- Malalignment of the components and/or soft tissue imbalance may cause excessive wear and early implant failure.

Precautions related to operating information in the package insert (professional labeling) for the BHR include:

- The surgeon should be thoroughly familiar with the implants, instruments, and procedure before performing surgery. Contact Smith & Nephew for the surgical technique manual or procedural training.
- Associated trials and templates should be used for verification of component size. If an appropriate component size cannot be found during pre-operative planning, do not use this type of implant.
- Complete pre-closure cleaning of the implant site (complete removal of bone chips, bone fragments, metallic debris, etc.) is critical to prevent wear of the articular surfaces.
- Using instruments other than the associated BHR instruments may result in inaccurate placement.
- Examine instruments for wear or damage before use. While rare, intra-operative instrument breakage can occur. Instruments that have experienced excessive use or force may be susceptible to breakage.

Precautions related to the hydroxyapatite-coated acetabular implants in the package insert (professional labeling) for the BHR include:

- Do NOT allow the HA-coated, porous-surfaced acetabular component to contact any substance other than the device packaging, clean gloves, or the patient's tissue.
- Do NOT use cement with these HA-coated, porous-surfaced implants.
- Take care to achieve a stable press fit. The HA-coated, porous surface is not a substitute for cement and is not intended to compensate for inadequate implant fixation.

Precautions related to patient education in the package insert (professional labeling) for the BHR includes:

- Warn the patient of the surgical risks, possible adverse effects, and possible operative complications that can occur with joint arthroplasty.
- Warn the patient of the limitations of artificial joint replacement devices.
- Caution the patient to protect the joint replacement from unreasonable stresses and to follow the treating physician's instructions. In particular, warn the patient to strictly avoid high impact activities such as running and jumping during the first pre-operative year while the bone is healing.
- Warn the patient that artificial joint replacement devices can wear out over time, and may require replacement.

Precautions related to packaging in the package insert (professional labeling) for the BHR include:

- Implants should be accepted only if received by the hospital or surgeon with the factory packaging and labeling intact. If the sterile barrier has been broken, return the component to Smith & Nephew, Inc.

Precautions related to sterilization in the package insert (professional labeling) for the BHR include:

- Implant components are supplied sterile to a Sterility Assurance Level (SAL) of 10-6. Metal components are sterilized to a minimum of 25 kiloGrays of gamma irradiation. All components are supplied in protective packaging. Inspect packages for punctures or other damage prior to surgery.
- Instruments used to implant the device system are supplied non-sterile and must be sterilized prior to use using one of the following validated, recommended methods:
    - Prevacuum Flash Cycle: 4 pulses (Maximum = 26.0 psig (2.8 bars) & Minimum = 10.0 inHg (339 millibars)) with a minimum exposure time of 4 minutes at 270°F to 275°F (132°C to 135°C), followed by a 1 minute purge
    - High Temperature Gravity Cycle: 270°F to 275°F (132°C to 135°C) with a minimum exposure time of 10 minutes, followed by a 1 minute purge and at least 15 minutes of vacuum drying.
    - Prevacuum Cycle: 4 pulses (Maximum = 26.0 psig (2.8 bars) & Minimum = 10.0 inHg (339 millibars)) with a minimum exposure time of 4 minutes at 270°F to 275°F (132°C to 135°C), followed by a 1 minute purge and at least 15 minutes of vacuum drying.

Precautions related to resterilization in the package insert (professional labeling) for the BHR include:

- DO NOT RESTERILIZE implant components. Contact your local Smith & Nephew, Inc. Sales Representative regarding procedures to return components.

5.0 POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse effects may occur in association with most any artificial hip replacement surgery including the BHR System:

- Cardiovascular complications including venous thrombosis, pulmonary embolism, or myocardial infarction,
- Sudden, pronounced, intraoperative blood pressure decrease due to the use of bone cement,
- Hematoma or damage to blood vessels resulting in large blood loss.
- Delayed wound healing,
- Infection,
- Temporary or permanent nerve damage resulting functional and/or sensory deficits in the affected limb,
- Metal sensitivity reactions or allergic reactions or metallosis,
- Dislocation or subluxation leading to post-operative joint instability (which may be caused by malpositioning of the implants, or muscle or fibrous tissue laxity),
- Component loosening or migration due to trauma, loss of fixation, malalignment, or bone resorption,
- Limb length discrepancy,
- Increased hip pain and/or reduced hip function.
- Fatigue fracture of the implants as a result of excessive loading, malalignment, or trauma,
- Osteolysis and/or other peri-prosthetic bone loss,
- Unintended bone perforation or fracture occurring either intra-operatively or post-operatively as a result of trauma, excessive loading, osteolysis, or osteoporosis,
- Periarticular calcification or ossification,
- Wear or deformation of the articular surface as a result of excessive loading or implant malalignment.

Any of these adverse effects may require medical or surgical intervention. Rarely, complications may lead to death.

6.0 ALTERNATIVE PRACTICES OR PROCEDURES

Depending on individual circumstances, alternative procedures may include non-surgical treatment such as reduced activity and/or pain management; other surgical treatments that do not involve use of an implant such as a Girdlestone procedure; or use of other commercially available resurfacing systems or total hip replacement systems.

7.0 MARKETING HISTORY

The first BHR hip resurfacing procedure was performed on July 30, 1997. Since its European market introduction in 1997 through its current worldwide distribution, the BHR has been implanted in over 33,358 hip resurfacing procedures in the following countries as of May 2004.

Australia	Hong Kong	Norway
Austria	India	Portugal
Belgium	Ireland	Romania
Bermuda	Israel	South Africa
Canada	Italy	Spain
Denmark	Japan	Sweden
Egypt	Korea	Switzerland
Germany	Netherlands	

In addition to several BHR reports by McMinn *et. al.*[67, 24] and Richardson JB *et al.* [76], findings from several other clinical studies have been published in peer-reviewed journals or have been presented at scientific and professional symposia.

Back *et al*[15]. reported findings from a prospective study of the first consecutive 231 primary BHR procedures performed at the Melbourne (Australia) Orthopaedic Group, and followed to a mean of 33 months. At a mean follow up of 33 months, survivorship was 99.14 %. Ebied, Journeaux, and Pope[32], of the Royal Liverpool University Hospital, UK, reported a prospective study of 100 BHR resurfacing procedures. Mean follow-up period was 17 months, with 73 hips followed to 12 months and 22 hips followed to 2 years. One revision was reported in a patient with difficult dysplasia. DeSmet[26] and colleagues at the Ghent University Hospital, Belgium, reported their study of 200 primary Birmingham hip resurfacing procedures performed from 1998 to 2000. The length of follow up ranged from 6 months to 3.5 years. One BHR procedure resulted in femoral neck fracture at 3 weeks postoperatively, requiring revision. Early results are available from a

series of 41 BHR procedures performed by Tessari and colleagues[88] of the Universita di Milano and the Hospital S. Raffaele. Glyn-Jones *et al*[40]. conducted a study to predict the long-term failure of the BHR using roentgen sterophotogrammetric analysis (RSA). Migration of the femoral head was analyzed for 22 patients with a standard BHR. Kishida *et al*[57]. conducted a clinical study comparing the effects of BHR resurfacing arthroplasty to total hip arthroplasty on the bone mineral density of the femur in 26 procedures in 25 patients with either osteoarthritis or osteonecrosis.

8.0 SUMMARY OF PRECLINICAL STUDIES

8.1. Performance Standards

There are no mandatory performance standards for metal-on-metal resurfacing hips. However, Smith and Nephew conforms to the following voluntary performance standards in the manufacture of the BHR System:

ISO 5832 Part 4: Specification for Cobalt Chromium Molybdenum casting alloys

British Standard 7254 Part 5: Orthopedic implants - production of castings made of Cobalt Chromium Molybdenum Alloy

British Standard EN10 002/1: Tensile testing of metallic materials -- method of test at ambient temperature

BS HC100: Inspection and Testing Procedure for Iron, Nickel, Copper, Cobalt and Refractory Metal based alloy castings

ASTM E 8: Standard test methods for tension testing of metallic materials

ASTM F75-01: Specification for cast Cobalt Chromium Molybdenum Alloy for surgical implant applications

8.2. Biocompatibility Studies

The chemistry of the BHR device is defined in ISO 5832 Implants for Surgery – Metallic Materials – Part 4, and ASTM F75 Specification for Cobalt-Chromium-Molybdenum Alloy for Surgical Implant Applications. The chemical composition is as follows:

Chromium 26.5-30%	Molybdenum 4.5-7%	Nickel 1% max.	Iron 1% max.
Carbon 0.35% max.	Manganese 1% max.	Silicon 1% max.	Cobalt balance

Technical specifications for hydroxyapatite coating of the BHR acetabular cup meet the requirements for ISO 13779-1, ISO 13779-2, and ISO 13779-4 (draft). Since the device is comprised of well-accepted materials for a permanent implant, and meets the ISO standard, additional biocompatibility testing is not required.

8.3. Articulating Wear

A tribiological study of the BHR was conducted to analyze volumetric wear rates for 5 million cycles. The study used a hip joint simulator to compare the volumetric wear rates of five active and one dynamically loaded control specimens, together with a hip friction simulator to study how the friction varied before, during and after the wear test. In addition, surface topography of the bearing surfaces before and throughout the wear simulator study were evaluated.

All femoral head prostheses were 50mm outer diameter size components. The joints were tested in the anatomical position (the femoral component being below the acetabular component) with the acetabular component oriented at 33^0 to the horizontal. The force vector applied provided a minimum load of 100 N and the maximum load was 2975 N. Five stations were subjected to dynamic loads and motions while the control station experienced dynamic loads, but no tangential motions.

Over the 5 million cycles, the average wear rate was 1.33 mm^3/million cycles. Initially the wear rate was high compared with later cycles (0.5 to 1 million cycles, 3.00 mm^3 /million cycles), but by 3-5 million cycles the wear rate had reduced to 0.4mm^3/million cycles. This was associated with the development of fluid film lubrication and consequent lowering of the friction levels.

At the start of the testing, the sample joint had a friction factor that was 0.081 ± 0.006. After 1 million cycles, the familiar mixed lubrication Stribeck curve began to form with the friction factor falling to 0.03 at the highest viscosity. At 2 million cycles this had fallen to 0.015 and a substantial fluid-film seemed to have formed though not a complete one. This became stable by the 3 million cycles mark. Friction measurements taken again at 5 million cycles were similar to those at 3 million cycles, with fluid film lubrication being maintained.

As supplied, the heads exhibited surface topography with irregular shaped peaks often seen as rectilinear arrays that looked like carbides within the CoCrMo. The peak-to-valley heights (PV) averaged 0.320 (SD 0.081) μm. These surfaces are typical for this alloy system where the surface has “relief polishing” due to the differences in hardness between the carbide and matrix phases. At the end of the test the PV values had generally increased for the heads. In the case of the cups, some increased and some decreased. However, the positively skewed distribution had generally worn to a negative one by the end of the test, indicating that most variations from the mean plane

were in the form of scratches whilst the peaks had been smoothed. The skew had decreased for all the cups also but still remained slightly positive.

In summary, the wear rates of the BHR hip resurfacing device are within the range and, in fact, at the low end of the range of rates found for other metal-on-metal bearings. There is strong evidence that the tribiological aspects of the joint improve with "running-in" and that this has a marked effect on the lubrication mechanisms where a considerable amount of the joint will be separated by a pressurized film of synovial fluid, and only a small number of asperites penetrating the film of fluid. Thus wear rates will be expected to reduce as the wear process proceeds.

8.4. Kinematics

The ROM test procedure was performed according to that described in Annex A of ISO 21535: 2002 (EN 12563: 1998). A rationale for components and methods as representative of "worst case" scenario determined the 58mm femoral head size paired with the 64 or 66mm acetabular cup to have the smallest angular displacement. For the purpose of this test the 66mm cup was utilized.

Flexion-Extension	Abduction-Adduction	Rotation
106.50	73.75	106.50
106.42	73.42	106.42
105.42	73.50	106.17
107.00	73.58	106.67
106.50	73.75	107.00
MEAN 106.37	MEAN 73.60	MEAN 106.55
StdDev 0.58	StdDev 0.15	StdDev 0.31
ISO Min 80.00	ISO Min 60.00	ISO Min 90.00

Under conditions of the test, the design of the 58mm BHR femoral head and 66mm acetabular cup has been demonstrated to comply with the ROM performance requirements specified in the international standard ISO 21535: 2002.

8.5. Stress Analysis

While the BHR has been designed to minimize necessary bone resection of both the acetabulum and femoral head, the component design and materials utilized maintain sufficient material volume to withstand potential forces. The design minimizes the potential for local stress risers

due to the absence of a long stressed, intramedullary stem. Both instrumentation and surgical techniques are developed to allow checking of all cuts, etc., and to make appropriate corrections as necessary. The manufacturer believes that the potential for surgical error, resulting in increase implant stress, is minimized by the policies on product labeling, operative technique and training of user surgeons on use of the device.

Static strength testing found the average maximum load for dysplasia fixation screws was 88.4lbf (393 N) and 1099.6 lbf (4890 N) for the bridging cup flange; concluding the loads measured during testing under worst-case conditions indicate both components should be able to withstand predicted in vivo loads. The femoral head demonstrated an average yield point of 5620 N (1263 lbf) and was also judged to withstand predicted in vivo loads. Fatigue testing of five femoral stems at 75 ksi (517 MPa) for 5 million cycles showed no deformation or cracking.

8.6. Sterilization

Sterilization of the BHR components is performed in accordance with the applicable regulations. These provisions include conformance with standards, including:

- The Code of Practice for the Validation and Routine Monitoring of Sterilization by Ionizing Radiation: U.K. Panel on Gamma and Electron Irradiation;
- BS EN 552:1994, Sterilization of Medical Devices - Validation and Routine Control of Sterilization by Irradiation;
- EN 46O02:1997, Quality Systems - Medical Devices - Particular Requirements for the Application of BS EN ISO 9002;
- ISO 11137:1995, Sterilization of health care products - Requirements for validation & routine control - Radiation & Sterilization

The principal sterilization process is the Gamma Irradiation utilizing Cobalt 60. This complies with GMP recommendations.

8.7. Shelf Life Testing

Shelf life testing was performed to verify sterile packaging integrity equivalent to five years.

9.0 SUMMARY OF CLINICAL STUDIES

9.1. Background

The primary source of clinical data supporting this PMA is a consecutive series of 2,385 BHR cases performed from July 1997 through May 2004 by Derek J. W. McMinn, FRCS, Birmingham Nuffield Hospital, Edgbaston, Birmingham, UK. Clinical assessments (modified HHS) were obtained on the first 1,626 BHR cases (surgeries between July 1997 and March 2002).

For purposes of data analysis for this PMA, the data from these 2,385 cases are grouped into 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.

Where practical, data are presented for each of these 3 cohorts separately, and then for the combined X-ray/Oswestry cohort (124+1502=1626 cases) and the combined X-ray/ Oswestry/McMinn cohort (124+1502+759=2385 cases).

The data from these 2,385 cases are included in two studies and an overall assessment that demonstrate the safety and effectiveness of the BHR through 5 years follow up:

- Survivorship Study: The primary study demonstrates the survival of the first consecutive 1,626 BHR procedures, performed from July 1997 through March 2002 (X-ray + Oswestry cohorts). These hips are included in the primary study cohort because, in addition to having the longest potential of follow-up, these hips were followed independently by the Oswestry Outcomes Centre at the Robert Jones and Agnes Hunt Orthopaedic Hospital, NHS Trust, Oswestry, Shropshire UK.
- Five Year Radiographic Assessment Study: The radiographic assessment includes the first consecutive 124 BHR procedures, performed from July 1997 through December 1997. These

124 hips are a subset of patients in the Survivorship Study. A prospective study was designed to obtain independent, objective, quantifiable data for the analysis of 5-year radiographic results for the BHR procedures performed during the first 6 months of BHR implantations.

- Safety Assessment: For the analysis of safety, this PMA includes adverse event findings for all 2,385 BHR procedures performed from July 1997 through May 2004.

9.2. Primary Study: Survivorship

The primary study is a 5 year survivorship study of the BHR that includes the first consecutive 1,626 BHR procedures performed from July 1997 through March 2002. These procedures are followed annually, independent of Mr. McMinn's routine clinical follow up, by the Oswestry Outcomes Centre. Data are available for 546 of the 601 BHR procedures eligible for 5 year follow up (90.8%).

It is noted that the data for BHR procedures performed after March 2002 are now being collected at the National Health Services Centre, where the Oxford Hip Score is used to collect clinical outcomes data[1]. Since only Oxford Hip Scores are available for the more recent 759 BHR procedures performed by Mr. McMinn, these data are not pooled with findings for the 1,626 procedures followed by the Oswestry Outcomes Centre.

9.2.1. Study Objective

The primary objective of this clinical study of 1,626 BHR procedures is to demonstrate the safety and effectiveness of the Birmingham Hip Resurfacing (BHR) arthroplasty system through 5 years post implant, measured by the survivorship of the implant.

9.2.2. Study Design

The BHR Survivorship Study was based on a collection of information maintained in the Oswestry Outcomes Centre database. The primary effectiveness measurement for this clinical study is the survivorship of the BHR system to a maximum of 5 years. The primary outcome measurement was therefore identified as a revision arthroplasty procedure, and the individual patient success criterion was identified as freedom from revision. The secondary effectiveness

[1] After the UK's National Institute for Clinical Excellence (NICE) decided in favor of reimbursement for the BHR, BHR cases are followed by the UK's National Health Services (NHS) Center. The NHS,however, uses the Oxford hip score, which is not similar to the Harris Hip Score. In addition, Smith & Nephew does not have access to the NHS's Oxford hip score data.

measurement is the clinical assessment of outcome by the Oswestry-modified Harris Hip Score (OSHIP).

9.2.2.1. Investigators / Investigational Sites

The Oswestry Outcomes Centre maintains a registry of 5,000 BHR procedures performed worldwide. Of all of the data included in the Oswestry Outcomes Centre registry, only the data from the the 1,626 BHR procedures performed by Mr. McMinn from July 1997 through March 2002 are included in the Survivorship Study. The decision to include data only from patients treated by Mr. McMinn was made for several reasons:

- Although the Oswestry Outcomes Centre records information regarding complications, deaths, or revisions, these data may not be routinely tracked: follow up by the Oswestry Outcomes Centre is accomplished by self-administered patient questionnaire. Therefore, a comparison of the data from the Oswestry Outcomes Centre database to the data from Mr. McMinn's clinical records provides additional assurance that an accurate, up-to-data survivorship status is known for each procedure.
- The data set from this single surgeon is as large as (or larger than) multi-surgeon and multi-site data sets typically provided to support PMAs for hip arthroplasty devices in the US.
- The size of this data set and the length of follow up provides reasonable assurance that complications and adverse events associated with the BHR device would have been detected within the study population.

9.2.2.2. Data Collection

The primary source of clinical data supporting this PMA is the 2,385 BHR cases performed by Mr. Derek McMinn from July 1997 through May 2004. For purposes of data analysis for this PMA, the data from these 2,385 cases are grouped into 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.

Where practical, data are presented for each of these 3 cohorts separately, and then for the combined X-ray/Oswestry cohort (124+1502=1626 cases) and the combined X-ray/ Oswestry/McMinn cohort (124+1502+759=2385 cases).

Follow-up through 5 years for the 1,626 cases (combined X-ray/Oswestry cohorts) was contracted to and independently conducted by the Oswestry Outcomes Centre. The follow-up parameters include:

- OSHIP Score: Pain, function, and range of movement self-assessments were collected from each patient using the Oswestry-modified Harris Hip Score (OSHIP) questionnaire.
- Patient satisfaction: Patient satisfaction data were collected through an additional question at the end of the OSHIP questionnaire.
- Adverse events: Complication, death, and revision data were retrieved from both the records of the Oswestry Outcomes Centre and from the records of the McMinn Centre.

Of the total 2,385 cases, follow-up for the most recent 759 BHR cases was conducted by the UK National Health Service rather than by the Oswestry Outcomes Centre (McMinn cohort). Therefore, OSHIP scores are not available for these patients. However, safety data are available for these 759 cases:

- Death, revision, and complications information that has been retrieved from the McMinn Centre files. The McMinn Centre collected revision, complication, and death data by recording the findings of pre- and post-operative patient visits to the Centre in patient records.

Note that the McMinn cohort data are used as part of the safety analyses within this PMA. Any analysis of the OSHIP effectiveness measure, however, necessarily excludes the 759 cases of the McMinn cohort, because OSHIP scores were not collected for this cohort.

The X-ray cohort includes the first 124 BHR cases performed by Mr.McMinn. Radiological data were collected for these cases according to a prospective protocol for x-ray review that included the following parameters:

- Medial and lateral migration
- Acetabular orientation.
- Femoral and acetabular radiolucencies
- Heterotopic bone formation

9.2.2.3. Secondary Data Sources

An additional though less complete source of clinical data included in the PMA consists of 3,374 BHR cases performed by 140 surgeons worldwide (other than 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 cohort (OSHIP scores, patient satisfaction), but differs in that complication, death, and revision data were retrieved from only from the records of the Oswestry Outcomes Center.

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 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.

9.2.3. Study Population: Survivorship Study

9.2.3.1. Demographics

Patients in the survivorship study (X-ray/Oswestry 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 $\leq$ 65 years old, and 127 (8%) were performed in patients > 65 years old.

One thousand one hundred and eleven (1,111) of the X-ray/Oswestry 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

9.2.3.2. Subject Accountability

The following table provides accountability data for all 1,626 cases in the X-ray and Oswestry cohorts.

Accountability – X-ray/Oswestry Cohort

Oswestry Outcomes Centre Follow Up (Evaluated / Expected)

	X-ray (n=124)	Oswestry (n=1502)	TOTAL (n=1626)
1 year	101/123 (82.1%)	1137/1493 (76.2%)	1238/1616 (76.6%)
2 year	51/123 (41.5%)	1192/1484 (80.3%)	1243 /1607 (73.3%)
3 year	122/122 (100%)	1067/1227 (87.0%)	1189/1349 (88.1%)
4 year	119/122 (97.5%)	773/885 (87.3%)	892/1007 (88.6%)
5 year	112/119 (94.1%)	434/482 (90.0%)	546/601 (90.8%)

9.2.3.3. Baseline OSHIP Scores

For the 1,626 procedures included in the Survivorship Study, baseline OSHIP Scores are available for 1,311 of the 1,626 procedures (81%). Scores ranged from 7 to 96, with a mean score of 59.8 (±13.87). The average baseline score is slightly higher than that usually documented for total hip arthroplasty patients, consistent with the indication for use and patient selection criteria for hip resurfacing rather than total hip replacement.

Baseline OSHIP Scores – X-ray/Oswestry cohort
All Procedures

Total procedures	1626
Total available baseline scores	1311
Mean	59.8
Median	63.0
Standard deviation	13.87
Minimum score	7.0
Maximum score	96.0

9.2.4. Study Findings

9.2.4.1. Primary Effectiveness Measurements – Survivorship

The table below presents the estimates of survivorship for the X-ray/Oswestry cohort calculated according to Peto's adjusted method. The estimated percent of procedures remaining free from revision at 5 years after the BHR procedure is 98.4% (95% confidence interval, 97.3% - 99.5%). Therefore, the overall study success rate at 5 years for the Survivorship Study is 98.4%

Percent of Subjects without Revision by Year
X-ray/Oswestry Cohort (N = 1,626)

Year	Estimated Percent of Procedures with no Revision	95% Lower Bound	95% Upper Bound	p-value
1	99.4	99.0	99.8	<0.0001
2	99.0	98.5	99.5	<0.0001
3	98.7	98.0	99.3	<0.0001
4	98.6	97.8	99.3	<0.0001
5	98.4	97.3	99.5	<0.0001

When findings for the additional 759 cases not included in the Survivorship Study (McMinn cohort) are added to the survivorship analysis, the survivorship rates are nearly the same. The estimated percent of all 2,385 procedures remaining free from revision at 5 years is 98.5% (95% confidence interval, 97.4% - 99.6%). The success rate at 5 years for the all 2,385 BHR procedures is 98.5%.

Percent of Subjects without Revision by Year
X-ray/Oswestry/McMinn Cohort (N = 2,385)

Year	Estimated Percent of Procedures with no Revision	95% Lower Bound	95% Upper Bound	p-value
1	99.4	99.1	99.8	<0.0001
2	99.1	98.7	99.6	<0.0001
3	98.8	98.2	99.4	<0.0001
4	98.7	97.9	99.4	<0.0001
5	98.5	97.4	99.6	<0.0001

Twenty four (24) of the 1,626 BHR procedures in the Survivorship Study (X-ray/Oswestry) cohort had undergone revision at last known follow up (1.47%). For all 2,385 BHR procedures (X-ray/Oswestry/McMinn cohorts) there are 27 revisions (1.13%).

Revisions – All Cohorts

	X-ray[1] (n=124)	Oswestry (n=1502)	McMinn (n=759)	TOTAL (n=2385)
1 year	1	9	3	13
2 year	0	5	0	5
3 year	1	4	0	5
4 year	0	1	0	1
5 year	0	1	0	1
5+ year	2	0	0	0
TOTAL	**4**	**20**	**3**	**27**

[1]Two additional revisions occurred in the X-ray cohort after the 5 year OSHIP score was obtained by the Oswestry Outcomes Centre. Therefore, the adjusted revision rate for the x-ray cohort is 4/124 (3%).

The most common reason for revision was femoral neck fracture, which occurred in 10 of the 2,385 cases. Late infections requiring revision occurred in 8 cases. Collapse of the femoral head occurred in 6 cases; avascular necrosis occurred in 2 cases, and dislocation was the reason for revison in 1 case.

Time to Revision / Reason for Revision

All Cohorts

Reason for Revision	Time to Revision in Years					
	n	**Mean**	**StdDev**	**Median**	**Minimum**	**Maximum**
Femoral neck fracture	10	0.198	0.144	0.149	0.025	0.383
Infection	8	3.119	1.397	2.713	1.706	5.394
Collapsed femoral head	6	2.172	1.393	1.821	1.131	4.901
Avascular necrosis	2	0.661	0.041	0.661	0.632	0.690
Dislocation	1	0.003		0.003	0.003	0.003
TOTAL	27	1.530	1.615	1.131	0.003	5.394

9.2.4.2. Secondary Effectiveness Measurements

The Oswestry-modified Harris Hip (OSHIP) Score is the secondary outcome measurement for the Survivorship study. For purposes of comparison to published reports of total hip arthroplasty, individual patient success is defined as an OSHIP Score of 80 or greater. However, to provide additional information about the outcome of a BHR resurfacing procedure, which is typically performed in patients who are younger and more active than traditional THR patients and who may have higher baseline scores than traditional THR patients, results are also presented with the individual success criterion adjusted to 90 or greater.

The tables below provide the OSHIP Score summary for all procedures in the X-ray/Oswestry cohort, followed by tables for only the unilateral procedures in this cohort.

Summary of OSHIP Scores by Year
X-ray/Oswestry Cohort (n = 1,626)

	Baseline	**1 Year**	**2 Year**	**3 Year**	**4 Year**	**5 Year**
Total hips	1626	1616	1607	1349	1007	601
Total evaluated	1311	1238	1243	1189	892	546
Mean	59.8	96.3	96.8	96.2	96.2	95.0
StdDev	13.87	7.08	7.01	7.53	7.49	9.24
Median	63.0	100.0	100.0	100.0	100.0	99.0
Minimum	7.0	42.0	34.0	43.0	41.0	30.0
Maximum	96.0	100.0	100.0	100.0	100.0	100.0

At 5 years follow up, 467 of 546 BHR procedures (85.5%) had OSHIP Scores of 90 and above. Five hundred and nine (509) of the 546 (93.2%) had scores of 80 and above.

Summary of OSHIP Scores by Category and Year
X-ray/Oswestry Cohort (N = 1,626)

	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
Total hips	1626	1616	1607	1349	1007	601
Total evaluated	1311	1238	1243	1189	892	546
Excellent (90-100)	0.4%	89.1%	91.8%	88.4%	88.6%	85.5%
Good (80-89)	2.7%	7.6%	5.2%	6.9%	7.1%	7.7%
Fair (70-79)	20.0%	1.7%	1.5%	2.8%	2.7%	3.5%
Poor (60-69)	37.9%	1.0%	0.7%	1.3%	1.1%	1.6%
Very Poor (<60)	39.1%	0.6%	0.7%	0.7%	0.6%	1.6%

OSHIP Score Findings are essentially equivalent when data for only unilateral procedures are tabulated.

Summary of OSHIP Scores by Year
X-ray/Oswestry Cohort, Unilateral Procedures Only (n = 1,111)

	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
Total hips	1111	1103	1100	927	687	395
Total evaluated	892	835	842	818	607	360
Mean	60.1	96.6	96.8	96.2	95.9	94.8
StdDev	13.14	6.75	7.30	7.46	8.01	9.68
Median	63.0	100.0	100.0	100.0	99.0	99.0
Minimum	9.0	42.0	34.0	43.0	41.0	30.0
Maximum	91.0	100.00	100.00	100.00	100.00	100.00

At 5 years follow up, 307 of 360 unilateral BHR procedures (85.3%) had OSHIP Scores of 90 and above. Three hundred and thirty four (334) of the 395 (92.7%) had scores of 80 and above.

Summary of OSHIP Scores by Category and Year
X-ray/Oswestry Cohort , Unilateral Procedures Only (n = 1,111)

	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
Total hips	1111	1103	1100	927	687	395
Total evaluated	892	835	842	818	607	360
Excellent (90-100)	0.2%	90.7%	92.0%	88.3%	87.1%	85.3%
Good (80-89)	2.6%	6.7%	4.9%	7.5%	8.1%	7.5%
Fair (70-79)	19.6%	1.4%	1.7%	2.4%	2.6%	3.3%
Poor (60-69)	39.1%	0.4%	0.6%	1.1%	1.3%	2.2%
Very Poor (<60)	38.5%	0.8%	0.8%	0.7%	0.8%	1.7%

9.2.4.3. Primary Safety Measurements - Adverse Events

Adverse event data were collected from the clinic records maintained at the McMinn Centre, from operative reports and surgery forms, and from comments provided by patients completing the OSHIP questionnaire. The following table summarizes all adverse events for all 2,385 BHR procedures.

Complications and Adverse Events
All Procedures (n=2,385)

Event	*n*	%
Wound exudate	589	25%
Pain	367	15%
Other	328	14%
Urinary retention / UTI	235	10%
Limp	211	9%
Stiffness, weakness, flexion deformity, restricted ROM	206	9%
Drop in hemoglobin	182	8%
Pyrexia, temperature, chills, fever	177	7%
Localized events at implant site (clicking, etc.)	75	3%
Localized events at incision site (redness, hardness, etc.)	74	3%
Heterotopic ossification	56	2%
Radiological report comments	53	2%
Postoperative infection	41	2%
Hypotension	37	2%
AVN femoral neck	35	1%
Component migration / loosening	21	<1%
Cardiac event	21	<1%
Collapse of femoral head	15	<1%
Late infection	15	<1%
Fracture femoral neck	13	<1%
Prosthesis dislocation	8	<1%
Postoperative deep vein thrombosis	8	<1%
Other thromboembolism events	7	<1%
Impingement	3	<1%
Not applicable (pre-existing condition)	3	<1%
Postoperative pneumonia	2	<1%

Deaths: A total of 20 deaths have occurred, occurring at intervals ranging from 0.7 to 6.0 years after the BHR procedure. In no case was a death related to the BHR procedure.

9.2.5. Summary of Findings from the Survivorship Study

The overall study success rate at 5 years for the Survivorship Study (X-ray/Oswestry Cohorts) is 98.4%.

Twenty four of the 1,626 BHR procedures in the Survivorship Study (X-ray/Oswestry) cohort had undergone revision at last known follow up (1.47%). For all 2,385 BHR procedures (X-ray/Oswestry/McMinn cohorts) there were 27 revisions (1.13%). The estimated percent of procedures in the X-ray/Oswestry cohort remaining free from revision at 5 years after the BHR procedure is 98.4% (95% confidence interval, 97.3% - 99.5%).

The most common reason for revision was femoral neck fracture, which occurred in 10 of the 2,385 cases. Late infections requiring revision occurred in 8 cases. Collapse of the femoral head occurred in 6 cases; avascular necrosis occurred in 2 cases, and dislocation was the reason for revison in 1 case.

At 5 years follow up, 467 of 546 BHR procedures (85.5%) had OSHIP Scores of 90 and above. Five hundred and nine (509) of the 546 (93.2%) had scores of 80 and above. For unilateral procedures only, 307 of 360 unilateral BHR procedures (85.3%) had OSHIP Scores of 90 and above at 5 years follow up. Three hundred and thirty four (334) of the 395 (92.7%) had scores of 80 and above.

Therefore, with a survivorship of 98.4% at 5 years, and an OSHIP Score $\geq$90 for 85.5% of the 456 procedures followed to 5 years, the results of the BHR System provide reasonable assurance that the device is safe and effective in hip resurfacing.

9.3. 5 Year Radiographic Assessment Study

9.3.1. Study Objective

The primary objective of this radiographic study is to supplement the Birmingham Hip Resurfacing (BHR) survivorship study by determining the rate of radiographic failures at 5 years post implant.

9.3.2. Study Protocol

Radiographic data were collected for these cases according to a prospective protocol for x-ray review that included the following parameters:

- Medial and lateral migration
- Acetabular orientation.
- Femoral and acetabular radiolucencies
- Heterotopic bone formation

9.3.3. Investigators / Investigational Sites

Nick Evans, FRCR, Consultant Radiologist, The Royal Orthopaedic Hospital NHS Trust, Birmingham, was selected as the Independent Reviewer and Primary Investigator for this study. Dr. Evans performed all radiographic measurements and assessments included in this study.

9.3.4. Study Population

The BHR was introduced into commercial distribution in the United Kingdom (UK) in July 1997, and the first BHR implant procedure was performed on July 30, 1997. Through December 31, 1997 a total of 124 BHR procedures were performed in 113 patients by Derek McMinn, FRCS, and all 124 procedures are included in this study.

9.3.4.1. Demographics

Patients ranged in age from 27.8 to 75.3 years (average age 52.8 years). Eighty-one (65.3%) of the procedures were performed in male patients and 43 (34.7%) were performed in female patients. Eleven of the 113 patients (9.7%) underwent bilateral BHR arthroplasty.

Demographics

Patients	Procedures	Age (Average, Range)	Bilateral (Patients)
Female (*n*=41)	43	52.5 (27.8 – 69.2)	2
Male (*n*=72)	81	52.9 (34.2 – 74.3)	9
ALL (*n*=113)	124	52.8 (27.8 – 74.3)	11

The majority of BHR procedures were performed for osteoarthritis of the hip (92/124, 74.2%); additional indications included hip dysplasia (22/124, 17.7%) and avascular necrosis (7/124, 5.6%).

Diagnostic Indication for Arthroplasty

Diagnosis	*n*	*%*
OSTEOARTHRITIS	92	74.2
DYSPLASIA	22	17.7
AVASCULAR NECROSIS	7	5.6
INFLAMMATORY ARTHRITIS	2	1.6
OTHER	1	0.8
TOTAL	**124**	**100**

9.3.4.2. Subject Enrollment and Accountability

A total of 124 BHR procedures were performed from July 30, 1997 through December 31, 1997. One patient who underwent bilateral BHR procedures died at 4 years postoperatively of causes unrelated to the BHR procedures; 4 of the 124 BHR procedures (3.2%) have undergone revision. Therefore, 118 procedures (124 hips - 2 hips due to death - 4 revisions = 118 hips) were eligible for 5 year radiographic evaluation of the BHR. One hundred and eight (108) of the 118 hips surviving to 5 years had 5 year radiographs available for independent review (91.5%).

Accountability for radiographic data and accountability for patient follow-up (OSHIP scores) are independent of each other. In this series, one additional hip had OSHIP evlaution but did not have radiographic data. Therefore, five year OSHIP Scores are available for 112 of 119 (94.1%) hips surviving to 5 years; one hip underwent revision at 5 years 6 months post implant, shortly after the 5 year OSHIP questionnaire was completed. Therefore, the 5 year OSHIP follow up rate for hips not undergoing revision is 112/118, or 94.9%.

Subject Enrollment and Accountability

	Baseline	6 Month	1 Year	2 Year	3 Year	4 Year	5 Year
Theoretically Due[1]	124	124	124	124	124	124	124
Deaths	-	0	0	0	0	0	2
Revisions	-	1	0	0	1	0	2
Expected[2]	124	123	123	123	122	122	118
Evaluated by OSHIP[3]	82	44	101	51	122	119	112
OSHIP % Follow Up	66.1	35.8	82.1	41.4	100	97.5	94.9[5]
Evaluated by x-ray[3]	124[4]	NA	NA	NA	NA	NA	108
X-ray % Follow Up	100.0	NA	NA	NA	NA	NA	91.5

[1]Theoretically due is the number due at each interval based on the date of surgery and date of database closure
[2]Expected is the number theoretically due at each interval based on the date of surgery and date of database closure
[3]Evaluated is the number with follow up data recorded.
[4]Portable x-ray films taken immediately following the BHR procedure are available for 89 of the 108 patients with 5 year radiographs. Many of these films are of poor quality. The radiograph taken at the first clinical follow up office visit is also used for baseline measurements.
[5]OSHIP scores are available for one hip that was revised shortly after the 5 year follow up interval.

9.3.5. 5 Year Radiographic Assessments

9.3.5.1. Assessment of Radiographic Lucencies

Lucencies around the femoral metaphyseal stem were assessed using the method described by Amstutz et al. This system uses a scoring system of 0 to 9 points, describing the location(s) and degrees of radiolucencies in three zones along the short metaphyseal stem. Acetabular radiolucencies were identified using a similar 0 to 9 point scoring system applied to three zones around the acetabulum, as described by DeLee and Charnley. A score of 8 or 9 points was defined as a radiographic failure.

Femoral Component Lucencies: One hip had a 9 point femoral component lucency at 5 years, and was therefore classified as a radiographic failure. Three additional hips had less significant femoral lucencies. One hip appeared to have had a 5 point femoral lucency at the immediate post-operative radiographic assessment; exact measurement was difficult due to the poor quality of the film. A grade 5 femoral lucency was also seen on the 5 year film. One hip was found to have a Grade 2 lucency, and one hip was found to have a 1 point lucency.

Acetabular Component Lucencies: Two hips had 8 point acetabular component lucencies at 5 years, and were therefore classified as radiographic failures. In one hip the 8 point lucency was associated with acetabular cysts that were apparent on the preoperative films which progressed

over time. In the second hip, in which a dysplasia cup had been implanted, the 8 point lucency was associated with the possible development of an early protrusio. Three hips had less significant acetabular lucencies. These included 1 point lucencies in two hips, in one of which an acetabular cyst had developed; and one 2 point lucency.

9.3.5.2. Change in Orientation / Migration

In only one hip was a orientation noted that was classified as radiographic failure. This hip, in which a 5 degree change in acetabular orientation was measured, is also the hip in which a 8 point acetabular lucency and possible protrusio was noted.

9.3.5.3. Heterotopic Ossification

Heterotopic bone formation was graded according to the Brooker classification system. Twenty one hips were classified Brooker I and 5 hips were classified Brooker II. Two hips had heterotopic ossification classified Brooker III. No hip was found to have Brooker IV heterotopic ossification.

9.3.5.4. Other Radiographic Findings

Bone resorption of the medial femoral neck was reported in 3 hips. In no case was the resorption associated with any other notable radiographic findings. Bone cysts were seen in the femoral head and acetabulum of one hip with a 8 point acetabular lucency, as previously described. A cyst at least 3 centimeters in size was also seen in the acetabulum of one hip with a 1 point acetabular lucency and a 5 year OSHIP score of 99.

9.3.5.5. Summary of 5 Year Radiographic Study Findings

The study protocol defined radiographic failure as the presence of incomplete or complete radiolucencies in all zones (score of 7 or 8) and/or migration of the component of greater > 2 mm and/or a change in acetabular angle $\geq$ 5 degrees. Therefore, 3 of the 108 hips (2.8%) are classified as radiographic failures at 5 years. None of the three radiographic failures required an implant revision.

Independent Radiographic Review Findings
BHR Procedures (n=108)

Finding	Incidence
Femoral Lucencies	
• Failure: Grade 9	1 (0.9%)
• Other	
o Grade 5 pre-op and post-op	1 (0.9%)
o Grade 2	1 (0.9%)
o Grade 1	1 (0.9%)
Acetabular Lucencies	
• Failure: Grade 8[1]	2 (1.8%)
• Other	
o Grade 2	1 (0.9%)
o Grade 1	2 (1.8%)
Change in orientation / migration	
• 5 degree change in orientation with Grade 8 acetabular lucency[1]	1 (0.9%)
Heterotopic Ossification	
• Brooker IV	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

9.4. Comparison Data

9.4.1. Study Objective

The objective of this summary is to provide comparison data for the clinical study of the BHR. Recent clinical reports in the literature exist for two other (non-BHR) metal-on-metal hip resurfacing products (Amstutz *et al.*[14] and Nevelos *et al*[73]). However, although the comparison of the clinical data in these reports to the BHR clinical data in this PMA would be appropriate, the products are no legally approved for marketing in the US. Thus, the Sponsor selected clinical studies of FDA pproved ceramic-on-ceramic total hip replacement (THR) products as comparison data.

9.4.2. Identification and Selection of Comparison Data

Based on the protocol for selecting references, the following published reports of clinical studies were selected for comparison data.

Author / Reference	Title
D'Antonio J *et al*: J Arthroplasty June 2002 Vol 17 No. 4	New experience with alumina-on-alumina ceramic bearings for total hip arthroplasty
Garino JP: COOR October 2000 No. 379	Modern ceramic-on-ceramic total hip systems in the United States: early results

9.4.3. Investigators / Investigational Sites

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.

9.4.4. Study Population

Demographics

Author	Patients	Procedures	Age (Average)	Bilateral Procedures
D'Antonio J *et al*	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 n 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**

9.4.4.1. Subject Enrollment and Accountability

Subject Enrollment and Accountability

Author	Mean follow-up (range)	Number of pts 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) • 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), • 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"

9.4.5. Comparison Data Findings

9.4.5.1. Primary Outcome Measurements - Revisions

D'Antonio *et al.* report 4 revisions in 338 ceramic-on-ceramic procedures (1.2%) followed for a mean of 3 years (range 2 – 4 years), and 8 revisions in the 151 control procedures (5.2%) followed to a mean of 3 years (range 2 – 4 years). An additional ceramic-on-ceramic procedure was noted to have an unstable femoral component and femoral subsidence, and this procedure was identified as a candidate for revision, bringing the revision / potential revision rate to 1.4% at a mean follow up of 3 years. An additional control procedure is also identified as a candidate for revision, bringing the control group revision / potential revision rate to 6%.

The indications for revisions in the ceramic-on-ceramic procedures included femoral fracture requiring revision of the femoral head and stem; recurrent dislocation requiring revision of the acetabular component, insert, and femoral head; and infection requiring revision of all components in two procedures.

In the series reported by Garino, 4 revisions were performed in the 333 procedures followed from 18 to 36 months (1.2%). Three of the revisions occurred early: one was performed for anterior instability and early dislocation; one for eccentric liner malpositioning; and one was performed at 6 weeks for cup migration in a patient with severe osteoporosis. One revision was performed for late deep infection at approximately one year postoperatively.

9.4.5.2. Radiographic Assessments

The following table summarizes radiographic findings reported for the D'Antonio study.

Radiographic parameter	System 1 ABC with porous (n=162)	System 2 ABC with HA (n=169)	System 3 CoCr on PE (n-149)
Femoral radiolucent line - zone 1	4 (2.5%)	4 (2.4%)	6 (4.0%)
Femoral radiolucent line - zone 7	2 (1.2%)	1 (0.6%)	0
Stem subsidence	0	1[1] (0.6%)	0
Unstable stem fixation	0	1[1] (0.6%)	0
Acetabular radiolucent line			
Zone 1	10 (6.2%)	1 (0.6%)	10 (6.7%)
Zone 2	3 (1.9%)	0	7 (4.7%)
Zone 3	25 (15.4%)	0	35 (23.5%)
Acetabular radiolucent line - all 3 zones	0	0	0
Acetabular shell migration	0	0	1[2] (0.7%)
Unstable acetabular component	1 (0.6%)	0	1[2] (0.7%)

[1] Same femoral component
[2] Same acetabular component

Garino reported that radiographic assessments showed no loose components, and no components with significant wear or fractures of the ceramic pieces in any patients. However, one case of acetabular migration is reported as a complication.

9.4.5.3. Secondary Outcome Measurements - Harris Hip Scores

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: 95.4 mean score (n=166)
- ABC System 2: 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.

9.4.5.4. Primary Safety Measurements - Complications and Adverse Events

Complications and Adverse Events: D'Antonio *et al.*

Event	ABC System 1 (n=166)	ABC System 2 (n=172)	Control (n=151)
Pain	9%	8%	7%
Limp	2%	4%	3%
Femoral fracture	2.4%	1.2%	1.2%
Dislocation	2.3%	3.4%	4.2%
Heterotopic bone	2.9%	3.4%	6.1%
Interoperative insert chip	2.9%	2.3%	NA

Complications and Adverse Events: Garino

Event	Incidence (%)	# of patients
Prosthesis dislocation	1	3
Femoral calcar trochanter fracture	1	3
Eccentric liner seating	1	2
Liner chipped during insertion	1	3
Acetabular migration	<1	1
Shell seated deeper than reamer	<1	1
Foot drop	<1	1
Superficial infection	<1	1
Deep infection	<1	1
Bursitis	<1	1
Thrombosis	<1	1
Fracture vertebrae	<1	1
Local pain	<1	2
Other local complications	2.5	8

9.4.6. Conclusions Drawn from the Comparison Data

D'Antonio *et al.* and Garino report very similar findings for their studies of ceramic-on-ceramic THR. In both studies, the revision rate is 1.2%; length of follow-up in the D'Antonio study is 2 to 4 years and in the Garino study it is 1½ to 3 years. The mean Harris Hip Score is greater than 90 for both studies. Therefore, both ceramic-on-ceramic THR systems appear to perform satisfactorily in a relatively young patient population.

9.5. Comparison of Survivorship Study Findings and Comparison Data

9.5.1. Demographics

There was no difference in the mean age for the three studies. As anticipated, each of the 3 studies enrolled a relatively younger patient population than traditional THR studies, in which the mean age may be 60 to 70 years of age.

Comparison of Study Findings: Ages

Study	Mean Age
Survivorship Study • X-ray/Oswestry cohort	53
Radiographic Study	52.8
Control Study • D'Antonio *et al.* • Garino	 53 52

9.5.2. Enrollment and Accountability

Each of the three studies included follow up data for at least 95% of the total enrolled population, even when follow up extended through 5 years as was the case for the BHR. For the control studies, Garino simply stated that all of the 333 patients enrolled in the study continued to be followed, with none lost to follow up.

Comparison of Study Findings: Accountability

Study	Total Enrolled	Follow up
Survivorship Study • X-ray/Oswestry cohort	 1,626	 90.8% (5 yrs)
Radiographic Study	124	91.5% (5 yrs)
Control Study • D'Antonio *et al.* • Garino	 319 333	 95.9% (2 yrs) "100%"

9.5.3. Baseline Characteristics

Although the BHR and ceramic-on-ceramic THR systems are indicated for use in younger, more active patients, the baseline Harris Hip Scores may have been slightly lower for the ceramic-on-ceramic THR procedures than the OSHIP Scores for the BHR procedures. This is consistent with the rationale that a resurfacing procedure is an intervention that takes place before degenerative

changes affect healthy bone stock in the femur; therefore, the symptoms associated with progressive degeneration are expected to be less severe for a resurfacing population.

Comparison of Study Findings: Baseline OSHIP/Harris Hip Scores

Study	Mean OSHIP/ HHS
Survivorship Study (OSHIP) • X-ray/Oswestry cohort	 59.8 (±13.87)
Radiographic Study (OSHIP)	55 (±13.0)
Control Study (HHS) • D'Antonio *et al.* • Garino	 Not reported 44

9.5.4. Primary Outcomes Measurements

Similarly low revision rates were reported for the BHR Survivorship Study, the BHR Radiographic Study, and the Control Studies. The difference in the revision rate for the Radiographic Study is not clinically significant. However, the length of follow differs among the three studies: follow up for the ceramic-on-ceramic THR studies is somewhat less than that for the BHR Survivorship Study and the BHR Radiographic Study.

Reasons for revisions also differed between the BHR studies and the ceramic-on-ceramic THR studies, primarily because of the general differences between resurfacing and THR devices.

Comparison of Study Findings: Revision Rate

Study	Follow Up Interval	Total Revisions
Survivorship Study • X-ray/Oswestry cohort	 2 to 5 years	 24/1,626 (1.47%)
Radiographic Study	5 years	4/124 (3.2%)
Control Study • D'Antonio *et al.* • Garino	 2 – 4 years 18 – 36 months	 4/338 (1.2%) 4/333 (1.2%)

9.5.5. Secondary Outcomes Measurements

Comparison of Study Findings: Radiographic Findings

Study	Follow Up Interval	Radiographic Findings
Radiographic Study (n=97)	5 years	
• Acetabular component		
o Lucencies		5 (4.6%)
o Unstable		0
• Femoral component		
o Lucencies		4 (3.7%)
o Unstable		0
D'Antonio *et al.* (n=331)	2 – 4 years	
• Acetabular component		
o Lucencies		8 (2.4%)
o Unstable		1 (0.3%)
• Femoral component		
o Lucencies		11 (3.32%)
o Unstable		1 (0.3%)
Garino (n=333)	18 – 36 months	None*

*no cases of acetabular or femoral lucencies or migration reported under radiographic findings; one acetabular migration reported under complications

The incidence of radiolucencies was low for all three studies. However, the data for the BHR procedures are based on 5 year follow up findings, compared to 2 to 3 year mean follow up for the published studies. As a result, it is possible that the results for the comparative studies may be worse over time.

Comparison of Study Findings: OSHIP/Harris Hip Scores

Study	Follow Up Interval	Mean OSHIP/Harris Hip Score
Survivorship Study (OSHIP)		
• X-ray/Oswestry cohort	5 years	95.0 (±9.24)
Radiographic Study (OSHIP)	5 years	86.2 (±16.22)
Control Study (HHS)		
• D'Antonio *et al.*	2 – 4 years	95.4; 96.6
• Garino	18 – 36 months	97

Mean Harris Hip Scores or OSHIP Scores at follow up were above 90 for all 3 studies; again the only difference is in the length of follow up for the BHR Survivorship Study and the BHR Radiographic Study compared to the ceramic-on-ceramic THR studies.

9.5.6. Primary Safety Measurements

Relatively low morbidity rates were reported for the BHR and the THR studies. This may be related more closely to the general good health associated with a younger patient population than usually undergoes hip arthroplasty. None of the deaths in any of the studies were related to the arthroplasty procedure, and no serious perioperative events such as deep vein thrombosis or postoperative pneumonia occurred in any of the patients in any of the studies.

9.5.7. Conclusions Drawn from Comparisons of Study Findings

Ceramic-on-ceramic THR systems are commercially available devices in the U.S.; findings from two studies of two of the devices approved for use are included in a literature control for the clinical studies of the BHR included in this PMA. Despite the obvious differences between the BHR resurfacing arthroplasty system and the ceramic-on-ceramic THR systems, these devices are all designed and indicated for use in younger, more active patients requiring hip arthroplasty.

Revision rates, postoperative Harris Hip or OSHIP Scores, and radiographic findings were similar for the BHR studies and the ceramic-on-ceramic studies. Therefore, there appear to be minimal differences in the clinical outcomes for the BHR and for the ceramic-on-ceramic THR systems.

9.6. Analysis of Data for Statistical Significance

The study demonstrated evidence of the sustained response through 5-years for the BHR in terms of revision rates and OSHIP scores. Adverse events observed for the BHR are consistent with adverse events observed for other hip replacements. Hence, the study provides evidence of the clinical efficacy of the device.

This study summarizes the revision rates and OSHIP results through five years of follow-up. Kaplan-Meier estimates were obtained for the revision rates using all available follow-up data for each of the cohorts. The two-sided 95% confidence bound for the survival rate was provided in order to obtain the lower bound for the percent of subjects with no revision yearly through 5 years. Statistical testing using the Wilcoxon test, Log-Rank test, and proportional hazards models were used to assess the homogeneity of the survival results across cohorts and selected subgroups of subjects. OSHIP scores were evaluated in the year they were assigned. For the OSHIP, observed results were summarized, results by visit were summarized using a repeated measures

model, and an analysis of covariance was performed for selected subgroups on the 2+ Year results. Survival and OSHIP results for subjects without a baseline OSHIP were evaluated.

The results were initially presented for unilateral and bilateral hips combined; however, additional analysis was conducted for the unilateral hips. The overall survival rate (i.e. hips that did not require revision) for all hips at 5-years has 98.6 (97.3, 99.8) and for bilateral hips the result was 98.2 (95.7, 100) Unilateral hips performed similarly with a survival rate of 98.7 (97.3, 100). Since the study demonstrated overall results with a lower bound less than 5%, the survival analysis supported the efficacy of the BHR. Reasons for revision appear to be linked to the time of the event. Early revisions are likely to be a result of fractures, and later revisions are likely to result from infections or a collapsed femoral head.

A number of covariates were evaluated for association with outcome to evaluate whether the population of hips were poolable or were predictors of poor response. There were few significant responses, but overall there were a limited number of revisions which could affect power. Initially, proportional hazards models were used, but the Wilcoxon test and Log-Rank test were added to check the consistency of results since all of the assumptions of proportional hazards analyses might not be met. Of special interest, unilateral and bilateral hips were not significantly different (p=0.512 log-rank, p=0.7985, Wilcoxon). The reason for resurfacing was possibly associated with outcome. For alls hips, AVN was somewhat significant (p=0.0415 log-rank, p=0.2282, Wilcoxon) and was significant for the Log-Rank test in unilateral hips (p=0.0182 log-rank, p=0.1570, Wilcoxon) even though this accounted for 3 revisions in subjects with AVN. Inflammatory arthritis had a similar hazard ratio to AVN, but a smaller sample size.

For the OSHIP score, the mean change from baseline was between 36.5 (year 1) and 38.1 (year 5) for all hips and 36.4 (year 1) and 37.5 (year 5) for unilateral hips across the five years with no evidence of a clinically significant reduction in effect over time. A repeated measures analysis observed similar results. There was evidence that the subjects without baseline values had somewhat lower post-baseline OSHIP scores which could be associated with somewhat lower baseline values. Overall survival in all hips with baseline OSHIP scores was 98.6 and was 98.3 in hips without baseline results. The results for unilateral hips were 98.7 in hips with baseline OSHIP and 97.4 in hips without baseline OSHIP. An analysis of variance was used to determine if OSHIP scores were related to any covariates. Significant factors were cohort, gender, baseline OSHIP, and median BMI. None of these factors represented changes in scores that were close to

the mean improvement baseline observed for the majority of subjects. Hence, the OSHIP analyses support the overall performance of the BHR.

Adverse events were evaluated by cohort and time. The summaries showed some differences in overall rates between the cohorts. With the lack of another hip resurfacing product to compare against, the interpretation of adverse events was based on a qualitative comparison to the general profile of complications expected from other hip implants. The profile did not appear to provide an unexpected burden of adverse evnts in association with use of the BHR. Radiographic results from the X-Ray cohort did not suggest the occurrence of asymptomatic deterioration.

The revision, OSHIP, and safety results for BHR suggest the product is performing well for primary hip resurfacing arthroplasty.

9.6.1. Conclusions Drawn from the Statistical Analysis

The revision rates in the major subject cohorts considered together established that the revision for the BHR to be less than 5% through five years. The BHR cases arose from Dr. McMinn's practice. Of this set of 2385 hips, 1626 hips from 1414 subjects partipated in the OSHIP survey conducted by the Owsestry Outcome Center. The revision rate in these set of subjects was of a primary interest because response to the survey allowed an active response that would indicate whether a revision had occurred or not. Further, these subjects had a considerably longer follow-up than the other McMinn cohort which consisted mostly of more recent BHR cases. An additional focus was taken on the 1111 unilateral hips. For all unilateral and all hips combined in the X-Ray and Oswestry cohorts, the revision rate was found to be acceptable.

Analyses were conducted to evaluate the homogeneity of revision results across the cohorts and selected characteristics of subjects receiving a BHR and there was little evidence of statistically significant differences in the revision rates. The limited number of revisions may have limited the power of these investigations. The hips whose reason for resurfacing was AVN may have had an indication of higher revision rates. In other cases, certain cohorts of subsets of hips may have been too small to obtain a lower bound for the revision rate of less than 5%. For example, the X-Ray cohort alone could not meet the criteria, but consisted of only 124 subjects. Biological mechanisms for differences in subsets of the hips being different should be considered in

conjunction as well before completely dimissing or accepting differences in performance in the subsets of subjects.

The subject follow-up for the X-Ray and Oswestry cohorts was calculated based on the observed last visit in the Oswestry Outcome Center survey. This mail based survey did not include a definition for lost to follow-up and put forth considerable effort to obtain subject follow-up. As a proxy for lost to follow-up information, the number of subjects with their last two visits missing were identified in the analysis. A total of 84 hips met this criteria. The demographic profile of these subjects was generally similar to the other subjects**.** So, of the overall hips, the number potentially unavailable for further follow-up is generally low (84 out of 1626). While there is little reason to think these subjects are missing because of poor BHR performance, they represent a sample which could have a missed event.

The radiographic (X-Ray) cohort demonstrated excellent findings on independent review of 5-year X-Rays. Demographic characteristics were generally similar, but not identical to the other hip cohorts. The revision rate was slightly higher than other Owestry and McMinn cohorts and one event did occur very soon after 5-years that produced a rate lower than 95%. Given the slightly higher revision rate but lack of significant X-ray findings at 5-years, this results of the review support the performance of the BHR.

OSHIP survey results were available for many hips followed by the Oswestry Outcome Center and support the efficacy of the BHR. In general 85.5 % of the subjects had scores greater than or equal to 90 and 93.2% of subjects had scores greater than or equal to 80 at five years. There was some missing baseline data, but the majority of OSHIP scores for the 3-year, 4-year, and 5-year visits were available. Hence, the OSHIP results supported the performance of the product. There was some evidence that the hips without baseline values probably had a lower initial value because they were observed to have lower post-baseline means. Whether this related to a mechanism for missing data at the later visits was unknown. However, exact estimates of means or change from baseline values need to take that into consideration. Given the vast majority of OSHIP scores were generally high, the OSHIP survey results support the value of the BHR as a treatment.

Statistical testing and confidence bounds were not performed for the adverse events. Events were summarized according the there relative time. The acceptability of event rates and consistency of results compared to THR or other implants was left to a clinical review.

In summary, the study results provide reasonable assurance of the safety and effectiveness of the BHR System through 5 years.

10.0 PANEL RECOMMENDATION

11.0 CDRH DECISION

12.0 APPROVAL SPECIFICATIONS