A PROSPECTIVE CONTROLLED MULTI-CENTER STUDY ON

M2A MAGNUM TOTAL HIP ARTHROPLASTY

SPONSOR: Zimmer Biomet

Protocol#: INT.CR.RROW2
Revision 2 (July 21, 2015)

GENERAL INFORMATION

Research Team

Principal Investigators (Japan)
Dr. Kenji Ohzono

Principal investigators are responsible for the overall project and performing the surgical procedures in all study groups. Responsible for applying for ethical and management approval, recruitment of patients, obtaining patient consent, managing postoperative care of patients and adverse event reporting.

Study Sponsors

Biomet Japan

Study sponsors take responsibility for initiation, management, and/or financing of a clinical studies at investigational sites

Study Monitor in Japan

Takahito Nakai

Study monitors are responsible for carrying out the monitoring procedure as indicated in the protocol.

STUDY OBJECTIVE

The primary objectives of this clinical study include:

- Evaluate clinical efficacy and performance of M2A Magnum in Asian population in comparison to competitors' similar products.
- Investigate potential advantages of M2A Magnum compared to M2A Taper (28mm and 32mm) in terms of Range of Motion, Dislocation while maintaining the same function improvement and pain reduction.
- Investigate Metal-ion release and renal function in M2A Total Hip Arthroplasty.

DEVICE DESCRIPTION

M2A Magnum

The M2a-Magnum™ Large Metal Articulation is an ultra-high performance metal-on-metal articulation offering superior joint mechanic restoration and full compatibility with Biomet's clinically proven hip stems. Unlike ceramic-on-ceramic or traditional metal-on-polyethylene bearings, the M2a-Magnum™ system offers the stability and ROM of a big ball (≥38mm) in acetabulums as small as 44mm.

- Allows for significant wear reduction compared with metal or ceramic-on polyethylene and the potential for higher stability and range of motion (ROM)
- Features PPS® Porous Plasma Spray surface coating and full hemisphere geometry with four sets of paired fins
- Six neck length offsets from -6 to +9mm
- Available in shell sizes from 44-66mm (2mm increments) and head sizes 38-60mm (2mm increments)

M2A Taper (28mm or 32 mm)

The M2a-Taper Acetabular System consists of a titanium outer shell with cobalt chromium (Co-Cr-Mo) metallic liner, which articulates with a cobalt chromium (Co-Cr-Mo) modular femoral head. The system is all metal – there is no polyethylene in the design.

The outer surface of the acetabular shell is covered with a porous coating of Titanium (Ti-6Al-4V) per ASTM-F136 which ensures immediate component fixation and maximum bone-to-implant contact. The plasma sprayed surface consists of particles which are bonded together to form a random pattern of interconnecting pores. The Co-Cr-Mo liner fits into the Ti outer shell by means of a taper. The locking mechanism consists of a three-degree taper with a maximum engagement of 0.075 inches. The shell has inner diameters of either 28mm or 32mm. The 28mm inner diameter is available in shell sizes 48mm through 70mm. The 32mm is available in shell sizes 52mm through 70mm.

Bi-Metric XR and Taperloc can be used with M2A Taper and M2A Magnum in the study.

STUDY DESIGN

The study is designed as a prospective, controlled multi-center study..

Hypotheses:

Study Hypotheses are established based on the primary objectives. Specifically:

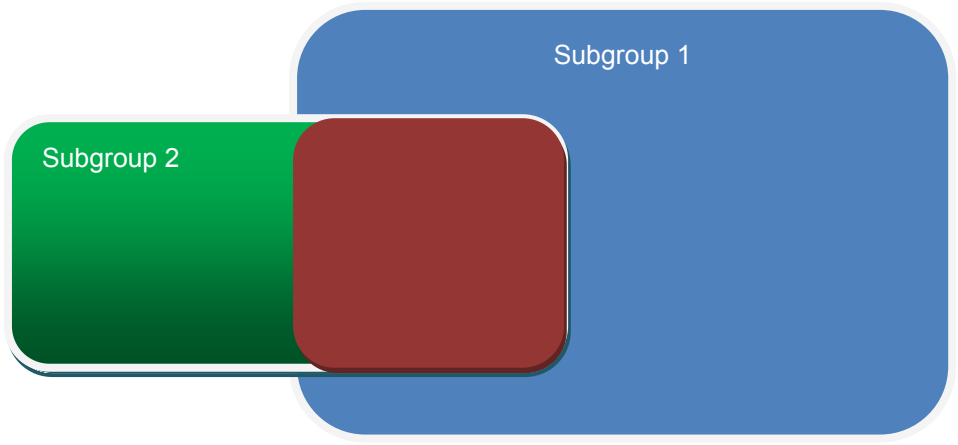
Hypothesis 1 – M2A Magnum will achieve the range of survivorships of competitors' products at 2 year postop *(based on the only available information on competitors' products).*

Hypothesis 2 – M2A Magnum will have better Range of Motion compared to M2A Taper (28mm or 32mm) at 1 year postop

Hypothesis 3 – M2A Magnum will have lower dislocation rate than M2A Taper (28mm or 32mm) at 5 year postop

Accordingly the study will include 2 subgroup studies. The relationship between the 2 subgroups is illustrated in the following table and graph:

Subgroup	Objectives	Trial Group	Control Group	Design	Endpoint(s)
1	Evaluate long term performance and size fit of M2A Magnum in Asian population and in comparison with competitors' similar products.	M2A Magnum .	Published data on Competitors' similar product – ASR.	Single arm cohort with Objective Performance Criteria (published data)	Survivorship, HHS, UCLA, Patient Satisfaction, cup seating, neck angle at immediate postop (part of radiographic assessment).
2	Compare early ROM, Clinical Outcomes, Metal-ion release and dislocation between M2A Magnum and M2A Taper w/ conventional head sizes	M2A Magnum	M2A Taper	RCT	HHS, ROM, UCLA, Dislocation and Metal-ion release, renal function, MRI Assessment[, survivorship



The study will be conducted over a period of 12 to 15 years. Patients from subgroups 1 and 2 will be followed at immediate postop, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years.

PATIENT SELECTION

All subjects, regardless of sex, race, or geographic location, must fit into the scope of the Inclusion / Exclusion criteria to be eligible for the study. If required per applicable regulations, all participants must sign an Informed Consent to be enrolled into the study.

Inclusion Criteria

Patients suitable for primary Total Hip Replacement
Patients with degenerative joint disease (inflammatory or non-inflammatory) or any of the composite diagnoses of:

a. Osteoarthritis
b. Avascular necrosis
c. Legg Perthes
d. Rheumatoid Arthritis
e. Diastrophic variant
f. Fracture of the pelvis
g. Fused hip
h. Slipped capital epiphysis
i. Subcapital fractures
j. Traumatic arthritis

Patients aged over 20 years old.
Patients with limited co-morbidity – ASA I – III
Patients must be able to understand instructions and be willing to return for follow-up
Patients willing to provide blood and urine samples for metal ion analysis at follow-up

Exclusion Criteria

Pre-existing metal implants
Absolute contraindications include: infection, sepsis, and osteomyelitis.
Relative contraindications include:
1) uncooperative patient or patient with neurologic disorders who are incapable of following directions,
2) osteoporosis,
3) metabolic disorders which may impair bone formation,
4) osteomalacia,
5) distant foci of infections which may spread to the implant site,
6) rapid joint destruction, marked bone loss or bone resorption
apparent on roentgenogram, and
7) vascular insufficiency, muscular atrophy, or neuromuscular disease.
8) pregnancy

ENDPOINTS

	SUBGROUP 1	SUBGROUP 2
PRIMARY ENDPOINTS*	Survivorship at 2 year postop	Dislocation (5 year postop), Range of Motion at 1 year postop.
SECONDARY ENDPOINTS	<u>At all follow-up visits:</u> Survivorship up to 10 year Harris Hip Score Radiographic Assessment Patient Satisfaction – EQ5D UCLA Complications including revisions	<u>At all follow-up visits:</u> Survivorship up to 10 year (for Magnum arm) Harris Hip Score. Radiographic Assessment Patient Satisfaction – EQ5D UCLA Complications including revisions Metal Ion release MRI assessment to all available patients at 5 year follow-up. ADDITIONAL IMAGE ASSESSMENT FOR SYMPTOMATIC PATIENTS

*For sample size calculations.

PARTICIPANT POPULATION (SAMPLE SIZE)

Participant population is determined based on primary/secondary endpoints of each subgroup following superiority or non-inferiority methodologies. Minimum sample sizes are determined in order to prove the hypotheses.

<u>Primary Endpoint Accumulative Dislocation Rate at 5 year postoperative</u>

Superiority test – time to event

Null Hypothesis: H_0 $p_t = p_c$

Alternative Hypothesis: H_a $p_t = p_c + d$

p_t = accumulative dislocation rate (1.8%)[2] in the trial group (Magnum) at 5 year postoperative.

p_c = accumulative dislocation rate (6.5%)[2] in the control group (M2A Taper) at 5 year postoperative.

$\alpha = 0.025$ Significance Level (97.5% confidence)

$\beta = 0.20$ 80% Power

$Z_{1-a/2} = 2.24$
$Z_{1-\beta} = 0.84$

N = 150 per group.

Due to nature of this endpoint (occurrence of dislocation), it is not expected there will be significant lost to follow-up and patients usually come back to their operating surgeons for complications if any.

Primary Endpoint Range of Motion at 1 year postoperative

Superiority test

Null Hypothesis: H_0 $\mu_t = \mu_c$

Alternative Hypothesis: H_a $\mu_t = \mu_c + d$

μ_t: mean of ROM in the trial group at 1 year postoperative.

μ_c: mean of ROM in the control group at 1 year postoperative.

$\alpha = 0.025$ Significance Level (97.5% confidence)

$\beta = 0.20$ 80% Power

$Z_{1-a/2} = 2.24$
$Z_{1-\beta} = 0.84$

d = 3.3 (degrees) Clinically Relevant Difference in ROM based on literature.

$\xi = 7.1$ Estimate standard deviation of ROM at 1 year postoperative. This value is based on results (preop and 1 year postop) from literature

N = 95 (including 7.5% lost to follow-up) per group

RANDOMIZATION

Patients will be randomized to receive M2A Magnum (trial group), or M2A Taper (control group). Patients have an equal opportunity of being assigned to the trial group or control group. Specifically:

In case of unilateral patients, the affected side of hip will be randomized to one of two groups. In case of bilateral patients, both sides of hip will be randomized to the same device (M2A Taper or M2A Magnum).

The randomization will occur via a random number generator (manual or computer). Block randomization will be used. Blocks of K patients will be created where K = 4. The possible sequences are AABB, BBAA, ABAB and BABA. Two sets of randomization blocks will be followed by unilateral and bilateral patients respectively. For unilateral patients, A or B represents the device assigned to affected side of the hip. For bilateral patients, A or B represents the device assigned to both affected sides of the hip.

The doctor or other health care professional does not choose the participants for each group. For Patients satisfying inclusion criteria, randomization will occur by retrieving the next randomly generated group assignment.

INSTITUTIONS

there will be 5 sites recruiting 150 Magnum cases and 150 M2A Taper cases.

PARTICIPANT DATA MANAGEMENT

The following table summarizes data collection required during the course of the study.

	PRE-OP	OP	IMMEDIATE POST-OP	3 MO	6 MO	1 YR	2 YR	3 YR	4 YR	5 YR	7 YR	10 YR
Informed Consent	X						X*					
Demographic and Historical Record	X											
Operative Record		X										
Metal ion concentrations in blood and urine	X			X	X	X	X	X	X	X	X	X
Renal function (Creatinine Clearance Test)	X			X	X	X	X	X	X	X	X	X
Harris Hip Score (Including ROM)	X			X	X	X	X			X		X
Postoperative Thigh Pain				X	X	X	X			X		X
EQ5D	X			X	X	X	X	X	X	X	X	X
UCLA Activity Score	X			X	X	X	X	X	X	X	X	X
Radiographic Assessment	X		X	X	X	X	X	X	X	X	X	X
MRI Assessment										X		
Additional Image Assessment (MRI / CT)	As needed (for symptomatic patients only: having pain/discomfort on hip, higher ion concentration than 7ppb or suspect of ARMD etc)											
Complications & Revisions	Anytime											

* Informed consent will be obtained at the time of 2 year follow-up to continue to participation of the study.

METAL ION ANALYSIS

Blood (serum) and urine will be collected at predetermined follow-up periods (3m, 6m, 1y, 2yr[3-5], , 3y, 4y, 5y, 7 yr and 10y) to measure metal ion levels released (Co and Cr) from the articulating surfaces of M2A Magnum or M2A Taper cases. To create a baseline, blood (serum) and urine samples will also be taken preoperatively.

All patients agree to the invasive procedure of giving blood and will provide blood and urine samples for measurement of metal ions pre-operatively. Patients with an existing metal implant or fixation device will be excluded. The analysis of metal ion concentrations within both blood and urine will be conducted. Blood and urine sample collection and metal ion analysis follow the protocol included in the Appendix I.

Metal ion analysis will be conducted separately for unilateral and bilateral patients.

RENAL FUNCTION ANALYSIS

Creatinine and creatinine clearance tests measure the level of the waste product creatinine in your blood and urine. These tests tell how well your kidneys are working. The substance creatine is formed when food is changed into energy through a process called metabolism. Creatine is broken down into another substance called creatinine, which is taken out of your blood by the kidneys and then passed out of your body in urine. See a picture of the kidneys.

Creatinine is made at a steady rate and is not affected by diet or by normal physical activities. If your kidneys are damaged and cannot work normally, the amount of creatinine in your urine goes down while its level in your blood goes up.

A creatinine clearance test measures how well creatinine is removed from your blood by your kidneys. A creatinine clearance test gives better information than a blood creatinine test on how well your kidneys are working. A creatinine clearance test is done on both a blood sample and on a sample of urine. eGFR /Creatinine clearance will be calculated, analyzed as described in Guideline for Chronic Kidney Disease (published by Japanese Society for Nephrology)[7] Renal function analysis will follow the protocol in Appendix I. All patients entered into the study agree to the invasive procedure of giving blood and urine samples for measurement of creatinine at preoperative and various postoperative visits.

Renal function will be conducted separately for unilateral and bilateral patients.

PARTICIPANT EVALUATION SCHEDULES

All study Participants are expected to return for clinical, metal ion analysis and radiographic evaluation at specific follow-up intervals. The following table summarizes the schedule for post-operative follow-up time intervals:

Evaluation Schedule		
Interval	**Follow-Up Window**	**Months Post-Op Range**
Immediate Post-Op	± 2 weeks	Immediate post-op < 2 weeks
3 months follow-up	± 1 month	2-4
6 month follow-up	± 1 month	5-7
1 year follow-up	± 2 months	10-14
2 year follow-up	± 2 months	22-26
3 year follow-up	± 3 months	33-39
4 year follow-up	± 3 months	45-51
5 year follow-up	± 3 months	57-63
7 year follow-up	± 3 months	81-87
10 year follow-up	± 3 months	117 - 123

COMPLICATIONS (ADVERSE EVENTS)

All adverse events, device related (*see Risk Analysis Section)* or non-device related, are to be recorded. Anticipated adverse events are defined, but not limited to, the following:

- Operative side hip manipulations or injections
- Operative side dislocations
- Operative side aspiration of joint fluids
- Falls
- Accidents- motor vehicle, motorcycle, ATV, etc.
- Death
- Any event in which the subject requires hospitalization or outpatient medical attention, including but not limited to: myocardial infarction, cerebral vascular accident, pulmonary emboli, gastrointestinal disorders, or a new diagnosis of a chronic condition (lung disease, renal disease, cancer, diabetes mellitus, hematological abnormalities, etc.).

RADIOGRAPHIC PROTOCOL

Radiographic Views
The study requires a full pelvic anteroposterior (AP) view and a lateral view.

Assessment Procedure
Assessments will be recorded on the radiographic assessment form at Immediately post-op, 3months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years.

The radiographic films will be marked for measurements as described in the following "Measurement angles and reference points" section for immediate post-operative time period only.
The immediate post-operative film will be used as an index (bench mark) for subsequent follow-up assessments.

The radiographic assessment definitions are as follows:

Full-pelvic Anteroposterior (AP) Radiograph: This radiographic view will be obtained with the patient placed in the supine position with the bilateral hip joint in a neutral position. The radiation beam must be centered on the pubic symphysis. The X-ray should include the total prosthesis, including the entire length of the femoral stem.

Lateral Radiograph: A cross-table lateral radiograph will be obtained with the patient placed in the supine position with the contralateral hip flexed to 90^{o} or maximally. The direction of the radiation beam is parallel to the examination table and is at 45^{o} to the long axis of the body. Again, the X-ray should include the total prosthesis, including the entire length of the femoral stem.

Radiolucency or Radiolucent Lines: A radiographic clearing or line not exceeding 2 mm in width at the bone/implant interface.

Osteolysis: A progressive radiolucency greater than 2 mm in width in one or more zones not present on immediate post-operative radiographs and/or a peri-acetabular bony destructive lesion that is progressive in nature.

Migration: Medial or superior movement of the acetabular component exceeding 4 mm as compared to immediate post-operative radiographs.

Subsidence: A vertical settling or sinking of the femoral component exceeding 5 mm as compared to immediate post-operative radiographs.

Ectopic (Heterotopic) Ossification: Abnormal bone formation following surgery or trauma.

Heterotopic Ossification Classification: The Brooker classification is utilised to categorise the various levels of ossification:

- Class I: represents islands of bone w/in soft tissues about hip
- Class II: includes bone spurs in pelvis or proximal end of femur leaving at least 1 cm between the opposing bone surfaces
- Class III: represents bone spurs that extend from pelvis or the proximal end of femur, which reduce the space between the opposing bone surfaces to less than 1 cm
- Class IV: indicates radiographic ankylosis of the hip

Measurement angles and reference points

Acetabular angle of inclination (α)
The acetabular angle of inclination (α) is measured on an AP pelvic radiographic view. An inter-teardrop line and an intersecting line across the outer edges (medial and lateral edges) of the acetabular cup are drawn. The angle of inclination is measured at the intersection of these two lines (see Figure 1). An angle of less than 60° is considered normal and the change in position is measured over time. As stated in the clinical investigation plan, a change in angle of inclination of more than 4° over time will be considered a failure.

Acetabular cup position and migration (superior and medial)
The acetabular cup migration is measured on an AP pelvic radiograph (see Figure 1). The cup position in both the superior-inferior and medial-lateral direction must be measured from the immediate post-operative radiograph. The measurements will be made using the method described by Nunn *et al*[1]. To determine the acetabular position in the superior-inferior direction (*Ay*), the vertical distance between the centre of the cup (determined by bisecting the intersecting line across the outer edges of the acetabular cup) and the inter-teardrop line is measured. The medial-lateral position (*Ax*) is the measured horizontal distance between the point *x*, directly below the centre of the cup, and the nearest teardrop. All measured distances must be corrected for magnification. Migration of the acetabular component in both the superior and medial direction will be calculated by comparing the change in distance over time. A change in the distance of more than 4 mm will be considered a failure.

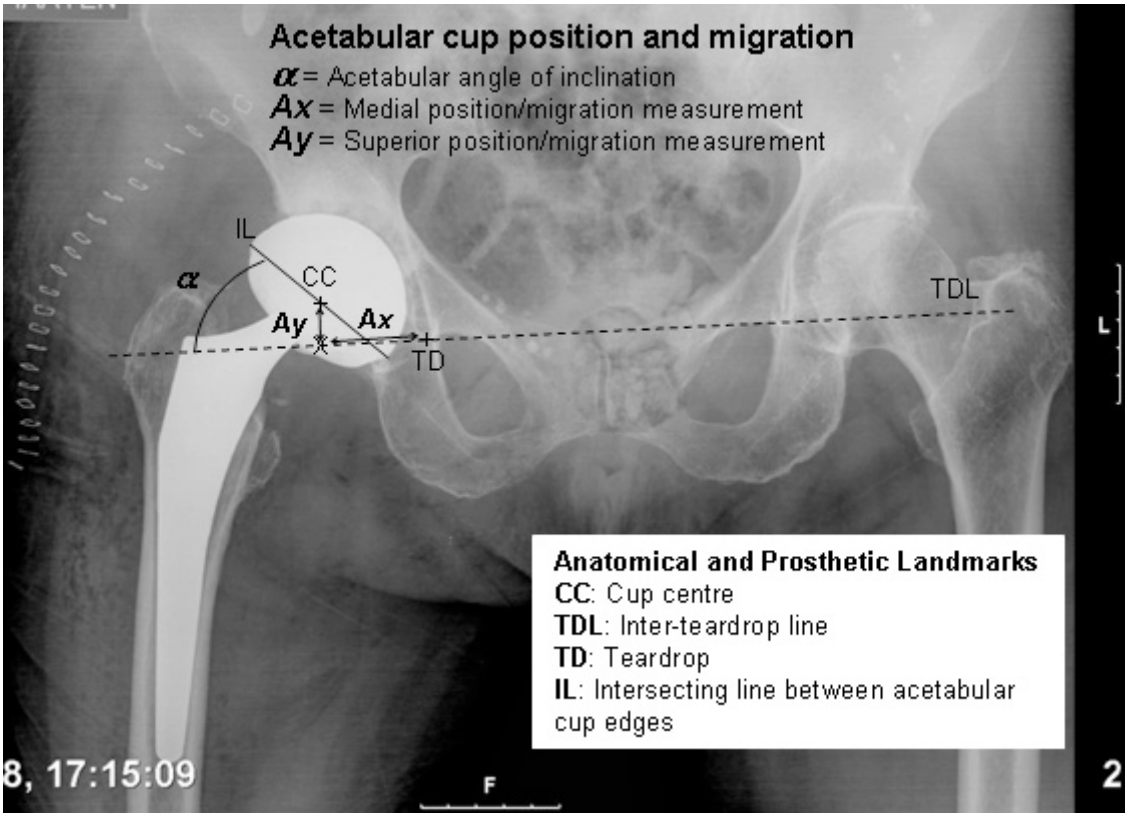


Figure 1. Measurement of acetabular component position, angle of inclination and migration.

Acetabular cup version angle (β)
The version angle of the acetabular cup (β) will be measured on the lateral X-ray using the method described by Arai *et al*[2]. A line perpendicular to the horizontal plane of the radiograph

[1] Nunn D, MAR Freeman, PF Hill and SJW Evans, "The measurement of migration of the acetabular component of hip prostheses". The Journal of Bone and Joint Surgery 71B (4), pp 629-631, 1989.
[2] Arai N, S Nakamura and T Matsushita, "Difference between 2 measurement methods of version angles of the acetabular component". The Journal of Arthroplasty Vol 22 No 5, pp 715-720, 2007.

and an intersecting line across the outer edges (medial and lateral edges) of the acetabular cup are drawn. The version angle (∠) is measured at the intersection of these two lines (see Figure 2). This technique allows an estimation of anteversion (shown in Fig 2), neutral position or retroversion of the acetabular component[3].

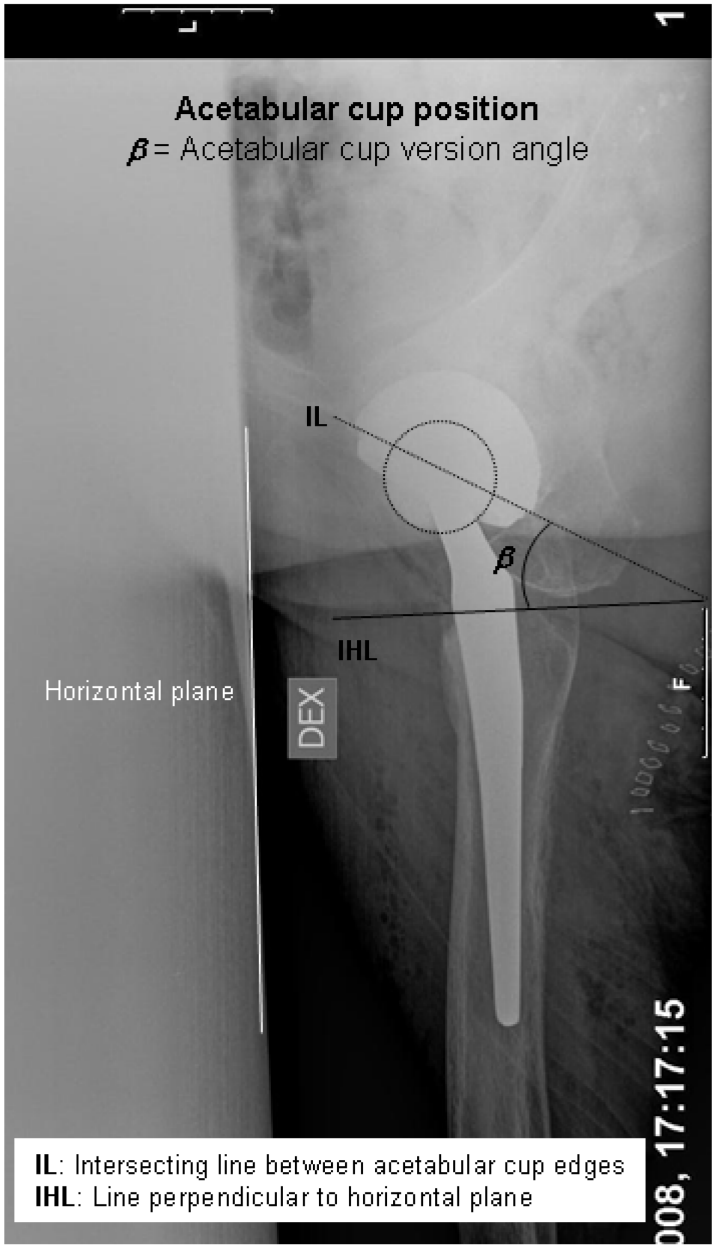


Figure 2. Measurement of acetabular cup version angle.

[3] Woo RY and BF Morrey, "Dislocations after total hip arthroplasty". The Journal of Bone and Joint Surgery 64, pp 1295-1306, 1982.

Femoral stem position and subsidence

To determine the position of the femoral stem the immediate post-operative radiograph will be measured. The measurements will be made using a modified version of the method described by Sutherland *et al*[4]. The vertical plane is parallel with the femoral canal. The vertical distance from the level of the superior tip of the greater trochanter to the level of the centre of the femoral head (*Fy1*) and the vertical distance from the shoulder of the femoral stem and the most proximal point on the lesser trochanter (*Fy2*) will be measured to determine the vertical position of the femoral stem (see Figure 3). The measured distances must be corrected for magnification. Subsidence of the femoral stem will be calculated by comparing a change in the vertical distances measured over time and a change in distance of greater than 5 mm will be considered a failure.

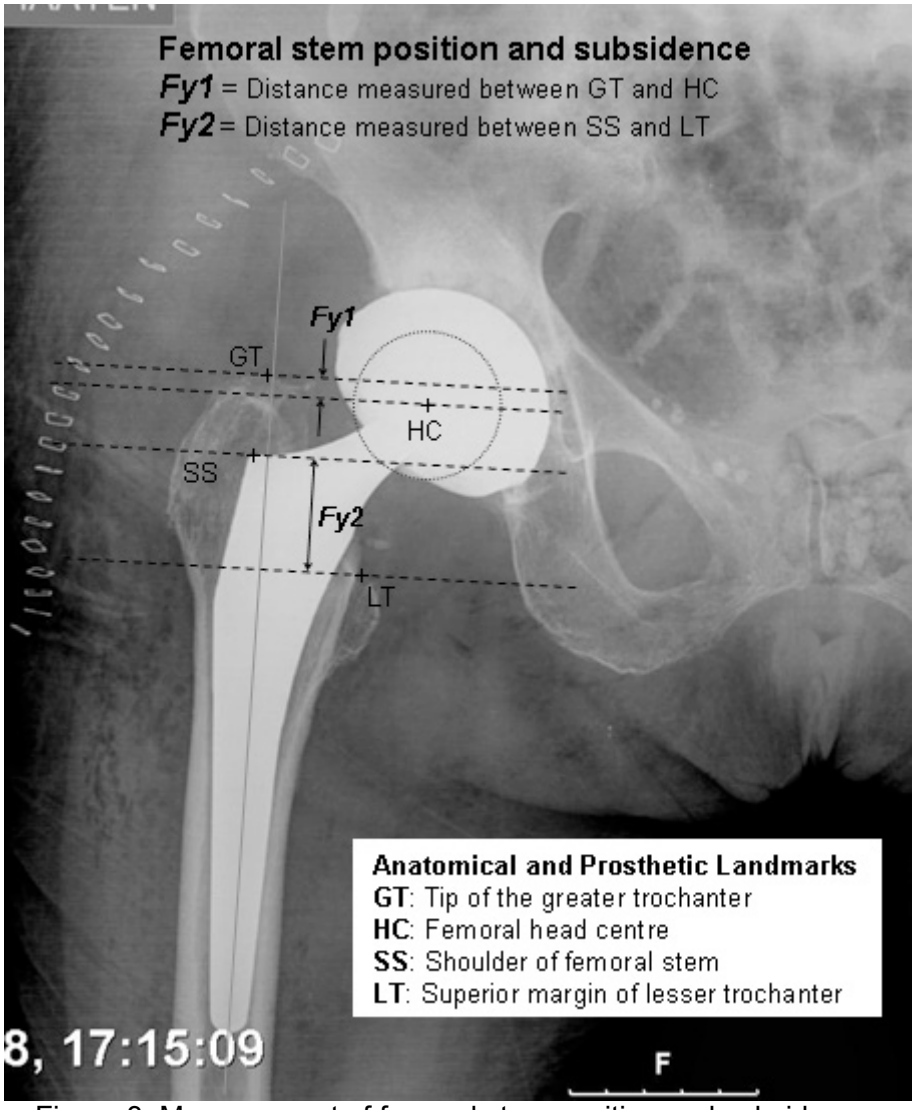


Figure 3: Measurement of femoral stem position and subsidence.

[4] Sutherland CJ, AH Wilde, LS Borden and KE Marks, "A ten-year follow-up of one hundred consecutive Muller curved-stem total hip-replacement arthroplasties". The Journal of Bone and Joint Surgery 64A, pp 970-982, 1982.

Radiographic Radiolucency Measurements

Radiolucencent lines at the bone-implant interface and evidence of osteolysis will be measured on both AP and lateral radiographs. The standard fourteen (14) Gruen zones will be used to record radiolucency surrounding the femoral component and the three (3) acetabular zones described by DeLee and Charnley will be used to record radiolucency surrounding the acetabular component (see Figure 4). The apparent thickness of the radiolucency within these zones will be recorded. Evidence of osteolysis (radiolucency > 2mm thickness) in the peri-prosthetic tissue of the acetabular or femoral component will be considered a failure.

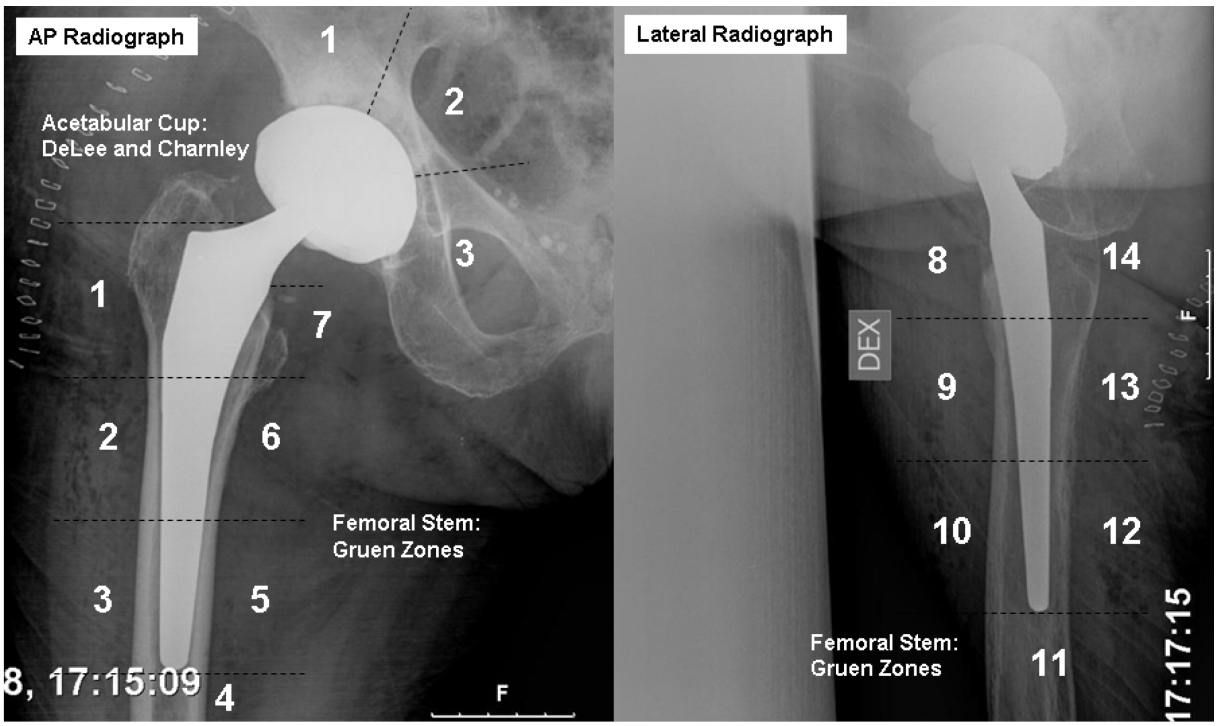


Figure 4: Radiographic zones for assessment of femoral and acetabular component radiolucency.

DATA COLLECTION

All sites will be required to complete and submit case report forms on Biomet's online database, Joint Assist 2.0, in a timely manner. Forms will be monitored for completeness and accuracy.

Further, it is imperative that the investigator answers all questions on the case report forms. All data should be accurate, indelible, legible, dated on the date of entry, and signed by initials, and/or formal signature by the authorized personnel documenting the data.

MONITORING PLAN

Prior to commencing the study the Monitor will provide the investigators with the necessary information to enable him/her to carry out his responsibilities. This information includes but not limited to:

- Investigator Brochure i.e. study protocol, investigator responsibilities, device information, etc.
- Ethical Committee Approval Information.

- Case Report Forms.
- Patient Consent Forms
- EDC user manual

The monitor of the evaluation periodically reviews the post-operative follow-up dates on all subjects for each evaluator. A follow-up schedule is then sent to each investigator, which illustrates any follow-up, reports which are due or missing. Every effort is made to assure that follow-up reports are completed in a timely manner, including contacting the evaluator by post, telephone or by personal visit when necessary. Also, during the course of the evaluation, the monitor will conduct periodic discussions with the investigator or staff to ensure that the evaluation is being conducted in accordance with the protocol. The monitor will maintain records of each visit or discussion.

CONFIDENTIALITY

To ensure study patients' privacy, all patients will be identified by unique identification numbers. All case report forms will only include patient IDs. It is the responsibility of the investigator to maintain a list of patient identification and Joint Assist 2.0 ID numbers.

Further the Joint Assist database is restricted, allowing a doctor to only view and enter data from his own patients. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

RISK ANALYSIS

This clinical study is to collect data on the THA w/ Magnum Acetabular, which is intended to help the participant gain mobility and decrease pain. Risks associated with this hip system include general surgical and hip arthroplasty risks. Due to the investigational nature of the system, there are unknown risks.

General Surgical Risks

As with any surgical procedure, there are risks involved with total joint replacement surgery. Potential adverse events include, but are not limited to: early or late infection perhaps necessitating device removal; component dislocation; damage to nerves and blood vessels; fracture of the bone or device; device loosening; allergic reactions to the metallic devices; phlebitis; long-term swelling; pulmonary embolization; and delayed wound healing. Other potential adverse effects include: prolonged illness; hematoma; wound dehiscence and/or drainage; the need for blood transfusions and/or further surgery; or permanent pain; deformity; and inconvenience. Risks associated with the anesthetic are those such as permanent brain damage, pneumonia, blood clots, and heart attack. Rarely some adverse events may be fatal. These possible adverse events are not unique to the Magnum System and, as stated above, may occur with any total joint replacement surgery.

As with any joint replacement post-operative activity, limitations may be imposed depending upon the participant's age, general health, baseline (pre-operative) activity level and baseline (pre-operative) condition of the hip and other joints.

Minimization of Risk

With the increased understanding of failure modes for total hip arthroplasty, pre-clinical testing and clinical results found in the literature, it is believed that none of the previously mentioned adverse events will occur in significant numbers. This study has reduced the potential risk to the participant through the following methods:

1. By defining a participant population that limits the exposure of the device to participants conforming to the proposed indications, exclusions, and age requirements
2. The surgical technique has been developed to help eliminate potential operative difficulties.

Reference:

1. Australian Orthopaedic Association (AOA) Hip and Knee Arthroplasty Report 2008.
2. Daniel J. Berry, Marius von Knoch, Cathy D. Schleck and William S. Harmsen, Effect of Femoral Head Diameter and Operative Approach on Risk of Dislocation After Primary Total Hip Arthroplasty, *J Bone Joint Surg Am.* 2005;87:2456-2463
3. Engh CA Jr, MacDonald SJ, Sritulanondha S, Thompson A, Naudie D and Engh CA; 2008 John Charnley award: metal ion levels after metal-on-metal total hip Arthroplasty: a randomized trial. Clin. Orthop. Relat. Res. 2009 Jan 467 (1): 101-11.
4. Daniel J, Ziaee H, Pradhan C, Pynsent PB, McMinn DJ. Blood and urine metal ion levels in young and active patients after Birmingham hip resurfacing arthroplasty: four-year results of a prospective longitudinal study. JBJS Br. 2007 Feb;89(2):169-73
5. Antoniou J, Zukor DJ, Mwale F, Minarik W, Petit A, Huk OL. Metal ion levels in the blood of patients after hip resurfacing: a comparison between twenty-eight and thirty-six-millimeter-head metal-on-metal prostheses. JBJS Am.2008 Aug;90 Suppl 3:142-8.
6. MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, Leung F; Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clin Orthop Relat Res. 2003 Jan;(406):282-96.
7. Guideline for Chronic Kidney Disease (CKD) http://www.jsn.or.jp/ckd/pdf/CKD01.pdf

Appendix I

Metal Ion Level and Renal Function Analysis Protocol (To be determined with SRL)