**PROTOCOL TITLE**

‘Migration in Total Hip Arthroplasty with a Cemented BiMobile cup: Better stability with more cement?’

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| **Short title** | **Be-Mobile** |
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| **Coordinating investigator/project leader** | ***L.W.A.H. van Beers, MSc*** |
| **Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)** | ***Prof. dr. R.W. Poolman***<br>***Orthopaedic Surgeon***<br>***OLVG, Amsterdam*** |
| **Sponsor (in Dutch: verrichter/opdrachtgever)** | ***OLVG*** |
| **Subsidising party** | ***Link Hamburg*** |
| **Independent expert (s)** | ***Prof. dr. J.C. Goslings***<br>***Surgeon***<br>***OLVG, Amsterdam*** |
| | |

**PROTOCOL SIGNATURE SHEET**

| **Name** | **Signature** | **Date** |
|---|---|---|
| **Sponsor or legal representative:**<br>***<please include name and function>*** | **Prof. dr. M.A.A.J. van den Bosch**<br>**Board of Directors, OLVG** | |
| **Principal Investigator:**<br>***<please include name and function>*** | **Prof. dr. R.W. Poolman**<br>**Orthopaedic surgeon, OLVG** | |

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **ABR** | **ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)** |
| **AE** | **Adverse Event** |
| **AR** | **Adverse Reaction** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CT** | **Computed Tomography** |
| **CV** | **Curriculum Vitae** |
| **DSMB** | **Data Safety Monitoring Board** |
| **GCP** | **Good Clinical Practice** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent Form** |
| **EC** | **Ethical Committee** |
| **RSA** | **Roentgen Stereophotogrammetry Analysis** |
| **(S)AE** | **(Serious) Adverse Event** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **THA** | **Total Hip Arthroplasty** |
| **Wbp** | **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)** |
| **WMO** | **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

## SUMMARY

**Rationale:** Total hip arthroplasty (THA) is a commonly performed surgery in patients with end-stage osteoarthritis (OA) of the hip. Although it is known as a successful procedure, (recurrent) dislocation after THA is a major problem and results in a deterioration in quality of life. Dislocation after THA is the number one cause of early revision surgery.

Dual-Mobility (DM) acetabular cups should provide more stability and biomechanically reduce the risk of (early) dislocation. Potential disadvantages of DM cups are increased liner wear, psoas impingement and loosening. This might result in more revision surgery at mid- and longer-term follow-up for the cemented cups. If the cemented fixation technique improves, this might diminish the disadvantages of more revisions due to loosening in cemented cups. High quality evidence guiding the best technique for cemented fixation is however lacking. The risk of implant loosening might be reduced by increasing the amount of cement used for cup fixation. It is currently unknown whether size of the implant, and thereby the amount of cement, affects stability and survival. To fill this gap in knowledge, this study will compare cup migration, as an indicator for loosening, in a new dual mobility cup (BiMobile, Waldemar Link GmbH & Co. KG, Hamburg, Germany), using a larger or smaller cup size (and thereby different amounts of cement: approximately 2mm or 4mm cement mantle). These results will also be compared with the Avantage cup (ZimmerBiomet), which is yet considered as a standard dual mobility cup in the Netherlands. Migration will be measured with Rontgen Stereophotogrammetry Analysis (RSA), which is currently the gold standard for measuring early migration and predicting long term survival. A relatively new and less intensive way to measure migration of prostheses is the use of computer tomography (CT) scans, however there is still little scientific evidence on how accurately this can be done. This study therefore also measures the accuracy with which migration is measured, between CT scans and RSA.**Objective**: The main objective of this study is to compare the (early) migration of the cemented BiMobile cup at two year post-surgery between two different cup sizes after standard optimal reaming, and consequently adjusting the cement mantle into circa 2 or 4 mm, in patients with a primary cemented THA. Additionally, the results of the BiMobile cup will be compared to the Avantage cup, which is placed with a standard cup size, resulting in a cement mantle of approximately 2 mm.

**Study design:** A prospective single centre blinded randomised controlled trial.

**Study population:** At the outpatient clinic of OLVG, all patients who meet the criteria to undergo a cemented THA will be screened for the in- and exclusion criteria detailed in section 2.

**Intervention (if applicable)**:

Group A: 25 patients will receive a cemented THA with a BiMobile dual mobility cup, in a standard size after optimal reaming, resulting in a cement mantle of approximately 2mm.

Group B: 25 patients will receive a cemented THA with a BiMobile dual mobility cup, in one size smaller than standard after optimal reaming, resulting in a cement mantle of approximately 4mm.

Group C: 25 patients will receive a cemented THA with an Avantage dual mobility cup, in a standard size after optimal reaming, resulting in a cement mantle of approximately 2mm.

**Main study parameters/endpoints:** Migration of the acetabular cup at two year postoperative, measured with RSA. RSA x-rays will be collected at discharge, 6 weeks, 6 months, 1 year and 2 years after surgery. CT scans will be collected at discharge and 2 years after surgery.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The risk for patients participating in this study is minimal, above the known risks for a THA procedure. In addition to the benefits from the primary hip arthroplasty procedure, patients might benefit from fact that all study patients receive a dual mobility acetabular cup, instead of a unipolar acetabular cup. Dual mobility cups are assumed to reduce the risk of hip dislocation. Patients may undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance. The devices that will be used, are CE marked and will be used according to it's labelling. The effective radiation dose per RSA-radiograph is 70 µSv. Five RSA radiographs (70 µSv per radiograph) and two computed tomography (CT) scans (0.3 mSv) will be taken over 5 years of follow-up, additionally to standard care. With this study, a total of 0.95 mSv is taken into account. The annual natural exposure is 2.5 mSv.

## INTRODUCTION AND RATIONALE

Total hip arthroplasty (THA) is commonly performed in patients with end-stage osteoarthritis (OA) of the hip. THA is known as a highly successful procedure that improves the patients' physical functioning and reduces pain. Although it is known as a successful procedure, (recurrent) dislocation after THA is a major problem and results in a deterioration in quality of life.(1) Dislocation after THA is the number one cause of early revision surgery. At one year follow-up 34.5% of all (N=2035) revisions between 2011 and 2015 in the Netherlands were due to dislocation.(2) Most dislocations occur during the first year after surgery, of which approximately 50% occurs within the first 3 months postoperative.(3-6) In a focus group with healthcare professionals and patients in four Dutch hospitals, patients indicated that the prevention of hip dislocation is important to them.

Dual-Mobility (DM) acetabular cups are thought to provide more stability and biomechanically reduce the risk of (early) dislocation compared to regular unipolar acetabular cups.(7-10) Potential disadvantages of DM cups are increased liner wear, psoas impingement and loosening. This might result in more revision surgery at mid- and longer term follow-up for the cemented cups, which has been demonstrated in the Dutch and Australian orthopaedic registries.(11, 12) If the cemented fixation technique improves, this might reduce the number of revisions due to loosening in cemented cups. High quality evidence guiding the best technique for cemented fixation is however lacking. There is evidence that enough bone should be removed, including the removal of the subchondral bone plate; this is known as optimal reaming.(13) The risk of implant loosening might be reduced by increasing the amount of cement used for cup fixation. However, it is currently unknown whether the amount of cement, which depends on the size of the cup, affects stability and survival.(14) To fill this gap in knowledge, this study will compare micro migration of the cup, as an indicator for loosening, in a new dual mobility cup (BiMobile, Waldemar Link GmbH & Co. KG, Hamburg, Germany), using a larger or smaller cup size (and thereby different amounts of cement: approximately 2 millimeter (mm) or 4 mm cement mantle). These results will additionally be compared with the Avantage cup (ZimmerBiomet), which is considered as the standard dual mobility cup in the Netherlands.(15, 16) Migration will be measured with Rontgen Stereophotogrammetry Analysis (RSA), which is currently the gold standard for measuring early migration and predicting long term survival of the implant. A relatively new and less intensive way to measure migration of prostheses is the use of computer tomography (CT) scans, however there is still little scientific evidence on how accurately this can be done.(17-21) This study therefore also measures the accuracy with which migration is measured, between CT scans and RSA.

## 1. OBJECTIVES

The main objective of this study is to compare the (early) migration of the cemented BiMobile cup up to two year post-surgery between two different cup sizes after standard optimal reaming, and consequently adjusting the cement mantle into circa 2 or 4 mm, in patients with a primary cemented THA. Additionally, the results of the BiMobile cup will be compared to the Avantage cup, which is placed with a standard cup size, resulting in a cement mantle of approximately 2 mm.

Secondary objectives are to analyze patient reported outcome measures (PROMs), device-related complications, pain, satisfaction, reoperations and implant survival. All secondary variables will be measured up to five year postoperative.

**STUDY DESIGN**

A prospective single centre double blinded randomised controlled trial, to compare the BiMobile cup with a standard amount of cement (standard cup size) after optimal reaming, with the BiMobile cup with a larger amount of cement (one size smaller cup) after optimal reaming.

A third randomised group will receive the Avantage cup, with a standard amount of cement (see figure 1).

All patients will be followed-up until 5 years after surgery. The study will be conducted in OLVG Amsterdam.

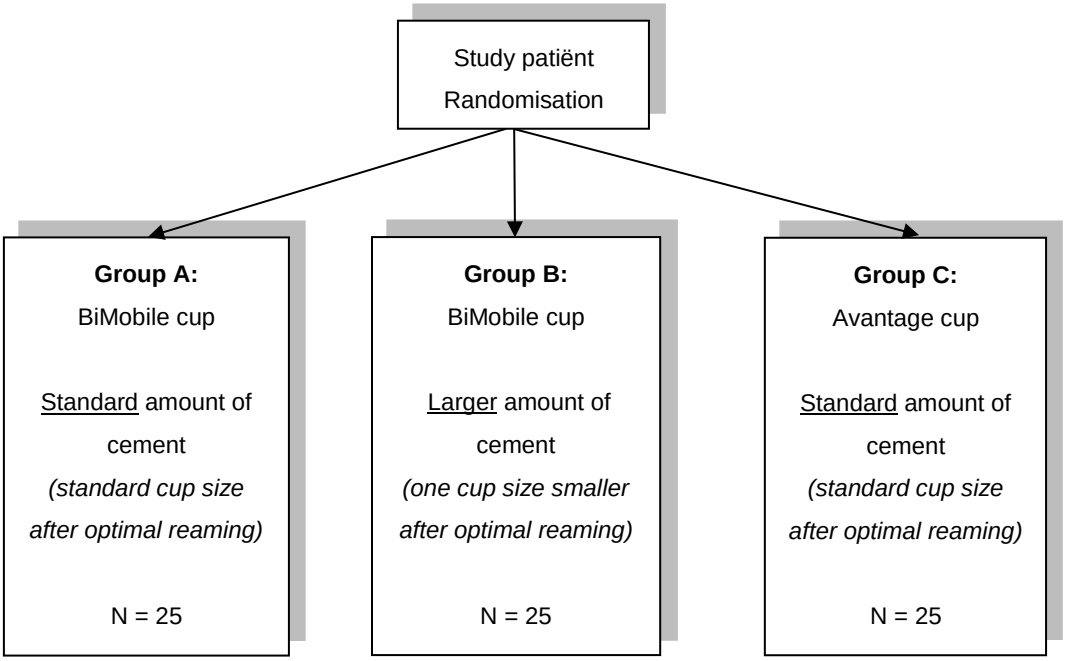


Figure 1. Flowchart with the three arms of the BiMobile study.

# 2. STUDY POPULATION

## 2.1 Population (base)

At the outpatient clinic of OLVG, all patients that meet the criteria to undergo an elective primary cemented THA will be screened for the following in- and exclusion criteria.

## 2.2 Inclusion criteria

- Patient requiring an elective primary cemented THA.
- Male patient ≥70 years old and female patient ≥65 years old.
- Ability and willingness to follow instructions and to return for follow-up evaluations.
- The patient is able to understand the meaning of the study and is willing to sign informed consent.
- Understanding the Dutch language.

## 2.3 Exclusion criteria

- The patient is morbidly obese, defined as Body Mass Index (BMI) of ≥ 40.
- The patient is expected to need lower limb joint replacement for another joint within one year.
- The patient has a systemic or metabolic disorder leading to progressive bone deterioration.
- The patient has a deformity or disease located in other joints than the hip that needs surgery and that is limiting their ability to walk.
- The patient has an active or suspected latent infection in or around the hip joint.
- The patient's bone stock is compromised by a disease or infection which cannot provide adequate support and/or fixation to the prosthesis.
- The patient is unable or unwilling to sign informed consent for this study.
- The patient is deemed unsuitable for participation in the study based on the investigator's judgment.

## 2.4 Sample size calculation

Based on current RSA studies and the high degree of sensitivity and accuracy of measurements of migration, relatively small patient groups should show statistical significant outcome.(22) A standardized phantom experiment for the model-based RSA, was performed with an acetabulum cup (Delta-TT cup, LINK) under simulated *in-vivo* conditions (Table 1). In such a phantom experiment, there is no actual movement between the components and the bone, therefore, the observed relative motions represent the

measurement error of these specific components using model-based RSA. These standard deviations are good estimations for the accuracy of the method that can be achieved *in-vivo*. The relative motions presented in table 1 are smaller than the accepted relative motions presented by Baad-Hansen et al.(23)

Table 1: Relative motions of the Delta-TT cup with respect to the acetabulum bone markers calculated using the elementary geometric shape (EGS) model (n = 10).

| | **Translations (mm)** | | | **Rotations (deg)** | | |
|---|---|---|---|---|---|---|
| | **Trans (x)** | **Long (y)** | **Sag (z)** | **Trans (x)** | **Long (y)** | **Sag (z)** |
| **Mean** | 0.001 | 0.003 | -0.009 | -0.069 | -0.033 | 0.033 |
| **St. dev** | 0.094 | 0.041 | 0.074 | 0.182 | 0.276 | 0.396 |
| **Min** | -0.145 | -0.048 | -0.113 | -0.410 | -0.493 | -0.833 |
| **Max** | 0.170 | 0.098 | 0.101 | 0.137 | 0.314 | 0.618 |

Sample size calculation based on a t-test was done, assuming normal distribution of migration data and standard deviation of translation of 0.3 mm within the patient collective at two years follow-up.(23) When the sample size in each group is 25, a two group 0.05 t-test will have 90% power to reject the null hypothesis that the two cups are not equivalent (= the difference in means, is 0.3 mm or farther from zero in the same direction) in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0 and the common standard deviation is 0.3 mm. This difference of 0.3 mm translation can be considered as a clinically relevant difference.

For the cup rotations, the highest standard deviation was 0.8 degree within the patient collective at two years follow up.(23) When the sample size in each group is 25, a two group 0.05 t-test will have 90% power to reject the null hypothesis that the two cups are not equivalent (= the difference in means, is 0.8 degree farther from zero in the same direction) in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0 and the common standard deviation is 0.8 degree.

## 3. TREATMENT OF SUBJECTS

Treatment group A:

25 patients will receive a cemented THA with a BiMobile dual mobility cup, in a standard size after optimal reaming, resulting in a cement mantle of approximately 2 mm.

Treatment group B:

25 patients will receive a cemented THA with a BiMobile dual mobility cup, in one size smaller than standard after optimal reaming, resulting in a cement mantle of approximately 4 mm.

Treatment group C:

25 patients will receive a cemented THA with an Avantage dual mobility cup, in a standard size after optimal reaming, according to the investigator's brochure, resulting in a cement mantle of approximately 2 mm.

### 3.1 Investigational product/treatment

BiMobile cup

The BiMobile acetabular cup is a new cemented dual mobility cup (Waldemar Link GmbH & Co. KG, Hamburg, Germany). We will randomize between two different sizes of cups, resulting in approximately a 2 mm or 4 mm cement mantle.

Regardless of randomization group, a 28 mm ceramic head (Biolox Delt, Ceramtec) will be used. The anatomic Lubinus SPII stem will be used in all randomisation groups. The SPII stem (Waldemar Link GmbH & Co. KG, Hamburg, Germany) is the most used cemented stem worldwide, with excellent results (survival up to 20 yr of 93.3%(24)), and can therefore be considered as the gold standard in cemented hip arthroplasty. For both stem and cup high viscosity cement will be used.

All participating orthopaedic surgeons will have experience with placing a dual mobility cup.

### 3.2 Surgery

The prostheses are placed according to the instruction manual by an experienced surgeon using a posterolateral approach and instrumentation.

### 3.3 RSA procedures

Roentgen Stereophotogrammetric Analysis (RSA) will be used to determine the micromotion of the components with respect to the bone. For this purpose, one-millimetre-diameter tantalum beads will be inserted in the surrounding bone of the prosthesis during surgery using a special insertion instrument.

The RSA X-ray which is taken one or two days after surgery is used as baseline. When there are not enough markers visible in the baseline RSA X-ray and this does not improve by placing the patient in another position, the patient will be excluded from the study (secondary exclusion criterium).

### 3.4 Use of co-intervention (if applicable)

Not applicable.

### 3.5 Escape medication (if applicable)

Not applicable.

# 4. INVESTIGATIONAL PRODUCT

## 4.1 Name and description of investigational product(s)

The LINK BiMobile Dual Mobility System is a new cemented acetabular cup (Waldemar Link GmbH & Co. KG, Hamburg, Germany). The metal shell is made from biocompatible and resilient EndoDur™ CoCrMo material and is mirror polished on the inner surface to minimize wear. The cemented BiMobile™ Cup has a satin finished surface.
The Standard UHWMPE Liner can be combined with 22 mm or 28 mm CoCrMo or ceramic Link® Prostheses heads. For this study, a 28 mm ceramic head will be used, regardless of randomization.

## 4.2 Summary of findings from non-clinical studies

Extensive product information of the implants can be found in the Product Rationale folder and Surgical Technique folder which are included as attachments 12.1 and 12.2.
Preclinical tests were performed for the Primary Implant Stability, Range of Motion, Functional and Interface analysis, Toxicity, Liner snap-in force, Wear testing and Transport Validation. For detailed information please consult the attachments.
In conclusion, all conducted investigations showed no irregularities and all established acceptance criteria were passed. The conducted studies imply that if the surgical technique is followed, the BiMobile acetabular cup system is safe to use. Hence, the BiMobile acetabular cup system and all corresponding instruments were evaluated as safe for the clinical application.

## 4.3 Summary of findings from clinical studies

No clinical studies have been conducted with the BiMobile cup. Current study will be the first clinical trial with this implant.

## 4.4 Summary of known and potential risks and benefits

Primary hip arthroplasty has important benefits, e.g. reduced pain and improved range of motion. Patients in the current study undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance and the potential decreased risk of dislocation due to the dual mobility cup instead of a regular unipolar cup.

The effective radiation dose per RSA-radiograph is 70 µSv. Five RSA radiographs, over 5 years of follow-up, will be taken additionally to standard care. Two computed tomography (CT)

scans of the hip will be made postoperative. The effective radiation dose per CT of the hip is 0.3 mSv. With this study, a total of 0.95 mSv is taken into account. The annual natural exposure is 2.5 mSv.

### 4.5 Description and justification of route of administration and dosage

Not Applicable

### 4.6 Dosages, dosage modifications and method of administration

Not Applicable

### 4.7 Preparation and labelling of Investigational Medicinal Product

Not Applicable

### 4.8 Drug accountability

Not Applicable

## 5. NON-INVESTIGATIONAL PRODUCT

### 5.1 Name and description of non-investigational product(s)

Avantage cup

Avantage is a Dual Mobility Acetabular System introduced by Biomet in 1998, to address patients with high risk of dislocation. Since 2005, the Avantage system has been the N°1 cementless and cemented dual mobility cup on the market.(25, 26)
In OLVG, the Avantage cup (ZimmerBiomet, Warsaw, IN) is used as the standard dual mobility acetabular cup. After optimal reaming, a standard size cup will be placed.

### 5.2 Summary of findings from non-clinical studies

The Avantage cemented cup has an Orthopaedic Data Evaluation Panel (ODEP) ‘5A’ rating, indicating that there is strong evidence of at least 5years follow up for this implant.(15) This rating means that a minimum cohort of 250 hips is studied (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) demonstrating Kaplan-Meier survivorship data of better than or equal to 95% (showing confidence limits on the data with the lower limit of 90%) at the benchmark of five years.
In The Netherlands, the Dutch Orthopaedic Association (NOV) has given a ‘1B’ rating, indicating that this implant has a revision percentace of 5% or less, with a follow up of 5 years.(16)

Furthermore, studies have been carried out to test strength, wear resistance and prevention of oxidation.(25)

### 5.3 Summary of findings from clinical studies

A good survival of 96.3 – 96.9% is shown in multiple studies.(25, 27)
In The Netherlands in 2016, an Avantage cup was used in 5.3% of all (N=9005) cemented THA's.(28)

### 5.4 Summary of known and potential risks and benefits

The Avantage cup is already used in standard care in most hospitals in The Netherlands. The ODEP rating 5A and NOV rating 1B indicate that this implant can be used in usual care.(15, 16) Revision rate at five years postoperative 4.0% (3.0-5.3).(11)

### 5.5 Description and justification of route of administration and dosage

Not applicable

### 5.6 Dosages, dosage modifications and method of administration

Not applicable

### 5.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

### 5.8 Drug accountability

Not applicable

# 6. METHODS

## 6.1 Study parameters/endpoints

### 6.1.1 Main study parameter/endpoint

Migration of the acetabular cup at two year postoperative, measured with RSA and CT. RSA X-rays will be collected at discharge, 6 weeks, 6 months, 1 year and 2 years after surgery. Low-dose CT scans of the hip will be collected at discharge and 2 years after surgery.

### 6.1.2 Secondary study parameters/endpoints (if applicable)

Physical functioning, quality of life, pain and patient satisfaction will be scored with PROMs, consisting of: numeric rating scale (NRS) for pain in rest and during loading, Hip disability and Osteoarthritis Outcome Score Physical Short form (HOOS-PS), EQ-5D and an anchor question about general daily functioning. All PROMs will be collected prior to surgery, at 6 months, 1 year, 2 years and 5 years after surgery. All implant related (serious) adverse events including reoperations and survival of the THA (cup and stem component) will be collected up to 5 years after surgery.

### 6.1.3 Other study parameters (if applicable)

Surgical characteristics such as surgical time, blood loss and implant size will be collected from the surgical report. Prior to surgery demographic data and medical history will be collected. Standard radiographs will be used for analysing the quality of the cement mantle (i.e. cement cracks, cortical hypertrophy), component position, rate of radiolucent lines (>2 mm), loosening and subsidence. In addition, CT scans will be used to assess cement mantle thickness and to compare the accuracy with which migration is measured, between CT scans and RSA.

## 6.2 Randomisation, blinding and treatment allocation

After signing informed consent, the patients will be randomized in one of the three study groups by the researcher, using an online randomisation program (CASTOR). Patients will be blinded for group allocation. The principal investigator and the participating surgeons may divert from the randomization scheme based on intra-operative findings. Any deviation from the assigned treatment group will be reported as a deviation from protocol.

### 6.3 Study procedures

During the pre-operative visit, patients who are potential candidates for this study will be screened to determine if they meet the inclusion / exclusion criteria. If the patient is a candidate, the investigator will propose participation in the study to the patient, according to GCP guidelines. Patients must sign an ethical committee (EC) approved study informed consent form (ICF) prior to participating in any study related activities. Once the subject has consented, pre-operative data will be collected including: demographics and medical history, NRS for pain in rest and during loading, HOOS-PS, EQ-5D and standard X-rays. A computed tomography (CT) scan will be taken at discharge and 2 years postoperative. The RSA X-rays will be taken at discharge, 6 weeks, 6 months, 1 year, and 2 years postoperative). Also the patients are asked to fill out questionnaires. See table 2 for an overview of all measurements and follow-up moments.

An independent party, RSA*core* of the Department of Orthopaedics of LUMC will be responsible for the analysis of the RSA images. A study site specific standard operation procedure (SOP) to make RSA radiographs will be available at the department of radiology. The anonymous RSA images can be directly uploaded to the secure website of the RSA*core*. It is desirable that the images are uploaded as soon as possible, especially the direct postoperative RSA images, because RSA*core* is then able to provide direct feedback about the quality of the images. In case the RSA images are not of good quality or too many markers are missing and the patient is still present, the RSA images can be retaken. After analysis, RSA*core* will send back a report. RSA*core* will perform the RSA related data analysis and will provide an interim report when the 1 year postoperative data is complete and a final report after 2 years.

Table 2: Overview of follow-up moments.

| **Evaluation moment** | **Pre-op** | **Intra-op** | **Dis-charge** | **6 wk** | **6 mth** | **1 yr** | **2 yr** | **5 yr** |
|---|---|---|---|---|---|---|---|---|
| *Time window* | | | | *±4d* | *± 2 wks* | *± 4 wks* | *± 8 wks* | *± 16 wks* |
| **Preoperative (Inc./Ex. Criteria)** | x | | | | | | | |
| **Surgical Details** | | x | | | | | | |
| **PROMs** | x | | | | x | x | x | x |
| **RSA röntgenanalysis** | | | x | x | x | x | x | |
| **CT** | | | x | | | | x | |
| **AP and LAT X-rays** | x | | x | | | | | |

| | |
|---|---|
| **(Serious) Adverse Device Events, if necessary, Study termination** | Anytime |

PROMs: Patient Reported Outcome Measures, RSA: Rontgen Stereophotogrammetry Analysis, CT: Computed Tomography, AP: Anterior-Posterior, LAT: Lateral.

### 6.3.1 RSA procedure

The RSA set-up consist of two synchronized roentgen tubes positioned approximately 1.5 meter above two roentgen cassettes (35 X 43 cm) at a 20° angle to the vertical. Both roentgen tubes simultaneously expose the roentgen film (Figure 2). A calibration box is used to calibrate the experimental set-up.

The RSA X-ray which is taken one or two days after surgery (before loading) is used as baseline. Since the tantalum beads are fixed in the bone around the implants, the position of the implant relative to the bone can be calculated. Taking these bone markers as reference points, the spatial translations and rotations of the component during follow-up can be calculated.(22, 29) The bone markers need to be well fixated in the bone. Bone markers are defined unstable when they move more than 0.3 mm with respect to the other bone markers. Unstable markers will be excluded from analysis.(30) When there are not enough markers visible in the baseline RSA X-ray and this does not improve by placing the patient in another position, the patient will be excluded from the study (secondary exclusion criterium).

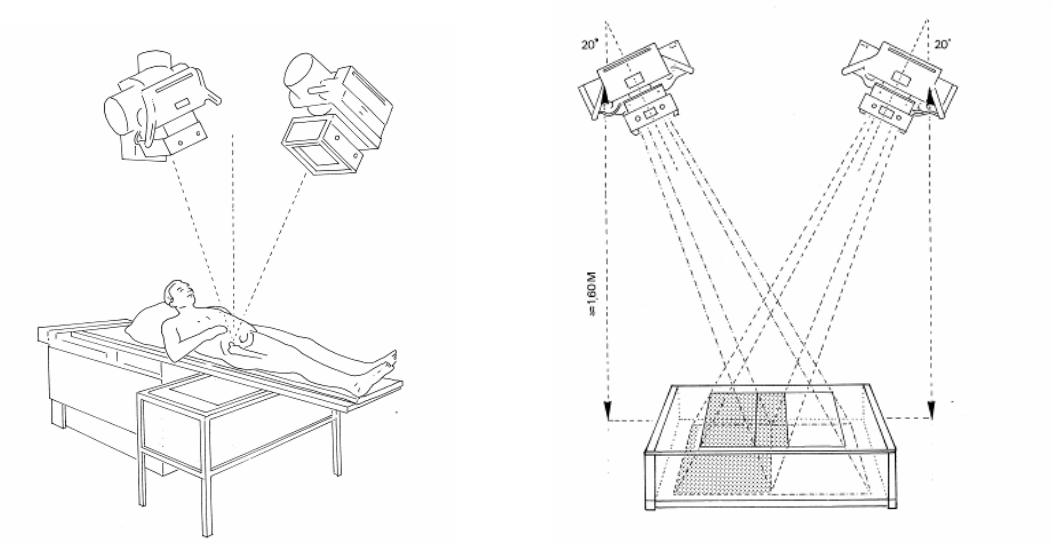


Figure 2: A uniplanar RSA arrangement. Two X-ray tubes are focused on the joint under examination. A calibration cage is placed underneath the X-ray table. It holds two X-ray films positioned next to each other.(22)

### 6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. They will be asked for the reason for withdrawal, but do not have to answer if they do not want to. Furthermore, the investigator can decide to withdraw a subject from the study for urgent medical or other reasons.
When a patient withdraws from the study, all data collected prior to the moment of withdrawing will be used for study analysis, unless the patient also withdraws consent for use of this data.

#### 6.4.1 Specific criteria for withdrawal (if applicable)

### 6.5 Replacement of individual subjects after withdrawal

Subjects for which not enough markers are visible on the first RSA-radiograph will be excluded from the study. These patients will be replaced, to ensure that a minimum of 25 patients per group remain.
Subjects who withdraw from the study for other reasons than the amount of visible markers will not be replaced, as long as a minimum of 20 patients per group remains. Otherwise, additional subjects will be recruited.

### 6.6 Follow-up of subjects withdrawn from treatment

The study data of withdrawn patients will be used until the moment of drop-out, unless a patient objects to this.
Patients will be treated according to the best medical judgment of the orthopaedic surgeon, regardless of the study protocol or withdrawal from the study.

### 6.7 Premature termination of the study

Because the devices used in this study are CE marked and will be used according to its labeling, there are no preconceived reasons for premature termination of the study. Upon the principal investigator's decision to terminate or suspend the study, the involved parties and EC will be notified promptly, stating the reasons.

## 7. SAFETY REPORTING

### 7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited EC without undue delay of a temporary halt including the reason for such an action. The study will be suspended

pending a further positive decision by the accredited EC. The investigator will take care that all subjects are kept informed.

## 7.2 AEs, SAEs and SUSARs

### 7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the RSA procedure or implants. Only relevant adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. The following AE's are directly related to the surgical procedure, and will therefore not be recorded by the investigator: nausea, headache, pain, haemorrhage and wound leakage.

### 7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs, as defined above, to the sponsor without undue delay after obtaining knowledge of the events.

The investigator will report the SAEs, as defined above, through the web portal *ToetsingOnline* to the accredited EC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

### 7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

### 7.3 Annual safety report

Not applicable.

### 7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

### 7.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

The additional risk of the use of the BiMobile cup over and above the risks of standard care, as well as the risk of extra X-rays and the placement of tantalum beads, are deemed to be negligible and therefore no DSMB will be established.

## 8. STATISTICAL ANALYSIS

Descriptive data will be summarized by treatment group. For parameters represented by continuous variables, the summaries will consist of the mean, median, standard deviation, interquartile range, minimum, and maximum values. For categorical variables, the number and percentage in each category will be presented.

Continuous outcome variables and their differences will be analysed with parametrical statistical techniques, unless the normality assumption does not seem reasonable for the data, in which case non-parametric techniques will be considered. A two-sided 0.05 alpha level will be used.

A paired t-test will be used to measure the differences in translations and rotations between RSA and CT.

Actions will be taken to minimize the amount of missing data. If data is missing, this will be handled according to the instructions of the specific measurement instrument, or if not available, imputation techniques will be used to replace the missing data.

### 8.1 Primary study parameter(s)

The main study parameter is the early migration (translational and rotational movements) of the BiMobile 2 mm cement acetabular cup and the BiMobile 4 mm cement acetabular

cup after two years. RSA data (discharge, 6 weeks, 6 months, 1 year and 2 years postoperatively) will be analysed using repeated measures ANOVA or mixed models if certain data points are missing. The null hypothesis is that there is no significant difference in mean migration at all time points. The alternative hypothesis is that the mean migration is significantly different at one or more time points.

### 8.2 Secondary study parameter(s)

Secondary study parameters concern physical functioning, quality of life, pain, patient satisfaction, device-related complications, reoperations and implant survival. Furthermore, early migration will be compared between the BiMobile 2 mm cement acetabular cup and the Avantage 2 mm cement acetabular cup. The secondary outcomes,will be analysed in the same manner as the primary study parameter, except for implant survival, which will be analysed using Cox regression analysis.
CT data (discharge and 2 years postoperatively) will be analysed using repeated measures ANOVA or mixed models if certain data points are missing.

### 8.3 Other study parameters

Other study parameters concern surgical characteristics, demographic data, medical history, standard radiographs (to assess the quality of the cement mantle) and CT scans (to assess the cement mantle thickness and to compare with RSA outcomes). These parameters will be analysed and presented in a descriptive manner.

### 8.4 Interim analysis (if applicable)

Interim analyses will be performed when 15 patients have reached the 6 months postoperative evaluation point. The number of SAE’s will be analysed. Results of the interim analysis will be discussed with the PI, and reported to the EC. In case of unexpected high number of SAE’s, appropriate actions will be taken.

ETHICAL CONSIDERATIONS

### 8.5 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice guidelines.

### 8.6 Recruitment and consent

During the pre-operative visit, patients that are possible candidates for this study will be screened to determine if they meet the inclusion / exclusion criteria. If the patient is a candidate, the investigator (or his designated representative) will propose participation in the study to the patient, according to GCP guidelines.
Patients must sign a EC approved study informed consent form prior to participating in any study related activities. The patients will be given adequate time to consider their decision (>1 week).

### 8.7 Objection by minors or incapacitated subjects (if applicable)

*Not applicable.*

### 8.8 Benefits and risks assessment, group relatedness

In addition to the benefits from the primary hip arthroplasty procedure e.g. reduced pain, improved range of motion, patients might benefit from the type of acetabular cup that is used in this study. All study patients receive a dual mobility acetabular cup, instead of a unipolar acetabular cup. Dual mobility cups are assumed to reduce the risk of hip dislocation. Patients may undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance.
The effective radiation dose per RSA-radiograph is 70 µSv. Five RSA radiographs, over 5 years of follow-up, will be taken additionally to standard care. Two CT scans of the hip will be made postoperative. The effective radiation dose per CT of the hip is 0.3 mSv. With this study, a total of 0.95 mSv is taken into account. The annual natural exposure is 2.5 mSv.

### 8.9 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

### 8.10 Incentives (if applicable)

Patients will only receive a travel expenses compensation for extra hospital visits due to this study.

## 9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 9.1 Handling and storage of data and documents

Data will be handled confidentially and anonymously. Each subject will be given an identification code and only research personnel involved in the logistics of the study will have access to the subject identification code list which can be used to link the data to the subject. The code is based on consecutive numbers. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). Data will be kept for 15 years after the end of the study.

### 9.2 Monitoring and Quality Assurance

Monitoring of the study will take place at least once during the total study duration, by an monitor of OLVG, according to guidelines set by the OLVG. This means that at a minimum the contents of the study ‘trial master file’ with all required documents will be monitored.

### 9.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited EC has been given. All amendments will be notified to the EC that gave a favourable opinion.
All substantial amendments will be notified to the EC and to the competent authority.
Non-substantial amendments will not be notified to the accredited EC and the competent authority, but will be recorded and filed by the sponsor.

### 9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited EC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 9.5 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited EC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the EC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited EC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited EC.

### 9.6 Public disclosure and publication policy

All publications and other public disclosures of the research data by the investigators will be made independent from the subsidizing party.

## 10. STRUCTURED RISK ANALYSIS

There is minimal risk associated with participating in this study over and above that of the primary hip arthroplasty procedure. Serious complications may be associated with any total joint replacement surgery. These complications include, but are not limited to: infection; genitourinary disorders; gastrointestinal disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction or death.
The devices are CE marked and will be used according to its labelling. Patients will be treated in the best medical judgment of the surgeon, regardless of the study protocol.
Assessment involves questionnaires, investigator assessments, RSA-radiographs a CT scan and anterior-posterior and lateral radiographs. The patient's burden from the study consists of two extra CT scans, three extra visits which consist of RSA-radiographs and questionnaires (at 6 months, 1 and 2 years), and at 5 years only questionnaires will be send to the patient. In addition to the benefits from the primary hip arthroplasty procedure e.g.

reduced pain, improved range of motion, patients might benefit from the type of acetabular cup that is used in this study. All study patients receive a dual mobility acetabular cup, instead of a unipolar acetabular cup. Dual mobility cups are assumed to reduce the risk of hip dislocation. Patients may undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance.
The effective radiation dose per RSA-radiograph is 70 µSv. Five RSA radiographs, over 5 years of follow-up, will be taken additionally to standard care. Two computed tomography (CT) scans of the hip will be made postoperative. The effective radiation dose per CT of the hip is 0.3 mSv. With this study, a total of 0.95 mSv is taken into account. The annual natural exposure is 2.5 mSv.

# 11. Attachments

## 11.1 Product Rationale Folder BiMobile

## 11.2 Surgical Technique Folder BiMobile

## 11.3 Brochure Avantage

## 12. REFERENCES

1. Enocson A, Pettersson H, Ponzer S, Tornkvist H, Dalen N, Tidermark J. Quality of life after dislocation of hip arthroplasty: a prospective cohort study on 319 patients with femoral neck fractures with a one-year follow-up. Qual Life Res. 2009;18(9):1177-84.
2. http://www.lroi-rapportage.nl/heup-overleving-1-jaarsrevisie-redenen-voor-revisie 2017 [updated 2017. Available from: http://www.lroi-rapportage.nl/heup-overleving-1-jaarsrevisie-redenen-voor-revisie.
3. Hailer NP, Weiss RJ, Stark A, Karrholm J. The risk of revision due to dislocation after total hip arthroplasty depends on surgical approach, femoral head size, sex, and primary diagnosis. An analysis of 78,098 operations in the Swedish Hip Arthroplasty Register. Acta Orthop. 2012;83(5):442-8.
4. Meek RM, Allan DB, McPhillips G, Kerr L, Howie CR. Epidemiology of dislocation after total hip arthroplasty. Clin Orthop Relat Res. 2006;447:9-18.
5. Phillips CB, Barrett JA, Losina E, Mahomed NN, Lingard EA, Guadagnoli E, et al. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. J Bone Joint Surg Am. 2003;85-A(1):20-6.
6. Woo RY, Morrey BF. Dislocations after total hip arthroplasty. J Bone Joint Surg Am. 1982;64(9):1295-306.
7. Bouchet R, Mercier N, Saragaglia D. Posterior approach and dislocation rate: a 213 total hip replacements case-control study comparing the dual mobility cup with a conventional 28-mm metal head/polyethylene prosthesis. Orthop Traumatol Surg Res. 2011;97(1):2-7.
8. Boyer B, Philippot R, Geringer J, Farizon F. Primary total hip arthroplasty with dual mobility socket to prevent dislocation: a 22-year follow-up of 240 hips. Int Orthop. 2012;36(3):511-8.
9. Farizon F, de LR, Azoulai JJ, Bousquet G. Results with a cementless alumina-coated cup with dual mobility. A twelve-year follow-up study. Int Orthop. 1998;22(4):219-24.
10. Philippot R, Camilleri JP, Boyer B, Adam P, Farizon F. The use of a dual-articulation acetabular cup system to prevent dislocation after primary total hip arthroplasty: analysis of 384 cases at a mean follow-up of 15 years. Int Orthop. 2009;33(4):927-32.
11. http://www.lroi-rapportage.nl/heup-overleving-1-3-en-5-jaarsrevisie-per-thp-component-gecementeerd-acetabulumcomponent 2017 [updated 2017. Available from: http://www.lroi-rapportage.nl/heup-overleving-1-3-en-5-jaarsrevisie-per-thp-component-gecementeerd-acetabulumcomponent.
12. https://aoanjrr.sahmri.com/documents/10180/275066/Hip%2C%20Knee%20%26%20Shoulder%20Arthroplasty 2017 [updated 2017. Available from: https://aoanjrr.sahmri.com/documents/10180/275066/Hip%2C%20Knee%20%26%20Shoulder%20Arthroplasty.
13. Flivik G, Kristiansson I, Ryd L. Positive effect of removal of subchondral bone plate for cemented acetabular component fixation in total hip arthroplasty: a randomised RSA study with ten-year follow-up. Bone Joint J. 2015;97-B(1):35-44.
14. Hernigou P, Daltro G, Lachaniette CH, Roussignol X, Mukasa MM, Poignard A. Fixation of the cemented stem: clinical relevance of the porosity and thickness of the cement mantle. Open Orthop J. 2009;3:8-13.
15. http://www.odep.org.uk/products.aspx 2017 [Available from: http://www.odep.org.uk/products.aspx.
16. https://www.orthopeden.org/downloads/76/classificatie-heupprothesen-2017.pdf 2017 [Available from: https://www.orthopeden.org/downloads/76/classificatie-heupprothesen-2017.pdf.
17. Broden C, Sandberg O, Skoldenberg O, Stigbrand H, Hanni M, Giles JW, et al. Low-dose CT-based implant motion analysis is a precise tool for early migration measurements of hip cups: a clinical study of 24 patients. Acta Orthop. 2020;91(3):260-5.
18. Eriksson T, Maguire GQ, Jr., Noz ME, Zeleznik MP, Olivecrona H, Shalabi A, et al. Are low-dose CT scans a satisfactory substitute for stereoradiographs for migration studies? A preclinical test of low-dose CT scanning protocols and their application in a pilot patient. Acta Radiol. 2019;60(12):1643-52.

19. Olivecrona H, Maguire GQ, Jr., Noz ME, Zeleznik MP, Kesteris U, Weidenhielm L. A CT method for following patients with both prosthetic replacement and implanted tantalum beads: preliminary analysis with a pelvic model and in seven patients. J Orthop Surg Res. 2016;11:27.
20. Otten V, Maguire GQ, Jr., Noz ME, Zeleznik MP, Nilsson KG, Olivecrona H. Are CT Scans a Satisfactory Substitute for the Follow-Up of RSA Migration Studies of Uncemented Cups? A Comparison of RSA Double Examinations and CT Datasets of 46 Total Hip Arthroplasties. Biomed Res Int. 2017;2017:3681458.
21. Scheerlinck T, Polfliet M, Deklerck R, Van Gompel G, Buls N, Vandemeulebroucke J. Development and validation of an automated and marker-free CT-based spatial analysis method (CTSA) for assessment of femoral hip implant migration: In vitro accuracy and precision comparable to that of radiostereometric analysis (RSA). Acta Orthop. 2016;87(2):139-45.
22. Valstar ER, Gill R, Ryd L, Flivik G, Borlin N, Karrholm J. Guidelines for standardization of radiostereometry (RSA) of implants. Acta Orthop. 2005;76(4):563-72.
23. Baad-Hansen T, Storgaard Jakobsen S, Soballe K. Two-year migration results of the ReCap hip resurfacing system-a radiostereometric follow-up study of 23 hips. Int Orthop. 2011;35(4):497-502.
24. https://registercentrum.blob.core.windows.net/shpr/r/-rsrapport-2015-B1dTcO3Pe.pdf 2017 [updated 2017. Available from: https://registercentrum.blob.core.windows.net/shpr/r/-rsrapport-2015-B1dTcO3Pe.pdf.
25. http://www.biomet.co.uk/medhome-uk/hip/hips-primary/cemented-acetabular/avantage-cemented. 2017 [Available from: http://www.biomet.co.uk/medhome-uk/hip/hips-primary/cemented-acetabular/avantage-cemented. 2017. .
26. Eucomed data reports. Period: 2005-2013. [Internet]. 2017.
27. Fresard PL, Alvherne C, Cartier JL, Cuinet P, Lantuejoul JP. Seven-year results of a press-fit, hydroxyapatite-coated double mobility acetabular component in patients aged 65 years or older. Eur J Orthop Surg Traumatol. 2013;23(4):425-9.
28. http://www.lroi-rapportage.nl/hip-total-hip-arthroplasty-surgery-most-frequently-registered-components. 2017 [Available from: http://www.lroi-rapportage.nl/hip-total-hip-arthroplasty-surgery-most-frequently-registered-components. 2017. .
29. Kaptein BL, Valstar ER, Spoor CW, Stoel BC, Rozing PM. Model-based RSA of a femoral hip stem using surface and geometrical shape models. Clin Orthop Relat Res. 2006;448:92-7.
30. Garling EH, Kaptein BL, Geleijns K, Nelissen RG, Valstar ER. Marker Configuration Model-Based Roentgen Fluoroscopic Analysis. J Biomech. 2005;38(4):893-901.