RESEARCH PROTOCOL

Comparison Of Posterolateral and direct Anterior approach in uncemented total hip arthroplasty: treatment outcome and cost-effectiveness

COPA study

08-01-2015

COMPARISON OF POSTEROLATERAL AND DIRECT ANTERIOR APPROACH IN UNCEMENTED TOTAL HIP ARTHROPLASTY: TREATMENT OUTCOME AND COST-EFFECTIVENESS

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Pharmacy	Not applicable

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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**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
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.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
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**
DAA	**Direct Anterior Approach**
PLA	**PosteroLateral Approach**
NOV	**Nederlandse Orthopaedische Vereniging (Dutch Orthopaedic Society)**
MIS	**Minimal Invasive Surgery**
THA	**Total Hip Arthroplasty**
MCA	**Medisch Centrum Alkmaar (Medical Centre Alkmaar)(participating hospital)**
VAS	**Visual Analogue Scale**
OHS	**Oxford Hip Score**

(3D) CT	**(3 Dimensional) Computed Tomography**
QoL	**Quality of Life**
MRI	**Magnetic Resonance Imaging**
EQ-5D	**EuroQol 5 Dimensions quality of life test**
BMI	**Body Mass Index**
HOOS	**Hip dysfunction and Osteoarthritis Outcome Score**
NFU	**Dutch Federation of Academic Centers (Nederlandse Federatie van Universitaire centra)**

SUMMARY

Rationale: Total hip arthroplasty (THA) is one of the most commonly performed orthopaedic surgeries. Recently, several studies have shown that the surgical approach to the hip known as the anterior or Huter approach could result in faster rehabilitation and more patient satisfaction after THA. The anterior approach allows the surgeon to reach the hip joint from the front, as opposed to the posterolateral approach, in which the joint is reached from the back. This way, no muscles are dissected, and the hip can be replaced without detachment of any muscle from the pelvis or femur. This study aims to compare the direct anterior approach (DAA) with the posterolateral approach (PLA) in patients undergoing uncemented THA. The main focus will be clinical, functional and surgical outcome and cost-effectiveness.

Objective: The objective of the study is to compare the DAA for THA with the standard PLA with respect to clinical, functional and surgical outcome and cost-effectiveness among patients, aged over 18 years, needing hip replacement.

Study design: The proposed study is a single centre, parallel group randomised clinical trial with balanced randomisation (1:1), and with a follow-up of two years after surgery.

Study population: Patients, aged over 18 years, suffering from osteoarthritis, who are a candidate for uncemented THA.

Intervention (if applicable): Total hip arthroplasty using the posterolateral and direct anterior approach.

Main study parameters/endpoints: The main study parameter of the study is the clinical outcome during the two years of follow-up after surgery. The clinical outcome is defined in terms of pain and function of the hip in relation to different activities of daily life.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients included in the study will follow the regular surgical and rehabilitation protocols. All patients will be asked to fill out several questionnaires at the regular visits to the outpatient clinic and will be send additional questionnaires in between. This will cost no more than 10 minutes each time. The risks involved with the intervention are no different from the normal risks involved with THA. In addition, 15 patients in each treatment group will have one MRI and another 15 in each group one CT scan performed. The study will not provide personal benefits or cause increased pre-, intra- and postoperative risks to the participating patients, but future patients may benefit from the results of the study performed. Ultimately this will result in more insight in total hip arthroplasty.

1. INTRODUCTION AND RATIONALE

In the Netherlands, approximately 25.000 total hip arthroplasties (THA) are performed each year [1]. It is estimated that the number of THA procedures will increase to 50.000 per year in 2030. Although there is general agreement about the surgical procedure, there is still debate about the surgical approach to be used to reach the hip joint. In their guideline 'Totale Heup Prothese' (meaning THA), The Dutch Orthopaedic Society (NOV) is not able to indicate one of the approaches as preferable [2]. Of the standard approaches, the posterolateral approach (PLA) is the surgical technique most often used. The hip joint is approached from behind, for which several muscles need to be detached, which requires a healing process. It also may increase the risk of incomplete healing, resulting in pain and a decrease in quality of walking and quality of life.

Currently, there is a strong tendency for surgical techniques to be improved and minimally invasive surgery (MIS) techniques are of interest. MIS is aimed at minimizing local soft-tissue trauma and shortening of hospital stay and rehabilitation time. One of the MIS techniques, the direct anterior approach (DAA), is used more and more for replacing the hip joint. Using the DAA, the hip joint is reached from the front and is replaced through the natural interval between the muscles, with much less muscle damage. Due to minimal soft tissue damage, length of hospital stay and rehabilitation time might be shortened when using the DAA. Also, this approach might result in a faster recovery of gait and mobility, and thus might affect the quality of life of (older) people needing a THA. The DAA is now common practice in a limited number of hospitals in the Netherlands.

The existing evidence with respect to the effectiveness of the DAA is limited. The length of hospital stay was found to be 3-5 days less for the DAA compared to other approaches [3-5]. Two studies did not find a difference but reported already relatively short stays of 3-4 days [6,7]. Also, two of three studies found more DAA patients to be discharged home, compared to other approaches [3,5,6]. Mainly in the short term, the DAA is associated with less postoperative pain and consumption of pain medication [4,8], a faster recovery time [9] and a more rapid recovery of hip function [10]. After 6 months, however, generally no differences between the DAA and other approaches are found for clinical parameters [5,7]. In a systematic review, de Verteuil et al. [11] concluded that DAA for total hip arthroplasty has small peri-operative advantages in terms of blood loss and operation time. They may be associated with a shorter hospital stay and faster recovery.

As a pilot study, we analysed our own patient files for differences between the DAA and PLA in a cohort of patients operated between January 2012 and December 2012 by a single surgeon in our hospital. A total of 80 patients (83 hips) undergoing THA using PLA (N=38) or DAA (N=45) were analysed. Patients operated with the DAA had a significantly shorter LOS (p=.009) and 3 times more adequate acetabular cup inclination (p=.004). Patients operated with the PLA had shorter operation time (p<0.001 and blood loss (p<0.001). Complications and follow-up measurements did not show significant differences between the two approaches. Differences between the pre-surgery and 1 year follow-up measurements were also comparable (submitted data).

The innovative character of the present study is that this is the first randomised controlled trial on this topic that will include clinical, functional and surgical outcomes as well as the cost-effectiveness of the DAA compared to standard PLA. Therefore, the results of this study will add knowledge of

effectiveness and economic knowledge of health care costs, not known so far, related to THA. The DAA is relatively new and only performed by a limited number of orthopaedic surgeons in a limited number of hospitals in the Netherlands. This study might resolve the debate whether the DAA or the PLA is the preferred type of surgery. If the DAA proves to be cost-effective, patients, surgeons and society will benefit. Patients will experience health gain by faster recovery and faster discharge to home. Physicians will be able to choose the most efficient intervention. Society will benefit because of a cost-reduction due to less days of hospital stay and shorter rehabilitation time.

2. OBJECTIVES

Primary Objective:

To compare the direct anterior approach (DAA) for Total Hip Arthroplasty (THA) with the standard posterolateral approach (PLA) with respect to clinical outcome among patients needing hip replacement.

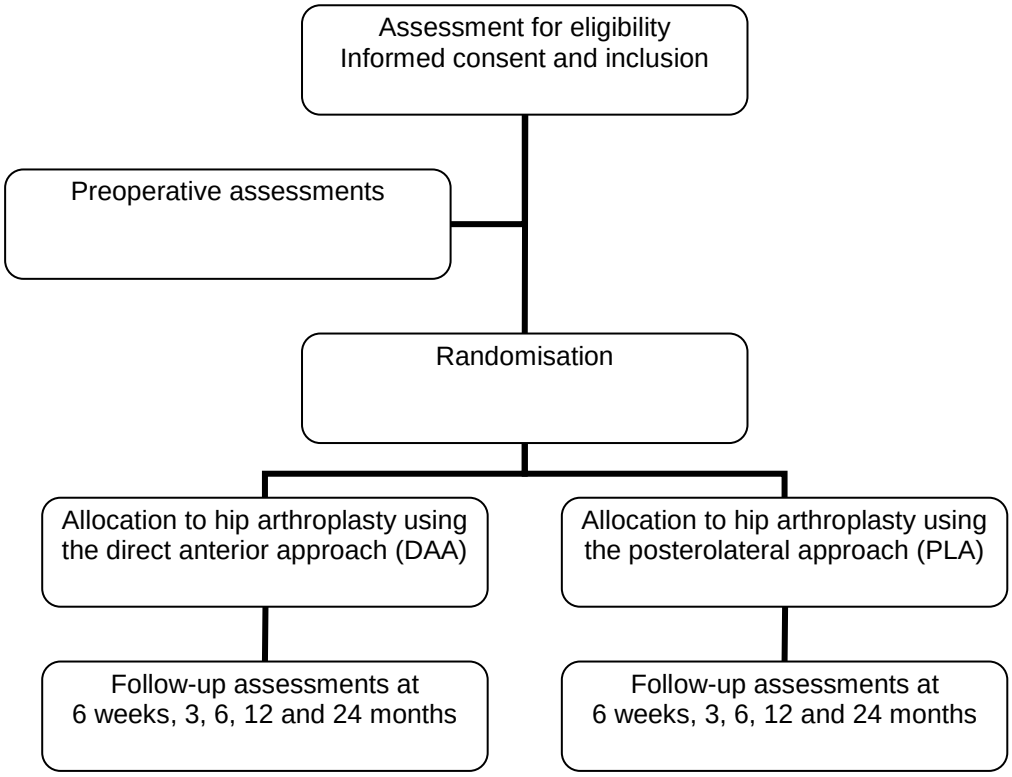
Secondary Objectives:

To compare the direct anterior approach (DAA) for Total Hip Arthroplasty (THA) with the standard posterolateral approach (PLA) with respect to functional and surgical outcome and cost-effectiveness among patients needing hip replacement.

3. STUDY DESIGN

The proposed study is a single centre (Medisch Centrum Alkmaar, MCA) parallel group randomised controlled trial, with balanced randomisation (1:1 DAA:PLA), with a follow-up of two years after surgery alongside an economic evaluation. The study will take place between 2014 and 2018 in the Medical Centre Alkmaar. The surgical procedures will be performed by three orthopaedic surgeons.

Figure 1: Flow chart of the study design



4. STUDY POPULATION

4.1Population (base)

Study participants are patients aged over 18 years, reporting to the outpatient department with clinical and radiographic signs of osteoarthritis of the hip. The surgeon together with the patient will decide if uncemented THA is appropriate. The study will be performed in Medical Centre Alkmaar, where in 2013 665 hip replacements were performed, of which about 80% were uncemented total hip replacements. There are currently three orthopaedic surgeons that perform both the DAA and PLA, who will participate in the current study. Each surgeon performs about 100 total hip replacements each year.

4.2Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Willing and able to participate in the study protocol;
- Age between 18 and 80 years
- ASA Physical Status I & II
- Diagnosed with osteoarthritis of the hip
- Subjects for who it is decided that they will undergo an uncemented THA at Medical Centre Alkmaar.
- Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained.
- Subjects, who, in the opinion of the Clinical Investigator, are able to understand this clinical investigation, cooperate with the investigational procedures and are willing to return for all the required post-treatment follow-ups.

4.3Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients with previous surgery to the ipsilateral or controlateral hip;
- Patients with posttraumatic changes of the pelvis or femur;
- Patients with inflammatory arthropathies;
- Patients diagnosed with osteoporosis
- Patients diagnosed with rheumatoid arthritis
- Patients who suffer from insulin dependant diabetes
- Patients who lack understanding of the Dutch language
- Patients who are treated for or diagnosed with neurological or muscle disorders which make assessment of pain and gait not possible

4.4Sample size calculation

The primary outcome is the clinical outcome. As we expect faster recovery for the DAA compared to the PLA, but an equal outcome in the long term, we want to detect a significant difference at 3 months. We calculated the sample size using the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) and the VAS score for perceived pain. Both these measurements are included in the Patient Related Outcome Measures (PROMs), which are currently the nationwide standard for the evaluation of orthopaedic treatments in the Netherlands used by hospitals and insurance companies.

The HOOS is a disease specific measure assessing pain and function of the hip in 5 different subscales (symptoms, pain, activities of daily living (ADL), sports & recreation, quality of life). In each subscale patients can score up to 100 points, with 0 points being the worst score and 100 points the best. To detect a clinically relevant difference of 7 points in the HOOS symptoms, pain or ADL subscales and using a standard deviation (SD) of 15 points [12-14] with a two-sided 5% significance level and a power of 80%, a sample size of 72 patients per group is necessary. To detect a difference in VAS score (0-10) of 1 point, i.e. a score of 2.5 SD 2 for the PLA and 1.5 SD 2 for the DAA [15] with a two-sided 5% significance level and a power of 80%, a sample size of 64 patients per group is necessary. Given an anticipated dropout rate of 20% during the 2-year follow-up, we will recruit 2 times 86 patients, 172 patients in total.

5. TREATMENT OF SUBJECTS

5.1Investigational product/treatment

For THA, two approaches are compared: the DAA and the PLA. Both approaches are regularly performed in hospitals and clinics in the Netherlands and in Medical Centre Alkmaar specifically. Therefore no specific surgical learning curve is expected for either of the procedures. The PLA is the most commonly used approach overall in the Netherlands.

For the DAA, the patient is placed in a supine position. The hip capsule is reached from the front, utilizing the internervous plane, located between the sartorius muscle and tensor fascia latae muscle superficially, and between the rectus femoris muscle and gluteus medius muscle more profoundly.

For the PLA, the patient is placed in the lateral position. The hip capsule is reached from the back, after incising the tensor fascia lata muscle and gluteal fascia, blunt dissection of the gluteus maximus muscle, and releasing the insertions of the piriformis, gemelli and obturator externus tendons.

For all operations the same hip prosthesis (CORAIL® Total Hip System, DePuy Synthes, Warsaw, Indiana, United States of America) will be used. All procedures will be performed using a standard operating table.

Intra- and postoperatively patients will be treated according to the standard clinical hip replacement protocol implemented in the MCA. For a detailed description of the standard postoperative pain protocol see appendix.

5.2Use of co-intervention (if applicable)

Not applicable

5.3Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational medicinal product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Primary study parameters are the clinical outcome parameters:

- Hip pain and symptoms assessed using the symptoms, pain and activities of daily living (ADL) subscales of the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) after three months
- Perceived pain in the week before the moment of assessment, assessed using a Visual Analogue Scale (VAS) after three months

8.1.2 Secondary study parameters/endpoints

Secondary study parameters are the clinical, functional and surgical outcome parameters and cost-effectiveness:

- Hip pain and symptoms assessed using the sports & recreation and quality of life subscales of the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS)
- Length of hospital stay
- Quality of life assessed using the EQ-5D
- Functioning during daily living assessed using the HOOS
- Quality of walking assessed during a timed up and go test and a two times 50m walk using inertial sensors
- Operation time, blood loss, and other parameters of the surgical procedures
- Cup and stem positioning assessed using standard radiography
- Cost-Effectiveness assessed using the cost-questionnaire
- Muscle status assessed using MRI in a sample of 15 patients from each group
- Positioning of the implant assessed using CT scans in a sample of 15 patients from each group.
- All complications related to the surgery and rehabilitation
- Productivity costs
- Direct medical costs (costs of additional radiography, medical consumption)

Other study parameters

Patient characteristics such as age, gender, stature, bodyweight, side of operation (left or right), smoking.

8.2 Randomisation, blinding and treatment allocation

When one of the participating orthopaedic surgeons, together with the patient, decides that uncemented THA is appropriate, the patient will receive information concerning the study. After one week the patient will be called to ask whether he or she wants to participate. If the patient agrees that he or she wants to participate, signing of the informed consent and afterwards the collection of baseline measurements will take place during the next outpatient clinic visit. After receiving informed consent, the patient is included in the study and baseline measurements will be taken. After this, the patient will be randomly allocated to either the direct anterior approach (DAA) or the posterolateral approach (PLA). Randomisation will be computer-generated in Medoc Research software (SDS Medical, The Hague) with a 1:1 allocation and a block size of 10. The allocation of the patient will then be stored in the patient file and the bureau of planning is informed of the allocation to plan the surgery. After randomisation and baseline measurements have been performed, the participant is informed of being allocated to either the DAA or the PLA group, since the location of the surgical

incision makes it impossible to blind patients for group allocation. The surgeon performing the procedure will know of the treatment allocation as it is also impossible to blind the surgeon. Evaluation of radiological examinations will be done by a blinded researcher. The first 30 subjects in each groups will alternately be allocated to receive a CT or an MRI.

8.3Study procedures

Pre-operative assessment

After inclusion participants will be asked to fill in a questionnaire. A general questionnaire containing questions about demographic characteristics of the participants, and validated questionnaires to assess clinical and functional outcomes and cost-effectiveness will be used. The Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) [13] will be used to assess pain, symptoms and function of the hip in relation to different activities of daily life. Also, a Visual Analogue Scale (VAS) will be used to assessed perceived pain in the previous week. To assess quality of life, the participant will be asked to fill in the EQ-5D [16,17]. A part of the questionnaire will be dedicated to questions concerning the financial costs associated with the hip problems of the participants to assess the cost-effectiveness of the approaches for hip arthroplasty. This part of the questionnaire is generally applied in cost-effectiveness studies and at some points specifically adjusted to hip problems.

In addition to the self-reported HOOS, the quality of movement and walking will be quantified to assess functional outcome. Basic balance and gait performance will be tested using the timed “up & go” (TUG) test, instrumented with inertial sensors to measure trunk accelerations, and a two times 50 meter walk at their preferred walking speed, also instrumented with inertial sensors [18-22]. For the TUG test [23], in short, participants will be asked to stand up from a chair, walk for 3 meters, walk back to the chair and sit down on the chair. The time needed to perform the TUG as instructed will be registered. In addition, the participants will wear inertial sensors (McRoberts Dynaport Hybrid, Dimensions 87 x 45 x 14 mm, Weight 74 grams), which will be attached to the trunk using a comfortable elastic belt with Velcro fixation. The inertial sensors measure the accelerations of the trunk. Pre-operatively, standard radiographs of the pelvis (anterior posterior or AP and lateral views) are performed.

Assessments during surgery and hospital stay

Operation parameters such as operation time and blood loss will be registered. During the first 3 days after surgery, again radiographs of the pelvis will be taken from the participant as part of standard protocol. The total time of hospital stay will be registered.

Follow-up assessments

The questionnaire including the HOOS, VAS, EQ-5D and complications has to be completed by the participant at the regular follow-up visits at the orthopaedic outpatient department at 6 weeks (± 14 days) and 12 months (± 31 days). In addition, the participants have to fill in this

questionnaire at 3, 6 and 24 months for which the questionnaire will be sent to the participants by mail or email. Participants will be able to return the questionnaire without any costs. The questionnaire concerning the financial costs will be followed up at 3, 6, 9 and 12 months.
At the regular visit to the orthopaedic outpatient department at 6 weeks, radiographs of the pelvis will be taken according to the standard protocol (AP and lateral views). In addition to standard protocol a 3D-CT scan will be performed to establish the cup and stem positioning of the hip prosthesis in a sample group. At the regular visit to the orthopaedic outpatient department at 12 months, balance and gait performance will again be tested using the TUG test and the two times 50 meter walk, both instrumented with inertial sensors. Also at 12 months radiographs of the pelvis will be made, and in a different sample group an additional MRI without contrast will be made to assess the cup and stem positioning of the prosthetic hip and the status of the hip muscles. This way patients do not need an extra outpatient clinical visit and potential end-stage tissue damage can be visualized on MRI imaging. [24] By means of these results it is possible to analyse prosthetic positioning and muscle status against clinical results for both groups.

Table 1: Overview of the time schedule of the assessment of the study parameters

	1	2	3	4	5	6	7	8	9
Location	**OC***	**IC***	**IC**	**OC**	**Q***	**Q**	**Q**	**OC**	**OC**
Assessment	**Pre-op**	**Operation**	**Day 1-3**	**6 weeks**	**3 months**	**6 months**	**9 months**	**12 months**	**24 months**
Window				± 14 days	± 31 days	± 31 days	± 31 days	± 60 days	± 60 days
Parameter									
Demographic characteristics	x								
Clinical outcome									
HOOS	x			x	x	x		x	x
VAS	x		x	x	x	x		x	x
Hospital stay			x						
EQ-5D	x			x	x	x		x	x
Complications			x	x	x	x		x	x
Functional outcome									
HOOS	x			x	x	x		x	x
Quality of walking	x			x				x	
Surgical outcome									
Operation parameters		x							
Pelvic radiography	x		x	x				x	
CT (sample group)				x					
MRI (sample group)								x	
Economic parameters	x				x	x	x	x	

*OC: Outpatient Clinic; C: Inpatient Clinic; Q: Questionnaire sent to patient

8.4Withdrawal of individual subjects

Withdrawal is not to be expected, as a standard implant is being used and follow-up is close to routine follow-up of total hip arthroplasty following the protocol of the Medical Centre Alkmaar. Participants can stop participating in the study at any time for any reason if they wish to do so without any consequences. Patients who withdraw from the study will have the reason for their withdrawal recorded, if given, on the case report forms (CRF's). The postoperative assessments include standard evaluations according to the clinical protocol, so every attempt must be made to ensure that all the participants return for these controls. The researchers and/or the treating specialist involved can decide to withdraw a participant from the study for urgent medical reasons.

8.4.1Specific criteria for withdrawal

Not applicable

8.5Replacement of individual subjects after withdrawal

If a participant withdraws from the study, he/she will not be replaced.

8.6Follow-up of subjects withdrawn from treatment

Participants who stop participating but do not withdraw their consent will be followed according to the standard clinical protocol currently used for patients with a total hip arthroplasty for recording of any adverse events. The patient shall not be asked to perform study related activities. It will be noted in the patient file if the patient no longer wishes to participate or if the patient has withdrawn informed consent.

8.7Premature termination of the study

If the research team has signals that one of the approaches for hip arthroplasty is associated with a significant complication rate, a preliminary analysis will be performed. Since both procedures are already performed as standard procedures in the MCA it is not expected that the complication rate in one of both procedures will exceed the current registrated rate. In 2012 550 primary total hip arthroplasties were performed in the MCA. At the time of writing this protocol, complications were registered for 395 patients, of whom 8 (2,0%) had a complication of any kind. When 86 patients are included the amount of complications shall be compared to 2012. If, against expectations, the complication rate of luxations and/or infections per subgroup is more than twice the total complication rate of 2012 or the complication rate for both groups combined is more than twice the rate of 2012 (4%) we shall abort the trial format. Furthermore, odds ratios will be calculated for the major complications, such as dislocation or infection, in both groups. In case of a significant difference of the odd ratio from one, the randomisation will be ended.

9. SAFETY REPORTING

9.1Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2AEs, SAEs and SUSARs

9.2.1Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to one of the two approaches for hip arthroplasty. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2Serious adverse events (SAEs)

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

- 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;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

If prolongation of hospital stay is due to logistical reasons (e.g. a patient is placed on a waiting list for a place in a rehabilitation centre), it will not be reported as an SAE. Prolongation of hospital stay or re-hospitalizations due to infection or luxation of the hip prosthesis are considered a standard risk in THA. In addition, a retrospective analysis in the Medical Centre Alkmaar (see introduction section) showed no differences in the occurrence of these events between DAA and PLA. Therefore they will not be reported as an SAE.

9.2.3Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3Annual safety report

Not applicable

9.4Follow-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

9.5[Data Safety Monitoring Board (DSMB) / Safety Committee]

A DSMB was not deemed necessary for this study as the treatment is non-critical and does not carry substantial additional risks as stated above.

10.STATISTICAL ANALYSIS

The intention to treat (ITT) population consists of all patients that are assigned randomized irrespective of being treated according to the protocol but at least underwent a THA. The per-protocol (PP) population comprises those patients of the ITT population who underwent a THA according to treatment allocation and have a score on the primary outcome variable.

10.1Primary study parameter(s)

Continuous study parameters are described in terms of means and standard deviations if the data are normally distributed. If the data are not normally distributed then they are described in terms of median, interquartile range and minimum and maximum values. Categorical study parameters are described as proportions.

It shall be investigated if THA using DAA leads to better values of the (primary) clinical outcome parameters postoperatively and at follow-up compared to THA using PLA. In case parametric assumptions are not violated, standard parametric statistical methods will be applied (GLM (General Linear Model)), otherwise non-parametric methods will be used. The same procedure is performed for differences in changes in the primary study parameters at follow-up compared to preoperative values within one patient. Categorical outcome parameters will be analysed using Chi-square tests. If possible, 95% confidence intervals for the relevant estimates will be calculated.

In addition to the univariate analyses, the longitudinal differences (effects of time) in the primary study parameters between the participants that received a THA using the DAA or PLA will be analysed in multiple regression models using random coefficient analyses. In these analyses the longitudinal differences between the two surgical procedures is studied accounting for the participation of three surgeons and possible confounding and effect modification of other determinants of the outcome parameters. The random coefficient analyses account for the dependency of the repeated measurements of the longitudinal study.

10.2Secondary study parameter(s)

The secondary study parameters (functional and surgical parameters) are to be analysed in the same manner as the primary study parameters.

In addition the cost effectiveness analysis (CEA) will be performed alongside the trial from a societal perspective. We will compare the differences in total costs between DAA and PLA to difference in effect (pain/VAS and symptoms/HOOS). We will also perform a cost-utility analysis based on the EQ-5D using Dutch tariffs. All relevant costs of the interventions, other direct medical costs (e.g. rehabilitation and medication) and productivity losses are assessed using cost-questionnaires at 0, 3, 6, 9 and 12 months after surgery. Bootstrapping will be used for pair-wise comparison of the mean differences in total costs. Cost-effectiveness and cost-utility ratios will be estimated using bootstrapping techniques and graphically presented on cost-effectiveness and cost-utility planes. Acceptability curves will also be presented.

A budget impact analysis will be conducted according to the ISPOR international guidelines and from different perspectives (health care, society). Available Dutch epidemiological data will be used to estimate the incidence and prevalence. The current and future mix of interventions

(different implementation levels) will be used to estimate long-term financial consequences. Costs will be estimated using tariffs from the Dutch Care Authority. Different scenarios using different care and population mixes will be modelled and sensitivity analyses performed.

10.3Other study parameters

Not applicable

10.4Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (2008), in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Subjects shall be informed using a study patient information document at least five days before the procedure to ensure an informed decision for consent and inclusion. Inclusion shall be done by competent orthopaedic surgeons, residents or nurse practitioners / physician assistants who will be trained in informing about the study in a research meeting. Signing of informed consent has to be done prior to any study related activities.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

This study might provide evidence for a surgical technique which will improve clinical, functional and surgical outcome and cost effectiveness after total hip arthroplasty for all patients in need of total hip arthroplasty in the future and at minimum risk and no extra cost for most patients in this study.

A total of 60 patients will undergo an additional CT or MRI. The average mean radiation exposure during a CT-scan of the pelvis is 7.4 mSv (milliSievert) (range 4.0 – 13). [25] Thus, 30 patients will be exposed to this additional radiation. For comparison: background radiation exposure in the Netherlands is around 2 mSv per year. [26]

11.5 Compensation for injury

Both DAA and PLA are procedures that are common practice in the Medical Centre Alkmaar. Most of the patients will undergo the normal follow-up protocol, but a subgroup of 60 patients will undergo an additional CT or MRI. Therefore the sponsor/investigator has a liability insurance for the 60 patients that will undergo a CT or MRI which is in accordance with article 7, subsection 9 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data will be handled confidentially by the investigator. Each subject will receive an identification code, this code will be used to link the data to the subject. The key to the code will be safeguarded by the investigator. Data will be kept for fifteen years

12.2 Monitoring and Quality Assurance

Monitoring of the study will be conducted by a qualified GCP monitor from Trial Center Holland Health. For a detailed description of the monitoring plan see appendix.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC 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.

12.5 End of study report

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

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

No arrangements made between the sponsor and the investigator concerning the public disclosure and publication of the research data. Data will be published in a(n) (inter)national scientific journal. The CCMO statement on publication policy will be followed.

13. STRUCTURED RISK ANALYSIS

Not applicable

13.1 Potential issues of concern

Not applicable

13.2 Synthesis

Not applicable

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