RESEARCH PROTOCOL

COMPASS study

COMparison of Posterolateral and direct Anterior approach in uncemented total hip arthroplasty with a Short Stem prosthesis

A single center randomized controlled clinical trial (RCT).

June 02, 2017

COMparison of Posterolateral and direct Anterior approach in uncemented total hip arthroplasty with a Short Stem prosthesis

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Pharmacy	Not applicable

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TABLE OF CONTENTS

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**
COMPASS	**COMparison of Posterolateral and direct Anterior approach in uncemented total hip arthroplasty with a Short Stem prosthesis**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
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**

NWZ	**Noordwest Ziekenhuisgroep(participating hospital)**
VAS	**Visual Analogue Scale**
OHS	**Oxford Hip Score**
HHS	**Harris Hips score**
QoL	**Quality of Life**
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)**
NWZ	**Noordwest Ziekenhuisgroep location Alkmaar**

SUMMARY

The purpose of this randomized controlled study is to compare posterolateral approach (PLA) and direct anterior approach (DA) in total hip arthroplasty with the NANOS short stem for subsidence, functional outcome, quality of life and isometric hip abduction force over a follow-up period of 2 years.

1 INTRODUCTION AND RATIONALE

Background

Short-stems total hip prostheses, such as the NANOS prosthesis, pose possible advantages for active patients. Because a large part of the column femoris remains intact it is possible to create a more anatomical reconstruction of the hip joint. This leads to better off-set restoration which may improve hip abductor function[1,2]. A reduced capacity of the abductor muscles might result in aberrant hip abduction/adduction pattern during walking, which might be problematic in for example the regulation of medio-lateral balance during walking. Another advantage in active patients is that the NANOS stem fixates proximally in the femur leaving more bone stock for a possible subsequent revision. Because of the proximal fixation it is suspected that the NANOS causes less stress shielding of the trochanter region[3] and flexibility of the femur shaft is left intact leaving a natural capacity to bending forces on the femur shaft

The NANOS prosthesis was developed in 2002. Since its release positive results have been presented (table 1 and table 2) for complication rates and revision rates. Also, an ODEP 3A* rating was assigned in 2016.

Table 1: Summary of results of the NANOS prosthesis

Title/Reference	Author/s	Cases	Survival Rate	Follow-up	Other Relevant Data
Keep it short and simple – Ergebnisse einer Multicenter-Studie. Orthopädie im Profil 1/2007	A. Reinhardt	183	100 %	52 cases 2 years	No complications to date, HHS Preop 47.1, Postop 95.8
5 years clin. experiences of a neck preserving stem. Presentation Smith & Nephew Mediterranean Hip Meeting 2010, Greece	F. Parente	222	100 %	62 cases 3–5 years	No revision, no dislocation was observed in any of the stems
3 to 5 year results of NANOS neck preserving stem. Presentation 58th Annual VSO Meeting 2010, Germany	P. Ettinger M. Ettinger	68	100 %	68 cases 3–5 years	No revision, no migration was observed in any of the stems, HHS Preop 47.5, Postop 95
NANOS neck preserving stem an alternative system in endoprothetic implantation in younger patients. Presentation 58th Annual VSO Meeting 2010, Germany	K. Moussa H. Dinges	110	100 %	110 cases 2.5 years	No revision, no radiographic signs of loosening or migration were observed in any of the stems, HHS Preop n/a, Postop 94
Results after implantation of the NANOS neck preserving stem. Presentation 58th Annual VSO Meeting 2010, Germany	L. Engelmann	50	96 %	50 cases 3–6 years	No radiographic signs of loosening observed in any of the stems. Two joint revisions (cause was not reported). HHS Preop 47.3, Postop 97.8

Table 2 Cumulative Percent Revision of Primary Total Conventional Hip Replacement using a Mini Stem Prosthesis (Primary Diagnosis OA)

Femoral Component	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs
C.F.P.	9	123	4.1 (1.7, 9.5)	4.1 (1.7, 9.5)	4.9 (2.2, 10.6)	5.8 (2.8, 11.7)	7.9 (4.2, 14.7)
Mallory-Head	3	74	2.8 (0.7, 10.8)	6.3 (1.8, 20.4)			
Mayo	6	96	2.1 (0.5, 8.1)	4.2 (1.6, 10.8)	4.2 (1.6, 10.8)	5.7 (2.4, 13.4)	7.9 (3.5, 17.4)
Metha	4	100	3.3 (1.1, 9.8)	4.6 (1.7, 11.7)			
MiniHip	11	461	2.2 (1.2, 4.3)	3.2 (1.7, 5.8)			
Nanos	5	629	0.7 (0.3, 1.8)	0.9 (0.4, 2.2)			
Silent	2	50	4.0 (1.0, 15.1)	4.0 (1.0, 15.1)			
Taperloc Microplasty	5	230	1.9 (0.7, 5.1)	1.9 (0.7, 5.1)			
Other (2)	2	15	6.7 (1.0, 38.7)	6.7 (1.0, 38.7)	6.7 (1.0, 38.7)	6.7 (1.0, 38.7)	
TOTAL	47	1778					

The use of short stems corresponds with the trend of direct anterior and minimal invasive hip surgery we have seen last years. With these techniques more muscles are left intact and might therefore result in a better functional outcome, leading to shorter operation time, less perioperative complications and less muscle damage[4]. Thus, both the short stem total hip prostheses as well as the direct anterior and minimal invasive approaches in hip surgery can be considered relatively recent innovations in THA and both are aimed at improving functional and clinical outcome, mainly in the short term. However, the clinical and functional effectiveness of the combination, i.e. whether the use of short stem prostheses is even more effective when used during the direct anterior approach compared to when used during the regular posterolateral approach in THA, is as far as we know not yet investigated. Important parameters in THA which may be related to clinical and functional outcome are the level of fixation and positioning of the (short) stem, which are thought to be affected by surgical approach. In literature, it is well established that early migration (migration within two years after THA) of the stem is predictive for late aseptic loosening of the stem[5,6]. The computer-assisted Einzel-Bild-Roentgen-Analyse (EBRA) system was evaluated to detect stem migration of 1 mm with a specificity of 100% and a sensitivity of 78%[7]. This method is less invasive and easier to use in a clinical setting then the gold standard RSA method. A migration threshold of 1.5 mm after two years was found to be highly predictive for later aseptic loosening and significantly increased risk of revision[5]. Comparing the level of migration of the short stem of the hip prosthesis for the direct anterior approach and the posterolateral approach in THA might add to the knowledge base of the effectiveness of the

direct anterior approach and may help in evidence based clinical decision making when deciding for the best treatment option when a patient's hip needs to be replaced.

2. OBJECTIVES AND HYPOTHESIS

Primary Objective:

The primary objective of this study is to investigate whether the NANOS femoral stem placed by means of the direct anterior approach (DAA) results in a better rigid fixation at two years follow-up in comparison with the NANOS stem placed using the posterolateral approach (PLA) in patients with hip osteoarthritis who need a total hip arthroplasty (THA).. Also, stem position and off-set restoration will be taken into account.

Secondary Objectives:

The secondary objective is to compare THA with the short stem NANOS prosthesis using the DAA with the PLA for perceived pain, functioning of the hip, quality of life, isometric hip abduction force and quality of walking during the first two years after surgery.

Hypotheses:

- The NANOS short stem prosthesis will show less subsidence if placed by means of the DAA compared to the PLA at two years follow-up
- The NANOS short stem prosthesis will show better stem position if placed by means of the DAA compared to the PLA at two years follow-up
- The NANOS short stem prosthesis will show better off-set if placed by means of the DAA compared to the PLA at two years follow-up
- The NANOS short stem prosthesis will show lower pain scores if placed by means of the DAA compared to the PLA
- The NANOS short stem prosthesis will show a better functional outcome and range of motion if placed by means of the DAA compared to the PLA
- The NANOS short stem prosthesis will show higher maximum isometric hip abductor muscle force if placed by means of the DAA compared to the PLA
- The NANOS short stem prosthesis will show a better gait pattern in terms of hip joint angles and hip joint moments in the frontal plain if placed by means of the DAA compared to the PLA

3.STUDY DESIGN

This study will be a single center, randomized controlled clinical trial (RCT). This study contains two arms, one with patients treated by means of the DAA and one with patients treated by means of the PLA.
Two surgeons will be participating in this study. Both are senior hip orthopedic surgeons for the NANOS prosthesis and both orthopedic surgeons will perform the DAA and the PLA. If the indication for primary hip arthroplasty is established, patients will be asked if they want to participate. Patients who are interested in participating will get an appointment with the research nurse after one week. Then informed consent will be signed and patients will be randomized to one of the two study arms. Registry of data and block randomization will be executed via Castor.

As primary outcome we will use the migration of the NANOS prosthesis in mm as measured with EBRA-FCA software. In addition, we will investigate functional outcome and quality of life with the HOOS and EQ-5D questionnaires.
Basic balance and gait performance will be tested using the timed “up & go” (TUG) test, instrumented with inertial sensors to measure body segment accelerations and angles, and a two times 50 meter walk at their preferred walking speed, also instrumented with inertial sensors[8–12]. For the TUG test[13], 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 test as instructed will be registered. In addition, the participants will wear validated inertial sensors (McRoberts Dynaport Hybrid, Dimensions 87 x 45 x 14 mm, Weight 74 grams)[14], which will be attached to the lower back with Velcro fixation.
The study will take place between 2017 and 2020 in the Noordwest Ziekenhuisgroep location Alkmaar.

4. STUDY POPULATION

4.1 Patient selection (Study population)

Patients enrolled in this study will have at least one of the indications listed below and meet all of the inclusion criteria. Patients meeting any of the exclusion criteria are not eligible for this study. The surgeon together with the patient will decide if uncemented THA is appropriate. The study will be performed in Noordwest Ziekenhuisgroep Alkmaar, in which in 2013 665 hip replacements were performed, of which about 80% were uncemented total hip replacements.

4.2 Subject inclusion

Subjects must meet all of the following characteristics for inclusion in the study.

- Willing and able to participate in the study protocol.
- Patient requires Primary total hip replacement (THR) to the affected side, unilateral or bilateral.
- Patient agreed to participate in the study by signing the Informed Consent form.
- Age of patient at date of surgery 18 to 75 years.
- Patient is likely to comply with study follow-up requirements
- 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 Noordwest Ziekenhuisgroep Alkmaar.
- Subjects who are able to give voluntarily, 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.

4.3 Subject exclusion

Subjects with any of the following characteristics must be excluded from the participation in the study.

- Previous surgery to ipsilateral or contralateral hip.
- Patients with posttraumatic changes of the pelvis or femur;

- Patients with inflammatory arthropathies;
- Patients diagnosed with rheumatoid arthritis
- Patients who suffer from insulin dependent diabetes
- Patients who are treated for or diagnosed with neurological or muscle disorders which make assessment of pain and gait not possible
- Patients who use medication for osteoporosis
- Pronounced coxa valga with a femoral neck angle > 145º
- Pronounced coxa vara with a femoral neck angle < 125º
- History of infection in the affected joint; systemic infections
- 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
- Grossly insufficient femoral or acetabular bone stock in the involved hip where a revision cup is indicated
- Spinal disease with neurologic movement disorders
- Alcoholism or addictive disorders
- Body mass index (BMI) > 30
- Patient is pregnant or being pregnant during follow up intervals
- Patients who lack understanding of the Dutch language

4.4 Sample size calculation

The main hypothesis of this study is that the NANOS short stem prosthesis will show less subsidence if placed by means of the DAA compared to the PLA at two years follow-up. No previous studies have been published in which differences in subsidence between DAA and PLA are compared for short stem prostheses.

The study design of the present study is an RCT. We calculated our sample size based on the study of Budde et al.[15]. In this study a mean subsidence of 0.46±0.31mm was measured for the NANOS stem prosthesis after 2 years of follow-up. When assuming a mean subsidence of 0.46 mm in the PLA group and 0.25mm less subsidence in the DAA group, a sample size of 25 subjects in each group (a total of 50 subjects)is necessary to detect a difference with a power of 80% and a two-sided 5% significance level using an independent t-test.

Since the follow-up of patients is almost similar to the regular follow-up of patients that undergo total hip replacement, we do not expect a high number of patients that are lost to follow-up. Therefore, we will include 10% more patients, which resulted in 56 patients.

5. TREATMENT OF SUBJECTS

Two surgeons will be placing the NANOS stems. Both surgeons will use the direct anterior approach (DAA) and the posterolateral approach (PLA). Both surgeons have extensive experience with both these approaches and previous experience with the NANOS stem.

We will use a follow-up protocol that is similar to the NOV (Dutch orthopedic society) THA guidelines[16]. This protocol contains postoperative clinical and radiological visits at 8 weeks and one year. In addition, we will send patients functional evaluation questionnaire (HOOS, VAS) at 3 and 6 months. At 24 months we will schedule an additional clinical and radiological follow-up visit.

5.1 Investigational product/treatment

The NANOS short stem femoral component (Smith & Nephew, Memphis, Tennessee, United States of America) in combination with the R3 acetabular component (Smith & Nephew, Memphis, Tennessee, United States of America) will be placed. Both components are ODEP rated. The NANOS stem has previously been placed in the hospital in a research setting investigating short to medium survivorship and function and showed excellent results.

All patients will be submitted to standard postoperative physical therapy and analgesia protocols.

The prosthesis will be placed using a direct anterior or posterolateral approach. Both approaches are regularly performed in hospitals and clinics in the Netherlands and in Noordwest Ziekenhuisgroep location Alkmaar specifically. The two surgeons involved in the study have extensive experience with both approaches and perform at least 40 total hip replacements each year. Therefore, no specific surgical learning curve is expected for either of the procedures.

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.

The PLA is the most commonly used approach overall in the Netherlands. 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.

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

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. DESCRIPTION OF THE DEVICES

6.1 Implants

In this study, the NANOS neck preserving stem will be used in combination with a well-documented non-cemented acetabular cup the R3 (R3 smith & nephew,
Memphis, Tennessee, United States of America) which is on the NOV list of approved components.

6.2 articulation

Acetabular component will be the R3 (Smith & Nephew, Memphis, Tennessee, United States of America). All investigators will use a oxinium head and a highly corsslinked polyethylene insert (XLPE) insert. Head size will be 32 mm or 36 mm. The size of the head depends on the acetabular component. Smaller heads will only be used if the acetabulum requires a cup size in which 32 mm cannot be used.

6.3 instruments

The participating surgeons will only use instrument supplied by Smith & Nephew orthopaedics AG for the implantation of the NANOS neck preserving stem. All instruments will be used conform the instruction of the manufacturer.

6.4 Applicable norms and guidelines

Clinical Investigation: ISO 14155:1 and ISO 14155:2

Reporting: STROBE: Strengthening the Reporting of Observational Studies in Epidemiology).

7. NON-INVESTIGATIONAL IMPLANT

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

- Radiographic analysis will be done on standard AP and lateral view X-rays postoperative, 8 weeks, 12 months and 24 months. Only the two X-rays that are taken during the extra outpatient appointment at 24 months do not include the standard treatment for THR. To measure migration and stem positioning we will use the EBRA-FCA software system. A blinded practitioner of the department of radiology will mark nineteen reference points on the stem and femur. The software automatically defines all other parameters.

8.1.2 Secondary study parameters/endpoints

Secondary study parameters are the clinical, functional and surgical outcome parameters compared between the DAA and PLA:

- Perceived pain, measured using a Visual Analogue Scale (VAS) in the week before surgery, during hospitalization at days 1 to 3, at discharge, 8 weeks, three months, six months, one year after surgery and two years after surgery.
- 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) in the week before surgery, at 8 weeks, three months, six months, one year after surgery and two years after surgery.
- Hip range of motion in the week before surgery, at 8 weeks, three months, six months, one year after surgery and two years after surgery.
- Quality of life assessed using the EQ-5D in the week before surgery, at 8 weeks, three months, six months, one year after surgery and two years after surgery.
- Functioning during daily living assessed using the HOOS in the week before surgery, at 8 weeks, three months, six months, one year after surgery and two years after surgery.
- Hip abductor strength and gait quality before surgery, at 8 weeks and after 12 months.
- Length of hospital stay
- Operation time, blood loss, and other parameters of the surgical procedures
- All complications related to the surgery and rehabilitation
- Health status will be classified using the ASA score.
- Patient’s pre-operative status, surgical procedure as well as clinical and radiological outcome will be documented.

8.1.3 Other study parameters

Patient characteristics such as age, gender, stature, body weight, body length, side of operation (left or right), smoking and comorbidities.

8.2 Randomization, blinding and treatment allocation

When patients want to participate, informed consent will be signed. Baseline measurements will be registered and patients will be randomized to one of the two study arms. Patient or surgeon will not be blinded for type of treatment.

8.3 Study procedures

Pre-operative assessment

After inclusion participants will be asked to fill in the questionnaires. A general questionnaire containing questions about demographic characteristics of the participants, and validated questionnaires to assess clinical and functional outcomes will be used. The Hip Dysfunction and Osteoarthritis Outcome Score (HOOS)[17] 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 assess perceived pain in the previous week. To assess quality of life, the participant will be asked to fill in the EQ-5D[18,19].

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 body segment accelerations and angles, and a two times 50 meter walk at their preferred walking speed, also instrumented with inertial sensors[8–12]. For the TUG test[13], 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)[14], which will be attached to the lower back with Velcro fixation. The inertial sensors measure the accelerations and angles of the lower leg as well as stance and tilt of the pelvis. Pre-operatively, standardized calibrated radiographs of the pelvis (anterior posterior or AP and lateral views) are performed.

Measurement of subsidence:

The EBRA-FCA system measures subsidence offset and varus/valgus angulation using at least four standardized AP standing pelvic x-rays. It can detect axial subsidence of 1 mm with a specificity of 100% and sensitivity of 78%. This system has been validated for short stem hip implants and has been previously used for the NANOS stem. Progressive subsidence of >1.5 mm two years after prosthesis placement is an indicator for aseptic loosening[5,7,20]. Subsidence will be measured by independent and blinded radiologists.

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, on the second postoperative day standing AP radiographs of the pelvis will be made. The two orthopedic surgeons involved in the study have experience with placement of the NANOS stem. Each surgeon performs about 40 to 100 total hip replacements each year. Both surgeons are experienced in performing either the direct anterior approach or the posterolateral approach. The total time of hospital stay will be registered. Complications and adverse events are noted at discharge.

Follow-up assessments

A 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 8 weeks (± 14 days) and 12 months (± 31 days). In addition, the participants have to fill in the HOOS, VAS, EQ-5D at 3 and 6 months. the questionnaires will be sent to the patient's home by post or e-mail. Participants will be able to return the questionnaire without making additional costs.

At the regular visit to the orthopaedic outpatient department at 8 weeks, radiographs of the pelvis will be taken according to the standard protocol (standing AP and lateral views) extra attention will be given for correct patient positioning for later migration analysis. At the regular visit to the orthopedic 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 standardized standing AP radiographs of the pelvis and axial radiographs of the treated hip will be made. One additional clinical radiological follow-up visit will be scheduled 24 months after surgery. At that moment, the participant will be asked to complete the HOOS, VAS and EQ-5D and the stem positioning will be assessed using standing AP pelvis and axial hip x-rays.

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

	1**	2**	3**	4**	5	6	8**	9***
Location	**OC***	**IC***	**IC**	**OC**	**Q***	**Q**	**OC**	**OC**
Assessment	**Pre-op**	**Operation**	**Day 1-3**	**8 weeks**	**3 months**	**6 months**	**12 months**	**24 months**
Window				± 14 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
HHS	X			X			x	
Quality of balance and walking	X			x			x	
Surgical outcome								
Operation parameters		x						
Pelvic radiography	X		x	x			x	x

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

** Standard patient visit

*** Extra outpatient visit

8.4 Withdrawal 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 Noordwest Ziekenhuisgroep 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.

8.4.1 Specific criteria for withdrawal
Not applicable

8.5 Replacement of individual subjects after withdrawal
If a participant withdraws from the study, he/she will not be replaced.

8.6 Follow-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.

8.7 Premature termination of the study
Based on the Australian national register for THA, the NANOS prosthesis shows excellent low revision rates at 3 years of follow-up compared to other short stem prosthesis.

In a pilot study that was performed in our centre with the CORAIL femoral stem[21], we analysed our own patient files for differences between the DAA and PLA. We analysed a cohort of 80 patients (83 hips) that were operated between January 2012 and December 2012 by a single surgeon in our hospital. 38 patient received a prosthesis by means of a PLA and 45 by means of a DAA. 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. To our knowledge, few data is available on how surgical approach influences subsidence[22]. Glyn-Jones et al.[22] reported no difference in subsidence between the posterolateral approach and direct lateral approach. Given the abovementioned information, we consider an interim analysis as not necessary.

9. SAFETY REPORTING

9.1 Section 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 in insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, regardless of cause. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious 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 jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The principle investigator will report the SAEs and possible device related events through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the principle investigator 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.

9.2.3 Adverse device Effects

All adverse events device-related or not, most be recorded and evaluated on the basis of the relationship to the device. Specifically, all component removals (and/or revisions) whether device related (or not device related) depending on their frequency, medical significance and circumstance.

Adverse device effect: are defined as the following:

- Any device component failure (e.g. breakage)
- Device wear particle induced osteolysis inflammation etc. Wear debris may be metal and or hydroxyapatite in composition.
- Any device component experiencing dislocation subsidence subluxation or migration.
- Unintended fractures
- Nerve damage (as evidence immediate postoperative by motor/sensor deficit not present preoperatively).
- Large vessel damage (with large blood loss i.e. 1500ml).
- Hip pain is recorded as VAS score and ranked as an element in the HOOS. It is nog routinely categorized as an adverse event. Extreme or persistent hip pain leading to disability may however be reported as adverse event.
- Other adverse related events that are deemed device related and serious.

9.2.4 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. All adverse events have to be documented on the appropriate interval and case report from. 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. Thereby no interim analysis will be performed.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

To answer our primary research question, subsidence at two years will be used. Secondary measurements include subsidence at 8 weeks and at 12 months. The EBRA-software needs at least 4 similar radiographs to correctly measure subsidence. The subsidence will be measured in mm with one decimal point behind the comma. In order to determine if there is a difference between the mean amount of subsidence (measured with the EBRA FCA) of the posterolateral and direct anterior approach group an independent t-test will be carried out and the 95% CI for the mean difference will be determined. Pearson's *r* will be used to calculate the effect size. The assumption of normality will be checked by visual inspection of the q-q plot and the box plot of the data within the groups. A Shapiro-Wilks test will also be performed on the data within the groups. Homogeneity of variance will be checked using the Levene's test.

The effect of time (e.g. at 1 day, 8 weeks, 12 months and 24 months postoperatively) on the amount of subsidence (measured with the EBRA FCA) will be examined with a one-way between subjects ANOVA. Eta² will also calculated to determine the effect size. Tukey's HSD test will be used to identify where the specific differences occured between the two groups. It is also used to calculate the 95% CI for each difference between the means.

The outcome parameters will be 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.

10.2 Secondary study parameter(s)

For the secondary continuous outcomes, the differences in scores for the DAA and PLA groups at the different times will be statistically tested using unpaired t-tests or its non-parametric equivalent based on whether the difference scores violate parametric assumptions or not. Categorical outcome parameters will be analyzed using Chi-square tests. If possible, 95% confidence intervals for the relevant estimates will be calculated.

10.3 Other study parameters

Not applicable

10.4 Interim 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 (2013), 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 device which will improve clinical, functional and surgical outcome after total hip arthroplasty for younger and active patients in need of total hip arthroplasty in the future and at low risk and no extra cost for patients in this study.

11.5 Compensation for injury

Previous use of the NANOS stem has been previously done in a prospective trial and has not led to a higher complication rate than we see after regular THA. All patients will undergo the normal follow-up protocol and will attend one additional follow up visit. Since total hip placement procedures are common practice in the Noordwest Ziekenhuisgroep Alkmaar and the Nanos had been previously used by the collaborating surgeons. We do not suspect additional complications.

Although short to midterm results with the NANOS stem are favorable, there is no documented long term follow-up. Therefore, the investigator has a liability insurance for the 58 patients that will undergo Nanos placement 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. € 650.000,-- (i.e. six hundred and fifty thousand Euros) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euros) 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.

11.6 Incentives (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-proof monitor.

12.3 Amendments

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