Dutch Persona PS Multicenterstudy

PROTOCOL TITLE 'Dutch Persona PS Multicenterstudy'

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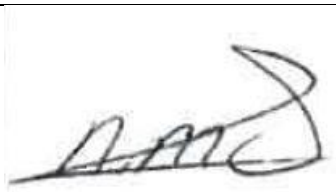
Coordinating investigator/contact Person: ***Mw. Dr. N.M.C. Mathijssen*** ***Reinier de Graaf Groep*** ***N.Mathijssen@rdgg.nl***		**21-11-2017**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

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**

SUMMARY

Rationale: TKA has demonstrated effectiveness with substantive and sustained improvement in quality of life for individuals with moderate to severe osteoarthritis, however, functional performance in patients 1 year after TKA remains lower than for healthy adults, with reports of an 18% slower walking speed, 51% slower stair-climbing speed, and deficits of nearly 40% in quadriceps strength. Additionally, certain limitations in knee design systems require surgeons to accept compromises which can result in surgical inefficiencies and challenges in seizing desired outcomes. Patient expectations and an ever emerging population with active lifestyle also add a new requirement and need for innovative designs that bring advantages over traditional implants. Personalized implants with critical features of natural movement, contoured shape, and unique anatomic and physiologic composition can address these requirements.

This study will evaluate the commercially available Zimmer *Persona* knee implant used in primary total knee arthroplasty, a more personalized knee implant.

Objective: The primary objective of this study is to obtain implant survivorship and clinical outcomes data for commercially available *Persona* knee implants used in primary total knee arthroplasty.

Study design: A prospective multicenter, non-controlled study of commercially available Zimmer *Persona* knee implants will be enrolled. Patients will be evaluated preoperatively, during hospital stay and at 6 weeks, 1 year, 2,3,4, and 5 years post-operative.

Study population: The study population will consist of 200 patients who qualify for primary total knee arthroplasty and who meet the inclusion/exclusion criteria for study participation.

Intervention (if applicable): The Zimmer *Persona* knee implant

Main study parameters/endpoints:

1. Implant survivorship based on removal of a study device.
2. Safety based on incidence and frequency of adverse events.
3. Clinical performance measured by overall pain and function,

quality of life data, radiographic parameters and survivorship.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Subjects participating in the study will have the same risks and benefits when not participating in the study.

1. INTRODUCTION AND RATIONALE

Osteoarthritis (OA) is the most common type of arthritis causing considerable disability across broad populations. The economic burden of arthritis, specifically osteoarthritis is enormous with an estimated cost of $60 billion in the United States and expected to increase to $100 billion by 2020.(1;2) The knee joint is the most common joint to develop OA and total knee arthroplasty (TKA) is the most frequently performed joint arthroplasty procedure for this condition.(3;4) With an increase in the prevalence of arthritis, obesity, and old age, a further demand for TKA is projected to increase substantially over the next few years. (5;6;7;8;9) In 2005, approximately 523,000 TKAs were performed nationally.(10) The American Academy of Orthopedic Surgeons (AAOS) and Kurtz et al,(11) have provided projections for future demand of TKA. In 2002, the AAOS had suggested an annual replacement load of 474,000 by the year 2030. In 2007, Kurtz et al,(11) described an annual demand of 3.5 million by 2030. While these projections vary widely, both suggest a strong increase in demand for TKA, prompting significant interest from surgeons, healthcare institutions and orthopedic device manufacturers interested to better understand the future technological and economic burden of TKA. Although, TKA has demonstrated effectiveness with substantive and sustained improvement in quality of life for individuals with moderate to severe osteoarthritis,(12;13) functional performance in patients 1 year after TKA remains lower than for healthy adults, with reports of an 18% slower walking speed, 51% slower stair-climbing speed, and deficits of nearly 40% in quadriceps strength.(14) Additionally, certain limitations in knee design systems require surgeons to accept compromises which can result in surgical inefficiencies and challenges in seizing desired outcomes.(15;16;17;18;19) Patient expectations and an ever emerging population with active lifestyle also add a new requirement and need for innovative designs that bring advantages over traditional implants. Personalized implants with critical features of natural movement, contoured shape, and unique anatomic and physiologic composition can address these requirements. The current concepts in TKA warrant a personalized orthopedics initiative by offering a finer ability in identifying and precisely addressing the unique needs of patients. It is through this introduction of high fidelity implants, morphologic designs and intelligent instrumentation that each patient's knee can be distinctively and accurately reconstructed, allowing for clinical outcomes to be better optimized. Furthermore, such personalized systems will empower the surgeon to advance performance by providing a leading design that efficiently accommodates surgeons' intraoperative needs with minimizing surgical trade-offs and maximizing efficiency. To address these clinical challenges and methodologically address new implant characteristics, a prospective, multi-center, longitudinal data collection model is being proposed. The objective of this study is to determine clinical performance/ outcomes and implant survivorship for commercially available Zimmer *Persona* knee implants used in

primary total knee arthroplasty. It is hypothesized that the implant survivorship is at least equal to the implant survivorship of the NexGen knee prosthesis (Zimmer) after 5 years, which is 96.5% (Results from Australian Orthopaedic Association National Joint Replacement Registry)

2. OBJECTIVES

The objective of this study is to obtain clinical performance (outcomes) data and survivorship for commercially available Zimmer *Persona* knee implants implanted in primary total knee arthroplasty. This will be done by analysis of validated outcome measurement tools, radiographs and adverse event data.

3. STUDY DESIGN

This is a prospective, multicenter, non-controlled clinical study designed to facilitate the collection and evaluation of pain, function, quality of life, radiographic assessment, and adverse event data. Up to 3 Dutch sites (Tergooi Ziekenhuizen, Medisch Centrum Alkmaar en de Reinier de Graaf Groep) will contribute to this study with a maximum of 200 implanted knees. Each Investigator will be skilled in total knee arthroplasty and experienced implanting the devices included in this study.

In order to avoid potential selection bias, each Investigator will offer study participation to each consecutive patient presenting as a candidate for primary total knee arthroplasty using the commercially available (CE marked and FDA cleared) Zimmer *Persona* knee implants and satisfying Inclusion/Exclusion criteria.

Candidates who express interest in study participation will be required to participate in the Informed Consent process and will not be considered enrolled in the study until the candidate has signed and dated the Informed Consent form. At this time the patient is considered enrolled into the study and is assigned with a Case ID.

All study subjects will undergo preoperative clinical evaluations prior to their total knee arthroplasty. The post-operative clinical and radiographic evaluations will be conducted postoperatively during hospital stay, at 6 weeks, 1 year, 2, 3, 4, and 5 years post-operative. The Investigator will review radiographs at each clinical evaluation interval to ensure radiographic evidence of adverse events is documented and reported to the EC and Sponsor as required.

4. STUDY POPULATION

4.1 Population (base)

Study population for primary statistical analysis will be comprised of males and females who require primary total knee arthroplasty, who satisfy the inclusion/exclusion criteria outlined in this section of the protocol and who have signed the Informed Consent form. In order to avoid potential selection bias, each Investigator will offer study participation to each consecutive patient presenting as a candidate for primary total knee arthroplasty using the commercially available (CE marked and FDA cleared) Zimmer *Persona* knee implants and satisfying Inclusion/Exclusion criteria.

4.2 Inclusion criteria

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

1. Patient is 18 to 75 years of age.
2. Patient qualifies for a primary total knee arthroplasty based on physical exam and medical history, including diagnosis of severe knee pain and disability due to at least one of the following:

a. Rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis

b. Collagen disorders and/or avascular necrosis of the femoral condyle

c. Post-traumatic loss of joint configuration, particularly when there is patellofemoral erosion, dysfunction or prior patellectomy

d. Moderate valgus, varus, or flexion deformities

e. The salvage of previously failed surgical attempts that did not include partial or total knee arthroplasty of the ipsilateral knee

3. Patient is willing and able to complete scheduled study procedures and follow-up evaluations
4. Independent of study participation, patient is a candidate for commercially available Zimmer *Persona* knee implants implanted in accordance with product labeling

4.3 Exclusion criteria

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

1. Patient is currently participating in any other surgical intervention studies or pain management studies
2. Previous history of infection in the affected joint and/or other local/systemic infection that may affect the prosthetic joint
3. Insufficient bone stock on femoral or tibial surfaces
4. Skeletal immaturity
5. Neuropathic arthropathy

6. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb
7. Stable, painless arthrodesis in a satisfactory functional position
8. Severe instability secondary to the absence of collateral ligament integrity
9. Rheumatoid arthritis *accompanied by* an ulcer of the skin or a history of recurrent breakdown of the skin
10. Patient has a known or suspected sensitivity or allergy to one or more of the implant materials
11. Patient is pregnant or considered a member of a protected population (e.g., prisoner, mentally incompetent, etc.)
12. Patient has previously received partial or total knee arthroplasty for the ipsilateral knee.

4.4 Sample size calculation

The study is a non-comparative case-series, therefore no sample size determination has been performed. A total of 200 patients will be included in this study, 50 patients for each site.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Zimmer Persona knee implants included in this study are commercially available (CE marked and FDA cleared) and have various component sizes to accommodate anatomical variation. They are intended for long-term implantation in accordance with product labeling. Please refer to the package insert for additional information and instructions.

When used in accordance with product labeling, the risks associated with the use of Zimmer *Persona* knee implants are similar to those of standard, metal-on-polyethylene knee systems used for the same clinical indication or purpose.

6. METHODS

6.1 Study parameters/endpoints

Primary endpoint:

- Implant survivorship based on removal of a study device.

Secondary endpoints:

- Safety based on incidence and frequency of adverse events.
- Clinical performance measured by overall pain and function, quality of life data, radiographic parameters and survivorship. Outcome measures are: Knee Society Objective Knee Score, KOOS score, EQ-5D, and Oxford Knee Score.

6.2 Randomisation, blinding and treatment allocation

Follow up takes place during hospital stay, at 6 weeks, 1 year, 2, 3, 4, and 5 years post-operative. Clinical evaluation will take place at these follow-up moments.

Evaluation	**Pre-operative**	**During hospital stay**	**6 weeks**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**
Medical History	✔							
Clinical evaluation	✔	✔	✔	✔	✔	✔	✔	✔
Radiographic	✔	✔		✔	✔	✔	✔	✔
Questionnaires	✔		✔	✔	✔	✔	✔	✔

Table 1. Study flow chart showing the required examinations and assessments.

6.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4 Replacement of individual subjects after withdrawal

If a subject withdraws from the study, no other subject will be invited for the study.

7. SAFETY REPORTING

7.1 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 insofar as suspension would jeopardise the subjects' health. 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 investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 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;
- 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 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 event. This is for a preliminary report with another 8 days for completion of the report.

7.3 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

8. STATISTICAL ANALYSIS

Performance of commercially available Zimmer *Persona* knee implants in primary total knee arthroplasty will be evaluated for pain, function, quality of life, and survivorship. Data collected in this study will be summarized descriptively and descriptive summaries will be the basis of any study reports issued. These summaries may be used for interim study reports and may also be used to support regulatory submissions, presentations, and/or publications. Additional surgical technique and instrumentation data may be collected and evaluated.

General Statistical Methods

Statistical methodology will consist of summarizing collected data descriptively. Categorical data (e.g., gender) will be summarized using counts and percentages, and 95% Confidence Interval (CI), over the time periods of interest. Continuous data, such as age, will be summarized by using means, medians, standard deviation, minimum, maximum, and 95% CI over the time periods of interest. Implant survival and return to function will be summarized using a Kaplan-Meier method and presented with rates (as percentages) and confidence intervals.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 7, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

All patients who will have a knee arthroplasty and who meets our inclusion criteria, will be invited to participate in the study by the orthopaedic surgeon. Patients will be given information of the study and an informed consent. Patients will be given time to think about participation as long as needed, but at least five days. After that, the patient will be contacted by phone and an appointment with the research nurse will be made. The research nurse will give extended information about the study and if the patient decides to participate, the informed consent will be signed. If the patient has additional questions, an appointment with the orthopaedic surgeon will be made.

9.3 Benefits and risks assessment, group relatedness

There are no benefits or risks for patients participating in this study.

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 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.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

A unique case identification number (Case ID) will be assigned to each participating subject/knee (bilateral subjects will be assigned a unique case ID number for each knee). This case ID will consist of the site number (1-Reinier de Graaf Hospital, 2—Tergooi, 3- Medisch Centrum Alkmaar) and the case number (1-50 for each site) (Thus, the first participant in Reinier de Graaf Hospital will be 1-1) This unique case ID number will be used throughout the study for identification. Case ID numbers will be assigned consecutively in ascending order per site. All patient related data will be kept encoded. On these forms the patients will only be tracked by the case ID. This code can only be decoded by the study center itself.

10.2 Monitoring and Quality Assurance

During the investigation, Zimmer will conduct periodic monitoring visits as needed and maintain contact with the Investigators and staff to monitor the study. To this end the Study Monitor requires access to the patient medicalrecords, Patient Consent Forms, original Case Report Forms, radiographs and relevant office notes during visits for monitoring purposes. The Clinical Monitor will report any noncompliance with the signed Clinical Trial Agreement, Clinical Investigation Plan, or any condition of approval imposed by the reviewing Ethics Committee to Zimmer.

10.3 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.

10.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority 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 and the Competent Authority.

10.5 Public disclosure and publication policy

Both the Clinical Investigator and the Sponsor have the right to publish or allow the results of the clinical trial to be published. The Clinical Investigator recognizes that the Sponsor has a special interest in the results of the clinical study and will submit manuscripts to the Sponsor prior to publication. If the Sponsor desires changes to be made, these are communicated to the Clinical Investigator within 1 month. Pooled data may be used for training and meetings.

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