PaTIO study : PhysiotherApeutic Treat-to-target Intervention after Orthopaedic surgery; A cost-effectiveness study.

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PROTOCOL TITLE 'PaTIO study : PhysiotherApeutic Treat-to-target Intervention after Orthopaedic surgery; A cost-effectiveness study.'

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TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE....8
2. OBJECTIVES....10
3. STUDY DESIGN....11
4. STUDY POPULATION....12
4.1 Population (base)....12
4.2 Inclusion criteria....12
4.3 Exclusion criteria....12
4.4 Sample size calculation....12
5. TREATMENT OF SUBJECTS....14
5.1 Investigational product/treatment....14
5.2 Use of co-intervention (if applicable)....14
5.3 Escape medication (if applicable)....14
6. INVESTIGATIONAL PRODUCT....15
6.1 Name and description of investigational product(s)....15
6.2 Summary of findings from non-clinical studies....15
6.3 Summary of findings from clinical studies....15
6.4 Summary of known and potential risks and benefits....15
6.5 Description and justification of route of administration and dosage....15
6.6 Dosages, dosage modifications and method of administration....15
6.7 Preparation and labelling of Investigational Medicinal Product....15
7. NON-INVESTIGATIONAL PRODUCT....16
7.1 Name and description of non-investigational product(s)....16
7.2 Summary of findings from non-clinical studies....16
7.3 Summary of findings from clinical studies....16
7.4 Summary of known and potential risks and benefits....16
7.5 Description and justification of route of administration and dosage....16
7.6 Dosages, dosage modifications and method of administration....16
7.7 Preparation and labelling of Non Investigational Medicinal Product....16
7.8 Drug accountability....16
8. METHODS....17
8.1 Study parameters/endpoints....17
8.1.1 Main study parameter/endpoint....17
8.1.2 Secondary study parameters/endpoints (if applicable)....17
8.1.3 Other study parameters (if applicable)....17
8.2 Randomisation, blinding and treatment allocation....17
8.3 Study procedures....17
8.4 Withdrawal of individual subjects....18
8.4.1 Specific criteria for withdrawal (if applicable)....18
8.5 Replacement of individual subjects after withdrawal....18
8.6 Follow-up of subjects withdrawn from treatment....18
8.7 Premature termination of the study....18

9. SAFETY REPORTING 19
9.1 Temporary halt for reasons of subject safety 19
9.2 AEs, SAEs and SUSARs 19
9.2.1 Adverse events (AEs) 19
9.2.2 Serious adverse events (SAEs) 19
9.2.3 Suspected unexpected serious adverse reactions (SUSARs) 20
9.3 Annual safety report 20
9.4 Follow-up of adverse events 20
9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee] 20
10. STATISTICAL ANALYSIS 21
10.1 Primary study parameter(s) 21
10.2 Secondary study parameter(s) 22
10.3 Other study parameters 22
10.4 Interim analysis 22
11. ETHICAL CONSIDERATIONS 23
11.1 Regulation statement 23
11.2 Recruitment and consent 23
11.3 Objection by minors or incapacitated subjects 23
11.4 Benefits and risks assessment, group relatedness 23
11.5 Compensation for injury 23
11.6 Incentives 24
12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION 25
12.1 Handling and storage of data and documents 25
12.2 Monitoring and Quality Assurance 25
12.3 Amendments 25
12.4 Annual progress report 25
12.5 Temporary halt and (prematurely) end of study report 25
12.6 Public disclosure and publication policy 26
13. STRUCTURED RISK ANALYSIS 26
13.1 Potential issues of concern 26
13.2 Synthesis 26
14. REFERENCES 27

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**

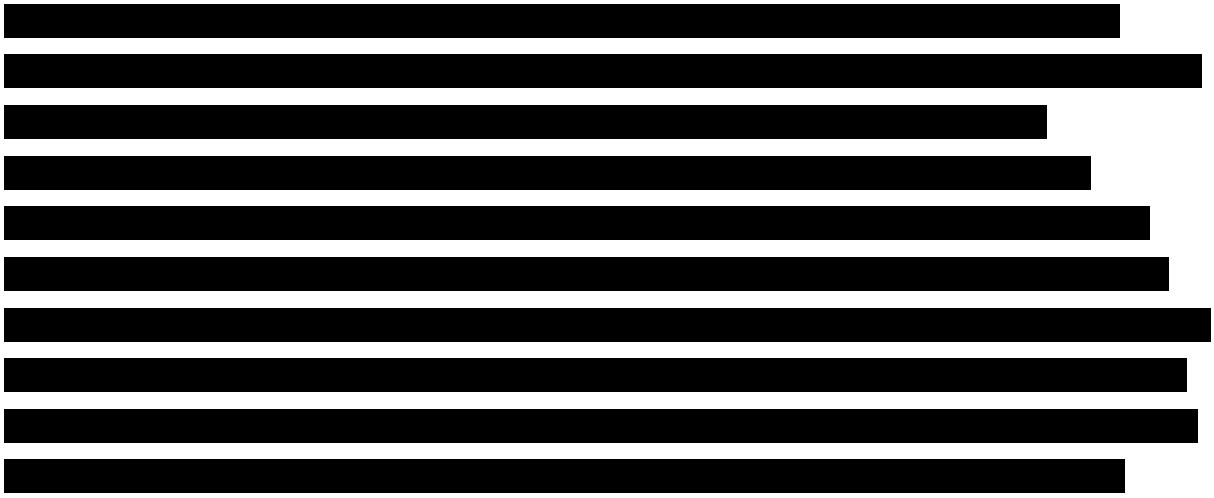
SUMMARY

Rationale: Postoperative physiotherapy (PPT) is a proven effective treatment strategy after total knee (TKA) and hip arthroplasty (THA), however research shows that there is no consensus regarding its timing, content and duration. We propose an optimized, personalized treat-to-target PPT which is based on the current scientific evidence and on expert opinion (focus group) and is presented in the form of a multidisciplinary care pathway.

Objective: To evaluate the cost-effectiveness of the optimized, treat-to-target PPT strategy in TKA and THA patients compared to usual PPT. The hypothesis is that with the optimized strategy superior functional outcome can be achieved to usual care, with lower costs (superiority study).

Study design: In a cluster randomized study design, we will compare the cost-effectiveness of two strategies regarding the provision of PPT following TKA/THA, usual PPT care and treat-to-target PPT. Patients scheduled for a primary TKA/THA and willing to comply with study protocol.

Intervention:



registered.

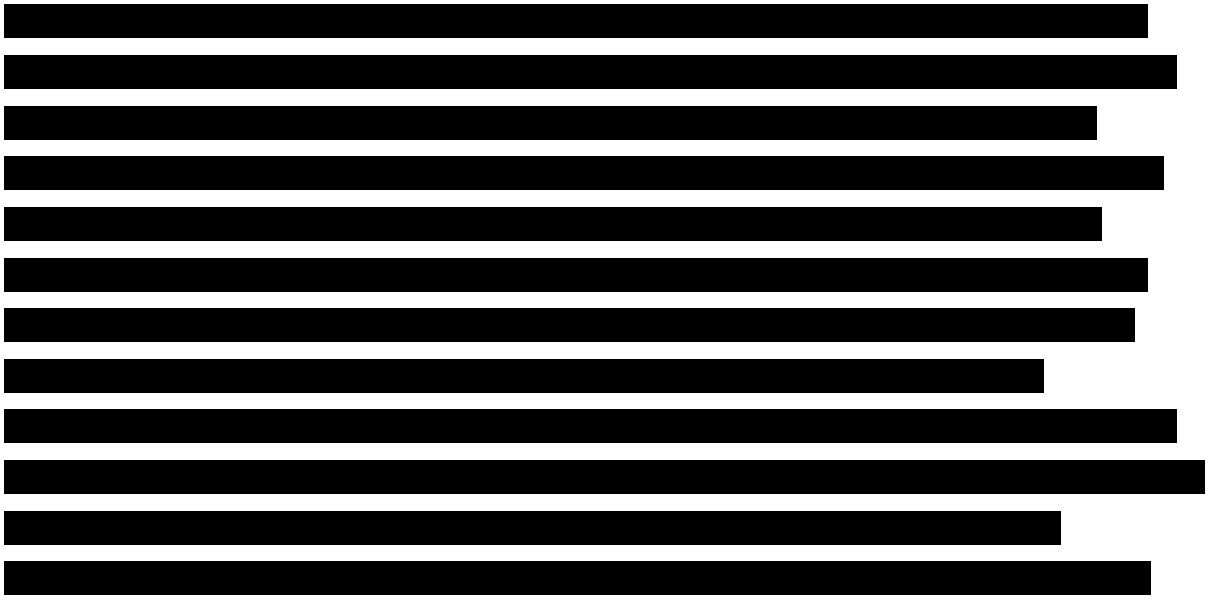
Usual care: Current PPT delivery.

Main study parameters/endpoints: The difference between both groups in change between baseline (two days after surgery) and 3 month postoperative KOOS-PS / HOOS-PS score, a measure of physical functioning.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will be asked to fill out questionnaires at 6 time points (10 minutes additional time per time point). At three time points the patients will be asked to perform physical performance tests. So additional time will be asked from the participating patients. In our view patients participating in this study will undergo no additional risks.

1. INTRODUCTION AND RATIONALE

Postoperative physiotherapy (PPT) after total knee or hip arthroplasty (TKA/THA) for osteoarthritis (OA) is an evidence-based, effective treatment, with several studies demonstrating its effectiveness in improving function, range of motion and quality of life[1-4]. Consequently, PPT plays an important role in achieving functional independence such as return to work[5, 6]. PPT following THA/TKA is advocated in guidelines of the Dutch Orthopaedic Association (NOV) and the Royal Dutch Society for Physical Therapy (KNGF). These guidelines state that PPT is recommended, including a post-discharge supervised (home) exercise program which should comprise muscle strengthening exercises and exercise focusing on functional levels. For THA a clinical pathway, including individual advice, support and postoperative rehabilitation is also recommended.
Recently we showed that >99% of patients receive PPT, with large majority (90%) having PPT in primary care[7]. Although in general PPT appears to be an effective treatment modality there is no consensus on several treatment aspects such as when to use which treatment modality, the timing of these treatment modalities, duration and frequency. As such, we showed considerable practice variation regarding the content of the treatment, i.e. extent to which (NOT)recommended treatment modalities were used. Also treatment frequency and duration varied, with patient-reported treatment duration being >12 weeks in 47%. This was also reported by other studies[7-10]. On societal level it is extremely relevant that the most optimal PPT treatment strategy is used, as it concerns >50.000 persons annually in The Netherlands[11]. Indeed, during the "Agenda Zorgevaluatie Orthopedie" meeting March 2015, initiated by the NOV, attended by among others, representatives of PTs and patients, this topic was among the Top-10 prioritized topics. Therefore more knowledge on optimized PPT strategies is necessary.



[redacted]

Therefore this study aims to compare the cost-effectiveness of optimized, tailored, PPT by using a treat to target strategy in combination with a clinical pathway that is embedded in the continuum of care with usual PPT care in THA/TKA, embedded in the continuum of care. We assume that with the optimized strategy faster recovery can be achieved, at lower costs. The results of this study can be used to develop and implement a nationwide care pathway for PPT after THA/TKA. Already 19 orthopaedic practices expressed their interest to participate in this project underscoring the willingness to address this topic, in close collaboration with PTs.

Health care efficiency problem

PPT is a proven effective treatment strategy after THA/TKA recommended in practice guidelines. [redacted]

Usual care

The provision of PT following THA/TKA is advocated in NOV and KNGF guidelines. About 99% of patients receives acute PPT, with 90% being treated in primary care[7]. PPT was provided in a secondary setting in about half of the patients. Patients and PTs reported however variation in content, duration and frequency. PPT duration ranged from 2-4 weeks till >12 weeks (in >47% of patients) with a weekly frequency of 2 sessions in 63% and 83% in patients and PTs respectively. In addition, we showed that the majority of PTs reported adherence to recommendations on PPT after THA/TKA, but also a high frequency of some not recommended treatment modalities[8].

See Figure 1 PPT after TKA/THA in appendix.

Patients

Patients with clinical and radiological knee or hip OA scheduled for primary TKA/THA.

2. OBJECTIVES

PPT is a proven effective treatment strategy after TKA and THA for end stage OA, and is recommended in several guidelines. However, research shows that there is no consensus regarding its timing, content and duration. We propose to integrate guideline recommendations and additional evidence in a personalized PPT treat-to-target strategy.

[redacted]

The treat-to-target PPT is based on the current scientific evidence and on expert opinion (focus group) and is presented in the form of a multidisciplinary care pathway.
The aim of the present proposal is to evaluate the cost-effectiveness of the optimized, treat-to-target PPT strategy in TKA and THA patients compared to usual PPT.
The hypothesis is that with the optimized treat-to-target strategy better functional outcome can be achieved compared to usual care with lower costs (we aim for a superiority study).

Primary objective

1. To assess whether the functional outcome of an optimized, personalized treat-to-target PPT strategy after TKA and THA is superior to usual care PPT after 3 months follow-up.
2. To assess whether an optimized, personalized PPT strategy is cost-effective compared to usual care PPT.

Secondary objective

To assess whether the functional outcome of an optimized, personalized treat-to-target PPT strategy after TKA and THA is superior to usual care PPT after 12 months follow-up.

To assess the difference in scores of OKS/OHS, NRS, EQ5D, performance tests, physical activity level, as well as anchor questions, and satisfaction question; between both groups.

3. STUDY DESIGN

The present proposal has a cluster design, and concerns a comparison of the cost-effectiveness of two cluster randomized strategies regarding the provision of physical therapy following TKA or THA, usual postoperative physiotherapy (PPT) care and treat-to-target PPT. To avoid dilution between the usual care PPT and treat-to-target PPT groups, randomization will take place on hospital level, meaning that all patients referred by one hospital will receive the same PPT intervention. The randomization will be stratified for the use or non-use of a fast-track protocol. The treat-to-target PPT intervention will be implemented by training of PTs. Patients will be followed for 12 months.

The following hospitals will participate in this trial: Erasmus MC (Rotterdam), HAGA Hospital (Den Haag), Leidsch University MC (Leiden), Máxima MC (Eindhoven/Veldhoven), MC Alkmaar, Medical Spectrum Twente (Enschede), Onze Lieve Vrouwe Gasthuis (Amsterdam), Spaarne Hospital (Heemstede), St Anna Hospital (Geldrop), St Elisabeth Hospital (Tilburg), Tergooi Hospitals (Blaricum), University MC Groningen, University MC Maastricht, Bergman Clinics (Rijswijk) and MC Leeuwarden. The duration of the present study is three years.

4. STUDY POPULATION

4.1 Population (base)

4.2 Inclusion criteria

Patients eligible for this trial are patients with clinical and radiological knee or hip OA who are scheduled for a primary TKA or THA, and willing to comply with the study protocol.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: TKA or THA for a diagnosis other than OA, uncontrolled cardiovascular disease or hypertension, history of neuromuscular disorder that affects lower extremity function, terminal illness, plans to have another joint replacement during study follow-up, not able to attend follow-up measurements, not able to attend the PPT in primary setting, serious psychiatric disorders, or insufficient command of the Dutch language, spoken and/or written.

4.4 Sample size calculation

Our primary research hypothesis is that the gain in physical function in our “treat-to-target” intervention will be superior to the gain in the usual care group at 3 months, measured by the HOOS-PS/KOOS-PS score. Currently, 19 hospitals expressed their interest to actively participate in our study.

No minimally clinical important difference (MCID) after postoperative physiotherapy in TKA/THA patients is yet available, only one study reported a MCID of 20 after TKA. As such our MCID is based on expert opinion, knowingly 10 points on the KOOS-PS and HOOS-PS.

The power calculation presented in this proposal is based on the proof of superiority. The standard deviation (SD) of the KOOS-PS and HOOS-PS 3 months after physiotherapy in TKA and THA patients has been reported to be on average 15.6 and 11.8 respectively [21-27]. For the intra cluster correlation coefficient we used an ICC of 0.06 which is generally reported in literature for hospital processes.

To detect superiority of the treat-to-target PPT intervention to usual PPT we assessed the required sample size based on the following assumptions, a MCID of 10 points, and a SD of 15.6. We propose a cluster RCT (randomization on Hospital level) with an intracluster correlation coefficient of 0.06 and in total 18 participating hospitals. Sample sizes of 90 in group one and 90 in group two, which were obtained by sampling 9 clusters with an average of 10 subjects each in group one and 9 clusters with an average of 10 subjects

each in group two, achieve 90% power to detect a difference between the group means of at least 10. The coefficient of variation of cluster sizes is 0,500. A two-sided t-test was used with a significance level of 0,050. This test used degrees of freedom based on the number of subjects. To account for a 25% of drop out 240 patients will be needed.

We also assessed the needed numbers to detect superiority of the treat-to-target PPT intervention to usual PPT for the outcome improvement of pain severity as assessed by the NRS. Based on a MCID of 1 point on the NRS , and a SD of 2 the needed numbers were assessed. Sample sizes of 117 in group one and 117 in group two, which were obtained by sampling 9 clusters with an average of 13 subjects each in group one and 9 clusters with an average of 13 subjects each in group two, achieve 91% power to detect a difference between the group means of at least 1. The standard deviation of subjects is 1,70. The intracluster correlation coefficient is 0,060. The coefficient of variation of cluster sizes is 0,500. A two-sided t-test was used with a significance level of 0,050. This test used degrees of freedom based on the number of subjects. To account for a 25% of drop out 312 patients will be needed.

Given the planned inclusion period of 12 months and the 19 centers participating and with an expected 100 inclusions a year (~2 per week), we expect to have sufficient numbers for our hypothesis. The length of the inclusion period is based on the inclusion rate of the assumed slowest including hospitals (UMCs).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

A) optimized personalized treat-to-target strategy: the physical therapeutic intervention is constructed based on existing protocols, current evidence for PPT interventions, and by an expert task force consisting of patients, PTs, orthopaedic surgeons, exercise physiologists and researchers. The final protocol has been registered. [redacted]

5.2 Use of co-intervention (if applicable)

NA

5.3 Escape medication (if applicable)

NA

6. INVESTIGATIONAL PRODUCT

NA

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

7. NON-INVESTIGATIONAL PRODUCT

NA

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

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The difference between both groups in change between baseline (two days after surgery) and 3 month postoperative KOOS-PS / HOOS-PS score will be used as primary outcome.

Besides, differences in medical consumption, adverse events, absence from work or decreased productivity, and patient costs, will be assessed.

8.1.2 Secondary study parameters/endpoints (if applicable)

Difference in scores of OKS/OHS, NRS, EQ5D, performance tests, physical activity level, as well as anchor questions, and satisfaction question.

8.1.3 Other study parameters (if applicable)

Preoperatively baseline characteristics will be recorded (age, gender, race/ethnicity, body mass index (BMI), educational status, marital status, living arrangements, employment status (full-time, part-time, unemployed) and musculoskeletal comorbidities, other co-morbidity, duration of complaints, previous surgery.

8.2 Randomisation, blinding and treatment allocation

To avoid dilution between the usual care PPT and treat-to-target PPT groups, randomization will take place on hospital level, meaning that all patients referred by one hospital will receive the same PPT intervention. Randomization will take place with help of a computer program. The randomization will be stratified for the use or non-use of a fast-track protocol. The randomization procedure will take place before the start of the inclusion period.

8.3 Study procedures

Patients who are scheduled for a TKA or THA will be informed about the study and invited to participate by the orthopedic surgeon before surgery. Besides the patients will receive written information. If they are willing to participate, they will be screened for eligibility. When the patient conforms to the inclusion criteria and gives written informed consent, preoperative measurements will be carried out. Preoperatively the usual questionnaires as recommended by the Dutch Orthopaedic Association (NOV), patient characteristics and physical therapy use will be recorded. At discharge after surgery possible prognostic factors and outcome measures will be collected.

Before the inclusion of patients will start, participating hospital will be randomized to group (a) providing usual PPT and group (b) providing treat-to-target PPT.
Follow-up measurements at 6 weeks, 3, 6, 9, 12 months will be performed.
Patients with a serious adverse events during surgery or directly thereafter, in which case a physiotherapeutic program (treat-to-target or usual care) cannot be followed, will still be included for the study and consequently, the follow-up measurements will be performed.

8.4 Withdrawal of individual subjects

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

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

8.6 Follow-up of subjects withdrawn from treatment

8.7 Premature termination of the study

NVT

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. 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, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. 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

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

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

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a

period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

SAE related to the surgical intervention (i.e. TKA or THA procedure) do not belong to the current study and will therefore not be reported through the web portal ToestingOnline to the accredited METC (Erasmus MC).

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

NA

9.3 Annual safety report

NA

9.4 Follow-up of adverse events

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

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

NA

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The study consists of two separate trials, namely one for TKA and one for THA patients. Both trials will be separately analysed.

The difference between both groups in change of KOOS/HOOS-PS between baseline and 3 month follow-up score will be used as primary outcome. Patients will be analyzed according to the intention-to-treat principle.

The primary analyses will be performed by using mixed models (change in KOOS/HOOS-PS during 3 months as dependent and intervention as independent variable).Change between baseline and 3 months follow-up score will be used as primary outcome. Hospital variable will be used to indicate the correlation structure in the model. Adjustments will take place for baseline values of KOOS-PS/HOOS-PS. Of variables of which a priori is known that they are associated with the change in KOOS/HOOS-PS, based on previous studies or based on a strong clinical rationale will be considered as covariates in the primary analysis. These covariates are age, gender, BMI, and surgical approach (anterior versus lateral and postero-lateral). The assumptions of constant variance and linear relationships will be assessed. Should any of these assumptions seriously fail then transformation of the dependent or independent variable(s) (where applicable) will be used. The choice of which transformation (e.g. square root, logarithm) will be used will be based on the specific distribution of the residuals.

COST EFFECTIVENESS ANALYSIS (CEA)

General considerations

We expect the personalized treat-to-target intervention to provide superior patient outcome, with lower healthcare use and societal costs. The economic evaluation will consist of a cost-utility analysis (societal cost per QALY), based on patient reports and with an undiscounted one-year time horizon. The analyses will follow the Dutch costing guidelines. Mean costs and effects will be statistically compared using two-sided bootstrapping, with multiple imputation to account for missing data. Costs will be related to patient outcomes using net-benefit analysis.

Cost analysis

Costs will be estimated from the societal perspective, including healthcare costs, patient and family costs, and productivity costs. The timing, contents, frequency and duration of PPT will be measured using the study registrations. Other costs will be reported by patients using quarterly questionnaires (including GP visits, outpatient visits, hospital days, medication, home and informal care, patient costs and productivity). Prices of

healthcare will be based on available price analyses, NZa prices and standard prices. Sensitivity analysis will be carried out on the perspective (societal or healthcare perspective) and the valuation of productivity (friction cost method or human capital approach).

Patient outcome analysis

In the economic evaluation, the impact on patients' disease burden will be quantified using quality-adjusted life years (QALYs). QALYs will be estimated from the quarterly EQ-5D-5L measurements, with Dutch tariff. Sensitivity analysis will be performed on the employed utility measure (Dutch EQ-5D-5L tariff or Visual Analogue Scale with power transformation).

BUDGET IMPACT ANALYSIS (BIA)

General considerations

In a cost-calculator spreadsheet model, budget impact will be evaluated from the perspective of the Dutch Budgettair Kader Zorg (BKZ), health insurers, and the different care providers. The analyses will follow the Dutch BIA guidelines.

Cost analysis

The analysis will take into account the current mix of treatments, with prices appropriate for the perspective, a 4-year time-horizon and dependent on the rate of uptake. Scenario analyses will be used to address uncertainty.

10.2 Secondary study parameter(s)

By using repeated measures mixed models analyses the course of the secondary outcome(s) over time of both interventions will be compared. The following time points will be used, baseline and follow-up measurements at 6 weeks, 3, 6, 9, 12 months.
Change in secondary outcomes will be used as dependent variable. As secondary outcomes will be used: change in KOOS/HOOS-PS; OKS/OHS, NRS, EQ5D, and performance tests.

10.3 Other study parameters

NA

10.4 Interim analysis

NA

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th version, date: October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Patients who are scheduled for a primary TKA or THA in one of the participating hospitals and fit to the inclusion and exclusion criteria will be informed about the study by the orthopedic surgeon before surgery. Besides the patients will receive written information and are invited to participate. If they are interested the research assistant of each hospital will contact them and screen on in-and exclusion criteria. When the patient conforms to the inclusion criteria and gives written informed consent, preoperative measurements will be carried out. Preoperatively the usual questionnaires as recommended by the Dutch Orthopaedic Association (NOV), patient characteristics and physical therapy use will be recorded. At discharge after surgery possible prognostic factors and outcome measures will be collected.

11.3 Objection by minors or incapacitated subjects

NA

11.4 Benefits and risks assessment, group relatedness

NA

11.5 Compensation for injury

The sponsor wishes to obtain dispensation from the statutory obligation to provide insurance, because participating in the study is without risks. Postoperative physical therapy is widely used following TKA/THA. Besides the treatment, subjects will undergo limited testing procedures; functional outcome is assessed with questionnaires, and functional performance tests and physical examination will be done (range of motion measurements). In our view patients participating in this study will undergo no additional risks. The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

11.6 Incentives

NVT

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data handling will be done with coded data, with the key (code to personal information linkage) only available to the local investigator. Persons who have access to the data include: investigators, research staff, monitoring and quality assurance personal.

12.2 Monitoring and Quality Assurance

The study will be monitored according to the monitoring plan (document K: onderzoek met verwaarloosbaar risico).

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 Temporary halt and (prematurely) end of study report

The investigator/sponsor 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 last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited 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

NVT

13. STRUCTURED RISK ANALYSIS

NVT

13.1 Potential issues of concern

NVT

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic considerations

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

NA

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