Exploring the Benefits of a 3D Patient-specific Alignment in Total Knee Arthroplasty

NCT number:

Not yet assigned

Document Title: Study Protocol and Statistical Analysis Plan

Document Date: 12/27/2025

Sponsor / Organization:

KU Leuven

Herestraat 49, B-3000 Leuven

Phone: **+32 50 66 48 00**

Email: info.brugge@kuleuven.be

Cover letter

Application Ethical Approval S67874 (RATKA CBO v1)

April 2023

Dear members of the PRS Review,
We would to present to you for approval our study titled 'Clinical and Biomechanical Outcome after Robotically-Assisted Total Knee Arthroplasty by Comparing Three Alignment Strategies' (S67874).
This study aims to compare the clinical, functional and biomechanical outcomes after the rehabilitation period following Total Knee Arthroplasty (TKA) of patients with either a Tibial Anatomic Alignment (TA TKA), Mechanical Alignment (MA TKA) strategy, or a new, updated 3D patient-specific alignment TA TKA strategy by controlling the orientation and position of the prosthesis for 3D patient-specific alignment to further optimize post-operative outcomes. Participant recruitment of this study takes place at the AZ Delta Hospital facility and the measurements after the rehabilitation period to evaluate the clinical and biomechanical outcomes take place at the Human Movement Laboratory, KU Leuven Campus Brugge.
The undersigned declares (1) to have taken note of the submitted documents and amendments, (2) to have no scientific or ethical objections, (3) there are no charges to the patient, health insurance, or hospital for participating to the study. Quality and safety standards for patient care in clinical research are not changed from those generally adopted by sponsors in their routine activities, consistent with Joint Commission International standards.

Yours sincerely,
Zhijun li

CLINICAL TRIAL PROTOCOL

Exploring the Benefits of a 3D Patient-specific Alignment in Total Knee Arthroplasty

RATKA_CBO

Version number: v *6* – **Date** *12/27/2025*

EudraCT Nr: Not yet assigned

'clinical trial' (EudraCT nr applicable): any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State - https://eudract.ema.europa.eu

Sponsor

KU Leuven

Herestraat 49, B-3000 Leuven

Coordinating Investigator

Prof. Kurt Claeys, PhD, PT, MT(Dept. Rehabilitation Sciences)

CLINICAL TRIAL PROTOCOL HISTORY

CTP / Amendment #	Date	Reason for amendment
Clinical Trial Protocol v1	31/10/2023	NA
Clinical Trial Protocol v2	11/06/2023	NA
Clinical Trial Protocol v3	14/11/2023	NA
Clinical Trial Protocol v4	15/11/2023	NA
Clinical Trial Protocol v5	27/11/2023	NA

LIST OF PARTICIPATING SITES

(if applicable)

List Of Participating Sites	Principal Investigator	Contact details
Dept. Rehabilitation Sciences	Kurt Claeys	Kurt.Claeys@kuleuven.be
AZ Delta Roeselare	Luyckx Thomas	thomas.luyckx@azdelta.be
Dept. Rehabilitation Sciences	Zhijun li	zhijun.li@kuleuven.be

SIGNATURES

*Form to be **repeated for every Participating Site** and signature of Prinicple Investigator. There can only be one (1) single Coordinating Investigator, while multiple Principal Investigator can be applicable (one (1) Principal Investigator per Participating Site) depending on the amount of Participating Sites.*

Title: Exploring the Benefits of a 3D Patient-specific Alignment in Total Knee Arthroplasty

Protocol: RATKA_CBO

The undersigned confirm that the following protocol has been acknowledged and accepted and that they agree to conduct the Trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in Directive 2001/20/EC or the Regulation 536/2014 as soon as applicable and any subsequent amendments, the ICH-GCP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical trials on medicinal products for human use as soon as applicable, the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the Trial without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Trial publicly available through publication or other dissemination tools, in accordance with this protocol without any unnecessary delay and that an honest accurate and transparent account of the Trial will be given; and that any discrepancies from the Trial as planned in this protocol will be explained.

Coordinating Investigator

Prof. Kurt Claeys, PhD, PT, MT

Name & Title	Signature	Date

Principal Investigator (Participating Site) (Principal Investigator is the same as Coordinating investigator in case of a monocentric trial)

Prof. Prof. Luyckx Thomas PhD, MD

Name & Title	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Annual Progress Report
AR	Adverse Reaction
CA	Competent Authority
CI	Coordinating Investigator
CM	Concomitant Medication
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
FAMHP	Federal Agency for Medicines and Health Products
FJS	Forgotton Joint Score
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LPLV	Last Patient Last Visit
MA	Mechanical Alignment
OKS	Oxford Knee Score
PCS	Pain Catastrophizing Scale
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Tibial Anatomic Alignment
TKA	Total Knee Arthroplasty
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VAS	Visual Analogue Scale

PI and CI shall each be referred to as « Investigator(s) »

FUNDING AND SUPPORT

Funder	Kind of Financial or Non-Financial Support
NA	

The protocol should include information regarding funding, institutional affiliations, , incentives for Trial participantss and information regarding provisions for treating and/or compensating Trial participants who are harmed as a consequence of participation in the Trial.

ROLES AND RESPONSIBILITIES

This was a multicenter study that included two centers, one is KU Leuven and the other is AZ Roeselare Hospital. All study terms were approved and adopted by both committees. The UZ/KU Leuven Ethics Committee has the authority to interpret all experimental terminology and contractual terms and is directly responsible to the research team. The AZ Roeselare Ethics Committee assisted the research team in collaborating on this study. The research team conducted the research in strict compliance with the ethics committee approval requirements. The AZ Roeselare Ethics Committee can feedback suggestions and requirements during the experiment to the UZ/KU Leuven Ethics Committee, and feedback the results to the research team through the recommendations after the UZ/KU Leuven Ethics Committee research discussion. The AZ Roeselare Ethics Committee shall not interfere directly with the research process of the research team.

The PI is responsible for the conduct of the Trial at his/her Participating Site, must protect the rights, safety and well-being of the participants and ensure adequate supervision of the conduct of the Trial at the Participating Site. If any tasks are delegated, the PI must maintain a log (see CTC website documenten/ISF: delegation of responsibilities log and training log) of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI must ensure that there is adequate and documented training for all Trial staff participating in the conduct of the Trial.

Kurt Claeys and Zhijun li is responsible for laboratory testing of patients as KU Leuven PI. Luyckx Thomas as the PI of AZ Delta Roeselare Hospital, who is responsible for introducing

patients to the laboratory of KU Leuven for testing and conducting questionnaire surveys in the outpatient clinic according to the patients' special requirements. Otherwise, all questionnaires will be followed up via phone call by Kurt Claeys or Luyckx Thomas.

It is the CI's responsibility to supervise the conduct of the Trial.

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Exploring the Benefits of a 3D Patient-specific Alignment in Total Knee Arthroplasty
Protocol Short Title Acronym	RATKA_CBO
Trial Phase (I, II, III, IV)	NA
Sponsor name	KU Leuven
Coordinating Investigator	Prof. Kurt Claeys, PhD, PT, MT(Dept. Rehabilitation Sciences)
Contact Adress CI	Spoorwegstraat 12, 8200 Brugge
Contact Email CI	Kurt.Claeys@kuleuven.be
Contact Phone CI	+ 32 16 37 65 62
EudraCT number	Not yet assigned
Other public database nr	
Principal Investigators and Participating Sites	Prof. Kurt Claeys, PhD, PT, MT(Dept. Rehabilitation Sciences) Prof. Luyckx Thomas, MD, PhD(AZ Delta Roeselare)
Medical condition or disease under investigation	knee osteoarthritis
Trial rationale	Implant positioning and component alignment in TKA is one of the determining factors in patient outcome. Currently, different alignment strategies in TKA surgery are used. Current literature does not show clear superiority. Recently, a new and individualized alignment strategy, Tibial Anatomic Alignment (TA), was introduced.
Primary objective	Clincal and biomechanical outcome in TA TKA versus MA TKA versus 3D patient-specific alignment TA TKA versus HC
Secondary objective(s)	Patient Satisfaction in TA TKA versus MA TKA versus 3D patient-specific alignment TA TKA versus HC
Trial Design	Cohort Study/Longitudinal Study
Endpoints	Clincal and Biomechanical Outcome, Satisfaction
Sample Size	3x15 = 45, HC=15
IMP, dosage and route of administration	NA
Active comparator product(s)	NA
Maximum duration of treatment of a Participant	One single visit with clinical and biomechanical testing within 2 years postsurgery

Maximum duration of Trial	4 year
Anticipate First Patient First Visit (FPFV)	1st February 2024
Anticipate Last Patient Last Visit (LPLV)	1st September 2027

TRIAL FLOWCHART

Schedule of Events – Trial specific Procedures / Assesments

Procedure/Assesment	Contact 1/ IC	Data Collection	Contact 2	Prospective Testing
Contacts	**1**		**2**	**3**
Informed consent	X			
Inclusion/Exclusion criteria	X			
Demographics		X		
Medical, Surgical history		X		
Collecting Data				
preop x-rays		X		
perop alignment & positioning		X		
surgical technique: cement, patella		X		
Appointment for testing			X	
Clinical Testing				
OKS-12				X
FJS-12				X
VAS Satisfaction				X
PCS				X
Tinetti				X
VAS Pain				X
Biomechanical Testing				
Gait and functional movement (forward lunge, squat) analysis: kinetic, kinematic, EMG				X

1 Background and Rationale

Briefly explain the background and issues/medical need of the Trial. Make a convincing case as to why the Trial would create valuable and useful scientific knowledge. What will be the expected benefits, risks and rationale why it is expected this Trial will have a positive benefit/risk balance.

- Postoperative function and patient satisfaction are becoming increasingly relevant in patients after knee arthroplasty surgery. Despite adequate pre- operative planning, improved surgical techniques and rehabilitation protocols, only 75%-85% of patients seems satisfied after TKA procedurs.
- Implant positioning and component alignment are determining factors in patient outcome. Currently, different alignment strategies in TKA surgery are used such as Mechanical Alignment (MA) and Kinematical Alignment (KA). MA is is still seen as the gold-standard alignment technique in TKA. However, recently KA is introduced because it restores more the patients individual joint orientation what is considered to be beneficial for soft tissue balance in the knee. In literature no clear superiority of one alignment technique is shown concerning clinical and functional outcome after knee arthroplasty procedures.
- A few years ago, an individualized alignment strategy, Tibial Anatomic Alignment (TA), was introduced and is supposed to be beneficial for soft tissue balance postoperative in knee arthroplasty patients. However, the benefits of TA in TKA on clinical and functional outcome remains up to date unclear prior to this study.
- New clinical insights following the implementation of this TA TKA strategy led very recently to a new, updated 3D patient-specific alignment TA TKA strategy by controlling the orientation and position of the prosthesis for 3D patient-specific alignment to further optimize post-operative outcomes.
- This project aims to compare the clinical, functional and biomechanical outcomes one-year post-surgery of patients with 3D patient-specific alignment TKA, TA TKA, healthy controls (HC) and MA TKA.

2 Trial Objectives and Design

2.1 Trial objectives

Formulate specific statements of the purpose of the Trial (i.e. aims and objectives). Define the primary research question, and address a specific hypothesis.

See also: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf

- **General objective**: to have more insights in the clinical en biomechnical outcome in patients with 3D patient-specific alignment TA TKA vs. TA TKA vs. MA TKA and vs. HC
    - **Specific Aim 1**: to have more insights into clinical outcome in patients with 3D patient-specific alignment TA TKA vs. TA TKA vs. MA TKA vs. HC
    - **Specific Aim 2:** to have more insights into biomechanical outcome in patients with 3D patient-specific alignment TA TKA vs. TA TKA vs. MA TKA vs. HC during gait and functional movements
- **Hypothesis**: a TA TKA strategy is expected to provide better clinical and functional outcomes for the patient at the end of the rehabilitation period (1 year post-surgery) compared to MA TKA. 3D patient-specific aligned TA TKA is expected to provide better clinical and functional outcomes for the patient at the end of the rehabilitation period compared to TA TKA or MA TKA, and closer to HC.

2.2 Primary Endpoints

- Clincal and functional outcome: VAS Satisfaction, VAS Pain, PCS, OKS, FJS
- Fall risk: Tinetti test
- Biomechanical outcome during gait and functional movements

2.3 Secondary Endpoints

- Significan differences will be set below the 0.05 (P-value=0.05).
- Compare a single task, calculate the mean and standard deviation, SPM (Statistical Parametric Mapping) filter out the places and periods of difference through one-way ANOA(analysis of variance), Paired t-test to determine if there is a difference between two groups.
- Independent t-test to identify other items that are independent between each two groups (P-value= 0.05).
- Compare multiple tasks. SPM (Statistical Parametric Mapping) two-way ANOA will used to do the test (P-value= 0.05).

2.4 Trial Design

Describe the design of the Trial to be conducted (eg double-blind, single-blind, open label, cross-over, parallel group,….). Describe also the scientific rationale for the Trial design. The use of figures or charts is recommended.

See also: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf

Cohort Study/longitudinal Study

45 patients that will be undergo a total knee replacement procedure, robotically-assisted. The participants will assigned to one of the three experimental groups: the MA TKA technique group (n=15), the TA TKA technique group (n=15), and the 3D patient-specific aligned TA TKA technique group (n=15) 3D patient-specific aligned technique will be used Patients were divided into three groups according to the definition of three alignments, which were determined by the surgeon responsible for the operation based on the surgeon's experience and adjusted based on the robot's detection of the patient's soft tissue condition. The final tibia osteotomy plan will ultimately determine which group the patient falls into and will be documented in the patient's case file. During tibial osteotomy, perpendicular to the mechanical axis was divided into MA group. When it is parallel to the tibial joint line, it is classified as TA TKA. When the tibial osteotomy is parallel to the joint line and tilted posteriorly, and when the femoral osteotomy copies the rotation axis of the femoral condyle axis, the direction of the femoral prosthesis copies the direction of the femoral condyle alignment, which belongs to 3D patient-specific aligned TA TKA. The specific osteotomy method will be recorded in the documented of surgical procedure and in the patient's medical record the patient's case by the surgeon. HC (n = 15), 15 healthy participants, matched for age and gender, were included in the study (Healthy participants, mainly grandparents of students at the Bruges Campus or parents of employees, eligible healthy controls can be matched and extracted on specific request in the Bruges Campus Gait Laboratory database). At one year of follow-up testing, clinical and biomechanical results will be evaluated in a movement analysis laboratory. Those responsible for follow-up studies will not be told which group the patients belong to (Investigators of testing and follow-up studies are blinded to which group the patients being tested or followed belong to.) Only after all tests are completed can researchers review the patient's case file. The researchers classified the

specific osteotomy methods recorded in the patient case files and then performed statistical comparative analyses. The criterion for judging and quantifying which of the three groups has better results is to test and compare which group obtains results that are closer to the healthy control group (P value = 0.05).

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

List details such as age, sex, disease, characteristics, baseline values, etc., under which a trial participant is deemed to be suitable (eligible) to participate in the Trial. Informed consent to participate must be stated as an inclusion criterion. It should be stated if women of child bearing age will be included and which suitable methods of contraception will be used to enable inclusion into the Trial. A simple list format is the preferred style.

Patients eligible for inclusion in this Trial have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures
2. Received a primary total knee replacement (incl. patella) robotically-assisted
3. Male or female
4. Age between 50 and 80
5. Able to walk independently

3.2 Exclusion criteria

List details such as prior/concomitant therapy, concomitant disease/disorders, diagnostics assessments, medical/lifestyle conditions, prior/concurrent clinical Trial, etc., under which a participant is considered to be unsuitable for inclusion into the Trial. It should be stated if women of child bearing age will be excluded. A simple list format is the preferred style.

Patients eligible for this Trial must not meet any of the following criteria:

1. Revision surgery
2. Patient with a history of neurological, psychiatric or neurodegenerative disease
3. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
4. Other musculoskeletal lesions that may affect the gait pattern

3.3 Expected Duration of the Trial

Specify the expected duration and define the end of the Trial for the Trial participant. This can be the full Trial duration e.g. first patient first visit to last patient last visit including follow up. Alternatively, for long running trials (e.g; oncology), the end of Trial can be defined at a specific time point at which the Trial will be regarded as completed even if patients are still in follow up. A simple table format is the preferred style. Make the distinction between the expected Trial duration at the site and the expected Trial duration for a single patient.

Trial duration at the site:

- 4 years

Trial duration for a single patient:

- One single visit with clinical and biomechanical testing within 2 years postsurgery

3.4 Screening failures

Describe the process when a participant will be considered as screen failure. (see CTC website documenten/ISF: screening log)

All participants that are considered for Trial participation and meet all of the inclusion criteria will be documented on the Screening Log, including Screen Failures. Participants who meet

one or more of the exclusion criteria **must not proceed** to be enrolled in the Trial and will be identified on the Screening Log as Screen Failure.

3.5 Consent withdrawal

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice to further treatment. This will be documented by the PI in the patient's medical record. The PI must take into account the consequences of such withdrawal: (1) use of personal data / study data, (2) use of human biological material already collected

4 Trial Procedures

4.1 Selection of Participants / Recruitment

Specify which department or Institution will recruit the participants and how the participants will be approached for inclusion and obtainment of such informed consent.

See also link: Adverteren / Rekruteren Richtlijnen

Patients of the orthopedic unit of AZ Delta Roeselare (Prof. Dr. T. Luyckx, Prof. Dr. P Winnock de Grave) will be recruited. Patients are contacted by phone and trial setup will be explained. If patient is willing to contribute, informed consent is sent by post to the patient. Once informed consent is completed and signed by the patient and sent back, patient will be invited for a test-moment at the movement analysis laboratory in KU Leuven Campus Bruges.

4.2 Consent

See also: Informed consent formulier (ICF)

The Trial can and will be conducted only on the basis of prior informed consent by the Trial participants. All participants will be informed about the aim of the study, possible adverse events, procedures and possible hazards to which the participant will be exposed, mechanism of treatment allocation (if applicable), strict confidentiality of any patient data, respective insurance coverages as required by local law and medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician.

The Investigator shall obtain a signed and personally dated informed consent form from participants or their legal representative(s) prior to their enrollment at their Participating Site. This means that informed consent must be obtained prior any procedure specifically conducted for the purposes of the Trial. It is emphasized in the information sheet that participation is voluntary and that the participant is free to refuse further participation in the Trial whenever he/she wants to. This will not have any impact on the participants subsequent care.

All originally signed obtained ICFs must be retained/archived in the ISF at the Participating Site and cannot be destroyed (even when a scanned copy is available) before expiration of legal archiving term (defined in section "Archiving"). Adequate information regarding a point of contact where the participant may obtain further information about the Trial will be provided in the ICF.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

4.3 Randomization Procedure / Code Break (if applicable)

Provide details of the randomization procedure to be used for each subject (e.g. central randomization procedures), the method used to generate the randomization schedule (e.g. computer generated), the source of the randomization schedule (e.g. sponsor, investigator, or other), and whether or not an Interactive Voice/Web Response System (IVRS/IWRS) will be used. Provide a description of the specific blinding procedures, if any, to

be used and where/how code break will be achieved if necessary. If blinding will not be used, include a statement to that effect.

No randomization procedure applicable. Researchers will use a blind method when conducting clinical and biomechanical testing on these 3 groups (researchers do not know which group the patients to be tested belong to). When all patients have completed all testing. During the data analysis process, the researchers learned which group the patients belonged to, as documented in the patient case file.Visit schedule and assessments

Describe the sequence of visits and applicable procedures/investigations in more detail to be performed as stipulated in the Trial flowchart. Also take possible re-screening and re-consenting procedures in mind. Applicable and allowed visit-windows can be added.

See Trial Flowchart

Procedure/Assesment	Contact 1/ IC	Data Collection	Contact 2	Prospective Testing
Contacts	**1**		**2**	**3**
Informed consent	X			
Inclusion/Exclusion criteria	X			
Demographics		X		
Medical, Surgical history		X		
Collecting Data				
preop x-rays		X		
perop alignment & positioning		X		
surgical technique: cement, patella		X		
Appointment for testing			X	
Clinical Testing				
OKS-12				X
FJS-12				X
VAS Satisfaction				X
PCS				X
Tinetti				X
VAS Pain				X
Biomechanical Testing				
Gait and functional movement (forward lunge, squat) analysis: kinetic, kinematic, EMG				X

5 Adverse Event Reporting

5.1 Definitions

5.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product,

whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

5.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

5.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Death
- A life-threateninga experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

[a] The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

5.2 Recording of adverse events (AEs)

The risk associated with the study-specific intervention is falling. The risk of subjects falling will be assessed and subjects will be assisted by handrails to minimize this risk. If the subject still has a tendency to fall, the experimental task will be stopped or the difficulty of the experimental task will be reduced.
The participant will be asked to report any adverse event related to the study-specific intervention to the study team. These reported events will be documented by the Investigator in the source documents and reported to the Sponsor through the (e)CRF.
The following minimum information should be recorded for each adverse reaction (AR):

- AE description
- start and stop date of the AR
- severity
- seriousness
- causality assessment to the study interventions
- outcome

5.3 Reporting to the Ethics Committee

The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the EC.

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC containing an overview of all SARs (Serious Adverse Reactions) occurred during the reporting period and taking into account all new available safety information received during the reporting period.

6 Statistics and Data Analysis

Describe the measures taken to avoid, or at least minimize, biases. Clearly define the study hypotheses which will be the object of statistical testing.

Hypothesis: TA TKA strategy is expected to provide better clinical and functional outcomes for the patient at the end of the rehabilitation period (1 year post-surgery) compared to MA TKA. 3D patient-specific aligned TA TKA is expected to provide better clinical and functional outcomes for the patient at the end of the rehabilitation period compared to TA TKA.

Three groups of patients after a TKA with a different alignment streategy are compared. To minimize biases all patients were operated with a same implant, same surgical approach and at the same hospital. Researchers will be blinded during clinical and biomechanical testing of the 3 groups.

6.1 Sample Size Determination

Give the number of participants to be enrolled, together with the rationale for the sample size (the "power calculation").

6.2 Power analysis showed that 45 participating patients would need to be recruited, 15 participants per treatment group. An additional 15 healthy participants are needed to compare which treatment regimen has results closer to those of healthy volunteers (Healthy participants, mainly grandparents of students at the Bruges Campus or parents of employees, eligible healthy controls can be matched and extracted on specific request in the Bruges Campus Gait Laboratory database).Statistical Analysis

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analysis, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analysis of the primary and secondary endpoints.

Describe the statistical methods to be employed, including timing of any planned interim analysis. Stipulate the level of significance that is to be used in each Trial analysis, together with the procedure(s) for accounting for any missing, unused, and spurious data. Procedures for reporting any deviation from the original statistical plan should be described and justified.

6.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Normality testing (Shapiro Wilk or Kolmogorov Smirnof test)
Secondary	Based on normality testing: unpaired T-test or Mann Whitney test
Exploratory	Regression or multivariate analysis

7 Data handling

Give details of whether paper or electronic CRF will be used, describe the proposed database etc. See website CTC: e-CRF).

Paper CRF, stored by Dr. Philip Winnock de Grave

Specify what kind of data will be collected (see definitions and links below):
http://wiki/display/public/muzlidoc/Gezondheidsgegevens+en+onderzoek

Data collection, management, storage, and backup will be performed by the doctoral researchers associated with this project (Zhijun Li), under the supervision of the PI (Kurt Claeys). The doctoral researcher associated with this project will be responsible for data documentation & metadata, under the supervision of the PI.

Participant identities will be linked to data using an alphanumeric code. The separate and uniquely double pass-word coded "Subject Identification Code List", which matches

identifying codes with the subjects' names, will be managed by the principle investigator (EM) and stored separately, using the Digital vault for private data service of the ICTS, KU Leuven. This system involves a secure and operating system in ICTS's special, secure environment for private data. The research record will be confidential, to the extent provided by federal, state, and local law. No one will see the record except people who have a right to see it. The participant will not be identified by name in any reports on this study.

Digital, pseudonymized data (i.e. coded and containing no personal information) will be stored on a Large Volume Storage (L-drive) of the KU Leuven, specifically developed to store large amounts of data for long periods of time. Only the investigators will have access to these files. The PI of this project (KC) will be the only one who can grant access to this network drive. Additionally, copies can be made on the individual work pc of the researchers involved in the project. Paper copies of the descriptive data and questionnaires will be stored in a secured locker at the Department of Rehabilitation Sciences, Campus Bruges of the KU Leuven. Only authorized personnel will have access to this locked storage room as they will need to be granted access by the PI (KC). Audio, video, kinematic data will be automatically encrypted and saved to a study dedicated laptop/tablet and to the secured KU Leuven's secure internal servers.

Back-up of the data will be provided via the university's secure network drive with automatic daily backup procedures. Additionally, a mirror of the data is provided in a second ICTS data centre for business continuity or disaster recovery purposes. The paper copies will be digitized and together with the digital data stored on the university's secure network drive with automatic daily backup procedures. Sufficient storage and backup capacity for the data is provided on the KU Leuven servers and networks.

At the end of the project, the files will be delivered to the principal investigator, who will continue to ensure their safekeeping. In accordance with the policy of KU Leuven, these files will be kept for at least another ten years after project completion. Data will be archived on the secured university's network drive (K-drive), which is specifically developed to archive data for long periods of time.

All data will be treated with strict confidentiality during the project. In order to guarantee the confidentiality of the information (including potentially personal data, whether or not from patients) and the privacy of those involved, the investigators will always handle Information with the utmost care and discretion within the framework of this study. The investigators will observe complete confidentiality at all times with regard to the information of which he/she has gained knowledge during the performance of this study.

In carrying out this research, the investigators commit themselves to the following duty of confidentiality:

- during and after completion of the study, the investigator accepts to strictly observe the duty of discretion with regard to the information that has been collected and the activities the investigator has participated in, and with regard to the patients, healthy volunteers, and staff members with whom the investigator comes into contact;

- the investigator will only process and collect data that are relevant and necessary for the study;

- the investigator will not share data with anyone not directly involved in this research;

- the investigator will take all necessary measures to protect the confidentiality of information and the privacy of data subjects;

- the investigator will handle the information carefully and responsibly and the access granted to information systems and digital data carriers.

The research data files will be strictly confidential, to the extent provided by federal, state, and local law. No one will see the research data except people who have a right to see it. In addition, participants will not be identified in any way at an individual level in any reports on this study.

The collection, processing, and disclosure of personal data, such as patient health and medical information are subject to compliance with the GDPR legislation (General Data Protection Regulation) and with the General Data Protection Regulation (EU Regulation 2016/679).

__Anonymous data__ are data that cannot be related to an identified or identifiable person and such data are consequently not personal data. Anonymous data can be collected (no identified or identifiable data are mentioned on questionnaire) or data can be anonymized after collection (once received and before analysis, all data which are related to an identified or identifiable data, are deleted). In case data are anonymized, no one (not even the Investigator / CI / Trial staff) can link the data to an identifiable person. The principles of data protection do not apply to "anonymous data", namely data which do not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable (by any person or by any means). When assessing anonymity you should take into account that GDPR applies to directly identifiable data (the data subject can be identified because of a name or another specific identifier) and to indirectly identifiable data (the data subject can be identified because in their combination the collected data allow to single out an individual). As such account should for example also be taken of the size of the population of which the individual is part. For example aggregated data, where information about many individuals are combined into broad classes, groups or categories, so that it is no longer possible to distinguish information relating to those individuals will most likely be considered as anonymous. Additionally, you should be aware that data can only be considered anonymized when it is not possible to re-identify the data subject. This means that no key is held to re-convert key-coded data. This also means that data cannot be anonymous to you, while they are not anonymous to the holder of the original source data.

__"pseudonymisation"__ means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person;

E.g. The participant's name or other identifiers should be stored separately from the Trial data and replaced with a unique code to create a new identity for the participant. In such a case data are encoded (pseudonymised) and solely the Investigator and his/her Trial staff shall be able to link the data to an identifiable person; the codelist must be retained in a secured place on site and can under no circumstances leave the site or be accessed by unauthorized persons.

***Personal data** means any information about an identified or identifiable natural person ("data subject"); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, a picture, an identification number (such as a phone number, even a professional phone number, a code, a bank account number), an online identifier (such as location data or an e-mail address, even a professional email address) or to on or more factors specific to the physical (such as a fingerprint), psychological, genetic, mental, economic, cultural, social identity of that natural person. They do not only include data having to do with individuals' privacy, but also data having to do with an individual's professional or public life.*

7.1 Data Collection Tools and Source Document Identification

***Source Documents:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH-GCP E6(R2) Documentation of source data is necessary for the evaluation and validation of clinical findings,*

observations and other activities during the Trial. Source documentation serves to substantiate the integrity of Trial data, confirms observations that are recorded in the eCRF and confirms the existence of Trial participants.

***Certified Copy:** A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. (ICH-GCP E6(R2)*

***Case Report Forms (CRF):** A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject. (ICH-GCP E6(R2)*

7.1.1 Operational aspects

7.1.1.1 Data collection

Source Data will be collected and recorded in the Trial participants files/medical records.

If applicable, worksheets may be used for the capture of some data to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation.

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately and complete.

(e)CRFs are provided by the sponsor for each subject. The Trial data will be transcribed by Trial Staff, as soon as possible after a subject visit, from the source documents into an (e)CRF in an pseudonymized manner using a unique identifier assigned by the Sponsor.

The eCRFs should be available for review at the next scheduled monitoring visit (if applicable).

7.1.1.2 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. All (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails are available to demonstrate the validity of the Trial data.

7.1.1.3 Data Management

The trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies.

7.1.1.4 Data Transfer

Any participant record or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor (see 8.1.2. legal requirements).

7.1.2 Legal requirements

All Source data will be kept on a secured location at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site shall treat all information and data relating to the Trial disclosed to them in this Trial as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Trial. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, as well as all Trial documents as specified in ICH-GCP Chapter 8, Essential Documents for the Conduct of a Clinical Trial, and all Trial documents as specified by the applicable regulatory requirement(s) in the TMF / ISF.
The Investigator will take measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the the European General Data Protection Regulation regarding data protection). The receiving party will agree to keep the transferred data confidential at all times.

7.2 Access to Data, Audit and Inspection

The Investigator will permit Trial-related monitoring, audits and competent authorities or other health authorities inspections, providing direct access to all relevant Source Data / Documents.

In addition (e)CRFs must be made available at all times for monitor, audit by the Sponsor's Trial auditor and for inspection by the competent authorities and other health authorities. The accuracy of the data will be verified by review of the Source Documents (if applicable and depending on the audit / inspection purposes).

7.3 Monitoring

Monitoring section only to be incorporated in the protocol if monitoring (by CTC or another CRO) is applicable. Please always check with CTC.)

Monitoring of the Trial will be conducted periodically by Trial monitors (independent from Trial staff). The Sponsor and Investigator/Participating Site will permit direct access to the Trial data and to the corresponding Source Data and documents to verify the accuracy of these data. The Trial will be monitored to ensure that the Trial is being conducted in compliance with GCP and current legislation, verify, among other procedures, that written informed consent has been obtained correctly, that the Trial procedures have been followed as shown in this protocol, and that the data have been recorded, for which the Source Data will be compared with the data recorded in the (e)CRF. More details about the monitoring strategy for this Trial are described in the Trial specific Monitoring Plan.

7.4 Archiving

As specified in ICH-GCP section 8.1 Addendum the Sponsor and Investigator/Participating Site should maintain a record of the location(s) of their respective Essential Documents (including but not limited to Source Documents, completed and final CRF and ISF / TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator / Participating Site should have control of all Essential Documents and records generated by the Investigator / Participating Site before, during and after the Trial.

The Sponsor is responsible for archiving trial specific documentation (such as but not limited to protocol, potential amendments, final report and database)according to ICH-GCP. Source data and site-specific study documents (such as but not limited to the originally signed ICFs) will be archived locally on site according to local practice, guidelines for at least 20 years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required. Destruction of Essential Documents will require authorisation from the Sponsor.

8 Ethical and Regulatory Considerations

8.1 Ethics Committee (EC) review & reports

See also link: https://www.uzleuven.be/nl/ethische-commissie/onderzoek

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in Directive 2001/20/EC or the Regulation 536/2014 as soon as applicable and any subsequent amendments, the ICH-GCP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical trials on medicinal products for human use as soon as applicable, the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

Before the start of the Trial, this protocol, the ICFs and other related documents e.g. advertisements and general practisioners information letters, will be submitted for review to the EC and to the relevant CA for Trial authorization (the below mentioned obligations shall only apply to the extent applicable). The Trial shall not commence until such approvals have been obtained.

The CI acknowledges that it is his responsibility to produce APR and he will do so by submitting to the EC/CA within 30 days of the anniversary date on which the favorable opinion was given, and annually until the Trial is declared ended.

The Investigator shall notify the EC/CA of the end of the Trial. Should the Trial be ended prematurely, the Investigator will notify the EC/CA and include the reasons for the premature termination within 15 days of the descision. The Investigator will submit a final report with the results, including any publications/abstracts, to the EC/CA within 1 year.

8.2 Peer review

Example: This Trial protocol was peer reviewed by certain independent experts. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies.

This Trial protocol was peer reviewed by certain independent experts. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies.

8.3 Regulatory Compliance

This Trial protocol and the conduct of the Trial in general is in compliance with applicable law, including but not limited to the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments.

8.4 Protocol / GCP compliance

See website CTC documenten/ISF: protocol deviation log and corrective action plan)

The Trial must be performed in accordance with the protocol, current ICH-GCP, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible.

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Protocol deviations which are found to frequently recur, will require (immediate) action. CI acknowledges that such recurring protocol deviations could be potentially classified as a serious violation.

It is understood that "a serious violation" is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the Trial; or
- the scientific validity of the Trial

8.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the applicable European Directives and Regulations regarding data protection. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws (Cfr. DPA in Annex).

Any personal data shall be treated as confidential at all times including during collection, handling and use, and that the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

8.6 Insurance

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies. In accordance with this Belgian law, the sponsor is unfailingly liable for any damage suffered by the participating patient and/or his beneficiaries that is directly or indirectly related to the trial. The sponsor of this study (KU Leuven) has taken out insurance to cover this liability.

8.7 Participants must pay for their own transportation to and from the laboratory. If a participant's participation in the study requires additional travel, that is, travel beyond routine care, travel expenses for these additional trips will be reimbursed.Amendments

See alsolink: https://www.uzleuven.be/nl/ethische-commissie/onderzoek

In accordance with the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor may make a non-substantial amendment at any time during a Trial. If the Sponsor wishes to make a substantial amendment to the clinical Trial agreement or the documents that supported the original application for the clinical Trial authorisation, the Sponsor must submit a valid substantial amendment to the Competent authority (CA) for consideration. If the Sponsor wishes to make a substantial amendment to the EC application or the supporting documents, the CI must submit a valid substantial amendment to the EC for approval. The CA and/or the EC will provide a response regarding the amendment within 28 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the CA and/or EC.

Any subsequent protocol amendments will be submitted to the EC and regulatory authorities for approval. No substantial amendment that require review by EC will be implemented until the EC grants a favorable opinion for the Trial. The CI acknowledges that amendments may also need to be reviewed and accepted by the Competent Authority before they can be implemented in practice at Participating Sites.

9 Publication Policy

Can be revised in compliance with the ethical aspects

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

For multi-centric Trials, it is anticipated that the primary results of the overall Trial shall be published in a multi-centre publication.

Participating Site is not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by Participating Site will be submitted to the Sponsor for review at least thirty (30) days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

10 Intellectual Property

Only to insert if no participating site agreement is signed and the protocol serves as contract between the parties

Any know how, inventions, methods, developments, innovations and discoveries, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor.

11 JCI

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by Sponsor in its regular activities, also in accordance with Joint Commission International standards, the Sponsor shall comply with the following

obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Trial; (b) the Sponsor will ensure that multi-center Trial reporting is reliable and valid, statistically accurate, ethical, and unbiased. The same requirements are applicable if multi-center Trial data and multi-center Trial results are provided to the INSTITUTION; (c) the Sponsor will not grant incentives, other than standard compensations and reimbursement of costs, to Trial participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Trial and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the Trial participants in accordance with all applicable laws.

12 References

1) Bourne R.B., Chesworth B.M., Davis A.M., Mahomed N.N., Charron K.D. **Patient satisfaction after total knee arthroplasty: who is satisfied and who is not?.** *Clin Orthop Relat Res.* 2010; **468**: 57-63

2) Eckhoff D.G., Bach J.M., Spitzer V.M., Reinig K.D., Bagur M.M., Baldini T.H., et al. **Three-dimensional mechanics, kinematics, and morphology of the knee viewed in virtual reality.** *J Bone Joint Surg Am.* 2005; **87**: 71-80

3) Insall J.N., Binazzi R., Soudry M., Mestriner L.A. **Total knee arthroplasty.** *Clin Orthop Relat Res.* 1985; **192**: 13-22

Appendices

Additional documents can be included as Appendix, such as ICF, PRO's, questionaires, scores, specific Trial information, additional guidelines (coding, classification, …) and scoring information, etc…

Appendix 1: The Forgotten Joint Score

FJS-12 score

The following 12 questions refer to how aware you are of your artificial hip/knee joint in everyday life. Please tick one answer from each question.

Are you aware of your artificial joint...

1. ... in bed at night?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

2. ... when you are sitting on a chair for more than 1 hour?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

3. ... when you are walking for more than 15 minutes?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

4. ... when you are taking a bath/shower?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

5. ... when you are traveling in a car?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

6. ... when you are climbing stairs?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

7. ... when you are walking on uneven ground?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

8. ... when you are standing up from a low-sitting position?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

9. ... when you are standing for long periods of time?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

10. ... when you are doing housework or gardening?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

11. ... when you are taking a walk/hiking?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

12. ... when you are doing your favorite sport?
○ never ○ almost never ○ seldom ○ sometimes ○ mostly

Appendix 2: Oxford Knee Score

PROBLEMS WITH YOUR KNEE

During the past 4 weeks.. ✓tick one box for every question

1 *During the past 4 weeks.....*
How would you describe the pain you usually have from your knee?

None	Very mild	Mild	Moderate	Severe
❑	❑	❑	❑	❑

2 *During the past 4 weeks.....*
Have you had any trouble with washing and drying yourself (all over) because of your knee?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

3 *During the past 4 weeks.....*
Have you had any trouble getting in and out of a car or using public transport because of your knee? (whichever you would tend to use)

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

4 *During the past 4 weeks.....*
For how long have you been able to walk before pain from your knee becomes **severe**? (*with or without a stick*)

No pain/ More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all - pain severe when walking
❑	❑	❑	❑	❑

5 *During the past 4 weeks.....*
After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Not at all painful	Slightly painful	Moderately painful	Very painful	Unbearable
❑	❑	❑	❑	❑

6 *During the past 4 weeks.....*
Have you been limping when walking, because of your knee?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
❑	❑	❑	❑	❑

Appendix 3: VAS Satisfaction

How satisfied are you with the result of your knee replacement surgery?

0_____10

Very dissatisfied Very satisfied

Appendix 4: VAS Pijn

How much pain have you experienced in the area of your operated knee during the last 4 weeks?

0_____10

No pain Unbearable pain

Appendix 5: Pain Catastrophizing Scale

	Not at all	To a slight degree	To a moderate degree	To a great degree	All ti
ırry all the time about whether the pain end	0	1	2	3	
el I can't go on	0	1	2	3	
terrible and I feel it's never going to get better	0	1	2	3	
awful and I feel that it overwhelms me	0	1	2	3	
el I can't stand it any more	0	1	2	3	
ırry that the pain will get worse	0	1	2	3	
ep thinking of other painful events	0	1	2	3	
xiously want the pain to go away	0	1	2	3	
n't seem to keep it out of my mind	0	1	2	3	
ep thinking about how much it hurts	0	1	2	3	
ep thinking about how badly I want the n to stop	0	1	2	3	
re's nothing I can do to reduce the nsity of the pain	0	1	2	3	
nder whether something serious may pen	0	1	2	3	

nination: Sum of 8, 9, 10, 11
gnification: Sum of 6, 7, 13
olessness: Sum of 1, 2, 3, 4, 5, 12

tal score of ≥30 indicates a clinically significant level of catastrophizing

Appendix 6: Tinetti Test

TINETTI BALANCE ASSESSMENT TOOL

Tinetti ME, Williams TF, Mayewski R, Fall Risk Index for elderly patients based on number of chronic disabilities. Am J Med 1986:80:429-434

PATIENTS NAME _____ D.o.b. _____ Ward _____

BALANCE SECTION

Patient is seated in hard, armless chair;

		Date		
Sitting Balance	Leans or slides in chair Steady, safe	= 0 = 1		
Rises from chair	Unable to without help Able, uses arms to help Able without use of arms	= 0 = 1 = 2		
Attempts to rise	Unable to without help Able, requires > 1 attempt Able to rise, 1 attempt	= 0 = 1 = 2		
Immediate standing Balance (first 5 seconds)	Unsteady (staggers, moves feet, trunk sway) Steady but uses walker or other support Steady without walker or other support	= 0 = 1 = 2		
Standing balance	Unsteady Steady but wide stance and uses support Narrow stance without support	= 0 = 1 = 2		
Nudged	Begins to fall Staggers, grabs, catches self Steady	= 0 = 1 = 2		
Eyes closed	Unsteady Steady	= 0 = 1		
Turning 360 degrees	Discontinuous steps Continuous	= 0 = 1		
	Unsteady (grabs, staggers) Steady	= 0 = 1		
Sitting down	Unsafe (misjudged distance, falls into chair) Uses arms or not a smooth motion Safe, smooth motion	= 0 = 1 = 2		
	Balance score		/16	/16

P.T.O.

13 Appendix 7: Data Processing Annex (DPA)

Definitions:

- "Protocol" means the document entitled "Clinical and Biomechanical Outcome after Robotically-Assisted Total Knee Arthroplasty by Comparing Three Alignment Strategies " containing the details of the academic study as developed by the Sponsor as approved by the relevant ethics committee.
- "Sponsor" means KU Leuven.
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
  - the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
  - other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ('Data Subject'), including without limitation pseudonimized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Protocol and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Subject's medical records, or other than provided in the instructions, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.

2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this

3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.

4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
   (i) accidentally or unlawfully destroyed, lost or altered,
   (ii) disclosed or made available without authorization, or
   (iii)otherwise processed in violation of Applicable Law.

5. The appropriate technical and organizational security measures must be determined with due regard for:
   (i) the current state of the art,
   (ii) the cost of their implementation, and
   (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Subjects pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)

7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with Data Processor, the findings as described under 8) (ii) below to the Data Controller.

9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

10. The Data Processor must without undue delay in writing notify the Data Controller about:
    (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
    (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or

(iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Subjects or from third parties.

11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 8) (ii)(a) above will contain at least the following information:
    (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Subjects concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
    (ii) the likely consequences of the Personal Data breach;
    (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.

12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).

13. The Data Processor must promptly reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Subjects under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.

14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of

a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.

16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.

17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA .