Protocol Full Title interventional trial with medication:

First Application of the Subcutaneous 'HEKcite' Therapeutic drug monitoring device in kidney transplantation patients.

Protocol Acronym/short title: FAST-H1

Version and date of final protocol: 30/09/2017

Trial identifiers

EudraCT Number: XXXXXXXX
NCT (clinicaltrials.gov): NCTXXXXXX

Sponsor: UZ Leuven

Name: UZ Leuven
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Principal Investigator:

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Signature

_____ _____

Principal Investigator Date

Print Name:

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1. Study Synopsis

Title of clinical trial	First Application of the Subcutaneous 'HEKcite' Therapeutic drug monitoring device in kidney transplantation patients.
Protocol Short Title/Acronym	FAST-H1
Study Phase if not mentioned in title	Phase II clinical trial
Sponsor name	UZ Leuven
Principal Investigator	Professor Johan Swinnen
Eudract number	NCTXXXXXX
Medical condition or disease under investigation	Kidney transplantation
Purpose of clinical trial	The purpose of this study is to assess accuracy and reliability of the HEKcite therapeutic drug monitoring device and compare these results with blood samples acquired at predetermined time points in kidney transplantation patients. To date, only static data via blood samples is available, and too many grafts are rejected because of lack of dynamic measurements. This HEKcite biosensor provides a dynamic measurement device

	which will improve drug compliance and the knowledge about receptor occupancy of therapeutic drugs in humans, and will eventually lead to fewer graft rejections, and thus better overall survival rates.
Primary objective	Assessment of the accuracy and reliability of the monitoring device compared to reference standard of care blood values.
Secondary objective (s)	To evaluate the mechanical stability of the HEKcite device To evaluate the biological stability of the HEKcite device after 6 months To evaluate the impact of the HEKcite device on drug compliance To evaluate the impact of the HEKcite device on graft functionality To evaluate the impact of the HEKcite device on patient' quality of life, assessed through KDQOL To evaluate the impact
Trial Design	Open-label, interventional trial
Endpoints	Graft survival [Time frame: 24 months] Urinalysis and GFR determination [Time frame: 24 months] Effects of immunosuppression weaning procedure on immunosuppression-related side effects (diabetes, hypertension, nephrotoxicity, hyperlipidemia) [Time frame: 24 months]
Sample Size	50
Summary of eligibility criteria	18 years to 75 years (adult, senior) Both sexes, no healthy volunteers

IMP, dosage and route of administration	Immunosuppressants, normal dosage, standard of care
Active comparator product(s)	None
Maximum duration of treatment of a Subject	24 months
Version and date of final protocol	20/09/2017
Version and date of protocol amendments	x

2. Background and rationale

3. Trial objectives and Design

3.1 Trial objectives

We aim to demonstrate the added value of the of the HEKcite therapeutic drug monitoring device and compare these results with blood samples acquired at predetermined time points in kidney transplantation patients. Accuracy and reliability of the monitoring device will be assessed by comparison to reference blood values.

Postop quality of life will be assessed using a KDQOL. Patient will fill a pre-printed form with the KDQOL at the day of surgery, and at every study visit. Patients will also reports the time and the dose of analgesics they are taking post operatively to control pain in that form. Patients will submit all the data to the surgeons at all follow-up appointments.

3.2 Primary endpoints

Graft survival [Time frame: 24 months]

3.3 Secondary endpoints

- Quality of life
- Urinalysis and GFR determination [Time frame: 24 months]
- Assessment of PK/PD data of immunosuppressants level in plasma [Time frame: 24 months]
- Assessment of influence of outside temperature on sensitivity and efficacy of HEKcite device [Time frame: 24 months]
- Effects of immunosuppression weaning procedure on immunosuppression-related side effects (diabetes, hypertension, nephrotoxicity, hyperlipidemia) [Time frame: 24 months]

3.4 Trial Design

An prospective, monocenter, open label, one-arm, interventional trial to assess the safety and efficacy of the HEKcite therapeutic drug monitoring device is proposed.

flowchart of routine practice is presented in figure 1.

At time of first presentation at the University Hospital of Leuven, campus Gastuisberg, more specifically at the department of nephrology (E409), a thorough clinical examination with urinalysis and a blood sample to examine the GFR value, is performed to confirm the diagnosis of end stage kidney disease (GFR < 15 ml/min/1.73 m^2). Next, patients are informed about their clinical condition and the proposed treatment plan. After patients have provided their written informed consent, a preoperative plan is prepared.

All patients will be treated by the local team of abdominal transplantation surgeons and nephrologists from the University Hospital of Leuven, campus Gasthuisberg. The principal investigator will be responsible for the training of all investigators, to ensure rehabilitation according to the protocol.

Operation plan

When determined if a patient is eligible for both transplantation surgery and placement of the HEKcite device in the forearm, the operative plan is assessed. Kidney transplantation surgery cannot always be planned in advance. If a kidney donor graft is easily accessible, dates and other important data are planned and if not, these are planned as soon as a kidney donor graft becomes accessible. As previously described, the choice of surgical technique is the responsibility of the surgeons.

The preferred forearm for the HEKcite device is determined, in accordance with the patient and the surgeon. Standard protocol is to implant in the right forearm, but patient preference will be considered, as well as certain criteria (amputation, nerve deterioration, ...) that make these standards impossible.

Placement of the HEKcite device by making a medio-lateral incision of approximately 1.5 cm. Next, the device is placed subcutaneously, ensuring neovascularization around and 'through' the device

itself. The device is expected to be encapsulated by fibrin fibers, ensuring safe preservation in the forearm.

Clinical evaluation

- Urinalysis, GFR determination are the basic parameters to determine renal function. These tests will be evaluated every study visit. Also, PK/PD data of immunosuppressants will be checked with blood samples at every study visit. Furthermore, the temperature will be checked to evaluate the effect of the outside temperature on the vasodilatation and vasoconstriction of the microvessels surrounding the HEKcite device, and thus the sensitivity and efficacy of the HEKcite device will be assessed in these different temperature-related circumstances at every study visit. Measurements of the temperature will be done with the ROMED® thermometer in all cases to avoid intervariability between thermometers.

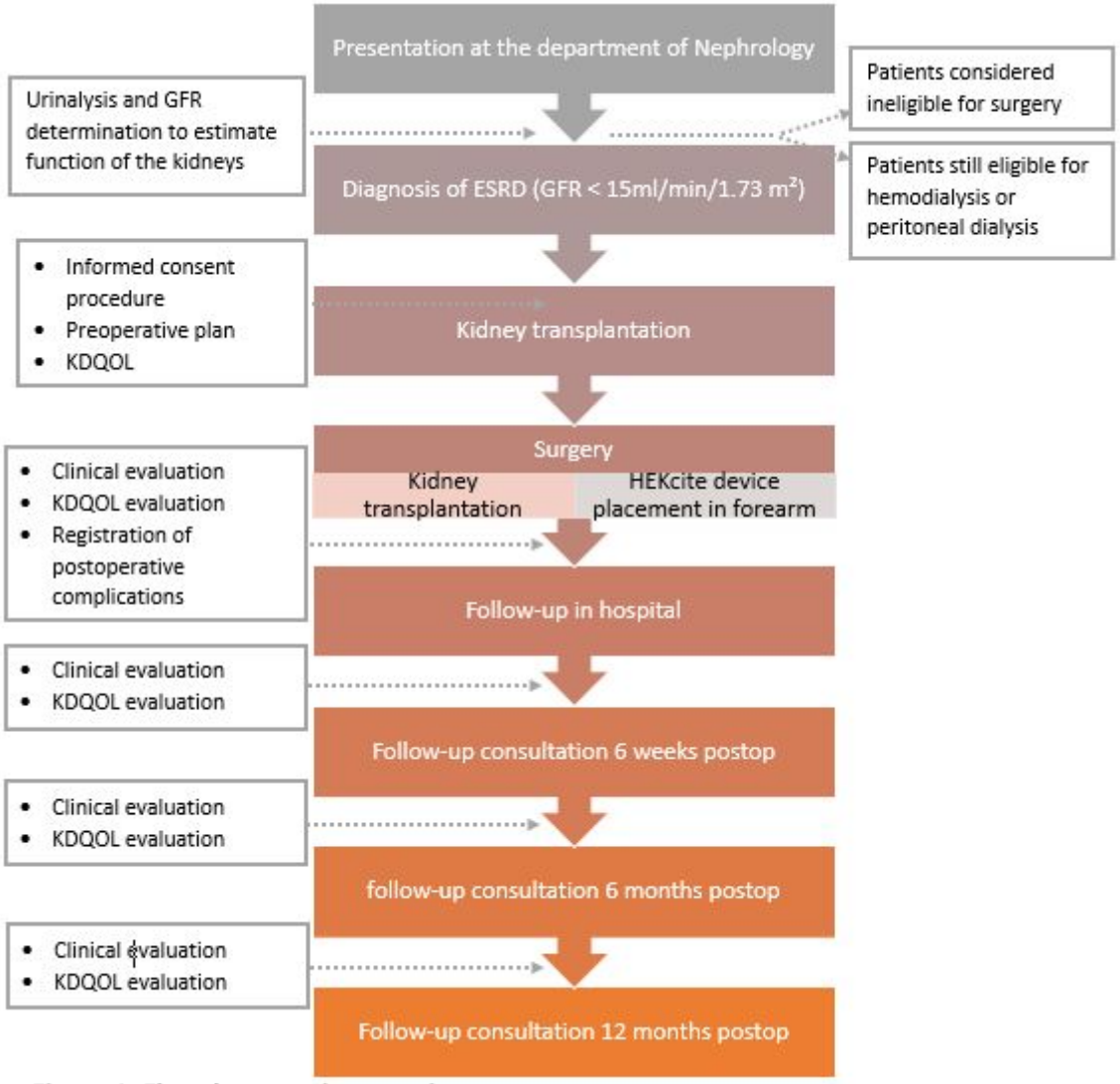

Figure 1: Flowchart routine practice

Abbreviations: ESRD: end-stage renal disease, KDQOL: kidney disease quality of life.

Since the choice for kidney transplantation depends largely on the patient condition, it is impossible to set one uniform surgical protocol.

Postoperative complications

Complications related to the transplantation surgery, the implant placement will be registered in the Case Report Form as serious adverse events (SAE) or adverse events (AE), according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v4,0 guidelines (available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-0614_QuickReference_5x7.pdf) Since all interventions are part of routine practice, registration of (S)AEs in the CRF is considered sufficient, and no notification of SAEs will be made to the ethics committee. An AE is any undesirable experience associated with the medical intervention that results in:

(1) Patient death;

(2) Life threatening;
(3) Requires patients hospitalization or prolonged hospialization;
(4) Results in a disability;
(5) Results in permanent damage;
(6) Results in congenital anomaly or birth defect.

Biological and mechanical stability of the HEKcite device

Biological and mechanical implant stability is determined through evaluation of the peri-implant infection rate, implant loss at routine consultations and at every study visit. In addition, long-term changes in biological and mechanical stability will also be examined clinically at 6 months after placement of the HEKcite device, and again at annual routine follow-up visits at 12 and 24 months.

3.5 Study center

University Hospital Gasthuisberg (Leuven).

3.6 Patient population

All consenting patients that require major kidney transplantation surgery, and require immunosuppressive therapeutic drugs after surgery.

3.7 Duration

We aim to initiate the trial in November 2017 and estimate a total recruitment period of one year to include at least 50 and a maximum of 60 eligible patients in this monocenter trial. Quality of life, biological implant safety will be measured for two years after placement of the HEKcite device. Parameters related to implant will be assessed at routine follow-up consultation until one year after placement of the HEKcite device.

3.6 Trial Flowchart

	Screen visit	Surgery (day0)	Day1	Week 1	Week 6	Month 6 postop	12 months postop	24 months postop
Informed consent	X							
Physical examination	X	X	X	X	X	X	X	X
Transplant surgery		X						

Device implantation surgery		X						
Urinalysis	X	X	X	X	X	X	X	X
Blood samples to determine PK/PD	X (baseline)		X	X	X	X	X	X
GFR determination	X	X	X	X	X	X	X	X
Temperature control (ROMED®)	X (baseline)	X	X	X	X	X	X	X
Peri-implant infection rate			X	X	X	X	X	X

4. Selection and withdrawal of subjects

4.1 Inclusion criteria

- Requires transplantation surgery (heart surgery such as bypass is allowed at the same time);
- Legal age;
- Both female and male patients;
- Patients with histologically or clinically confirmation of (urgent) need for kidney transplantation surgery;
- Patients not eligible anymore for long-term conventional dialysis;
- Signed informed consent prior to surgery;
- Willing to complete all follow-up requirements.

5.2 Exclusion criteria

- Patients not eligible tot he abovementioned criteria;
- Patients with medical contraindications for kidney transplantation surgery;
- Pregnant or nursing women;
- Have a history of transplantation surgery;
- Cannot return for required follow-up visits;
- Hypersensitivity to immunosuppressants;

- Acute preoperative neurological event (such as a stroke);
- History of substance abuse within one year or is a prison inmate;
- Participating in another study;
- Participation in a trial with an investigational product within the previous three months;
- Life expectancy less than five years.

5.3 Selection of participants

At time of confirmation of the need for kidney transplantation surgery, the local abdominal transplant surgeon and abdominal internist of the participating center in will consult whether the patient is indeed eligible for placement of the HEKcite therapeutic drug monitoring device. If the patients proves eligible, he/she will be informed or at least prior to the placement of the HEKcite device, the patient will be asked to give written informed consent for recording his/her data in the University Hospital Gasthuisberg Leuven database.

5.4 Withdrawal of subjects

Since the study comprises prospective collection of routinely-collected data in a database, no additional patient risk is expected. The in-house designed HEKcite protocol is based on the routinely-applied concept of implant loading, but consist of a custom-developed manufacturing process of the actual device. The anticipated side effects or toxicities are thus associated with the surgical placement of the device. They comprise postoperative complications at the transplantation site and device implant site (wound dehiscence, infection). The surgical techniques have been routinely carried out in transplant patients as standard of care in the University Hospital Leuven, campus Gasthuisberg.

Subjects are withdrawn from the clinical trial when they react allergic to the implantable device, when they suffer (Serious) Adverse Events, in case of poor compliance to the immunosuppressive therapy and in case of graft rejection. If withdrawal of the subject appears after screening but before surgical placement of the HEKcite device, the subject will be replaced. If withdrawal of the subject appears after surgical placement, the subject will also be replaced, but already received data will be used for statistical analysis. As the medical caretakers sees fit, poor compliance will also be a reason for withdrawal. In these cases the subject will be withdrawn and replaced, and the data will be used for statistical analysis.

5.6 Expected duration of trial

We aim to initiate the trial in November 2017 and estimate a total recruitment period of one year to include at least 50 and a maximum of 60 eligible patients in this monocenter trial. Quality of life, biological implant safety will be measured for one year after placement of the HEKcite device.

Parameters related to implant will be assessed at routine follow-up consultation until one year after placement of the HEKcite device.

5. Trial Procedures

6.1 By visit

At the screening visit, the informed consent procedure is started. At all other visits, the standard of care procedures for post transplantation patients will be followed. Next to these standard evaluations, the printed version of the KDQOL is filled in by the patients.

6.2 Laboratory tests

Urinalysis, together with the blood samples for both the PK/PD data and the GFR rate will be tested preoperative to have a reference of respectively concentration of immunosuppressants and kidney function. Thus, the patients will give urine and with the dipstick method, the color and clarity will be assessed. For more specific results, a blood sample will also be drawn from the patient to test for GFR rates. The temperature of the patients will be evaluated using ROMED® thermometer at all visits, in order to evaluate longitudinal the effect of temperature on the sensitivity and efficacy of the HEKcite device.

6. Assessment of efficacy

Blood samples are standard of care assessments to evaluate the concentration of the immunosuppressants. We will compare these results with the information we get from the application that is connected to the HEKcite device.

7. Assessment of Safety

8.1 Specification, timing and recording of safety parameters

Preoperatively, standard of care will be provided to the subject, in order to determine safety. P
atient will be informed about possible hazards. The surgery and extra implantation will once again be explained to ensure complete knowledge for the patient. Physical examination will be performed, together with urinalysis, baseline temperature, and baseline blood tests to determine GFR. These are all noted in the flowchart. During surgery itself, standard of care measurements will be provided and surgeon is allowed to take actions if any adverse reactions occur.

Postoperatively, standard of care measurements will be provided. Also, the patient will stay in the hospital as long as needed, as evaluated by the treating physician. Aside from the standard of care measurements, flow chart will be followed strictly in order to get the least variability in the study.

All adverse reactions are determined and reported to the appropriate regulations. If needed, patients can be excluded from the trial.

8.2 Procedures for recording and reporting adverse events (AE)

8.2.1 Definitions in Law of May 7, 2004 concerning experiments on the human person

Adverse reaction (AR): all 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;

Adverse event (AE): any untoward medical occurrence in a patient or subject of the treated group during an experiment, and which does not necessarily have a causal relationship with this treatment

Unexpected adverse reaction (UAR): an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product);

Serious adverse event (SAE) or serious adverse reaction (SAR): any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, and this, when it is a clinical trial, at any dose;

Suspected unexpected serious adverse reaction (SUSAR): is an AR that is serious and unexpected (meaning that nature or severity of the AR is not consistent with the Investigational Medicinal Product reference safety information, which is the Investigator's Brochure) and is judged by either the investigator or the sponsor as having a reasonable suspected causal relationship with the investigational medicinal product.

8.2.2 Notification of adverse events

The investigator shall report all serious adverse events immediately, after first kwowlegde, to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring

immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the terms specified in the protocol

For reported deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the minister if the experiment is being conducted in Belgium, if he so requests.

8.2.3 Notification of serious adverse reactions

The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the minister, to the competent authorities in all the Member States concerned in the case of a trial, and to the competent ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected unexpected serious adverse reactions shall be reported to the minister, to the competent authorities of all Member States concerned in the case of a clinical trial and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

The sponsor shall also inform the other investigators.

Once a year throughout the experiment, the sponsor shall provide the minister and the ethics committee in Belgium and those of the member States in whose territory the trial is conducted in the case of a multicentre trial, with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

Regarding those adverse events and serious adverse reactions the Principal Investigator will take all reasonable measures, in consultation with Sponsor, to protect subjects at risk following the occurrence of such events.

8.2.4 Adverse events that do not require reporting

Define here any AE's or SAE's that are expected and do not require reporting for this trial. For trials where the IMP is licensed, it is permissible to state that events or reactions listed in the SmPC do not need to be reported. Please define the period for AE reporting – eg randomisation, or first dose until 30 days post final IMP administration

8.3 Treatment stopping rules

8.4 Data monitoring committee (DMC)

Some indications for setting up a data monitoring committee:

- Life-threatening disease
- Patient population (e.g. pediatric population)
- Prior knowledge or strong suspicion that a treatment under consideration has the potential to harm patients
- Complex study design

For further information:
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf

8. Statistics

Wilcoxon-matched pairs test or repeated measures ANOVA will be applied to examine the evolution of QOL, assessed with the kidney disease quality of life (KDQOL), at respectively the two and three time-points for analysis of the primary endpoint hypothesis.

Statistical analysis will primarily consist of descriptive analysis. Wilcoxon-matched pairs test or repeated measures ANOVA will be applied to examine the evolution of different parameters at several time points. Regression analysis will be performed to examine the influence of different variables on biological and mechanical stability. All analysis will be performed using Prism® software (GraphPad Prism 5, Inc., La Jolla, CA) and SPSS software (version 21, IBM SPSS statistics, Chicago, IL).

9.1 Sample size

At least 40 patients will be enrolled in this clinical trial to ensure strong statistical analysis.

9.2 Randomisation

No randomization needed.

9.3 Analysis

A description of the statistical methods to be employed, including timing of any planned interim analyses should also be provided The level of significance that is to be used in each trial analysis must be stipulated, 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. The data set for any analysis must be clearly stipulated (eg “all subjects”, “randomised subjects”, “intent to treat”) and the population(s) should be clearly defined. Define the trial stopping rules if appropriate.

10. Quality assurance

Give details as to how QA will be maintained, mention SOP’s if available

11. Direct access to source data and documents

It will be specified, (or reference is made to another written agreement) that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients’ case sheets, blood test reports, X-ray reports, histology reports etc).

12. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements.This protocol and related documents will be submitted for review to Ethics Committee and to the Federal Agency for medicinal products for Clinical Trial Authorisation

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed

informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study 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 Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data)

Data are **anonymous** if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.
When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately (site file) from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

13. Data Management

Predefined patient demographic, clinical and surgical parameters will be prospectively collected by the local investigators at time of routine consultation, or surgical procedure. Urological parameters will be prospectively collected by the treating surgeon at time of clinical evaluation. Quality of life data, through assessment of the KDQOL questionnaire will be collected by the appointed health care employee as part of routine care.

All data will be registered on a paper CRF, that will be completed for every individual patient by the treating physician, prosthodontist or local study nurse. The CRF sections on 'recruitment', 'eligibility screening form', 'demographic info', 'diagnostic info', 'surgical characteristics', 'pre-prosthetic surgery' and 'implant characteristics' should be completed by the treating surgeon and/or resident during the consecutive consultations or at time of dictating of the medical letter to the general practitioner. The treating surgeon and/or resident are also responsible for the sections on 'recurrence of disease' or 'termination of participation'. The CRF section on 'rehabilitation' and 'annual follow-up' should be completed by the treating physician, if possible in close cooperation with the treating surgeon for evaluation of clinical evaluation, during the consecutive consultations.

QOL questionnaires should be added to the CRF form. If present, a study nurse could complete the CRF based on the completed medical files, in close cooperation with the treating surgeon.

Instructions on how to complete the CRF will be explained orally at the initiation visit, prior to trial start.

The IP will be the primary contact person for questions related to the trial. He/she will perform bi-annual monitoring visits to the participating centers to provide administrative support, and monitor the presence of written informed consent forms and data registration according to good clinical practice. At that time, the CRC will also be responsible for data-entry of the CRF's of recruited patients in an electronic MS Office Access database, that will be located on a shared account with limited access. For ease of communication, each of the participating centers will appoint one of the local investigators as trial representative, who will be the central contact person for all study-related communication. Appointment of the local trial representative is at the responsibility of the local site. After trial closure, all study-related documents will be stored centrally at the University Hospital Gasthuisberg Leuven.

A workchart is presented in Appendix H.

14. Translational research

Blood samples will be sent to the researchers in UZ Gasthuisberg Leuven.

15. Publication Policy

It is anticipated that the results of the overall Study shall be published in a monocenter publication, involving the data of the clinical site participating in the Study.

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.

Publications will be coordinated by the Investigator of Sponsor. 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.

Co-authorship will be granted based on the following four criteria, recommended by the International Committee of Medical Journal Editors (ICMJE):

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
(2) Drafting the work or revising it critically for important intellectual content; AND
(3) Final approval of the version to be published;

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

16. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

17. Financial Aspects

Since the 'HEKcite protocol' consists of routinely-performed surgical procedures, it is partly reimbursed by the 'Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV/ENAMI)'. Since the registered data is collected during routine-practice, no supplement reimbursement for the surgical preparation, surgical procedure, rehabilitation or consultations will be provided to the patient.

In case additional funding for the 'HEKcite protocol' is granted, an investigator fee will be accredited to the principal investigator, based on its contribtutions (e.g. number of recruited patients, completeness of the data provided,...). As reported in the Dutch clinical manual, XXX provide certain material without charge or at a reduced price for patients with the indication as specified in the inclusion criteria.