LEakage After primary Knee and hip arthroplasty; a randomized controlled study for finding the best way to treat wound leakage after primary arthroplasty (October 2016)

October 2016

PROTOCOL TITLE: LEakage After primary Knee and hip arthroplasty; a randomized controlled study for finding the best way to treat wound leakage after primary arthroplasty

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Sponsor (in Dutch: verrichter/opdrachtgever)	**Board of University Medical Center Groningen**

Subsidising party	**ZonMW**
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Laboratory sites <*if applicable*>	***NA***
Pharmacy <*if applicable*>	***NA***

PROTOCOL SIGNATURE SHEET

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AB	Antibiotics
ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
PJI	Prosthetic Joint Infection
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKA/THA	Total Knee Arthroplasty/Total Hip Arthroplasty
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen)

SUMMARY

Rationale: Persistent wound leakage after primary TKA/THA is associated with a Prosthetic Joint Infection (PJI). PJI is a serious complication of TKA/THA (2% overall incidence). PJI has major implications for a patient's quality of life and can need revision surgery. Revision surgery for PJI within one year after TKA/THA is necessary in at least 200 patients annually (0.4% of all patients). The costs involved are high (± € 30,000).
Persistent wound leakage can be treated both by means of nonsurgical- or surgical treatment. Both are currently applied as usual care. Nonsurgical treatment consists of bed rest, bandages, antibiotics. Surgical treatment consists of debridement, antibiotics and implant retention (DAIR)) on days 8-11 postoperative. The rationale for an early treatment of wound leakage is, that in case a PJI is present, adequate surgical and antibiotic treatment as early as possible is strongly associated with prosthesis survival. The dilemma is that not all postoperative prolonged wound leakages are a proxy for a PJI, wound leakage may also be a risk to acquire a PJI. Nonsurgical treatment is aimed at rest to help primary wound healing in order to prevent a PJI. So far the literature shows no evidence for the superiority of surgical over nonsurgical intervention.

Objective: To determine clinical and cost effectiveness and impact on disease-specific and general health-related quality of life of surgical intervention (DAIR on day 10) versus nonsurgical treatment in patients with persistent wound leakage. Primary endpoint will be revision surgery for PJI up to one year.

Study design: A multicenter randomized controlled trial comparing surgical with nonsurgical treatment in case of persistent wound leakage after primary TKA/THA.

Study population: Patients aged 18 or older after primary TKA/THA surgery with a persistent wound leakage at day 9 are eligible for participation in the study.

Intervention (if applicable): Nonsurgical treatment consists of bed rest, bandages, and wound care. Surgical treatment consists of DAIR on day 10. DAIR is meant to clean the prosthesis and the wound in order to conquer the possibility of infection.

Main study parameters/endpoints: The clinical and cost effectiveness of surgical intervention (DAIR day 10) versus nonsurgical treatment in patients with wound leakage after TKA/THA.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The goal of the study is to compare two standard clinical policies, which are currently both used as usual care in the Netherlands depending on the physician's or hospital's preference. The patients in our trial will be subjected to one of these policies. It is therefore not plausible that participation will lead to an increased health risk. There is no clear evidence for either treatment regimen. No extra hospital visits are required. The burden of DAIR consists of surgery on day 10. The prostheses is cleaned and it takes 1-1.5 hours. It's as such a safe procedure.

1. INTRODUCTION AND RATIONALE

Total Knee Arthroplasty/Total Hip Arthroplasty (TKA/THA) are highly successful procedures in patients suffering from end-stage osteoarthritis (OA), and results in improvement of joint function and quality of life, and pain relief. These procedures are amongst the most reliable and cost-effective surgical procedures, with more than 50,000 prostheses implanted every year in the Netherlands [LROI 2014]. Due to the aging population it is expected that these numbers will significantly increase in the coming decades. Woundleakage after TKA/THA can be a postoperative problem. Wound leakage is associated with prosthetic joint infection (PJI) which is considered a serious postoperative complication. In this study a comparison is made of the clinical and cost effectiveness of a surgical and non-surgical treatment strategy against persistent wound leakage after primary TKA/THA.

Persistent wound leakage (any wound leakage on or after day 5) after a primary THA/TKA is associated with PJI [Maathuis 2009]. In theory, this might be induced in the postoperative phase by an inflammatory response. The dilemma is whether the inflammatory response 1) is part of a normal postoperative healing process in a proinflammatory environment or 2) is a reaction to a minimal load of bacteria which will be resolved by the patients' immune response, or 3) the inflammatory response is a reaction to an overload of bacteria. The latter indicating presence of a PJI which should be treated by surgical intervention (and antibiotics), the so-called DAIR (Debridement, Antibiotics, and Implant Retention). Conversely, surgical wounds may also show prolonged leakage because of resorption of a hematoma, fatty necrosis, or anticoagulants use and take longer to heal without the need for surgery, but with the need of rest and proper wound care.

Thus, prolonged wound leakage can be interpreted as a sign of prosthetic joint infection, but according to other authors it may also be seen as a risk factor for a deep infection, since a leaking wound can be a *porte-d-entrée* for bacteria. The latter is explained by the retrograde infection pathway described by Weiss and Krackow 1993, i.e. a leaking wound can be a pathway for bacterial colonisation. Persistent wound drainage can therefore be seen as risk factor for infection or as potential imminent infection, with fluid production as reaction on the infectious process. The latter perspective would have a low threshold for performing surgical debridement and lavage [Vince 2007, Ghanem 2014]. Irrespective of the treatment modality chosen, consensus states that early adequate treatment should be started as soon as possible if a PJI is suspected [Vince 2007, Lonner 1999, Maathuis 2009, Jaberi 2008, Patel 2007, Saleh 2002, Ghanem 2014]. The treatment strategies toward wound leakage vary from non-surgical treatment (bed rest, pressure bandage, wound care) to surgical treatment (DAIR). In fact, nonsurgical treatment is aimed at stopping wound leakage and DAIR is aimed at treating deep wound infection.

DAIR is meant to clean the prosthesis and the wound, and eradicate biofilm in order to conquer the infection and escape revision surgery for infection. Bacteria attached to the implant encapsulate themselves in a slime layer (biofilm), invisible to the body's innate immune response and out of reach of antibiotics [Busscher 2013]. Antibiotics do not reach the bacteria in biofilm state and only work in combination with surgery. DAIR carries a risk (probably 1-2%) of causing a new infection; it requires anaesthesia and therefore patients are subject to the regular complication risks of surgery like anaesthesia-related problems and nerve or vascular injury. It is also hypothesized that DAIR is likely executed unnecessary, as the optimal timing for a DAIR has not been proven yet. Maybe if one waits longer, the wound will heal without surgical intervention. It is generally assumed that biofilm matures within two weeks, and a mature biofilm is more difficult to eradicate. Hence theoretically, if one aims at

removing a biofilm it is best done within this term. Every intervention at an early stage is aimed at preventing major revision surgery for PJI in the future, avoiding unnecessary interventions.
Revision surgery for PJI has major implications for a patient's quality of life (multiple surgeries, longer operating times, increased blood loss and more complications, lengthy hospital stays and long-term antibiotic treatment). In addition, the costs associated with revision surgery are high (± € 30,000) [Kurtz, Bozicz, Vanhegan 2012]. In the Netherlands, revision surgery within one year is necessary in more than 600 patients (0.9% TKA and 1.4% THA). According to the "Landelijke Registratie Orthopedische Implantaten" (LROI), infection is the reason for revision within one year in 25.8% TKA and 12.3% THA revision cases. A Danish register study evaluated underreporting of infection as reason for revision and found it to be at least 40% [Gundtoft 2015]. This leads to the assumption that at least 1/3 of revisions within one year are related to PJI (200 patients). The associated costs for revision surgery for PJI within one year are therefore estimated at € 6,000,000 (200 x € 30,000). However, the number of revisions for PJI is probably much higher with longer follow-up, as many PJI cases are caused by lower-virulence bacteria. PJI within two years is therefore still generally considered to be related to the primary surgery. This is expressed in the LROI figures for revisions for PJI: in 2014 there were 2541 TKA and 3574 THA revisions with infection as reason for revision, 15% and 11% respectively, on a yearly base. Considering 40% underreporting, it can be estimated that approximately 1064 patients need revision surgery for PJI, of whom at least 200 are operated within the first year of index surgery and the other 800 after the first year. So it can be concluded that the actual rate of PJI is probably largely underestimated, as was also discussed for the Danish National Hip register [Gundtoft 2015]. This underestimation will also be present for the Dutch Arthroplasty register (LROI), despite its completeness of over 97% [Steenbergen 2015].

OBJECTIVES
Primary Objective:
To determine the clinical and cost effectiveness of surgical treatment (DAIR day 10) versus nonsurgical treatment in patients with wound leakage after TKA/THA.

Secondary Objective(s):
To compare the impact of surgical treatment (DAIR day 10) with nonsurgical treatment on disease-specific and general health-related quality of life.

HYPOTHESIS:
Surgical treatment (DAIR on day 10) will result in a 50% reduction rate of revision for PJI up to one year after primary TKA/THA compared to nonsurgical treatment. Consequently surgical treatment is more (cost) effective compared to nonsurgical treatment. DAIR on day 10 will result in improvement of disease-specific and general health-related quality of life compared to nonsurgical treatment.

RESEARCH QUESTION:
Primary research question
What is the clinical and cost effectiveness of surgical treatment (DAIR day 10) versus nonsurgical treatment in patients with persistent wound leakage? Primary endpoint will be revision surgery for PJI up to one year.

Secondary research questions
What is the impact of surgical treatment (DAIR day 10) compared to nonsurgical treatment on disease-specific and general health-related quality of life at one year?

2. STUDY DESIGN

A nationwide multicenter randomized controlled trial comparing surgical treatment (DAIR day 10) with nonsurgical treatment in case of persistent wound leakage after primary TKA/THA. A randomisation on patient level will be executed. The randomization procedure will be designed and implemented by the Trial Coordination Center UMCG using the validated web-based system ALEA. Each user will receive an individual login code with which to randomize patients. The web application will return the allocated treatment. As a confirmation the web application will also send an e-mail to selected users containing the randomization information. The system is online 24 hours a day, 7 days a week.

3. STUDY POPULATION

3.1 Population (base)

All patients aged 18 or older that undergo TKA/THA surgery in the participating hospitals.

3.2 Inclusion criteria

All patients aged 18 or older after primary TKA/THA surgery with a persistent wound leakage at day 9 are eligible for participation in the study.

3.3 Exclusion criteria

-Mental or physical disability to fulfil study requirements.
-Insufficient command of the Dutch language.

3.4 Sample size calculation

The power analysis is based on the assumption that, in patients experiencing persistent wound leakage at day 9, PJI eventually will develop and will necessitate revision surgery in 20% of cases. It is hypothesized that surgical intervention (DAIR day 10) will prevent 50% of PJI and consequently 50% of revision surgery for PJI in comparison to the non surgical intervention. In order to detect this 50% difference with 80% power at a significance level of 0.05, 155 patients are needed in the surgical group and 155 in the nonsurgical group. With an expected dropout rate of approximately 20% a sample size of 194 patients per group is needed (total N=388).

4. TREATMENT OF SUBJECTS

Nonsurgical treatment
The nonsurgical treatment policy consists of relative rest (stop exercise, bed rest), wound care with sterile bandages and pressure bandage; hospital admission may be considered. On day 16 wound classification, clinical examination and CRP are performed. In case of persistent leakage at day 16, a DAIR according to study protocol is advised on days 17-20.

Surgical treatment
DAIR on day 10. DAIR is meant to clean the prosthesis and the wound in order to conquer the possibility of infection. DAIR consists of opening the wound, taking one culture from the fluid deep to the fascia and at least four deep-tissue cultures: two synovial and at least one around both components of the joint prosthesis. Only after taking cultures antibiotics are started and the hematoma and necrosis excised. Mobile parts (e.g. tibial insert, femoral head) are exchanged to make room for optimal debridement. The wound is lavaged thoroughly with 3-6 litres of saline. It is advised to use scrub sponges to mechanically clean all visible prosthetic parts. Povidone iodine solution or chlorhexidine solution may be used.

4.1 Investigational product/treatment
NA

4.2 Use of co-intervention (if applicable)
NA

4.3 Escape medication (if applicable)
NA

5. INVESTIGATIONAL PRODUCT
NA

6. NON-INVESTIGATIONAL PRODUCT
NA

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint
The primary clinical outcome is the percentage of prevented revision for PJI within one year and the involved costs.

7.1.2 Secondary study parameters/endpoints (if applicable)
Study parameters are wound class, temperature, CRP, culture results, second surgery. Patient parameters include BMI, ASA, smoking, medication.
Disease specific and general health related quality of life. The short HOOS and KOOS and the Oxford Hip and Knee Score will be used as disease-specific outcome instruments. The EQ-5D-5L will be used as a generic health-related quality of life questionnaire. To get an impression of pain an NRS will be used. All questionnaires are recommended by the Netherlands Orthopaedic Association (NOV) and are included in the standard Patient Reported Outcome Measure (PROM) for both TKA and THA patients. In Dutch hospitals it is standard procedure that patients fill in these questionnaires preoperatively and at 3, 6 and 12 months postoperatively.

7.1.3 Other study parameters (if applicable)

COST-EFFECTIVENESS ANALYSIS (CEA):
The cost effectiveness analysis typically integrates two quantities: 1. the additional costs (or savings) of the surgical protocol (DAIR) compared with the nonsurgical treatment, and 2. the additional health benefits. Based on these 2, a third metric is calculated: The Incremental Cost Effectiveness Ratio (ICER), which is the difference in costs, divided by the difference in effects.

Cost analysis
In the CEA, costs will include primary treatment (including home care) and health care associated with revision for infection in the first year (estimated from patient charts). Productivity losses will also be included. All items of resource use will be collected at the patient level, using CRFs and patient Questionnaires (iMCQ and iPCQ (www.imta.nl). Estimated productivity costs will include short-term losses due to hospitalization and lifelong losses due to mortality (using general Dutch labor participation and income data). Health care will be valued using standard prices [zorginstituut Nederland, 2015], with time and travel costs included in the CUA. Productivity losses will be valued using both the friction-cost method (primary analysis) and the human-capital method.

Patient outcome analysis
In the CEA, patient outcome will be measured by the incidence of revision for infection. In the CUA, in the trial-based analysis the impact on QALY loss will rely on trial results based on the EQ-5D-5L. The quality of life assessments in our own patients will be used to calibrate the literature estimates to our specific patient population.

7.2 Randomisation, blinding and treatment allocation

A randomisation on patient level will be executed. The randomization procedure will be designed and implemented by the Trial Coordination Center (TCC) UMCG using the validated web-based system ALEA. Each user will receive an individual login code with which to randomize patients. The web application will return the allocated treatment. As a confirmation the web application will also send an e-mail to selected users containing the randomization information. The system is online 24 hours a day, 7 days a week.

7.3 Study procedures

Nonsurgical treatment
Patients in the nonsurgical treatment group will be treated following a nonsurgical treatment policy. This policy consists of relative rest (stop exercise, bed rest), wound care with sterile bandages and pressure bandage; hospital admission may be considered. On day 16 wound classification, clinical examination and CRP are performed. In case of persistent leakage at day 16, a DAIR according to study protocol is advised on days 17-20.

Surgical treatment
DAIR on day 10. DAIR is meant to clean the prosthesis and the wound in order to conquer the possibility of infection. DAIR consists of opening the wound, taking one culture from the fluid deep in the fascia and at least four deep-tissue cultures: two synovial and at least one around both components of the joint prosthesis. Only after taking cultures are antibiotics started and the hematoma and necrosis excised. Mobile parts (e.g. tibial insert, femoral

head) are exchanged to make room for optimal debridement. The wound is lavaged thoroughly with 3-6 litres of saline. Scrub sponges are used to mechanically clean all visible prosthetic parts. Povidone iodine solution or chlorhexidine solution may be used as additional intraoperative antiseptic.

7.4 Withdrawal of individual subjects

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

7.4.1 Specific criteria for withdrawal (if applicable)

NA

7.5 Replacement of individual subjects after withdrawal

Subjects who withdraw will be replaced in order to maintain a sufficient sample size, although a drop-out rate of 20% has been accounted for.

7.6 Follow-up of subjects withdrawn from treatment

These subjects will be followed-up by usual care protocols.

7.7 Premature termination of the study

Since the study is comparing two ways of usual care, there are no reasons for premature termination of the study.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);

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

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:
- side-effects of antibiotics treatment
- elective hospital admission for nonsurgical treatment

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs not requiring reporting like mentioned above will be listed annually in a report.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

NA

8.3 Annual safety report

NA

8.4 Follow-up of adverse events

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

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

Since the study is comparing two ways of usual care a DSMB is not necessary.

9. STATISTICAL ANALYSIS

Statistical analyses will be performed with the help of IBM SPSS statistics 22. An intention to treat analyses will be performed. For all analyses a one–tailed significant level of $p < 0.05$ is considered to be statistically significant

9.1 Primary study parameter(s)

Clinical outcome

This study is designed as a randomized controlled trial. Every patient can be classified as nonsurgical or surgical. At least two measurements will be collected, namely before the

intervention (at day 9) and one year after the intervention. Between these two measurements additional information on the patient will be collected. The patient is also nested within a hospital, but the dependency of the measurements within the patient is our focal interest. The primary outcome of the study is revision surgery for PJI within one year (a binary variable). To take into account all these dependencies, multilevel logistic regression model with three levels will be used to analyse the data. The three levels are hospitals, patients and measurements, where measurements are nested within patients and patients are nested within hospitals. The effect of the intervention will be controlled with covariates such as age and gender.

9.2 Secondary study parameter(s)

Secondary outcomes are disease-specific and general health-related quality of life (ordinal variables). In line with the analyses of the primary outcome, a multilevel linear regression model with three levels will be used to analyse the data. The three levels are hospitals, patients and measurements, where measurements are nested within patients and patients are nested within hospitals. The effect of the intervention will be controlled with covariates such as age and gender.

9.3 Other study parameters

In the economic evaluation, primary aim will be to estimate the societal costs of the surgical strategy with a DAIR on day 10, and compare this to the costs of the nonsurgical treatment strategy. Secondary aim will be to estimate the cost effectiveness of the surgical strategy compared to nonsurgical treatment (from a societal perspective), based on the primary measure of effectiveness (number of infections prevented). Finally, a costs utility analysis will be performed based on EuroQol (5D-5L)-defined utilities.
Results of the cost effectiveness analysis will display the additional costs or savings with the surgical strategy in order to prevent one additional patient with an infection compared to nonsurgical treatment. Results of the cost utility analysis will display the additional costs or savings with the surgical strategy in order to gain one quality-adjusted life year (QALY) compared to nonsurgical treatment.
The time horizon of this study will be 12 months, therefore the analysis will not include discounting of costs and effects. Bootstrap resampling will be performed on the cost, and on the cost and effect pairs in order to calculate confidence intervals. Cost effectiveness acceptability curves will also be plotted, to estimate the probability of the surgical strategy being more cost-effective than the nonsurgical treatment strategy, for different amounts of money that a decision-maker may be willing to pay for one additional unit of effect (infection avoided, QALY).

BUDGET IMPACT ANALYSIS (BIA)
General considerations
A budget impact analysis will be conducted from a healthcare perspective as well as from a health insurance perspective. The basic case scenario will focus on a one-year impact at the national level. Scenario analysis will adopt a four-year horizon.

Cost analysis
A budget impact analysis (BIA) will be conducted to inform decision-makers about the financial consequences of the adoption and diffusion of the surgical strategy (DAIR) in

the Dutch healthcare system. The BIA will use a deterministic model. The model input parameters will be mainly based on results of the current clinical- and cost-effectiveness study and available literature. For the BIA, no additional patient level data will be collected.

The analyses will be conducted from various perspectives, including a direct medical perspective, a government and societal budgetary care perspective (overheidsperspectief), a budgetary care perspective limited to net bKZ expenditures ("netto bKZ-uitgaven"), and a health insurer's perspective. For the analysis from a direct medical perspective, only costs within the healthcare sector will be taken into account. Unit prices will be based on Dutch standard prices (2015 guidelines). For the other perspectives, national tariffs will be applied (NZa tariffs) and the scope of included costs will be limited to those relevant for the perspective concerned. The precision of costs will be in accordance with the described perspectives (€M).

The model will take into account changes in the availability and adoption of the surgical strategy by calculating the financial consequences of the following scenarios:

• Situation in which all patients receive the nonsurgical treatment strategy.
• Situation in which all patients receive the surgical strategy.
• Situation in which all patients are treated gradually according to the study protocol (DAIR).
• Situation in which treatment according to the study protocol (DAIR) is considered suitable and available for varying percentages of the targeted population.

For each of the presented scenarios, a time horizon of up to four years will be applied. Alternative time horizons will be addressed in sensitivity analyses. Costs will be calculated based on changes in resource use, valued against the price level relevant from the various perspectives. Discounting of future costs will not be applied in the BIA.

The model will allow additional analyses for subgroups of patients. These analyses include mainly the shift in the subgroups of patients based on indication, type of surgery, age, BMI, ASA, medication groups (anticoagulants, immunosuppressants) and comorbidity (e.g. diabetes). Budget information for relevant subgroups will be made available for decision-makers. The planned sensitivity analysis will address the main input parameters and assumptions of the model, and financial consequences of variations in model parameters will be calculated for each of the applied perspectives [Mauskopf, 2007].

9.4 Interim analysis (if applicable)

NA

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

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

10.2 Recruitment and consent

All patients aged 18 or older and scheduled to undergo TKA/THA surgery in the participating hospitals will be orally informed about the LEAK study by their physician or specialised nurse when he or she is placed on the planning list for TKA/THA. In addition the patient will receive written information in the form of a flyer with background information about the study.

At the day of hospitalization all TKA/THA patients will be informed again about the study orally by the independent local research physician/nurse. On day 5-7, in case of persisting wound leakage, patients will receive a patient information letter and oral information by an independent research physician/nurse about the study and they will be asked to think about participating.

On day 9-10, patients can communicate their final decision (yes or no) to the local independent research physician/nurse with respect to participation in the study. If patients agree to participate, written informed consent will be obtained.

In case their wound is still leaking at day 9-10, they will be randomized to nonsurgical or surgical treatment.

In case the wound is dry at day 9-10, or if patients have to undergo DAIR because of high clinical suspicion for infection (T>38.5, red indurated wound and pain), patients are not eligible to randomization but they can give permission to use their data for comparative analyses.

For the sake of facilitating logistics in the participating centres, consent and randomization are set at day 9 or 10; DAIR is set at day 10-11. In the general text, for easy reading, these terms are simplified to day 9 and day 10 respectively.

10.3 Objection by minors or incapacitated subjects (if applicable)

In case of incapacitated subjects, the subject will not be asked to participate.

10.4 Benefits and risks assessment, group relatedness

The goal of the study is to compare two standard clinical policies, which are currently both used as usual care in the Netherlands depending on the physician’s or hospital’s preference. The patients in our trial will be subjected to one of these standard policies. It is therefore plausible that participation will lead not to an increased health risk. The burden of participation in the trial can be considered minimal as treatment regimens within the study are in line with usual care strategies. No extra hospital visits are required.

10.5 Compensation for injury

Aangezien het onderzoek een vergelijking betreft van in Nederland gebruikelijke behandelingen op het gebied van de geneeskunst heeft de oordelend commissie, de METc UMCG , ontheffing van de verzekeringsplicht verleend zoals bedoeld in art. 4 lid 2 van het Besluit verplichte verzekering bij medisch wetenschappelijk onderzoek met mensen.

10.6 Incentives (if applicable)

NA

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Personal data will be handled confidentially. Every subject will receive a unique code, this code contains the number of the hospital (UMCG/ HAGAZiekenhuis, Onze Lieve Vrouwe Gasthuis etc.) followed by the
number corresponding with the study group (nonsurgical/surgical). This combination of three numbers will be supplemented with a unique sequence number. Data of each subject will be collected under this unique code. A unique subject identification list will be used to link the data to the subject. The key to the code is safeguarded by the coordinating investigator. All source documents will be entered in an electronic CRF.

11.2 Monitoring and Quality Assurance

Based on the negligible risk profile, minimal monitoring is considered adequate (according to the NFU standards). Monitoring digitally will be performed for critical data (e.g. completeness of questionnaires) and will be executed by an independent subject of the orthopaedic department, not related with the study, with relevant training and education.

11.3 Amendments

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

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

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

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The present study is investigator initiated. No arrangements are made between the subsidizing party and investigator concerning publication of the research data. Independent of the outcome, the results of the study will be published in international peer-reviewed scientific journals. Patient data will be presented anonymously in all publications and scientific journals. This prospective clinical trial will be registered in the ”Nederlands Trial Register” before the first patient is recruited.

12. STRUCTURED RISK ANALYSIS

NA

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