LEAK study: design of a nationwide randomised controlled trial to find the best way to treat wound leakage after primary hip and knee arthroplasty

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ABSTRACT

Introduction Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are highly successful treatment modalities for advanced osteoarthritis. However, prolonged wound leakage after arthroplasty is linked to prosthetic joint infection (PJI), which is a potentially devastating complication. On the one hand, wound leakage is reported as a risk factor for PJI with a leaking wound acting as a porte d’entrée for microorganisms. On the other hand, prolonged wound leakage can be a symptom of PJI. Literature addressing prolonged wound leakage is scarce, contradictory and of poor methodological quality. Hence, treatment of prolonged wound leakage varies considerably with both non-surgical and surgical treatment modalities. There is a definite need for evidence concerning the best way to treat prolonged wound leakage after joint arthroplasty.

Methods and analysis A prospective nationwide randomised controlled trial will be conducted in 35 hospitals in the Netherlands. The goal is to include 388 patients with persistent wound leakage 9–10 days after THA or TKA. These patients will be randomly allocated to non-surgical treatment (pressure bandages, (bed) rest and wound care) or surgical treatment (debridement, antibiotics and implant retention (DAIR)). DAIR will also be performed on all non-surgically treated patients with persistent wound leakage at day 16–17 after index surgery, regardless of amount of wound leakage, other clinical parameters or C reactive protein. Clinical data are entered into a web-based database. Patients are asked to fill in questionnaires about disease-specific outcomes, quality of life and cost effectiveness at 3, 6 and 12 months after surgery. Primary outcome is the number of revision surgeries due to infection within a year of arthroplasty.

Ethics and dissemination The Review Board of each participating hospital has approved the local feasibility. The results will be published in peer-reviewed scientific journals.

Trial registration number NTR5960; Pre-results.

INTRODUCTION

Osteoarthritis (OA) is the most recognised joint disorder worldwide and is recognised as a substantial source of disability.1 Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are highly successful and widely accepted surgical treatment modalities for advanced OA of the hip and knee. In 2015, 28 798 THAs and 27 082 TKAs were performed in the Netherlands2 and 310 800 THAs and 693 400 TKAs were performed in USA in 2010.3 4 The demand for joint arthroplasty continues to rise due to an ageing population and changing thresholds for surgery and is expected to keep increasing in the coming decades.5 Unfortunately, this results in higher absolute numbers of complications after joint arthroplasty. One of the most serious and potentially devastating complications is prosthetic joint infection (PJI).

Persistent wound leakage after primary THA or TKA is associated with PJI. Wound
leakage is induced in the postoperative phase by an inflammatory response. Conversely, surgical wounds may also show prolonged leakage for other reasons (hematoma, seroma or fatty necrosis) and take longer to heal without development of a PJI. Prolonged wound leakage is a risk factor for PJI as a leaking wound can be a porte d’entrée for micro-organisms (retrograde infection pathway). Bacteria can rapidly form a biofilm on the metal surface of the prosthesis, thereby decreasing the effectiveness of the host defence and antimicrobial therapy. It is estimated that in the Netherlands about 2200 patients annually (4% of ±55,000 THA/TKA) have wound leakage at day 9 after index surgery. As PJI is a serious and potentially devastating complication, prolonged wound leakage should be considered as potentially imminent PJI, with fluid production as a symptom or a risk factor for infection.

PJI has an enormous impact on patients as well as society, as it often results in septic revision surgery, requiring removal of the infected implant to eradicate the infection and hopefully allowing subsequent reimplantation. This septic revision surgery is accompanied by a large negative impact on the quality of life of patients and high healthcare costs (±€30,000 per patient with PJI in UK), due to extended hospital stays, costly surgical procedures, prolonged use of antibiotics and impaired function of the hip or knee. The Dutch Arthroplasty Register reports a total of 3809 THA and 2667 TKA revision surgeries performed in 2015. Revision surgery within 1 year of index surgery was necessary in more than 600 patients and at least 30% of these were PJI-related.

Persistent wound leakage can be treated by non-surgical and surgical treatment modalities. Non-surgical treatment can consist of relative rest (no exercise and bed rest), pressure bandages (hip spica or knee pressure bandage) and wound care with sterile bandages. Hospital admission can be required. Surgical treatment typically consists of debridement, antibiotics and implant retention (DAIR). A DAIR procedure is meant to clean the prosthesis and wound, including breaking down the biofilm, in order to treat the infection and render further infection treatment unnecessary. Treatment of persistent wound leakage varies considerably among Dutch hospitals, as confirmed recently by a nationwide questionnaire-based survey regarding both non-surgical and surgical treatment modalities. However, these modalities have never been studied comparatively.

Several authors have investigated the effect of DAIR for treatment of persistent wound leakage and reported various results and/or made (opinion-based) statements, generally in favour of early DAIR. The most recent PJI consensus meeting suggests five to seven days of wound leakage as the threshold to perform DAIR, but there is no solid evidence for this statement. Therefore, the optimal timing of DAIR is yet to be established, which could imply that either overtreatment or undertreatment may occur. As the treatment decision-making process is generally relatively easy in patients with severe wound leakage and a high suspicion of infection, this study particularly aims to provide evidence for the best treatment of patients with a low suspicion of infection.

As early DAIR is hypothesised to be helpful in treating or preventing infection and salvaging the implant, the objective of this study is to determine the clinical outcome and cost effectiveness of early surgical intervention (DAIR at day 9–10 after index procedure) versus non-surgical treatment in patients with prolonged wound leakage after primary THA/TKA. In addition, the impact on disease-specific and general health-related quality of life will be determined. Our hypothesis, based on the scarce literature mentioned above, is that performing a DAIR at day 9–10 will result in a 50% reduction rate of revision surgery for PJI up to one year after primary THA/TKA compared with non-surgical treatment.

METHODS AND DESIGN

Study design and procedure

A prospective nationwide multicentre randomised controlled trial (RCT) will be conducted. The study will be carried out in 35 hospitals throughout the Netherlands. All patients aged 18 or older and scheduled to undergo primary THA/TKA in the participating hospitals will receive written and oral information about the LEAKage After primary Knee and hip arthroplasty (LEAK) study. Patients with persistent wound leakage at day 5–7 after index surgery will be monitored carefully and receive non-surgical treatment. Clinical examination, wound classification and C reactive protein (CRP) will be carried out at day 5–7 and day 9–10. In case of persistent leakage at day 9–10 after index surgery, the patient will be included in the study (after signing the informed consent form) and randomised to either surgical treatment (DAIR at 9–10) or continued non-surgical treatment. Patients allocated to the non-surgical treatment group with persistent wound leakage at day 16–17 after index surgery will also be subjected to a DAIR, regardless of amount of wound leakage, other clinical parameters or CRP. Patients in the non-surgical treatment group with clear signs of infection (defined as temperature >38.5°C, increasing wound leakage, redness, pain and increasing CRP (>25% compared with day 9–10)) earlier than day 16–17 will receive surgical treatment at that time point. Patients with clear signs of infection earlier than or at day 9–10 after index surgery will receive surgical treatment without randomisation (see online supplementary figure 1). The extended version of the study protocol flowchart is enclosed in online supplementary figure 2.

Randomisation will be performed by a web-based system (developed by Interactive Studios, Rosmalen, The Netherlands), based on the software Apache and MySQL. Each participating hospital receives an individual login in order to register and randomise patients. A two-day time window for randomisation (day 9–10) is chosen to facilitate implementation of the protocol, as some patients undergo surgery on days of the week that result in follow-up moments in the weekend, which may
hamper inclusion. Since there is no uniform classification for wound leakage, experts in the field of PJI (the LEAK study group) developed a wound leakage classification system based on amount of wound leakage, called the LEAK-classification, consisting of four classes: LEAK class 0: dry wound, LEAK class 1: mild wound leakage (<2×2 cm in gauze per 24 hours), LEAK class 2: moderate wound leakage (>2×2 cm in gauze and no need for >1 absorbent gauze exchange per 24 hours) and LEAK class 3: severe wound leakage (need for >1 absorbent gauze exchange per 24 hours). Due to the nature of the study, patients and surgeons cannot be blinded. Data analyses will be performed blinded.

Inclusion and exclusion criteria
All patients aged 18 or older with persistent wound leakage at day 9–10 after primary THA/TKA surgery are eligible for inclusion and subsequent randomisation for the surgical treatment (DAIR at day 9–10) or continued non-surgical treatment. Exclusion criteria are mental or physical disability to fulfil study requirements and insufficient command of the Dutch language.

Surgical treatment
The surgical treatment consists of DAIR at day 9–10. DAIR consists of opening the wound and obtaining one culture from the intra-articular synovial fluid deep to the fascia and at least four deep-tissue cultures: two synovial and at least two around the components of the joint prosthesis. Empirical antimicrobial treatment in accordance with the local protocol is started after obtaining cultures and excising haematoma and necrosis. Mobile parts (eg, tibial insert, femoral head and acetabular liner) are exchanged and at least two around the components of the joint prosthesis. Implant level properties is advised.

Non-surgical treatment
The non-surgical treatment consists of relative rest (stop exercise and start bed rest), pressure bandages (hip spica or knee pressure bandage) and wound care with sterile bandages. The non-surgical treatment is optionally carried out in a hospital admission setting. Patients in the non-surgical treatment group do not receive antimicrobial treatment. In non-surgically treated patients clinical examination, wound classification and CRP are performed at day 16–17 after index surgery. A DAIR will also be performed on all patients with persistent wound leakage at day 16–17 after index surgery, regardless of amount of wound leakage, other clinical parameters or CRP.

Outcome measures
Primary outcome is the percentage of reoperations for PJI within one year of index surgery. Reoperation refers to any kind of septic revision surgery (one or two stage, Girdlestone, arthrodesis or amputation). In addition, any other PJI treatment modalities are recorded (repeated DAIR, start of suppressive antimicrobial treatment or watchful neglect).

Secondary outcomes are the impact of surgical treatment compared with non-surgical treatment on disease-specific outcome and general health-related quality of life and the economic evaluation (cost-effectiveness and cost utility) of the surgical and non-surgical treatment. Self-reported questionnaires will be used to measure these outcome parameters. All questionnaires used are recommended by the Netherlands Orthopaedic Association as a quality assessment tool of orthopaedic care and are included in the standard Patient Reported Outcome Measure (PROM) list for both THA and TKA patients. Randomised patients will fill in these questionnaires 3, 6 and 12 months after index surgery.

Clinical data
Clinical data will be recorded from randomised patients, patients who undergo surgical treatment earlier or at day nine because of clear signs of infection and patients with persistent wound leakage at day 5–7 but a dry wound at day 9–10 after index surgery. Data are recorded in the web-based database. Demographic characteristics, body mass index, American Society of Anesthesiologists score, immunosuppressant medication, diabetes and anticoagulants will be recorded. Further data include information about the index surgery, reoperation for PJI, postoperative complications, clinical signs of infection, use of antibiotics and measurement of CRP. For those patients who are allocated to surgical treatment, the course of the DAIR procedure and culture results will be recorded. In case of repeated DAIR procedures, the information will also be specified in the database. The clinical data are filled in by a physician of the participating hospital, to preserve doctor-patient confidentiality.

Disease-specific outcome and general health-related quality of life
Questionnaires that will be used to measure disease-specific outcome are the Hip and Knee disability and Osteoarthritis Score—physical function short form (HOOS-PS/KOOS-PS)16 17 and the Oxford Hip and Knee Score (OHS/OKS).18 19 General health-related quality of life will be measured by the EuroQol-5D-5L (EQ-5D-5L).20 21

The HOOS-PS and KOOS-PS are disease-specific PROMs derived from the original HOOS and KOOS questionnaires. These questionnaires inform after hip or knee disability in patients with osteoarthritis. The HOOS-PS consists of five items assessing physical function with interval-level properties. Questions are answered using a Likert scale, in which a higher score reflects more symptoms and limitations. The KOOS-PS contains seven items. Questions are answered using a Likert scale, with higher scores indicating more limitations in physical functioning. The raw scores are converted to a 0-to-100 scale with 100 as the best outcome. The Dutch language versions of the HOOS-PS and KOOS-PS are considered reliable and valid.16 17
The OHS and OKS are disease-specific PROMs. These questionnaires consist of 12 questions covering function and pain associated with the hip or knee. Questions are answered using a Likert scale. Scoring involves summing the total for each item to produce a final score between 0 and 48, with a higher score indicating greater disability. The questionnaires are considered reliable, valid and sensitive to clinically important changes over time and are available in the Dutch language. \(^{18,19}\)

The EQ-5D-5L is a widely used and valid generic instrument to measure general health-related quality of life and is validated in the Dutch language. \(^{20,21}\) The EQ-5D-5L consists of two parts. The first part consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored using a Likert scale. The combined scores of these five dimensions are converted to the EQ-5D index score. \(^{21}\) The second part consists of a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled ‘best imaginable health state’ and ‘worst imaginable health state’ anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by writing down the number representing the point on the EQ-VAS which best represents their own health on that day. \(^{20,21}\) The EQ-5D-5L is embedded in this study protocol, as it is especially useful in combination with the economic evaluation that will be conducted in order to calculate utilities.

### Economic evaluation

The primary aim of the economic evaluation will be to estimate the societal costs of the strategy to perform a DAIR at day 9–10 and compare this to the costs of a continued non-surgical treatment strategy. Secondary aim will be to estimate the cost effectiveness of the surgical treatment compared with non-surgical treatment (from a societal perspective), based on the primary measure of effectiveness (number of infections prevented).

Cost effectiveness analyses (CEA) and cost utility analyses (CUA) based on EQ-5D-5L-defined utilities will be performed to describe the financial consequences of both surgical and non-surgical treatment. All items of resource use will be collected at the patient level, using case record forms and the patient questionnaires Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ). The iMCQ is a generic instrument for measuring medical costs. The questionnaire includes 31 questions related to frequently occurring contacts with healthcare providers. \(^{22}\) The iPCQ is a standardised generic instrument for measuring and valuing productivity losses. The questionnaire includes 12 questions divided into three modules measuring productivity losses of paid work due to absenteeism, presenteeism and productivity losses related to unpaid work. \(^{23,24}\)

The CEA and CUA integrate two quantities: the additional costs (or savings) of surgical treatment compared with non-surgical treatment and the additional health benefits. Based on these two quantities the incremental cost effectiveness ratio is calculated, which is the difference in costs divided by the difference in effects. Results of the CEA will display the additional costs or savings with surgical treatment in order to prevent one additional patient with an infection compared with non-surgical treatment. In the CUA, the impact on quality adjusted life year (QALY) will rely on the results based on the EQ-5D-5L. Results of the CUA will display the additional costs or savings with surgical treatment in order to gain one QALY compared with non-surgical treatment.

Healthcare will be valued using standard prices, \(^{25}\) with time and travel costs included in the CEA and CUA. Productivity losses will be valued using both the friction-cost method (primary analysis) and the human-capital method (sensitivity analysis). The time horizon will be 12 months; therefore, the analysis will not include discounting of costs and effects. Bootstrap resampling will be performed on the cost as well as on the cost and effect pairs in order to calculate CIs. Cost effectiveness acceptability curves will be plotted to estimate the probability of surgical treatment being more cost-effective than non-surgical treatment, for different amounts of money that a decision-maker may be willing to pay for one additional unit of effect (infection avoided or QALY).

### Sample size

The power analysis is based on the assumption that 20% of patients with persistent wound leakage at day 9–10 will necessitate revision surgery. It is hypothesised that surgical treatment (DAIR at day 9–10) will prevent 50% of PJIs and consequently revision surgery compared with non-surgical treatment. In order to detect this 50% reduction with 80% power at a significance level of 0.05, 155 patients are required in the surgical treatment group and 155 in the non-surgical treatment group. With an expected dropout rate of approximately 20%, a sample size of 194 patients per group is needed, making up a total required patient group of 388 patients.

### Statistical analysis

Descriptive statistics will be used to analyse patient characteristics. The primary outcome of the study is revision surgery for PJI within one year of index surgery (a binary variable). At least two measurements will be collected, namely at the time of randomisation (at day 9–10) and one year after index surgery. The dependency of the measurements within the patient is our focal interest. To take into account other dependencies (eg, the hospital in which the patient is treated), a multilevel logistic regression model with three levels will be used to analyse the data. The three levels are hospitals, patients and measurements. As this study is designed as an RCT, every patient can be classified as a case (surgical treatment) or control (non-surgical treatment). The effect of the intervention will be controlled for relevant covariates such as age and gender. Intention-to-treat analyses will be conducted. Subanalyses will be performed for patients with wound leakage after THA and TKA separately, to gain insight into the effectiveness of the intervention. Moreover,
subanalyses will be performed within both treatment groups to distinguish between patients who initially received non-surgical treatment but were treated with a DAIR at day 16–17 versus patients who only received non-surgical treatment (non-surgical treatment group) and between patients who received one DAIR versus two DAIRs (surgical treatment group).

For all analyses, a one-tailed significant level of P<0.05 is considered to be statistically significant. All statistical analyses will be performed using SPSS V.24.0 for Windows (IBM, Armonk, New York, USA).

ETHICS AND DISSEMINATION

The Review Board of each participating hospital has examined and approved the local feasibility. The study will be conducted according to the principles of the Medical Research Involving Human Subjects Act (WMO), the Good Clinical Practice standard (GCP) and the Declaration of Helsinki. Eligible patients will be informed about the study and will sign an informed consent form in order to participate. Serious adverse events will be recorded and reported to an independent data and safety monitoring board. Auditing and monitoring will be carried out throughout the duration of the study. We began recruitment in February 2017 and expect to have completed recruitment by August 2018 and completed data collection by August 2019. The results of this study will be published in international peer-reviewed scientific journals.

DISCUSSION

Wound leakage is associated with PJI, with fluid production as a symptom or a risk factor for infection. With increasing numbers of joint arthroplasties worldwide, the number of PJs is rising as well. Without an evidence-based guideline, there is huge variation in clinical practice regarding the treatment of persistent wound leakage in the Netherlands and abroad, with both non-surgical and surgical treatment modalities being used (submitted data). The most recent PJI consensus meeting suggests 5–7 days of wound leakage as the threshold to perform a DAIR-procedure. Nevertheless, this statement remains unproven and comparative studies on early surgical intervention (DAIR) versus non-surgical treatment are lacking. There is a need for an unambiguous clinical guideline to treat persistent wound leakage.

Objective of the LEAK study is to determine the outcome of surgical treatment (DAIR at day 9–10) versus non-surgical treatment. Performing surgical treatment at day 9–10 is a compromise between the recommendation of the most recent PJI meeting and usual clinical practice in the Netherlands. In preparation of designing this RCT, we performed a survey among Dutch orthopaedic surgeons to evaluate current Dutch orthopaedic care for persistent wound leakage after joint arthroplasty. As only 17.2% of Dutch orthopaedic surgeons started surgical treatment after 5–7 days of wound leakage and 44.1% after 10 days of wound leakage, we decided to perform surgical treatment at day 9–10 after joint arthroplasty.

Based on the scarce literature available, the conservative assumption is that wound leakage is associated with revision for PJI in 20% of cases, and it is hypothesised that surgical treatment (DAIR on day 9–10) will reduce this to a 10% revision rate for PJI, that is, a 50% reduction within one year of primary THA/TKA compared with continued non-surgical treatment. It is hypothesised that in the long run (more than one year) even a larger reduction can be achieved, as many cases of PJI are caused by lower-virulence pathogens, and PJI within 2–5 years is generally considered as related to the index surgery. In this study, participating patients will be followed up for one year. This follow-up length is chosen because of restrictions from the subsidiary agency. Additional follow-up will be done through the Dutch National Registry for Orthopaedic Implants (LROI).

If the hypothesis as formulated in the LEAK study is confirmed, this will offer a firm body of evidence for the development of a guideline for treatment of prolonged wound leakage, eventually resulting in a lower percentage of PJs and therefore a significant improvement of physical functioning and health-related quality of life for patients with prolonged wound leakage. Moreover, from an economic perspective, it will lead to significant cost savings in orthopaedic healthcare. It is estimated that in the Netherlands about 2200 patients annually (4% of ±55000 THA/TKA) have wound leakage at day 9–10. It is hypothesised that the number of patients needing revision surgery for PJI with non-surgical treatment will be 200–400 compared with 100–200 with surgical treatment at day 9–10 after index surgery. Costs of standard treatment are difficult to estimate due to large variations in current clinical practices. Costs of the study intervention (DAIR) are about €3000. Additional savings include the avoided reinterventions, which amount to approximately €30000 per procedure. The hypothesised reduction in orthopaedic healthcare costs by implementing the LEAK study protocol is €300000 per year nationwide. This reduction in healthcare costs will be even greater considering the fact that PJI may develop later than one year after index surgery. Furthermore, it is hypothesised that performing surgical treatment (DAIR at day 9–10) can reduce the productivity loss associated with reoperations and can reduce the costs associated with prolonged home-care and informal care provided by relatives, which come in addition to the healthcare costs.

During the design of the LEAK study, the project team discussed using a non-inferiority design. This was discarded, as it is estimated that the effect of surgical treatment is sufficiently large to provide evidence for the superiority of performing an early DAIR procedure.

In conclusion, clinical practice for the treatment of persistent wound leakage varies considerably. The dilemma is that not all postoperative prolonged wound leakages are a proxy for PJI, but delaying surgical
treatment for too long may result in undertreatment and development of a PJI. At the present time, the literature shows no evidence for superiority of surgical over non-surgical treatment. The results of the current study will contribute to development of evidence-based guidelines on the optimal treatment and treatment timing of persistent wound leakage after THA and TKA.

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Disclaimer
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Competing interests
None declared.

Ethics approval
The study is approved by the Institutional Review Board of the University Medical Center Groningen (METc2016/418).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
Individual participant data that underlie the results reported in future articles will be available from the corresponding author on reasonable request after deidentification. Additionally, the study protocol, statistical analysis plan and analytic code will be available to researchers who provide a methodologically sound proposal, beginning 3 months and ending 5 years after article publication. Proposals should be directed to c.a.m.lowi@umcg.nl. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (https://www.protheoseinfeccties.nl).

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REFERENCES
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