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Comparison of **co**oled versus **co**nventional radiofrequency treatment of the **gen**icular nerves for chronic knee pain: a multicentre randomised controlled non-inferiority pilot trial (Cocogen trial)

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PROTOCOL TITLE: Comparison of **co**oled versus **co**nventional radiofrequency treatment of the **gen**icular nerves for chronic knee pain: a multicentre randomised controlled non-inferiority pilot trial

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
ALEA	**Trans European Network for Clinical Trials Services**
AP	**Anterior posterior**
AR	**Adverse Reaction**
ASRA	**American Society of Regional Anesthesia and Pain Medicine**
BMI	**Body mass index**
CEA	**Cost Effectiveness analysis**
DSMB	**Data Safety Monitoring Board**
EQ-5D-5L	**EuroQol 5 dimensions 5 level questionnaire**
ESA	**European society of Anaesthesiology**
EU	**European Union**
FDA	**Food and drug administration**
GPE	**Global perceived effect**
HADS	**Hospital Anxiety and Depression scale**
HRQOL	**Health Related Quality of Life**
IC	**Informed Consent**
IL	**Inferolateral**
IM	**Inferomedial**
IMMPACT	**Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials**
IMTA	**Institute for medical technology assessment**
IRB	**Institutional Review Board**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MQS	**Medication Quantification Scale**
NRS	**Numeric Rating Scale**
NSAID	**Non-steroidal anti-inflammatory drugs**
OA	**Osteoarthritis**
OKS	**Oxford Knee Score**
PCS	**Pain Catastrophizing Scale**
PGIC	**Patient Global Impression of Change**
QALY	**Quality- adjusted Life Year**
RCT	**Randomized controlled trial**
RF	**Radiofrequency**

(S)AE	**(Serious) Adverse Event**
SM	**Superomedial**
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	**Total knee arthroplasty**
VAS	**Visual analogue scale**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Knee osteoarthritis is a progressive degenerative process that affects joint cartilage and the subchondral bone. Approximately 10% to 30% of all osteoarthritis patients suffer from disabling symptoms such as pain, stiffness and loss of function leading to psychological and sleeping disorders and a diminished quality of life. (1-4) When conservative treatment fails to treat the symptoms, a total knee arthroplasty can be performed. (3, 6-9) Due to comorbidities or young age due to the limited lifetime of the prostheses used, the total knee arthroplasty procedure is not suitable for all patients. Also, persistent pain after a total knee arthroplasty is also possible. For these specific groups of patients a radiofrequent treatment of the genicular nerves (superolateral, superomedial and inferomedial) might be an alternative treatment option. Multiple researchers investigated the effect of conventional and later also, cooled radiofrequent treatment of the genicular nerves, with promising results for both techniques. (20-23) However, the techniques have never been compared in a randomised controlled trial.

Objective: The primary goal of this study is to provide an estimate of treatment effects, inclusion rate, and comparability of patients between hospitals to assess the feasibility of conducting a future randomised controlled non-inferiority trial to assess whether the effect of conventional RF treatment of the genicular nerves (superomedial, superolateral and inferomedial) of the index knee on knee pain relief is not inferior to the more expensive cooled RF treatment of the genicular nerves. A secondary goal is to estimate the initial costs and cost-effectiveness of conventional RF treatment compared to cooled radiofrequent treatment so as to determine the need, focus and scope of an economic evaluation alongside the RCT.

Study design This study is a prospective, multicentre, double blind, randomised controlled, non-inferiority pilot study.

Study population: Adult patients (> 18 years) with chronic, moderate to severe knee pain (NRS>4) due to osteoarthritis, radiological diagnosed to be graded 2-4 according to the Kellgren-Lawrence criteria on Rx or MRI or with persistent postoperative moderate to severe knee pain (NRS>4) after total knee arthroplasty.

Intervention (if applicable): One group is treated with a conventional radiofrequent treatment of the genicular nerves (SL, SM, IM) of the index knee. The other group is treated with a cooled radiofrequent treatment.

Main study parameters/endpoints: The primary study outcome parameter is the proportion of patients with a pain intensity reduction of at least 50% at 3 months post intervention compared to baseline. Pain intensity is measured by a Numeric Rating Scale. Secondary parameters include physical functioning, health-related quality of life, emotional outcome, patient satisfaction, side effects, duration effect, medication use, costs and cost

effectiveness. Inclusion rates per patient subgroup (osteoarthritis and post total knee arthroplasty) and per hospital will be monitored as well.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: After study enrolment and baseline intake, patients are treated and followed at 1, 3, 6 and 12 months after the initial intervention (total of 4 site visits, 1 online visit). Primary endpoint is 3 months post intervention. During the intake a physical examination is done. The treatment itself is performed without sedation and is generally well tolerated without side effects of complications. This study compares two active treatment therapies. Therefore, it is expected that patients from both treatment groups experience similar positive effects regarding pain relief and improved knee function.

1. INTRODUCTION AND RATIONALE

Osteoarthritis is one of the most prevalent chronic diseases and a leading cause of pain and disability. (1) The prevalence of radiographic evidence of knee osteoarthritis in persons older than 55 years varies, depending on which study, between 33 and 68%. Approximately 10% to 30% of those have significant pain and functional impairment. (2) Osteoarthritis is a progressive degenerative process that affects joint cartilage and the subchondral bone. The most important symptoms of knee osteoarthritis are pain, stiffness and loss of function leading to psychological and sleeping disorders and a diminished quality of life. (3, 4)

Treatment options can be divided into non-pharmacological, pharmacological, infiltrations and surgical. Non-pharmacological treatments consists of self-management, lifestyle changes, braces, transcutaneous electrical nerve stimulation, acupuncture and physiotherapy. Pharmacological therapy includes oral analgesics like paracetamol and non-steroidal anti-inflammatory drugs (NSAID). Patients that are unresponsive to these analgesics are sometimes prescribed strong opioids, although this should be reserved for exceptional cases due to increasing complications related to (ab)use of opioids. (5) Furthermore minimally invasive measurements such as intra articular injections of steroids or viscosupplementation could also provide short term relief. Unfortunately, conservative treatment is often insufficient or associated with side effects. If this is the case, total knee arthroplasty (TKA) can be performed. (3, 6-9)

TKA is not a guarantee of success given that the incidence of postoperative pain and functional limitation can raise as high as 53%. (10-16) Also, there is a group of patients that is not suitable to undergo surgery due to comorbidities or very young age due to the limited lifetime of the prostheses used. In those groups of patients radiofrequent (RF) treatment of the genicular nerves might be an alternative treatment option.

The sensory innervation of the anterior part of the knee is accomplished by articular branches of the femoral, saphenous, obturator, common peroneal, tibial and sciatic nerve. (17-19) Some of these articular branches are called the genicular nerves. Radiofrequent treatment of the genicular nerves is first described by Choi and colleagues in 2011. (17) They targeted the superomedial, superolateral and inferomedial genicular nerves for a conventional RF treatment because these branches are in close proximity with bony landmarks. This makes them a possible target using fluoroscopy. In this double blind randomised trial 38 elderly patient received a conventional RF treatment of 70°C for 90 seconds. They showed significant improvement in visual analogue score (VAS), Oxford knee score (OKS) and global perceived effect (GPE) at 3 months in comparison with placebo.

Since this first report, multiple publications have investigated the effect of conventional and later also, cooled RF treatment of the genicular nerves. (20-23) The use of cooled radiofrequency treatment was first described for the treatment of low back pain after which it found its introduction in the treatment of chronic knee pain in 2015. (22-26) The use of cooled electrodes increases lesion size by removing heat from adjacent tissue and allowing power delivery to be increased without tissue scarring and high impedance. (24) A prior study showed a higher success percentage and possibly a longer effect with the use of cooled radiofrequency. (23) On the other hand, the use of a cooled radiofrequency is associated with a higher product cost. In current practice, cooled RF is increasingly being used and is slowly replacing conventional RF treatment, despite evidence on its superiority. We however, hypothesize that the cheaper conventional RF treatment is not inferior to cooled RF, and may save substantial costs. A comparison between conventional and cooled radiofrequency has not been performed yet.

This protocol outlines a study using a prospective, multicentre, double blind, randomised controlled non-inferiority pilot design to yield important information for the design of a subsequent RCT to test if conventional RF treatment is not inferior to cooled RF, and also to assess the feasibility of conducting such a large RCT in two countries. In addition, we aim to estimate the initial cost-effectiveness of conventional RF treatment compared to cooled RF treatment. The current study is set up to reflect the proposed study design of the future study as close as possible, but results of this pilot study may lead to future design changes.

2. OBJECTIVES

The primary goal is to yield information to inform the design of, and evaluate the feasibility of, a future large randomised controlled non-inferiority trial to assess whether the effect of conventional RF treatment of the genicular nerves (superomedial, superolateral and inferomedial) of the index knee on knee pain relief is not inferior to the more expensive cooled RF treatment of the genicular nerves. The secondary goal is to estimate the initial cost-effectiveness of conventional RF treatment compared to cooled RF treatment so as to determine the need, focus and scope of an economic evaluation in the definitive RCT.

By first performing a pilot study we want to obtain an estimate of treatment effects and an insight into rates of inclusion. We will also be able to judge whether the international collaboration between a Belgian and 2 Dutch hospitals participating in this trial is feasible, and we'll be able to judge whether there are substantial differences in the populations of patients that both countries draw a sample from that may have an effect on the subsequent trial (e.g., the need for multilevel analysis or the need for stratified analysis).

By analysing treatment effect size we will be able to calculate a more accurate sample size for the future RCT. At the moment it is difficult to predict inclusion rates since the patient group of knee pain due to osteoartrose has variety of treatment options of which the investigated treatment is only one.

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3. STUDY DESIGN

This study is designed as a prospective, multicentre, double blind, randomised controlled non-inferiority pilot trial. The total follow up time is 12 months with follow up assessments at 1, 3, 6 and 12 months post intervention. It is estimated that the total duration of data collection will cover 2 year. Patients will be randomly selected for treatment with conventional RF treatment or cooled RF treatment of the SL, SM and IL genicular nerves. In total, three hospitals participate in this study: Ziekenhuis Oost-Limburg (Belgium), Maastricht UMC+ (Netherlands) and Rijnstate (Netherlands).

An overview of the main procedures that participants undergo is provided in figure 1, Appendix A.

4. STUDY POPULATION

4.1 Population (base)

Adult patients with chronic, moderate to severe anterior knee pain (NRS>4) due to osteoarthritis, radiological diagnosed to be graded 2-4 according to the Kellgren-Lawrence criteria on Rx or MRI or with persistent postoperative pain after TKA. (27,28) In the patients group with persistent pain after a TKA an extensive orthopaedic workout did not reveal any other therapeutic solutions. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of such damage. (29)

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years
- Able to understand the informed consent form and provide written informed consent and able to complete outcome measures.
- Chronic anterior knee pain (> 12 months) with an NRS > 4 on most or all days for the index knee either constantly or with motion.
- Unresponsive to conventional treatments continued during 12 months including physiotherapy, oral analgesics or intra-articular infiltrations.
- Radiologic confirmation of arthritis of OA grade of 2 (mild), 3 (moderate) or 4 (severe) noted within 6 months for the index knee according the Kellgren Lawrence criteria (27) diagnosed by an independent radiologist with experience in musculoskeletal imaging on Rx or MRI (28) or patients with total knee arthroplasty of the index knee with a negative orthopaedic workout.
- Other therapies (including surgical interventions) for pain in the index knee are allowed for the period of the study follow up as long as they are documented. This is necessary to correctly estimate the costs in the cost effectiveness analyses. Allowing patients to receive additional treatments will also improve the protocol compliance.
- Agree to provide informed consent and to comply with the requirements of this protocol for the full duration of the study

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patient refusal to comply to protocol procedures or schedule
- Local or systemic infection (bacteraemia)
- Evidence of inflammatory arthritis or an inflammatory systemic disease responsible for knee pain
- Intra-articular injections (steroids, hyaluronic acid, platelet enriched plasma, …) in the index knee during the 3 months prior to procedure
- Body mass index (BMI) > 40 kg/m^2
- Pregnant, nursing or planning to become pregnant before the treatment. Women of reproductive age will be tested on pregnancy prior to start of the study. Participants who get pregnant after the treatment during the follow up period will not be excluded.
- Chronic widespread pain
- Patients with psychosocial dysfunction will be referred for further psychological follow up prior to possible inclusion
- Allergies to products used during the procedure
- Uncontrolled coagulopathy defined as supratherapeutic dose of anticoagulation medication.
- Uncontrolled immune suppression
- Participating in another clinical trial/investigation within 30 days prior to signing informed consent
- Patient is currently implanted with a defibrillator, neuromodulator or other electrical devices
- Radicular pain in index leg
- Patient received previous conventional or cooled radiofrequency of the index knee

4.4 Sample size calculation

The primary aim of this study is to provide estimates of the effect sizes of the primary and secondary outcome measures, and to estimate the inclusion rate so that we have sufficient input to determine feasibility of a future RCT and to yield input for the sample size calculation. Further design aspects, such as the need for multilevel analysis based on clusters of patients within hospitals will be assessed as well. A rule-of-thumb suggests including 12 patients per group in case of a pilot study, so that preliminary data on effect sizes and feasibility can be obtained. (30) For our study, this means 12 patients in the conventional RF group and 12 in the cooled RF group, but separately for patients with osteoarthritis and for patients with knee pain after total knee arthroplasty. Hence, we will include a total of 48 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Procedure description

According to the recent ASRA and ESA guidelines on peripheral blockade in the anticoagulated patient, management should be based on site compressibility, vascularity, and consequences of bleeding, should it occur. (31) In the genicular radiofrequency treatment performed in this study, we judged this factors to be in favour of not stopping anticoagulation.

During the procedure the patient is monitored using pulse oximetry. No sedation is administered so the patient is able to communicate and report the stimulation adequate. The patient is placed in a supine position on a fluoroscopy table with the index knee flexed 10-15° by placing a cushion in the popliteal fossa. The procedure is performed under sterile conditions. The procedure is performed with a 100 mm long, 18 G straight RF cannula/introducer (Halyard) with a probe/electrode with a 10 mm active tip or with a 100 mm long, 17 G RF cannula/introducer with an 18 G cooled probe/electrode with a 4 mm active tip (Halyard/Coolief). No diagnostic block is performed since a recent study showed no prognostic value. (32) No corticosteroids are injected to decrease the risk of complications such as systemic effects and infection. (33) Using a high frequency linear ultrasound the superomedial, the superolateral and the inferomedial genicular nerve are targeted described as below. The inferolateral genicular nerve is not targeted because of its proximity to the common peroneal nerve with its motor branches.

<u>Superomedial genicular nerve</u>

The transducer is placed in a coronal orientation on the medial side of the proximal knee. After identifying the femoral medial epicondyle, the transducer is displaced proximally and centered to the junction between the epiphysis and diaphysis of the femur and the vastus medialis superficial to it, just anterior to the adductor tubercle. The superomedial genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superomedial genicular artery is visualised just above the bony cortex, the target point is next to this artery. If the artery is not visualised, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer was turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 ml lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior ‘in plane’ approach in the transverse plane until contact is made with the bony

cortex at the center of the femur. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is repositioned until sensory threshold is reached.

Inferomedial genicular nerve

The transducer is placed in a coronal orientation on the medial side of the distal knee to visualize the junction of the tibial medial epiphysis and diaphysis, the inferomedial genicular artery and the medial collateral ligament. If the inferomedial genicular artery is visualised just above the bony cortex beneath the medial collateral ligament at the midpoint between the tibial medial epicondyle and the tibial insertion of the medial collateral ligament, the target point is next to this artery. If the artery is not visualised, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer was turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 ml lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior ‘in plane’ approach in the transverse plane until contact is made with the bony cortex at the center of the tibia. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is repositioned until sensory threshold is reached.

Superolateral genicular nerve

The transducer is placed in a coronal orientation on the lateral side of the proximal knee. After identifying the femoral lateral epicondyle, the transducer is displaced proximally to image the junction between the epiphysis and diaphysis of the femur and the vastus lateralis superficial to it. The superolateral genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superolateral genicular artery is visualised just above the bony cortex, the target point is next to this artery. If the artery is not visualised, the junction between the epiphysis and diaphysis is the target point. The probe-to-target point distance is assessed with ultrasound. An out-of-plane entry point is marked perpendicular to the center of the probe at the assessed probe-to-target point distance. Consecutively, the transducer was turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetized with 1 ml lidocaine 2% at the estimated entry point. The

cannula is advanced using an anterior to posterior 'in plane' approach in the transverse plane until contact is made with the bony cortex at the center of the femur. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and produced paresthesia at a threshold of less than 0,5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, If no sensory stimulation threshold is obtained at this position, the transducer is repositioned until sensory threshold is reached.

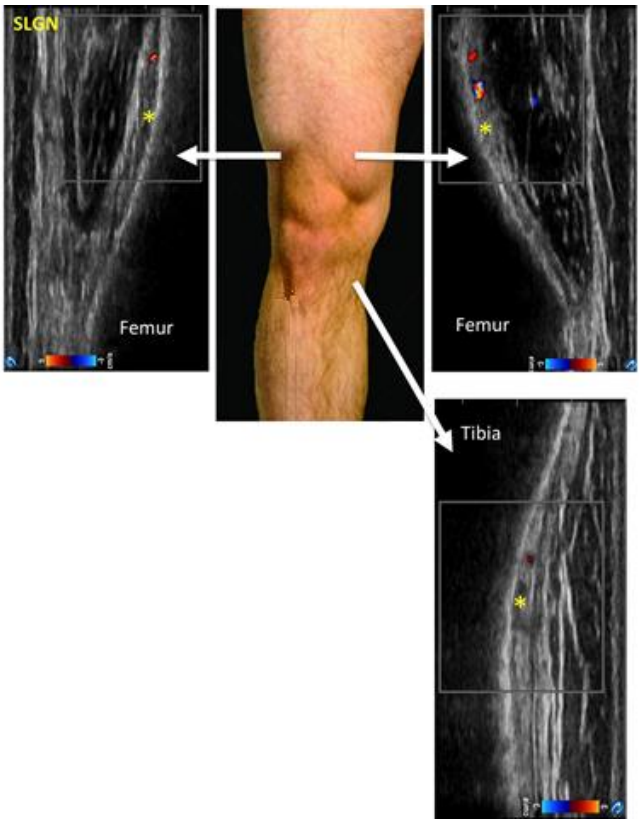

Fig. Ultrasound probe position and corresponding images for genicular radiofrequency treatment. Color Doppler shows the corresponding genicular arteries. Treatment sites are marked with yellow asterisks.

If all three target nerves were identified, a control fluoroscopy image is made to confirm the needle tip position. First, an AP view is made and the needle tip should be at the junction between the diaphysis and the epiphysis touching the bony cortex. Second, a lateral view is made where the needle tip should be within the 2 middle quarters of the femur width.

If the needle tip is confirmed to be in the correct position 1 ml of lidocaine 2% is injected before the start of a RF treatment. In the conventional radiofrequency group a treatment of 80°C at the tip is applied during 90 seconds at each nerve. In the cooled radiofrequency

group a treatment of 60°C measured at the tip and on average 80°C in the targeted tissue is applied during 150 seconds using the Coolief system.

After the procedure, the patient is transferred to the recovery. After 30 minutes without any events, the patient is discharged at home. Home medication is continued postoperative. Patient is informed about potential transient increase in pain due to neuritis and alarm symptoms (fever, swelling, bleeding and motor weakness).

5.2 Use of co-intervention

It is allowed to use other medication or undergo an intervention as long as documented to be able to adequate estimate costs.

5.3 Escape medication

The use of all medication is allowed as long as documented. This enables the researchers to adequate estimate costs.

6. NON-INVESTIGATIONAL PRODUCT

The medical products used in this study are used as in usual clinical practice. The 'CE certificates' and 'instructions for use' of each medical product are to be found in Appendix B and C.

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

The following is a summary description of the used study device. For additional information, please refer to the COOLIEF "Instructions for Use" (Appendix B). The COOLIEF™ system is composed of three primary components (collectively known as 'disposables') and is used in conjunction with the pain management generator, pump unit, connector cables (collectively known as 'Hardware') and dispersive electrodes (also known as 'grounding pads'):

- Cooled radiofrequency sterile tube kit (sterile, single use, non-body contact): it is used for closed-loop circulation of sterile water through a Halyard cooled radiofrequency probe. It includes a burette and tubing.
- Cooled radiofrequency introducer (sterile, single use, 100 mm, 17 gauge, straight): it is to be used with the probes only. The cooled radiofrequency introducer provides a path for the probe to the targeted nervous tissue.
- Cooled radiofrequency probe (sterile, single use, 18 gauge): it is inserted through an introducer into or near nervous tissue. The active tip extends 4 mm from the introducer and delivers energy. Sterile water circulates internally to cool the probe while it delivers radiofrequency energy. A thermocouple in the probe measures the cooled electrode temperature throughout the procedure.

The product is comprised of an electrically insulated shaft with an active tip that functions as an electrode for RF energy delivery, a handle, tubes with luer locks and a cable with a 7-pin connector. The introducer includes an insulated stainless steel cannula and a stylet. The tube kit is comprised of a burette and flexible tubing fitted with luer locks for connection to the probe.

The following is a summary description of the used control device. For additional information, please refer to the "Instructions for Use" (Appendix C). The control device to produce a conventional radiofrequency lesion is composed of two primary components and is used in conjunction with the same pain management generator, connector cables and dispersive electrodes (also known as grounding pads) (Halyard) as in the study group.

- Radiofrequency introducer (sterile, single use, 100 mm, 18 gauge, straight): it is to be used with the probes only. The radiofrequency introducer provides a path for the probe to the targeted nervous tissue.
- Radiofrequency probe (sterile, single use): it is inserted through an introducer into or near nervous tissue. The active tip extends 10 mm from the introducer and delivers energy. A thermocouple in the probe measures the electrode temperature throughout the procedure.

6.2 Summary of findings from clinical studies

The treatment performed with the COOLIEF™ system is a well-established method for delivering lesions into nervous tissue to accomplish neurotomy procedures to deactivate nerves that are responsible for transmitting pain signals. (24). The system uses water-cooled technology to deactivate pain transmission. (24)

6.3 Preparation and labelling of Non Investigational Medicinal Product

The probe, introducer, and tube kit are ethylene oxide sterilized and supplied sterile. These components can be packaged together in a kit or as separate components. The devices should be stored in a cool, dry environment. The 'Instructions For Use' (IFU) documents (Appendix B and C) are included in each kit.

7. METHODS

7.1 Study parameters/endpoints

Endpoints are chosen following the IMMPACT guidelines which recommend 6 core outcome domains in chronic pain research. (34) These domains are:

1. Pain
2. Physical functioning
3. Emotional functioning
4. Participant ratings of improvement and satisfaction with treatment
5. Symptoms and adverse events
6. Participant disposition

Furthermore, inclusion rate will also be monitored.

7.1.1 Main study parameter/endpoint

The primary study parameter is the proportion of patients with a pain reduction of at least 50% at three months post intervention. Pain intensity is expressed as a number from the numerical rating scale. Absolute NRS scores are also collected at each visit. A pain dairy of multiple NRS during 4 days will be collected to achieve a more complete and trustworthy idea of pain.

In this study we will use a threshold of 50% although IMMPACT guidelines only recommend a threshold of 30% because in the clinical setting the 50% threshold is most often used, as well in previous studies. This makes comparison within the literature easier.

NRS is a unidimensional, subjective measurement of pain intensity, expressed by the patient as a number between 0 and 10. It is a 11 point scale in which 0 equals no pain and 10 maximal pain. (35)

Furthermore, at one, three, six and twelve months post intervention the patients are also asked whether the pain is acceptable.

A month is defined as 30 days with 4 days before or after this timepoint.

At 12 months a time window of 2 weeks before and there the timepoint is accepted.

7.1.2 Secondary study parameters/endpoints

The secondary parameters are:

- Patient self-reported impression of change, measured by the Patient's Global Impression of Change (PGIC) at 1, 3, 6 and 12 months. The impression of change is measured using a 7 point likert scale. (36)

- The change in medication use, measured by the change in Medication Quantification Scale III (MQS III). The MQS is designed as a methodology of quantifying different drug regimens in 1992 and updated in 1998 (MQS II) and 2003 (MQS III) using detriment weights determined by surveying physician members of the American Pain Society. (37) This will be recorded at baseline, 1, 3, 6 and 12 months post intervention.
- The duration of pain relief. This is defined as the time interval in which a NRS reduction of more than 50% is obtained or in which the pain is still acceptable without the usage of other additional therapies (increase in MQS 3 score of more than 50%, intra-articular infiltration, operation)
- The change in physical function from baseline to 3, 6 and 12 months post intervention. This will be measured by the change in the Oxford Knee Score (OKS). (38) The OKS is a patient-reported measure assessing pain intensity and physical function. The list consists of 12 items scored from 1 to 5, with 0 representing normal function/ least symptoms. Objectively, knee function will be measured through goniometry by using the CJOrtho app and by 'timed up and go' test. (39, 40) The measurement of maximal knee flexion and extension is performed in a standardised manner and photos of each position will be kept for review. The 'Timed Up and Go' test assesses patients' functional mobility of the lower extremities. Participants are timed with a stopwatch while standing up from a chair, walking 3 meters (in a comfortable and safe way), come back and sit back in the chair.
  The objective parameters of physical function will not be obtained at 12 months.
- The change in health-related quality of life, measured by the change in EQ-5D-5L, between baseline and 6 and 12 months post intervention. (41) The EQ-5D-5L is a patient-reported generic measure of HRQoL comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses to the 5 items (one for each dimension) result in a patient's health state that can be transformed into a utility score ranging between 0 (death) and 1 (full health), representing the quality of life of the health state. (41). The EQ-5D-5L is assessed at baseline and at 1, 3, 6 and 12 months post intervention.
- Change in characteristic attitudes and symptoms of depression from baseline to 3, 6 and 12 months post intervention. This will be measured by the change in Hospital Anxiety and Depression Scale (HADS) and in Pain Catastrophizing Scale (PCS) from baseline to 6 and 12 months. (42, 43) HADS is developed to detect anxiety and depression in patients with physical health problems. The questionnaire consists of 14 items: 7 items to measure anxiety and 7 items to measure depression. The PCS is often used in clinical settings to measure catastrophic thinking related to pain. The 13 item questionnaire consists of 3 subscales (magnification, rumination and helplessness) and asks patients to

reflect on past painful experiences and to indicate the degree on which they experiences each of 13 thoughts of feelings on a 5- point scale (0 not at all and 4 all the time).

- Amount of Adverse Events and/or Serious Adverse Events. Active capture during each site visit to assess specific symptoms and adverse events that are relevant to chronic knee pain or RF treatment.
- Costs in both intervention groups. Costs include health care related costs (e.g. intervention cost, medication), costs to patients and family (e.g. travel costs, out-of-pocket payments), and costs due to lost productivity. Complete individual level hospital resource use data (e.g. surgical intervention, diagnostic procedures, hospital admissions, outpatient clinic visits) will be measured using medical records and by means of a self-developed questionnaire to be completed by patients, based on the iMTA Medical Consumption Questionnaire as recommended in the Dutch guideline for economic evaluation. (44) The questionnaire will have a recall period of 3 months and will be administered repeatedly at baseline, 3, 6 and 12 months post intervention. The Dutch manual for costing research will be used to determine prices for each volume of resource use. (45)
- Cost-effectiveness will be expressed using incremental cost-effectiveness ratios (e.g. incremental cost per QALY, incremental cost per reduced point on the pain score, and incremental costs per additional treatment success). QALYs (Quality Adjusted Life Years) will be calculated by multiplying life years with the health-related quality of life during these life years as measured by the EQ-5D-5L.
- At 12 months in the osteoarthritis group, we ask if a total knee arthroplasty is performed and if so at which timepoint.
- All used questionnaires to retrieve the above mentioned outcome parameters can be found in Appendix D.

7.1.3 Other study parameters

Inclusion rates will also be monitored.

7.2 Randomisation, blinding and treatment allocation

Final inclusion of a patient follows after written informed consent. Included patients will be subscribed by the central trial coordinator and the data management centre. The data management centre is responsible for the randomisation procedure, which will be performed with the software program CASTOR. Randomisation is justified because both treatments are similar with similar risks since the cooled radiofrequency is a modification of the conventional technique. The cooled radiofrequency however has the potential benefit of higher chance of therapy success (pain reduction) and longer duration of therapy success. Every patient from

or the total knee arthroplasty group, or the osteoarthritis group, will be divided into one of the treatment groups at random so that half of every patient population (TKA and OA) received cooled and half conventional radiofrequency treatment. The randomisation ratio is 1:1. Patients in group 1 will receive conventional RF treatment, and patients in group 2 are being treated with cooled RF treatment.

The patients are treated by a pain physician who is not involved in the follow- up treatment. The blinding of each patient enrolled in this study is tested approximately 30 minutes after the treatment by asking the patient what they think they have received. At the 6 months follow- up, the patient is deblinded.

7.3 Study procedures

Patients will be in follow up for 6 months. There are 4 site visits. T0 to collect baseline parameters after which the intervention is performed. T1 at one month post intervention. T2 at 3 months post intervention at which the primary endpoint is collected. T3 at 6 months post intervention.

Table 1 (Appendix E) provides an overview of all study procedures per follow up moment. There is a distinction between study procedures at site and study procedures at home.

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.

7.5 Premature termination of the study

Premature termination is only possible:

- if the judgement of the competent medical research ethics committee that has assessed the study is irrevocably revoked;
- if a reasonable case can be made for terminating the study in the interests of the health of the research subjects;
- if it transpires that continuation of the study cannot serve any scientific purpose, and this is confirmed by the medical research ethics committee that has issued a positive decision on the study;
- if one of the parties or the funder has been declared insolvent or a bankruptcy/winding-up petition has been filed in respect of one of the parties or the financier, or one of the parties or the financier is dissolved as a legal entity;

- if the principal investigator is no longer capable of performing the tasks of the principal investigator, and no replacement agreeable to both parties can be found;
- if one of the two parties fails to comply with the obligations arising from the agreement and, provided compliance is not permanently impossible, this compliance has not taken place within thirty days of the defaulting party receiving a written request to comply, unless failure to comply is not in reasonable proportion to the premature termination of the study;
- if circumstances beyond the control of the sponsor, investigator or funder make it unreasonable to require the study's continuation.

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 investigational intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The potential risks to subjects in which a radiofrequency neurotomy procedure is performed, regardless of the treatment modality, may include the following, all of which are anticipated adverse events that have been identified as possible complications of procedures involving lesioning of nervous tissue:

- Infection,
- Damage to collateral nervous tissue,
- Increased pain,
- Failure of technique,
- Superficial burns,
- Damage to collateral tissue (i.e., bruising or hematoma),
- Deafferentation dysesthesia
- Paralysis
- Allergy

Subjects should be instructed to contact the investigator immediately if an AE occurs. At each visit, the investigator should further query the subject to determine if any new adverse events have occurred. Adverse events will be assessed and reported from the time the subject signs consent until study exit according to the following procedure.

The investigator will assess the severity of each AE based on the following definitions:

Severity	Definition
Mild	An AE in which the subject is aware of signs or symptoms, but which does not interfere with the subject's usual activities of daily living, or is transient and resolves without treatment or sequelae.
Moderate	A sign or symptom which interferes with the subject's usual activities of daily living or requires treatment.
Severe	Any event listed as serious adverse event.

For each AE, the investigator will assess the causality/relationship to the received treatment according to the following criteria:

Relatedness	Definition
Possible	The association of the AE with the test article is unknown; other etiologies are also possible.
Probable	A reasonable temporal sequence of the AE with test article administration exists and based upon the medical professional's clinical experience, the association of the AE with the test article seems likely.
Definite	A causal relationship exists between the received treatment and the AE, and other conditions (e.g., concomitant illness, progression or expression of the disease state, reaction to concomitant medications) do not appear to explain the AE.

All AEs must be recorded in the subject's medical record and the appropriate eCRF. The description of the AE will identify the date of onset, date of remission, severity, causal relationship to the study treatment, action taken along with the results of any diagnostic procedures or laboratory tests, all treatments that were required and the outcome of the AE.

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;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

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

Sites will be instructed to follow their normal routine processes for adverse event reporting. However, serious adverse events will be specifically monitored for. The sponsor will report the possible, probable or definite related SAEs through the web portal 'ToetsingOnline' to the accredited METC that approved the protocol, within 7 days of first knowledge for SAE's 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. All reported SAE's will be mentioned to the accredited METC that approved the protocol in a yearly summary.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

These will be dealt with as any serious adverse reaction as described as above.

8.3 Annual safety report

N.A.

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 and Safety monitoring board

Given the nature of this study a Data and Safety Monitoring Board (DSMB) is not required based on the FDA guidance document, "Establishment and Operation of Clinical Trial Data Monitoring Committees" and EMA guideline "Guideline on data monitoring commitees". Monitoring of the data is requested and would be performed by a clinical research monitor (CTCM).

9. STATISTICAL ANALYSIS

Patient baseline characteristics will be described for both knee pain groups separately, and stratified by treatment allocation using mean and standard deviation or median and interquartile range for continuous variables, and count and percentage for categorical variables. Incomplete patients records will be imputed using multiple imputation to allow analysis on all randomised subjects.

All outcome measures will be computed on the intention to treat sample.

9.1 Primary study parameter(s)

The primary outcome, the proportion of patients reporting treatment success at 3 months after treatment, will be described per group as count with percentage and 95% confidence interval. In addition, we will report the mean change from baseline on the NRS, including standard deviation and 95% confidence interval. Furthermore, we will compute the difference in proportion of success between groups and the difference in mean change from baseline between groups, both with 95% confidence interval. The lower bound of the 95% confidence interval of the difference will be compared to the non-inferiority limit. However, the latter part will be used only for exploratory purposes, due to the nature of the study design (i.e. pilot study).

9.2 Secondary study parameter(s)

All hypothesis testing will be explorative in nature, and thus secondary to describing the outcome measures. The confidence interval of the difference between groups will be used to test non-inferiority of conventional RF compared to cooled RF. In case the point estimate of the difference in proportion of treatment effect between groups will be below the non-inferiority limit, this will be suggestive of non-inferiority. In that case, we will use the results of this study to calculate the necessary sample size for a future randomized controlled non-inferiority trial.

Other secondary study parameters (MQS III, PGIC, duration of pain relief, OKS, the Timed Up and Go test, goniometry, HADS, PCS, EQ-5D-5L, performance of a TKA and the amount of Adverse Events and/or Serious Adverse Events) will be reported as mean or percentage difference including 95% confidence interval. Hypothesis testing will be performed using the independent t-test for continuous variables, and Fisher's Exact test for categorical variables. This will only be regarded as explorative in nature.

COST EFFECTIVENESS ANALYSIS (CEA)

Economic evaluation comparing conventional to cooled RF treatment will be performed with a time horizon of 6 months. Cost-effectiveness will be assessed by evaluating the incremental cost-effectiveness ratios using several perspectives: societal cost per QALY (based on EQ-5D-5L), healthcare cost per reduced point on the pain score, and healthcare costs per additional treatment success. Standard bootstrap and sensitivity analysis will be performed to address uncertainty surrounding the findings.

9.3 Other study parameters

Descriptive statistics will be used to report inclusion rates in function of feasibility of a future RCT.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 8, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Potential eligible patients for this study are informed about the study by their pain physicians. If the patient shows interest in potential participation, the pain physician provides the patient with the patient information letter and asks permission for a researcher to contact the patient. During this conversation the researcher provides additional information and answers any questions the patient may have. The researcher asks the patient consent to contact the patient minimal 7 days later to ask whether the patient has any questions/ concerns and if the patient has made a decision whether or not to participate in the study. The patient can contact the researcher on his own discretion after the informative conversation if he decides to participate. If the patient decides to participate in the study, the patient is scheduled for treatment. Prior to the treatment both patient and researcher sign the informed consent document followed by baseline measurement.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable. Minors or incapacitated adults are excluded in this study.

10.4 Benefits and risks assessment, group relatedness

Patients in both treatment groups have the opportunity to benefit from positive treatment effects (pain relief, functional improvement, improved quality of life). The additional risks associated with either treatment options can be expected to be very low. Potential side effects of the treatment are haematoma, infection, temporary increase of pain, hypesthesia, paresthesia and neuralgia or paralysis, superficial burns, damage to collateral nervous tissue of soft tissue, failure of technique and allergy. (17, 23, 41)

Since the prevalence of osteoarthritis is rising, the burden of this disease and the risks and cost associated with total knee replacement are also rising. (46)(47) Therefore, there is a need for minimal invasive technique to treat osteoarthritis. In the recent literature there are different reports, primarily in the USA, about the effectiveness of cooled radiofrequency. In Europe there is at the moment no indication for this treatment due to the lack of reimbursement. Therefore there is a need for a randomised control trial with a head to head

comparison to evaluate if the newer modification of a radiofrequency treatment is as effective and also cost effective in comparison with the conventional radiofrequency treatment in Belgium and The Netherlands. This study has a scientific merit with minimal risk for the participants.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. So the sponsor has an insurance at each site which is in accordance with the legal requirements in the Netherlands (Article 7 WMO) and in Belgium (Article 29, Law 7 may 2004). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

(Proefpersonenverzekering, verzekeringsverklaring Model 1).

(Sponsor liability insurance MUMC+, CNA Insurance); Rijnstate, Medirisk)

10.6 Incentives

The study participants will not receive financial compensation for their study participation. Parking costs will be reimbursed with a maximum of 12,5 euro per visit. There will be no difference in costs in comparison with regular care due to participation in this study since both treatment groups are standard of care.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All data collected during this study will be handled confidentially. The data of each study participant will be coded (001, 002, 003 etc, 001M for MUMC+, 001R for Rijnstate, 001Z for ZOL). by use of a study number to secure data security and the privacy of study participants according to the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. A subject identification code list is safeguarded by the principal investigators. The principal investigator, monitors and researchers have access to the source data. The data will be kept for 20 years after completion of the study by the data management centre.

Data obtained from this study can be used in the future larger study on the treatment of chronic knee pain and only coded data of participants who gave informed consent will be used. This data, obtained from the current study, will be stored and can be used in other research about the treatment of chronic knee pain. Informed consent to use this data will be obtained.

11.2 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.

11.3 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.

11.4 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 8 weeks. The end of the study is defined as the last patients 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 and the competent authority 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 and the Competent Authority.

11.5 Public disclosure and publication policy

All study results will be published without restrictions. This means that patients grant the sponsor the right to publish the study results, based on their participation in the study. All members of the study groups agree that all study results will be published. No veto right exists. Both negative and positive results will be published. Before publication, all authors will have the opportunity to give comments on the manuscript. Data will be published as soon as possible after finishing data analysis.

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13. APPENDIX.

Appendix A

Participant flow diagram

Appendix B

'Instruction for use' of Coolief radiofrequency (Halyard)
'CE' of Coolief radiofrequency (Halyard)

Appendix C

'Instruction for use' of conventional radiofrequency (Halyard)
'CE' of conventional radiofrequency (Halyard)
'Instruction for use' of generator (Halyard)
'CE' of generator (Halyard)

Appendix D

Numerical rating scale
Pain and medication Dairy
PGIC
MQS III
Medication list
OKS
Goniometry
Timed up and go test
EQ-5D-5L
HADS
PCS
Cost diary

Appendix E

Table 1: Overview study procedures per site visit

Site visit	Study procedures at site	Study procedures at home
T0: baseline	- MQS III - Goniometry - Timed up and go test	- NRS - Is pain acceptable? - Medication list - OKS - EQ-5D-5L - HADS - PCS - Cost diary
T1: 1 months post intervention	- Adverse Events - MQS III	- NRS - Is pain acceptable? - PGIC - Medication list - EQ5-5D-5L - Cost diary
T2: 3 months post intervention	- Adverse Events - MQS III - Goniometry - Timed up and go test	- NRS - Is pain acceptable? - PGIC - Medication list - OKS - EQ-5D-5L - Cost diary - HADS - PCS
T3: 6 months post intervention	- Adverse Events - MQS III - Goniometry - Timed up and go test	- NRS - Is pain acceptable? - PGIC - Medication list - Cost diary - OKS - EQ-5D-5L - HADS - PCS
T4: 12 months	/	- NRS

post intervention		- Is pain acceptable? - PGIC - Medication list - Cost diary - OKS - EQ-5D-5L - HADS - PCS - Adverse Events - Performance of TKA?