Cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain: 12-month and cost-effectiveness results from the multicenter COCOGEN trial

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ABSTRACT

Background Radiofrequency (RF) treatment of the genicular nerves reduces chronic knee pain in patients with osteoarthritis (OA) or persistent postsurgical pain (PPSP) after total knee arthroplasty (TKA). The objective of this study is to compare long-term outcomes of cooled and conventional RF and perform an economic evaluation.

Methods The COCOGEN trial is a double-blinded, non-inferiority, pilot, randomized controlled trial that compared the effects up to 12 months of cooled and conventional RF in patients with chronic knee pain suffering from OA or PPSP after TKA following a 1:1 randomization rate. Outcomes were knee pain, functionality, quality of life, emotional health, medication use, and adverse events. A trial-based economic evaluation was performed with a 12-month societal perspective. Here, the primary outcome was the incremental costs per quality-adjusted life year (QALY).

Results 41 of the 49 included patients completed the 12-month follow-up. One patient in the PPSP cooled RF group had substantial missing data at 12-month follow-up. The proportion of patients with ≥50% pain reduction at 12 months was 22.2% (4/18) in patients treated with conventional RF versus 22.7% (5/22) in patients treated with cooled RF (p>0.05). There was a statistically significant difference in the mean absolute numerical rating scale at 12 months after cooled RF and conventional RF in patients with PPSP (p=0.02). Differences between other outcomes were not statistically significant. The health economic analysis indicated that cooled RF resulted in lower costs and improved QALYs compared with conventional RF in PPSP but not in OA. There were no serious adverse events.

Conclusions Both RF treatments demonstrated in approximately 22% of patients a ≥50% pain reduction at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective than conventional RF. Additionally, cooled RF has in patients with PPSP, as opposed to OA, greater effectiveness at lower costs compared with conventional RF.

Trial registration number NCT03865849.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conventional and cooled radiofrequency (RF) of the genicular nerves reduce therapy-resistant chronic knee pain in patients with osteoarthritis and persistent postsurgical pain; however, long-term effects of this treatment are unknown. Cooled RF is intrinsically more costly than conventional RF, and it is unknown whether a cooled RF treatment is cost-effective compared with conventional treatment.

WHAT THIS STUDY ADDS

⇒ This pilot randomized controlled trial adds long-term clinical and cost-effectiveness results of a comparison between cooled and conventional RF treatment of the genicular nerves to treat chronic knee pain.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A large, powered randomized controlled trial is necessary to prove statistical significance, identify which patients benefit the most, and address uncertainty induced by the small size of this pilot trial.

INTRODUCTION

Osteoarthritis (OA) of the knee is a degenerative disease of the cartilage and subchondral bone which leads to pain, loss of function, and potentially a lower quality of life and financial burden.[1–4] When conservative therapy fails to treat these symptoms, a total knee arthroplasty (TKA) is the last resort. However, not everyone is a suitable candidate for such a procedure because of comorbidities or young age. Patients with comorbidities have a higher perioperative risk, and postoperative revalidation can be difficult. Young patients have worse outcomes with a higher risk of revision.[5] Furthermore, up to 53% of patients develop persistent postsurgical pain (PPSP) after a TKA, forming a second cause of chronic knee pain.[6 7]

Chronic pain has a high impact on a patient's quality of life and is associated with a high

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socioeconomic cost.[3 4] Recently, radiofrequency (RF) treatment of the genicular nerves emerged as a minimally invasive treatment for chronic knee pain. By blocking nociceptive pain signals from the knee, through applying a RF current in proximity of the genicular nerves, a patient with knee OA or PPSP after TKA can obtain pain relief and improvement of knee function.[8 9] In addition to the conventional RF treatment, newer modality, cooled RF has been developed to create a bigger lesion size aimed to further improve the success rate and prolong the effect.[10] In a previous publication, both after a conventional and cooled RF treatment of the genicular nerves, a reduction of chronic knee pain in patients with OA and PPSP after TKA up to 6 months was described.[11] While this pilot trial was intrinsically underpowered, cooled RF resulted in a non-significant higher probability of pain reduction compared with conventional RF in the whole study population and in both subgroups (OA and PPSP). In the PPSP group, the discrepancy between the treatment success of cooled RF and conventional RF was higher when compared with the OA group. In another recent trial, cooled RF did not result in significantly higher long-term benefits when compared with conventional RF in patients with OA.[12] Other previous trials also indicate that RF of the genicular nerves leads to improved quality of life in patients with knee OA.[13–15] Whether cooled RF treatment is cost-effective compared with conventional RF in patients with therapy-resistant OA or PPSP is yet unknown.

In this manuscript, we present the 12-month clinical effectiveness results and the cost-effectiveness analysis of cooled versus conventional RF in therapy-resistant chronic knee pain due to OA and PPSP. The analysis is part of the COCOGEN pilot randomized controlled trial, of which the 6-month effectiveness results are published in a separate paper.[11] We hypothesized that at 12 months in both patient groups (OA and PPSP), knee pain after conventional RF treatment is not inferior to cooled RF and that cooled RF is cost-effective compared with conventional RF.

METHODS
Trial design
The COCOGEN trial was a randomized controlled, non-inferiority, pilot trial conducted in three participating centers (Hospital Oost-Limburg, Belgium; Maastricht UMC+, The Netherlands; and Rijnstate, The Netherlands) (online supplemental file 2). Patients were followed up to 12 months after treatment. Ethical approval was granted from the ethical committees of Hospital Oost-Limburg (19/0038U) and Maastricht UMC+ (NL69877.068.19/METC 19–031). The study was registered at ClinicalTrials.gov on 7 March 2019 (NCT03865849). Patients were enrolled between 10 February 2020 and 28 April 2021.

Participants, randomization, and blinding
Adult patients suffering from long-term (>12 months) chronic anterior knee pain due to OA and PPSP after TKA that were unresponsive to conventional treatments (physiotherapy, analgesics, or intra-articular infiltrations) were included in the trial (online supplemental file S1). After stratification per etiology of pain (OA and PPSP), participants were randomized into two treatment groups, the conventional and cooled RF groups, with an allocation ratio of 1:1 and variable block size of 2 or 4 in the online Castor electronic data capture application. In this double-blinded trial, both the patient and the outcome assessor were unaware of the patient's treatment allocation up to 6 months. After a systematic unblinding at 6 months, patients were followed up until 12 months after treatment. Patients were encouraged to continue other conservative care throughout the trial.

Intervention
Participants received RF treatment of the superomedial, superolateral, and inferomedial genicular nerves using a Halyard/Coolief RF generator.[16] No prognostic block prior to the treatment was used. Patients were not sedated, hemodynamically monitored, and positioned in a supine position on a fluoroscopy table with the index knee flexed 10–15°. The RF needle placement was guided by ultrasound, and the final position was controlled using fluoroscopy. The target point was the mentioned genicular nerves at the junction of the shaft and condyle of the femur and tibia. The subcutaneous tissue was anesthetized with 1 mL lidocaine 2% at each entry point before the introduction of the RF needle. After obtaining a sensory threshold (50 Hz) of ≤0.5 V and an absent response to motor stimulation (2 Hz) of 1.0 V, 1 mL of lidocaine 2% was injected at each genicular nerve. Each of the three nerves was treated with conventional RF using a 100 mm, 18-gage, straight RF introducer and one 10 mm active tip RF probe set at a temperature of 80°C for 90 s or with cooled RF using a 100 mm long, 17-gage, straight RF introducer and one 4 mm active tip, 18-gage cooled RF probe generating a temperature of 60°C at the tip of the probe for 150 s.

Study endpoints and data collection
Participants were assessed at baseline, 1, 3, 6, and 12 months after the procedure. Data were collected from the medical patient record, questionnaires, and functionality tests in an online patient case report form in the Castor data management tool.

The primary endpoint of the COCOGEN trial was the proportion of patients with ≥50% pain reduction at 3 months. We previously reported that 4 of 23 patients treated with conventional RF (17%) versus 8 of 24 with cooled RF (33%) (p=0.21) reached the primary endpoint at 3 months.[11]

The clinical outcomes at 12-month follow-up were the following: numerical rating scale (NRS), Oxford knee score (OKS), patient's self-reported impression of change measured by the Patient's Global Impression of Change (PGIC), health-related quality of life (HRQoL) expressed in Euroqol 5-dimension 3-level (EQ-5D-3L) questionnaire, mental health measured by the Hospital Anxiety and Depression Scale (HADS) and by the Pain Catastrophizing Scale (PCS), medication use assessed by the Medication Quantification Scale III (MQS III), and adverse events and incidence of a TKA.[17–23] The NRS score at each timepoint was the mean score of the previous 4 days except for the 12-month follow-up. At 12 months, patients were asked to report the NRS in rest and during movement. We reported the mean of these two.

Statistical methods
As COCOGEN is a pilot RCT, the rule of thumb of Julious was used to include 12 patients per treatment group amounting to a total of 48 patients.[24] The rule of thumb ensures enough participants to estimate treatment effects and measures of variance but may not ensure sufficiently high power for null-hypothesis testing. The effectiveness outcomes were analyzed following the per-protocol principle as this is more conservative for testing non-inferiority hypothesis. To test for non-inferiority, the mean NRS difference between groups, including 95% CI, was calculated at 12 months. The lower bound of the 95% CI of the difference was compared with the non-inferiority limit of 0.75 NRS points.[25 26] The analysis of the outcomes was
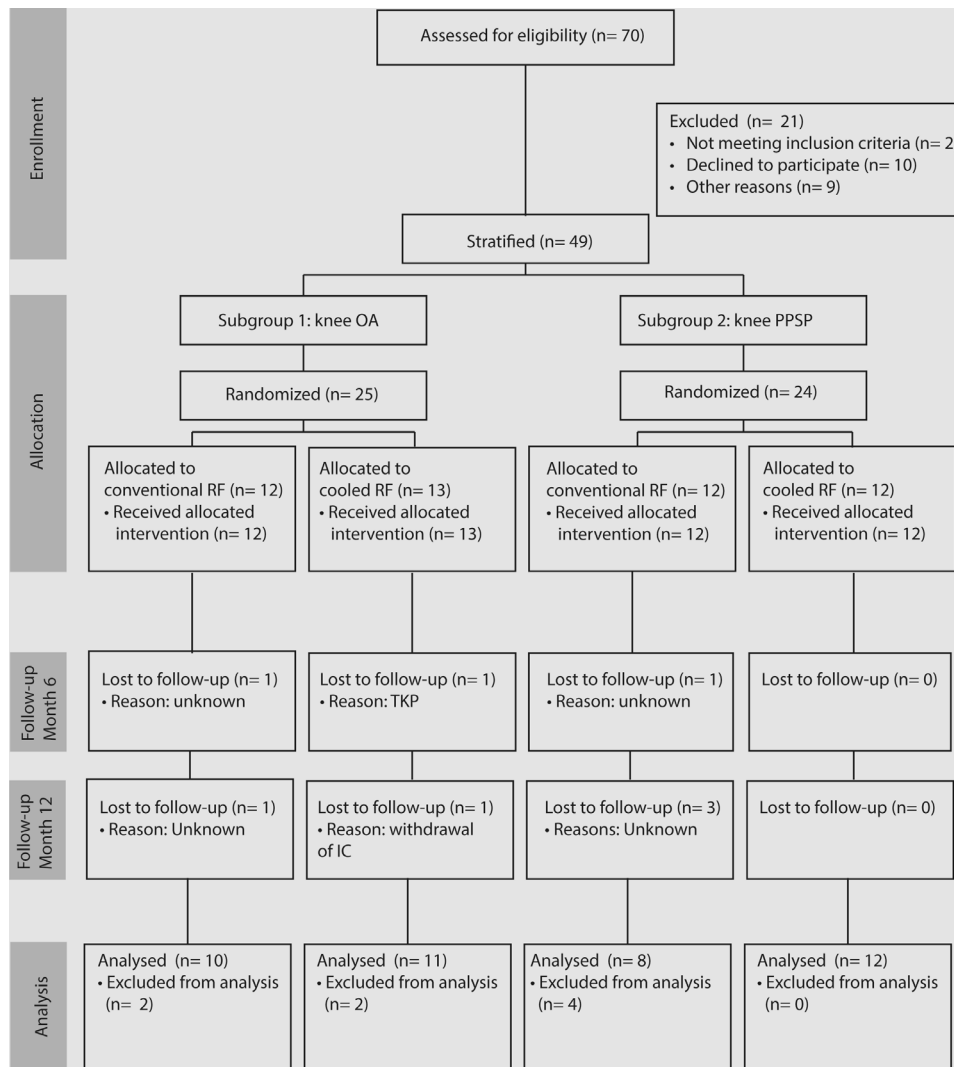
Figure 1 The Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months. IC, informed consent; OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; TKP, total knee prothesis.

exploratory due to the pilot nature of the trial. The proportion of patients achieving treatment success was calculated as percentage. The difference between groups was computed, including 95% CI, and Pearson's χ^2 test was used for the comparison between the treatment groups. We reported the secondary study parameters as mean or percentage of difference including 95% CI. The mean NRS at 12 months was calculated as the average score of the reported NRS during rest and during movement.

The economic evaluation

The economic evaluation was designed and analyzed to conform with the Dutch guidelines for health economic evaluation (HEE).[27] A cost-effectiveness analysis was performed for patients with OA and PPSP separately. The base case analysis was performed from a societal perspective and a time horizon of 12 months.

Health outcomes

The quality-adjusted life year (QALY) was chosen as the measure of the benefit of the cooled and conventional RF intervention. The QALY is the preferred health outcome in economic evaluations and is a combined measure of HRQoL and survival.[28] HRQoL was measured by the EQ-5D-3L.[29] The EQ-5D-3L is a patient-reported generic measure of HRQoL comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels reflecting the severity of the impact of the patient experiences. The patient's responses were converted to utility scores using the Dutch social tariff.[30] Subsequently, QALYs were calculated using the area under the curve of the time in which a certain health state was multiplied by the utility score of this health state. The EQ-5D was completed electronically at 1, 3, 6, and 12 months after treatment.

Resource use and costs

Resource use was classified into four main categories: RF intervention costs, healthcare resource use, costs to patient and family, and productivity costs. The cost of the RF interventions was calculated as the sum of the cost of a day hospitalization, the costs of the used material, and the cost of the medical personnel. Healthcare resource utilization included healthcare-related visits (eg, general practitioner, physiotherapist, and dietician), visits to other allied professionals (eg, social worker), use of home care (home nursing care and family care), inpatient hospitalizations, and emergency department visits. Patient and family costs included out-of-pocket expenses made by the patient (eg, for
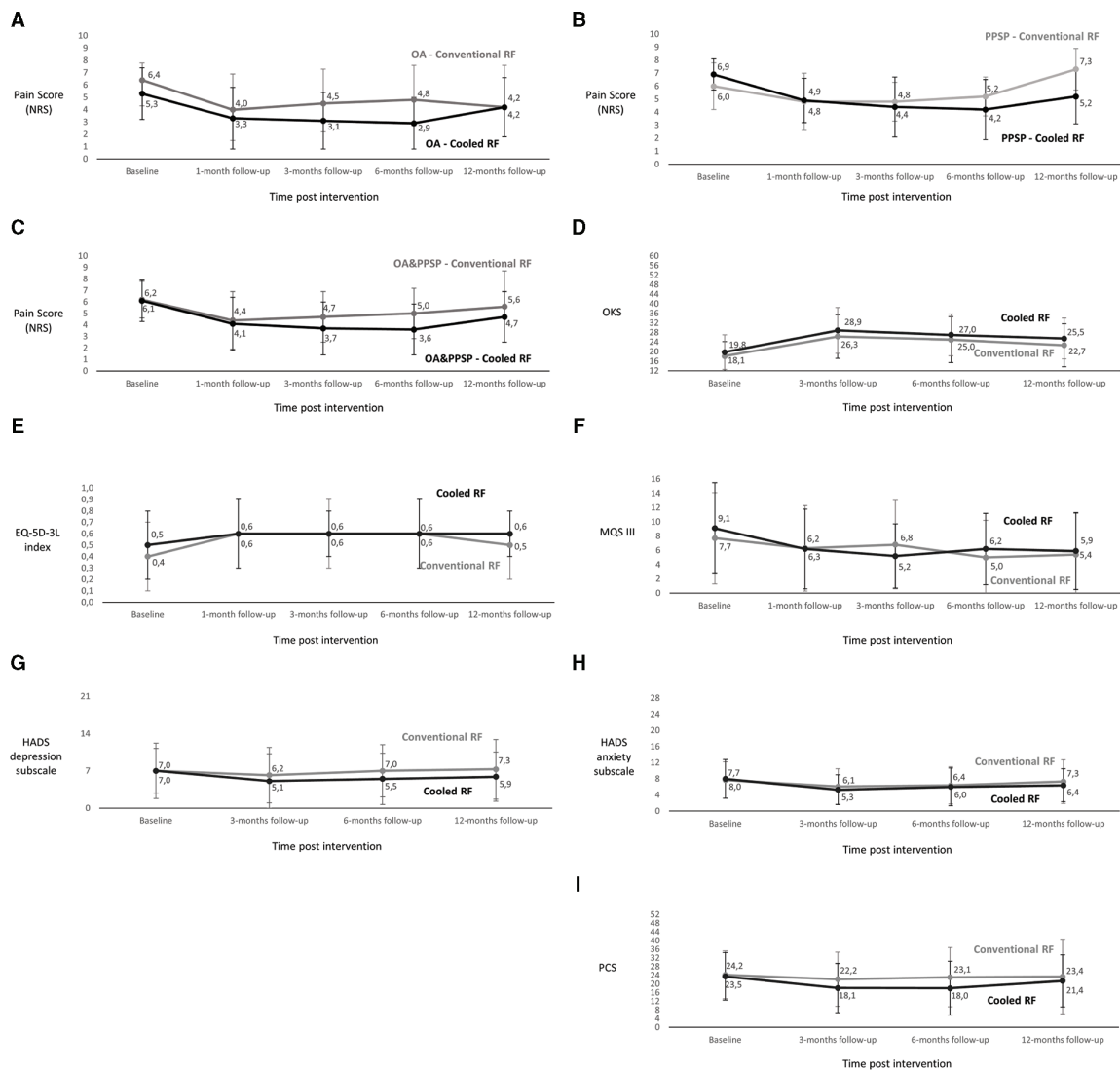
Figure 2 Evolution of the clinical outcomes during the 12-month follow-up of the COCOGEN trial. Vertical lines represent the standard deviation. NRS, numerical rating scale; RF, radiofrequency; OA, osteoarthritis; PPSP, persistent postsurgical pain; OKS, Oxford knee score; EQ-5D-3L, EuroQol 5-dimension 3-level; MQS III, Medication Quantification Scale III; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.

medication and braces) and informal care costs. Costs due to lost productivity included costs due to short-term and long-term absences from paid and unpaid work.

Data on other healthcare utilization, patient and family costs, and costs due to loss of productivity were collected electronically using an adapted version of the iMTA Medical Consumption Questionnaire (MCQ) and the Productivity Cost Questionnaire (PCQ) at baseline, 3, 6, and 12 months.[31 32] The recall period for the PCQ and MCQ questionnaires was 4 weeks and 3 months, respectively. The iMTA MCQ is a validated generic instrument for measuring resource use and includes questions on healthcare use, for example, consultation with healthcare professionals (medical doctor and general practitioner physiotherapist), interventions, hospitalizations, and informal care and out-of-pocket expenses. The costs of healthcare use were calculated by multiplying the resource use by the price per unit of resource using Dutch reference prices.[27] The unit price in euro for each cost category can be found in online supplemental file S2. The reference year to which all costs have been adjusted for the analysis is 2021. As the follow-up period did not exceed 12 months, no discount rate was applied. Costs of medication use were

calculated only based on the information the patients reported in the MCQ questionnaire and not linked to the MQS III score. The iMTA PCQ is designed and validated to assess productivity loss, by quantifying the hours of lost paid and unpaid work. Productivity costs were calculated using the friction cost method.[27]

Statistical analysis of HEE

Missing PCQ data were imputed based on paid work status at previous measurement and earlier/later responses (eg, if a respondent did not have paid work at baseline and the PCQ was missing at 3 months, 0 costs were imputed). Other missing cost and effect data were imputed using multiple imputations using the mice package for R.[33] The imputation model included randomization, age, sex, and cost variables at other time points. Less than 5% of data were missing; hence, 10 imputed datasets were generated.[34 35] Since the MCQ and PCQ were not administered at 9-month follow-up, the mean costs of 6 and 12 months were used to calculate the total 12-month costs for each respondent. Each of the imputed datasets was analyzed separately, and results were pooled using Rubin's rules.

Mean healthcare and societal costs and QALYs for the OA and PPSP subgroups acquired over the 1-year study period were reported using descriptive statistics.[36] The mean differences in costs and effects between cooled and conventional RF were estimated using linear regression models, adjusted for baseline differences and confounders, where appropriate.[37] To address the uncertainty surrounding the differences in costs and effects, non-parametric bootstrapping with 5000 replications was used to estimate their 95%CI.[38] If appropriate, the deterministic incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs between cooled and conventional RF. Non-parametric bootstrapping was used to plot the joint distribution of the difference in costs and QALYs in a cost-effectiveness plane, further exploring uncertainty. Finally, cost-effectiveness acceptability curves show the probability of the cooled RF being cost-effective compared with conventional RF for a range of ceiling ratios for QALY. Ceiling ratios reflect the maximum price health policymakers are willing to pay for an additional QALY. In the Netherlands, the Council for Public Health and Healthcare proposes an informal ceiling ratio between €20.000 and €80.000 per QALY, depending on the burden of disease.[39]

To assess the robustness of results, in addition to the base case analysis of the economic evaluation, additional analyses were performed: (1) an analysis from a healthcare perspective in which costs due to productivity loss and patient and family costs were excluded and (2) an analysis with a short-term perspective (6 months). All analyses were performed in R Studio. The reporting of this economic evaluation follows the Consolidated Health Economic Evaluation Reporting Standards guidelines.[40]

RESULTS
Participants
41 of the 49 included patients reported 12-month outcomes (10 in the OA conventional RF group, 11 in the OA cooled RF group, 8 in the PPSP conventional RF group, and 12 in the PPSP cooled RF group). Figure 1 depicts the Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months. In the OA group, 21 of 25 patients (84%) completed the study, while 20 of 24 patients (83%) of the PPSP group completed the study. One patient in the PPSP cooled RF group had substantial missing data at 12-month follow-up, including the NRS. Between 6 and 12 months, five additional patients dropped out. All randomized patients received the allocated treatment. There were no crossovers between the treatment arms. Baseline patient characteristics were presented in the previous publication.[11]

Effectiveness analysis
The evolution of the clinical outcomes during the 12-month follow-up is presented in figure 2.

Percentage of pain reduction
At 12 months, the percentage of patients that reached ≥50% pain reduction compared with baseline was 22.2% (4/18) after a conventional RF and 22.7% (5/22) after cooled RF (table 1). In both the OA and PPSP populations, the difference in percentage of patients that reached ≥50% pain reduction between cooled and conventional RF was not statistically significant. When using the recommended cut-off of ≥30% pain reduction by the 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' guidelines, only the difference between conventional and cooled RF in the PPSP group was statistically significant (p=0.045). The other differences were not statistically significant.

Numerical rating scale
Whole population: cooled versus conventional RF
The mean pain reduction (ΔNRS) (95%CI) of all patients treated with cooled RF at 12 months compared with baseline was −1.4 (−2.5 to −0.7). This change over time was statistically significant (p=0.018). The mean ΔNRS (95%CI) of all patients treated with conventional RF was −0.8 (−2.3 to 0.7). This change over time was not statistically significant (p=0.29). The mean absolute NRS at 12 months did not differ significantly (p=0.30) between cooled and conventional RF. The non-inferiority comparison between conventional and cooled RF was performed in the whole population due to the limited sample size of this trial. The point estimate difference in NRS was 0.9 at 12 months with 95%CI (−0.8 to 2.6). This includes the non-inferiority margin of 0.75 making it inconclusive at this point (figure 3).

Whole population: PPSP versus OA
The mean NRS of patients with PPSP decreased from 6.4 at baseline to 6.1 at 12 months. In these patients, the mean ΔNRS (95%CI) at 12 months compared with baseline was −0.6 (−1.8 to 0.6). This change over time was not statistically significant (p=0.30). The mean NRS of patients with OA decreased from 5.8 at baseline to 4.2 at 12 months. In these patients, the mean ΔNRS (95%CI) at 12 months compared with baseline was −1.6 (−2.9 to −0.2). This change over time was statistically significant (p=0.024). The mean absolute NRS at 12 months did not differ significantly (p≥0.05) between patients with PPSP and OA.

Table 1 The percentage of patients with ≥30% and ≥50% pain reduction after conventional and cooled RF at 12 months follow-up timepoints in each patient subgroup

	OA			PPSP			Whole group		
	Conv RF, n (%)	Cooled RF, n (%)	P value[*†]	Conv RF, n (%)	Cooled RF, n (%)	P value[*†]	Conv RF, n (%)	Cooled RF, n (%)	P value[*†]
≥50% pain reduction compared with baseline									
6 months	3/11 (27.3)	4/12 (33.3)	1.00	1/11 (9.1)	5/12 (41.7)	0.16	4/22 (18.2)	9/24 (37.5)	0.15
12 months	4/10 (40)	3/11 (27.3)	0.66	0/8 (0)	2/11 (18.2)	0.49	4/18 (22.2)	5/22 (22.7)	1.00
≥30% pain reduction compared with baseline									
6 months	4/11 (36.4)	5/12 (41.7)	1.00	1/11 (9.1)	5/12 (41.7)	0.16	5/22 (22.7)	10/24 (41.7)	0.17
12 months	4/10 (40)	4/11 (36)	1.00	0/8 (0)	5/11 (45)	0.045	4/18 (22.2)	9/22 (40.9)	0.21

*P value compares conventional RF with cooled RF procedure.
†Pearson's χ² test used to compare proportions.
OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency.

Non-inferiority graphic of the COCOGEN trial
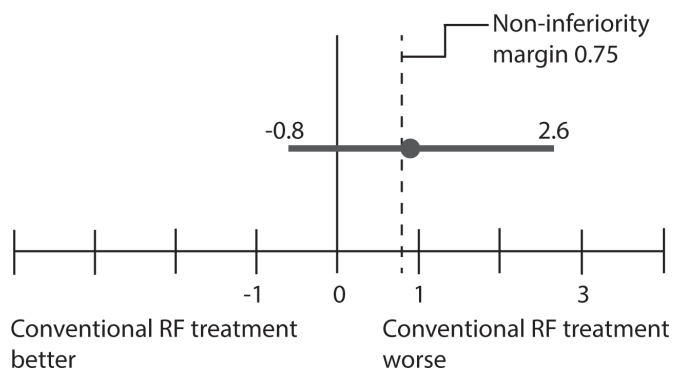Point estimate +0.9 with 95% CI of -0.8 to 2.6

Figure 3 Non-inferiority graphic of the COCOGEN trial.

Patients with PPSP: cooled versus conventional RF

In patients with PPSP treated with cooled RF, the mean ΔNRS (95%CI) at 12 months compared with baseline was −1.7 (−3.2 to −0.3). This change over time was statistically significant (p=0.03). In patients with PPSP treated with conventional RF, the mean ΔNRS (95%CI) at 12 months compared with baseline was 0.9 (−0.9 to 2.7). This change over time was not statistically significant (p=0.27). The mean absolute NRS at 12 months did differ significantly between conventional and cooled RF in patients with PPSP (p=0.02).

Patients with OA: cooled versus conventional RF

In patients with OA treated with cooled RF, the mean ΔNRS (95%CI) at 12 months compared with baseline was −1 (−3 to 0.9). This change over time was not statistically significant (p=0.26). In patients with OA treated with conventional RF, the mean ΔNRS (95%CI) at 12 months compared with baseline was −2.1 (−4.3 to 0). This change over time was statistically significant (p=0.05). The mean absolute NRS at 12 months did not differ significantly between conventional and cooled RF in patients with OA (p=0.41).

Other outcomes

In figure 2, we present the evolution of the other clinical effectiveness outcomes. The mean PGIC, OKS, EQ-5D-3L, HADS depression subscale, HADS anxiety subscale, PCS, and MQS III of the conventional RF and cooled RF group were not statistically significantly different at 12 months of follow-up. Mean scores of the other outcomes in the whole population at 12 months are presented per allocated RF treatment in online supplemental file S3.

Two patients with OA (one in the OA cooled RF group and one in OA conventional) underwent a TKA procedure between 6 and 12 months of follow-up. One additional patient with PPSP treated with conventional RF was treated with corticosteroids and capsaicin patch in the index knee between 6 and 12 months of follow-up. No patient with PPSP underwent a revision or other surgical reintervention of the total knee prothesis.

Safety analysis

There were no adverse events reported that were possibly or definitely related to the procedure at 12 months of follow-up. The infrapatellar hypoesthesia reported after a cooled RF at 6 months did not persist at 12 months.

Health-economic analysis

Participants

23 patients were included and analyzed in the PPSP subgroup and 24 in the OA group. The distribution of included patients in Belgium and the Netherlands was, respectively, 32 and 15. One patient with OA treated with cooled RF and one with PPSP treated with conventional RF were excluded from the analysis as no data were collected on resource use and costs at any of the follow-up moments. We present in online supplemental file S4 the baseline patient characteristics of the analyzed population.

Healthcare use

Costs from a societal perspective for each subgroup at 12 months are outlined in table 2. In PPSP, the two highest contributors to the considerably higher societal costs in the conventional RF group compared with cooled RF were the healthcare costs and the costs to patient and family (ie, out-of-pocket expenses and informal care costs). In the OA group, all three categories (healthcare costs, costs to patient and family, and productivity costs) contributed to the higher total societal costs of the cooled RF group compared with conventional RF.

Cost-utility analysis

In the PPSP group at 12 months after treatment, the difference between the mean QALYs estimated between cooled RF and conventional RF favored cooled RF. At 12 months, the patients with PPSP treated with cooled RF had fewer total costs with a higher gain in QALYs compared with the conventional RF group. Hence, cooled RF is the dominant treatment, and no ICER was calculated. In the OA group at 12 months after treatment, the difference in QALY between the cooled and conventional RF groups favored conventional RF (table 2). At 12 months, the patients with OA who were treated with cooled RF had more total costs with a lower gain in QALYs compared with the conventional RF group. As a result, cooled RF is inferior to conventional RF.

The bootstrapped estimates of incremental costs and QALYs are aggregated in the cost-effectiveness plane and represent uncertainty surrounding the cost and effect differences (figure 4). The majority of the data points in patients with PPSP cover the southeast quadrant indicating that when taking statistical uncertainty into account, cooled RF generates more health gains at lower costs, while most of the data points in the OA population cover the northwest quadrant indicating that cooled RF generally generates poorer health outcomes at higher costs. As a result, in PPSP, cooled RF is highly likely to be cost-effective, while in OA, cooled RF has a very low probability of being cost-effective in comparison with conventional RF at any willingness-to-pay threshold as visualized in the cost-effectiveness acceptability curves (figure 5).

Sensitivity analysis

The cost-utility analysis from the healthcare perspective (ie, excluding productivity costs and costs to patient and family) in the OA population showed that the difference in costs between cooled and conventional RF is substantially lower at 12 months compared with the societal perspective (table 2). Similarly, the cost-saving potential of cooled RF in the PPSP population is lower. However, the final results of the analyses (ie, whether the treatment was likely to be cost-effective) were unchanged.

The results from the 6-month analysis are available in online supplemental file S5 and are congruent to the conclusions reached during the 12-month analysis.

Table 2 Effectiveness outcomes and costs (€) presented per subgroup (OA and PPSP) and per RF modality after multiple imputation, based on 10 imputed datasets

Outcomes	Mean (SE)		Unadjusted mean difference (95% CI)*	Adjusted mean difference (95% CI)*
	Conventional RF	Cooled RF		
Outcomes for the OA group at 12 months after treatment				
QALY	0.604 (0.004)	0.558 (0.002)	−0.046 (−0.227 to 0.134)	−0.040 (−0.187 to 0.106)
Total healthcare-related costs	3405 (64)	4528 (125)	1123 (−2126 to 4372)	371 (−2627 to 3369)
Costs to patient and family	1018 (44)	3391 (85)	2373 (−600 to 5346)	876 (−839 to 2590)
Productivity costs/loss	3881 (0)†	6254 (0)†	2373 (−5266 to 10012)	2494 (−5544 to 10531)
Total societal costs	8303 (60)	14173 (159)	5860 (−3313 to 15052)	145 (−4485 to 14776)
Outcomes for the PPSP group at 12 months after treatment				
QALY	0.516 (0.002)	0.690 (0)	0.174 (0.014 to 0.334)	0.128 (0.008 to 0.247)
Total healthcare-related costs	4313 (216)	2499 (62)	−1814 (−4711 to 1083)	−1961 (−4848 to 925)
Costs to patient and family	2894 (67)	666 (30)	−2228 (−4518 to 62)	−2002 (−4268 to 258)
Productivity loss	3270 (0)†	2286 (0)†	−984 (−4258 to 2290)	−366 (−3680 to 2948)
Total societal costs	10477 (204)	5451 (62)	−5026 (−11022 to 970)	−4376 (−10124 to 1372)

Costs for each category were summed and the mean difference was calculated.

The sample size analyzed per subgroup was as follows: OA conventional RF (n=12), OA cooled RF (n=12), PPSP conventional RF (n=11), PPSP cooled RF (n=12).

*The uncertainty expressed in 95% CI around the mean costs and effects in each subgroup is calculated using non-parametric bootstrap simulations with 5000 replications.

Measurements are adjusted for baseline differences in EQ-5D index and costs (healthcare costs, patient and family costs, productivity costs, and total societal costs, respectively).

†These values have a SE of 0 since missing data in productivity costs were imputed separately before the multiple imputation procedure.

OA, osteoarthritis; PPSP, persistent postsurgical pain; QALY, quality-adjusted life year; RF, radiofrequency.

DISCUSSION

The 12-month data of the COCOGEN trial revealed no difference in treatment success (around 22%) between cooled and conventional RF in patients with chronic knee pain when treatment success is defined as pain reduction of ≥50%. In the OA and PPSP group separately, treatment success was not significantly different between the two RF modalities. In patients with OA, treatment success was higher (33.3%) than in the PPSP group (10.5%). Remarkably, in patients with OA, treatment success was higher at 12 months compared with 6 months possibly reflecting an artifact from the small sample size of this trial or a more fluctuating course of pain in patients with OA. In patients with

PPSP, treatment success diminished at 12 months in comparison with the 6-month results. When treatment success was defined as ≥30% pain reduction, there was also no significant difference between a conventional RF (22.2%) and a cooled RF (40.9%) in the whole population. In each population separately, the difference was more pronounced in the PPSP group. While there was no significant difference between conventional or cooled RF in patients with OA, this difference was statistically significant in patients with PPSP (0% treatment success after conventional RF, whereas 45% treatment success after cooled RF). Furthermore, only in patients with PPSP, there was a statistically significant reduction of the absolute NRS score after cooled RF (1.7 point
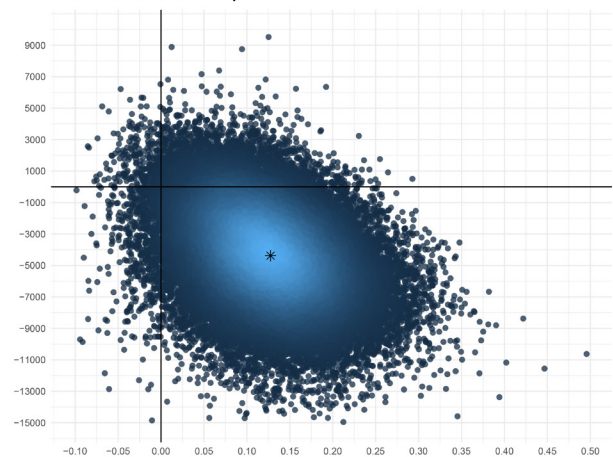
OA

Differences in costs (€)
(Cooled RF- Conventional RF)
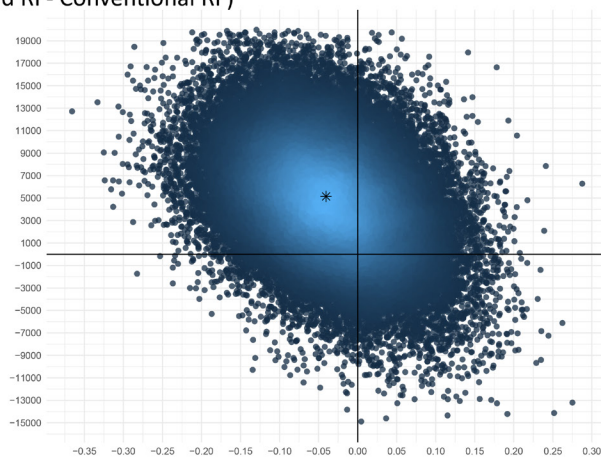
Differences in QALY (Cooled RF- Conventional RF)

PPSP

Differences in costs (€)
(Cooled RF- Conventional RF)

Differences in QALY (Cooled RF- Conventional RF)

Figure 4 The incremental cost-effectiveness planes for the osteoarthritis and persistent postsurgical pain population representing the cost difference (€) and differences in quality-adjusted life year estimated using EuroQol 5-dimension 3-level between cooled and conventional radiofrequency at the 12-month time point. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency ablation; QALY, quality-adjusted life year.

OA

Probability of cost-effectiveness

Willingness-to-pay: incremental costs (€) per QALY gained

PPSP

Probability of cost-effectiveness

Willingness-to-pay: incremental costs (€) per QALY gained
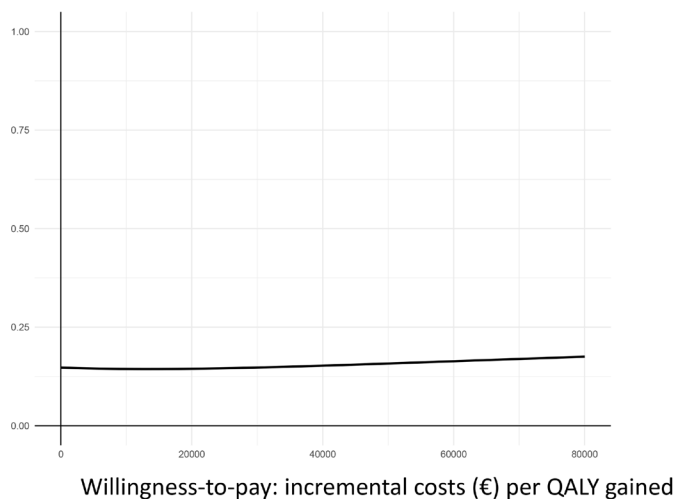
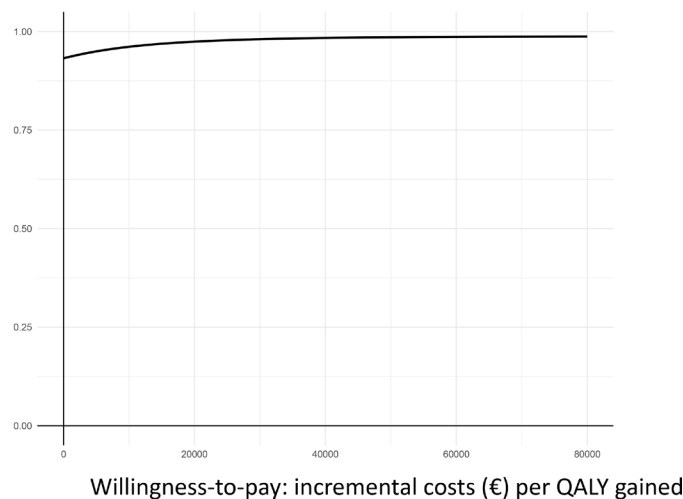**Figure 5** The cost-utility acceptability curve for cooled radiofrequency (RF) compared with conventional RF in the osteoarthritis and persistent postsurgical pain population at 12 months. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; QALY, quality-adjusted life year.

decrease), whereas this was not the case after conventional RF (0.9 point increase). A possible explanation could be that in PPSP, patients' anatomy is changed due to the total knee replacement in comparison with patients with OA probably resulting in more anatomical variability. Therefore, cooled RF, which creates a bigger lesion, could be more effective than conventional RF in PPSP. Another possible explanation could be that in the different populations, the etiology of pain is different. In a postoperative state, it seems logical that neuropathic pain dominates over nociceptive pain.[8 41 42] Other alternative strategies to improve treatment success include targeting more than three genicular nerves. At the moment, most studies target three nerves as originally described by Choi et al, but the optimal number of nerves to target should be further identified.[16 43 44]

In the cost-effectiveness analysis of the COCOGEN trial, we found that in the PPSP group, cooled RF resulted in a small gain in QALYs at 12 months compared with conventional RF. This was accompanied by a cost-saving potential when cooled RF was performed compared with conventional RF. In the OA group, however, cooled RF resulted in lower QALYs at 12 months and higher costs compared with conventional RF. The high societal costs in the OA group receiving cooled RF may be explained by their poorer health (ie, quality of life) post-treatment, compared with conventional RF, and this may lead to a higher level of care use and productivity loss and thus higher societal costs. Despite the limited number of patients included in this analysis, the findings of this trial indicate that cooled RF is likely to be cost-effective in the PPSP population but not in the OA population at decision-making thresholds used in the Netherlands.

Similar to the findings of other trials in the OA population, the NRS in the COCOGEN trial changed in a statistically significant manner when compared with baseline after cooled RF up to 12 months; however, the effect of cooled RF did not lead to a significant increase in the OKS score.[45 46] Our findings are also in line with the results of the study of Santana et al where the effectiveness of the conventional RF seemed to diminish at 12 months resulting in higher NRS scores.[13] Our data reflected a similar evolution after cooled RF, even though these differ from the results from Davis et al where treatment effect remained stable up to 12 months.[45]

A single trial by Qudsi-Sinclair et al reported long-term data of conventional RF in patients with PPSP patients up to 12 months.[47] The NRS change in the trial by Qudsi-Sinclair and the COCOGEN trial were congruent. The NRS decrease from baseline after conventional RF in the COCOGEN trial and in the trial of Qudsi-Sinclair et al is followed by a progressive increase in NRS from 6 to 12 months.

To date, a single economic evaluation has been published on RF of the genicular nerves. Desai et al performed a trial-based cost-effectiveness analysis comparing cooled RF with intra-articular steroid injections in patients with OA which strongly favored cooled RF.[15] When compared with Desai et al, the OA population in our trial has similar baseline OKS scores and an equivalent EQ-5D index. In contrast to Desai et al, however, we found that the improvement in EQ-5D utility after cooled RF was much smaller in OA and that healthcare costs, costs to patient and family, and productivity losses were higher, resulting in a high likelihood that cooled RF is not cost-effective in OA compared with conventional RF. These two trials have several methodological differences: Desai et al included healthcare costs only and used a mapping analysis to calculate EQ-5D utility based on the OKS. Generally, the disease-specific OKS is more sensitive to health changes in the OA population than the generic EQ-5D, which may explain the larger QALY gain.

No adverse events developed after both a conventional and a cooled RF at 12 months supporting the long-term safety of both treatments. Secondary outcomes including the quality of life (EQ-5D-3L), emotional health (HADS and PCS), and medication use did not change in a statistically significant manner between cooled and conventional RF up to 12 months.

Currently, there is an increase in research on RF of the genicular nerves and growing evidence that different RF modalities are effective. A comparison of the long-term effects of these interventions in relation to their costs is becoming imperative for the incorporation of this intervention in chronic knee pain decision-making algorithms to guide the optimal allocation of the

available healthcare resources. As mentioned previously, there are a limited number of trials that evaluate 12 months or longer follow-up of patients undergoing RF of the genicular nerves, and there are no prospective trials comparing cooled with conventional RF up to 12 months published until present.[13 45–48]

One of the main strengths of this trial is that it is designed in a pragmatic manner increasing the external validity of the results. Furthermore, this is the first published health economic analysis from a societal perspective comparing cooled and conventional RF in patients with therapy-resistant chronic knee pain. Despite this, no decisive conclusion can be derived based on these results due to the intrinsically small sample size of this pilot trial. This was evident in the effectiveness outcomes and subsequently in the health economic analysis resulting in increased uncertainty surrounding the outcomes. While bootstrap analyses can overcome some statistical uncertainty, results must be interpreted with caution due to the very small number of patients in each subgroup (OA and PPSPS) and the highly skewed nature of cost data. A second limitation of this study was the systematic unblinding after 6 months of follow-up, which may have had an influence on subjective outcome measures taken after unblinding. Third, the COCOGEN study was performed in Belgium and the Netherlands—encompassing two different health systems. There may be some differences in access to first-line and second-line care; however, cost prices are similar in both countries. Moreover, results are presented from both the societal and healthcare perspectives, in line with Dutch and Belgian guidelines, respectively. Fourth, in this trial, we did not include all costs of analgesics. Since we did not see meaningful differences in medication use on the Medication Quantification Scale V.3 score, we do not expect this to have influenced the trial findings. An inclusion of all costs of analgesics is however recommended in a future trial.

The COCOGEN trial was primarily designed as a pilot trial to guide further research. Future studies should be sufficiently powered for between-group comparisons with an inclusion of a sham procedure and a long follow-up to prove the effectiveness of the current technique and should include the collection of resource use and quality of life data to perform a cost-effectiveness analysis. At the moment, the COGENIUS trial (NCT05407610) is being conducted.[49] This is a powered trial that aims to compare conventional and cooled RF with a sham procedure in OA and PPSP with 2 years of follow-up.

CONCLUSIONS

In conclusion, the COCOGEN study showed that RF of the genicular nerves is safe and can result in ≥50% pain reduction in approximately 22% of patients with chronic knee pain at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective and cost-effective than conventional RF. Larger powered trials with the inclusion of a sham procedure and long follow-up should be conducted to support these findings.

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SUPPLEMENTARY MATERIAL S1

Inclusion and exclusion criteria of the COCOGEN trial.

Inclusion criteria:

- Adult subjects that suffer from moderate to severe (Numeric Rating Scale > 4) chronic anterior knee pain (> 12 months) due to OA or PPSP after TKA that was unresponsive to conventional treatments (physiotherapy, analgesics, or intra-articular infiltrations).
- For OA patients, a radiologic confirmation of Kellgren-Lawrence (KL) grade II to IV on X-ray or MRI was required.
- For PPSP after TKA patients, a negative orthopaedic workout was required.

Exclusion criteria were:

- Body mass index > 40 kg/m2
- Chronic widespread pain
- Untreated psychosocial disease
- Radicular pain in index leg
- Local or systemic infection (bacteraemia)
- Uncontrolled immune suppression
- Uncontrolled coagulopathy (defined as supratherapeutic dose of anticoagulation medication)
- Patient currently implanted with a defibrillator, neuromodulator or other electrical devices
- Allergies to products used during the intervention
- Evidence of inflammatory arthritis or an inflammatory systemic disease responsible for knee pain
- Intra-articular injections (e.g., steroids, hyaluronic acid, platelet enriched plasma) in the index knee during the 3 months prior to the start of the study
- Previous conventional or cooled radiofrequency of the index knee
- Pregnant, nursing or planning to become pregnant before the treatment
- Participation in another clinical trial/investigation within 30 days prior to signing informed consent
- Patients who refused to comply to protocol procedure.

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SUPPLEMENTARY MATERIAL S2

Table S2. Unit prince in Euro for each cost category (year 2021).

Price for each unit of cost category		Cost per unit (€)
Health care resource use [1]		
Health care related visit	General practitioner (visit)	37
	Occupational physician (visit)	71
	Other health care physician specialist (visit) [b]	101
	Physiotherapist (visit)	37
	Occupational therapist (visit)	37
	Dietician (visit)	37
	Homeopathist (visit)	37
	Psychologist (visit)	71
	Use of home care (home nursing care) (one hour visit)	56
	Use of home care (domestic help in housekeeping) (one hour visit)	26
	Use of home care (family care) (one hour visit)	16
	Inpatient day hospitalisation (day)	307
	Inpatient night hospitalisation (day)	529
	Emergency department (visit)	288
	Use of ambulance (trip)	572
Visit to other allied professionals	Social worker (visit)	72
RF intervention costs [a]		
	Cooled RF intervention	1127
	Conventional RF intervention	338
Costs for patients and family		
Out of pocket expenses	Warm medical dressing/compress	40
	Medical gel	20
	Analgetic medication (unit)	20
	Brace (unit)	75
Informal care	Informal care (per hour)	16
Productivity costs		
	Productivity loss for paid work (hour)	34.75
	Productivity loss for unpaid work (hour)	14

[a] The cost of the RF interventions (cooled and conventional RF) was calculated as the sum of the cost of a day
hospitalisation, the costs of the used material and the cost of the medical personnel.

[b] The cost price for a health care physician specialist visit was calculated as an average of all specialisations.

Abbreviations: RF, radiofrequency ablation.

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SUPPLEMENTARY MATERIAL S3

Table S3. The overall effectiveness outcomes at 12-months follow-up timepoints compared between conventional and cooled RF treatment of the genicular nerves.

	Baseline		6 months FU			12 months FU		
	Conv. RF	Cooled RF	Conv. RF	Cooled RF	p-value[a,b]	Conv. RF	Cooled RF	p-value[a,b]
Mean NRS [d] (SD)	6.2 (1.6)	6.1 (1.8)	5.0 (2.2)	3.6 (2.2)	0.13[c]	5.6 (3.1)	4.7 (2.2)	0.30[c]
Patients with significant improvement in PGIC, n (%)	-/24	-/25	5/22 (22.7)	9/24 (37.5)	0.28	3/18 (22.7)	8/22 (36.4)	0.29
Mean OKS score (SD)	18.1 (6.1)	19.8 (7.2)	25.0 (9.6)	27.0 (8.7)	0.47	22.7 (9.0)	25.5 (8.5)	0.31
Mean EQ-5D-3L score (SD)	0.4 (0.3)	0.5 (0.3)	0.6 (0.3)	0.6 (0.28)	0.62	0.52 (0.3)	0.6 (0.2)	0.19
Mean HADS depression subscale (SD)	7.0 (4.2)	7.0 (5.2)	7.0 (4.9)	5.46 (4.8)	0.31	7.3 (5.6)	5.9 (4.6)	0.38
Mean HADS anxiety subscale (SD)	7.7 (4.5)	8.0 (4.8)	6.38 (4.6)	6.0 (4.7)	0.79	7.3 (5.4)	6.4 (4.1)	0.55
Mean PCS score (SD)	24.2 (11.0)	23.5 (10.9)	23.1 (13.7)	18.0 (12.4)	0.20	23.4 (17.2)	21.4 (12.1)	0.67
Mean MQS III score (SD)	7.7 (6.4)	9.1 (6.4)	5.0 (5.2)	6.2 (5.0)	0.40	5.4 (5.8)	5.9 (5.4)	0.78

Abbreviations: Conv., Conventional; RF, radiofrequency; SD, Standard deviation; PGIC, Patient's Global Impression of Change; OKS, Oxford Knee Score; EQ5-5D-3L, EuroQol-5 Dimension- 3 Level; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; MQS III, Medication Quantification Scale III.

a: p-value compares conventional RF versus cooled RF procedure

b: Pearson's Chi-squared test used to compare proportions and Paired T-test used to compare means

c: p-value of mean paired difference between baseline and follow-up NRS

d: mean NRS at 12 months is calculated as the average score of the reported NRS during rest and during movement.

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SUPPLEMENTARY MATERIAL S4

Table S4. Baseline patient characteristics per subgroup (OA and PPSP) including baseline quality of life, pain scores and health care resource use in the intention to treat population.

	OA		PPSP	
	Conventional RF	**Cooled RF**	**Conventional RF**	**Cooled RF**
Sample size, n (%)	12 (50)	12 (50)	11 (48)	12 (52)
Female, n (%)	11 (92)	6 (50)	9 (82)	8 (67)
Mean age (SD) in years	62 (14.3)	61 (13.4)	65 (12.1)	65 (8.9)
Mean BMI (SD) in kg/ m2	32.6 (4.9)	28.6 (3.6)	29.2 (5.2)	28.2 (5.6)
Education level, n (%)				
Primary school	3 (25)	4 (33)	2 (18)	3 (25)
Secondary school	6 (50)	5 (42)	8 (73)	9 (75)
Higher education	3 (25)	3 (25)	1 (9)	0 (0)
Mean OKS score (SD)	16.3 (5.6)	21.8 (7.7)	20.1 (6.3)	17.1 (5.4)
Mean NRS score (SD)	6.4 (1.4)	5.3 (2.1)	6.3 (1.6)	6.9 (1.2)
Mean EQ-5D-3L score (SD)	0.444 (0.291)	0.431 (0.344)	0.369 (0.324)	0.494 (0.344)
Mean MQS III score (SD)	9.1 (5.9)	8.1 (6.4)	6.9 (6.8)	10.0 (6.5)

Data is reported in standard deviation (SD) unless otherwise specified. Abbreviations: BMI, Body Mass Index; OA, Osteoarthritis; PPSP, Persistent Post-Surgical Pain; OKS, Oxford Knee Score; NRS, Numerical Rating Scale; EQ-5D-3L, 3-level, 5- dimensions health related quality of life; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; MQS III, Medication Quantification Scale Version III.

SUPPLEMENTARY MATERIAL S5

Table S5. Results from the cost-utility analysis and sensitivity analysis for the conventional and cooled RF interventions in each population (OA and PPSP) at 6 months.

Outcome	ΔC (95% CI) [a]	ΔE (95% CI) [a]	CE plane				Probability of cost-effective procedure at €20.000 [b]	Is cooled RF cost-effective at €20.000? (Yes/No) [b]
			NE (%)	SE (%)	SW (%)	NW (%)		
OA population (n = 24)								
Societal perspective at 6 months	5017 (-2665; 12700)	-0.017 (-0.090; 0.056)	29	3	6	62	0.09	No
Health care perspective at 6 months	596 (-1853; 3045)	-0.017 (-0.090; 0.056)	20	12	20	48	0.27	No
PPSP population (n = 23)								
Societal perspective at 6 months	-1409 (-3499; 681)	0.035 (-0.031; 0.100)	7	77	11	5	0.92	Yes
Health care perspective at 6 months	-17 (-840; 805)	0.035 (-0.029; 0.102)	38	47	3	12	0.79	Yes

[a] The uncertainty expressed in 95% confidence intervals (CI) around the mean difference in costs and effects is calculated using regression analysis, adjusted for baseline differences, and non-parametric bootstrap simulations with 5000 replications.

[b] The probability of cost-effectiveness expresses the percentage of the 5000 bootstrap simulations in which cooled RF was cost-effective.

Abbreviations: OA, Osteoarthritis; PPSP, Persistent Post-Surgical Pain; RF, radiofrequency ablation; ΔC, difference in costs; CE, cost-effectiveness; NE, North-east; SE, South-east; SW, South-west; NW, North-west; CI, Confidence Interval.

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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)

(January 2021)

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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**

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NL69877.068.19   **Cocogen Trial**

(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

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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.

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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.

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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:

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- 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.

Superomedial genicular nerve

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

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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.

<u>Inferomedial genicular nerve</u>

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.

<u>Superolateral genicular nerve</u>

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

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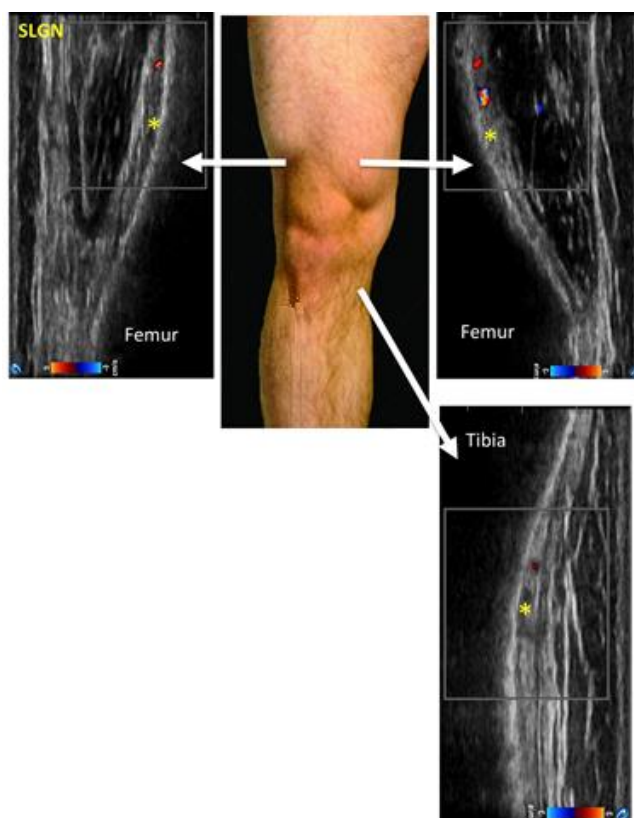
Fig. Ultrasound probe position and corresponding images for genicular radiofrequency treatment. Color Doppler shows the corresponding genicular arteries. Treatment sites are marked with yellow asterisks.

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

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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.

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- 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.

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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)

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- 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

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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;

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- 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).

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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.

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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.

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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

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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.

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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.

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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

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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

Supplemental material

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Reg Anesth Pain Med

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