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Comparison of conventional and cooled radiofrequency treatment of the genicular nerves versus sham procedure for patients with chronic knee pain: protocol for a multicentre, double-blind, randomised controlled trial (COGENIUS)

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ABSTRACT

Introduction The prevalence of chronic knee pain is increasing. Osteoarthritis (OA) and persistent postsurgical pain (PPSP) are two important causes of knee pain. Chronic knee pain is primarily treated with medications, physiotherapy, life-style changes and intra-articular infiltrations. A radiofrequency treatment (RF) of the genicular nerves is a therapeutical option for refractory knee pain. This study investigates the effectiveness and cost-effectiveness of conventional and cooled RF in patients suffering from chronic, therapy resistant, moderate to severe knee pain due to OA and PPSP.

Methods and analysis The COGENIUS trial is a double-blinded, randomised controlled trial with 2-year follow-up. Patients and outcome assessors are blinded. Patients will be recruited and treated in Belgium and the Netherlands. All PPSP after a total knee prothesis and OA patients (grades 2–4) will undergo a run-in period of 1–3 months where conservative treatment will be optimised. After the run-in period, 200 patient per group will be randomised to conventional RF, cooled RF or a sham procedure following a 2:2:1 ratio. The analysis will include a comparison of the effectiveness of each RF treatment with the sham procedure and secondarily between conventional and cooled RF. All comparisons will be made for each indication separately. The primary outcome is the Western Ontario and McMaster Universities Osteoarthritis Index score at 6 months. Other outcomes include knee pain, physical functionality, health-related quality of life, emotional health, medication use, healthcare and societal cost and adverse events up to 24 months postintervention.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of the University of Antwerp (Number Project ID 3069-Edge 002190-BUN B3002022000025), the Ethics committee of Maastricht University (Number NL80503.068.22-METC22-023) and the Ethics committee of all participating hospitals. Results of the study will be published in international peer-reviewed journals.

Trial registration number NCT05407610.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The COGENIUS trial is a powered, double-blind, multicentre, randomised controlled trial.
⇒ Both cooled and conventional radiofrequency treatments will be compared with a sham procedure.
⇒ Another strength is that a cost-effectiveness analysis will be performed.
⇒ All patients will undergo a run-in period of 1–3 months where all recommended conservative treatments for chronic knee pain will be optimised.
⇒ A limitation of the trial is that the follow-up is limited to 2 years after treatment.

INTRODUCTION

Chronic knee pain, defined as knee pain that persists or recurs for more than 3 months, is an increasing cause of pain and disability worldwide.[1–4] The main cause of chronic knee pain is osteoarthritis (OA) of the knee.[4 5] Therapy resistant knee pain after a surgical intervention on the knee, otherwise named persistent postsurgical pain (PPSP), is another important cause of chronic knee pain.[6 7]

Knee OA is a progressive degenerative disease, commonly diagnosed in adults over 50 years of age, that leads to pain, stiffness and loss of function of the joint.[8] The lifetime prevalence of OA is increasing due to the ageing of the population and an increase in obesity, which are well-known risk factors.[8–10] Due to the lack of disease-modifying drugs, the cornerstone of care for OA is conservative treatment.[9 11–13] This includes non-pharmacological care (education, lifestyle changes, exercise programmes, weight management), pharmacological care (non-steroidal anti-inflammatory drugs, paracetamol, duloxetine)

and/or intra-articular (IA) infiltrations with corticosteroids or hyaluronic acid.[12 13] Unfortunately, conservative care for knee OA is often insufficient or associated with side effects. Around 50% of patients who are first diagnosed with symptomatic knee OA are estimated to eventually undergo a total knee arthroplasty (TKA) in their lifetime.[14] Despite being an effective procedure, up to 20% of patients after primary TKA express dissatisfaction and experience moderate to severe PPSP.[6 7 15 16] Similar to OA, treatment of PPSP is symptomatic and limited to non-interventional conservative care.[6 7] The disease burden of patients with knee OA pain and PPSP refractory to conservative care is high and leads to sleeping disorders, psychological distress and a diminished quality of life.[17–19]

This underlines the need for improvement in treatment strategies for OA and PPSP. Growing research on a radiofrequency (RF) treatment of the genicular nerves, points to the potential of this treatment for patients with therapy resistant OA and PPSP.[20 21] An RF treatment blocks the transmission of painful stimuli from the sensory genicular nerves of the knee to the central nervous system by means of a thermal lesion created using RF current.[20 21] Since the first report on RF of the genicular nerves by Choi *et al* in 2011, the procedure has evolved to target the genicular nerves more accurately. Furthermore, different RF modalities have been introduced to clinical practice aiming to increase the effectivity of the treatment.[20 22 23] Conventional and cooled RF are the two most used RF modalities. Recent systematic reviews report that conventional RF treatment of the genicular nerves is an effective, well-tolerated and safe procedure in knee OA.[24–27] At the moment, literature on RF for knee PPSP is scarcer.[28] Furthermore, retrospective and pilot studies indicate a possible larger effectivity of cooled RF compared with conventional RF on knee pain. However, these have not been directly compared in powered prospective studies in both the OA and PPSP population.[29 30] Comparison of RF to a sham procedure is only tested in the relative small study of Choi *et al*.[31] Confirmation of superiority of RF treatment over a sham procedure in a larger trial is essential for the incorporation of an RF treatment in the clinical treatment algorithm for chronic knee pain.

To address the above-mentioned research questions, we aim to conduct a powered, randomised controlled trial that compares the effectivity of cooled RF versus conventional RF versus a sham procedure in patients with chronic knee pain because of therapy resistant OA or PPSP after a TKA. Our hypothesis is that cooled RF is superior to conventional RF and that both RF treatments are superior to a sham procedure in both populations at 6 months after intervention. Other objectives are to further determine the effects of the cooled RF versus conventional RF versus sham procedure up to 24 months in terms of pain reduction, physical functioning, medication use, other patient-reported outcomes and side effects of the performed interventions, and the cost-effectiveness.

METHODS AND ANALYSIS

Study design

The COGENIUS study is a three-arm, pragmatic, prospective, multicentre, double-blind (participant-blinded and assessor-blinded), randomised sham-controlled trial of estimated 4 years' duration. Four hundred patients with chronic moderate to severe anterior knee pain refractory to conventional treatments, 200 with knee OA and 200 with PPSP, will be included and followed up for a period of 24 months. Participants will be recruited and treated in 13 hospitals in Belgium and 2 hospitals in the Netherlands. Each patient will undergo a run-in period of 1–3 months to guarantee that conservative treatment is maximally carried out in all patients. Stratified per group (OA and PPSP), participants who fulfil the inclusion criteria after the run-in period will be randomly allocated to a conventional RF intervention, a cooled RF intervention or a sham procedure following a 2:2:1 ratio. Patients will be encouraged to continue usual care during the study. During the follow-up, patients will not be actively offered a repeat intervention. However, a repeat RF intervention will be allowed after the completion of the primary endpoint at 6 months as part of usual care. Figure 1 depicts the schematic flow of the patients in the COGENIUS trial. The study will follow the Standard Protocol Items Recommendations for Interventional Trials and the Consolidated Standards of Reporting Trials.[32 33] Design of the COGENIUS trial was preceded by a pilot trial, the COCOGEN study, comparing cooled to conventional RF in the OA and PPSP population.[29]

Participants and recruitment

Potential participants for the study will be identified by pain physicians in hospital centres after primary identification and referral from general practitioners, rheumatologists, orthopaedic surgeons, rehabilitation physicians and other pain physicians. The recruiting physicians will be informed about the study by means of information leaflets and scientific meetings. The potential participants will be screened by a researcher based on the inclusion and exclusion criteria presented in table 1. Before inclusion in this trial, PPSP patients are required to have undergone a negative orthopaedic workup. This constitutes an orthopaedic visit where mechanical prosthetic problems, joint infection, inflammatory or allergic response to implanted material and nerve damage are excluded. All assessments necessary for inclusion are performed as standard of care. After the acquirement of the informed consent (see online supplemental documents 1–3), the eligible patients will be enrolled in the run-in period.

The run-in period

A run-in period of approximately 1–3 months depending on the specific needs of the patient is planned to optimise the conservative care of the patients enrolled in the trial.

The run-in period includes education on OA or PPSP, physiotherapy following a standardised physiotherapy prescription, dietary weight management with possible referral to a dietician, self-efficacy and self-management programmes in patient organisations, use of gait aids and optimisation of the pharmacological treatment. All patients will be required to have undergone treatment

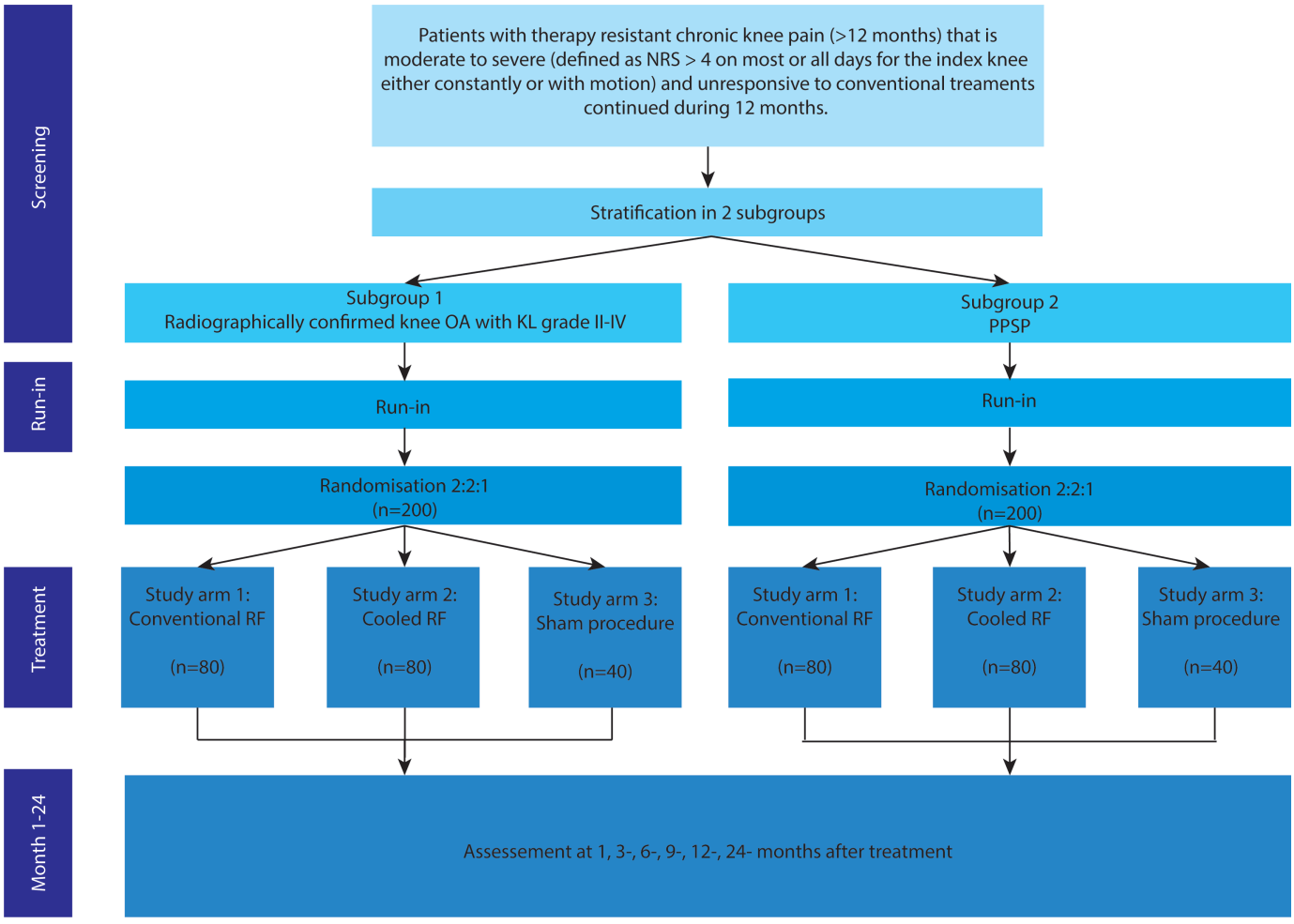

Figure 1 Schematic flow of the design of the randomised study comparing cooled RF to conventional RF to a sham procedure. KL, Kellgren-Lawrence; NRS, Numerical Rating Scale; OA, osteoarthritis; PPSP, osteoarthritis; RF, radiofrequency.

with the following medication for the knee pain before or during the run-in period if not medically contraindicated: topical and oral Non steroidal anti-inflammatory drugs (NSAIDs), paracetamol, tramadol and duloxetine. At the end of the run-in period, the success of conservative treatment will be evaluated. The participant will proceed to the randomisation and study intervention phase if the mean Numerical Rating Scale (NRS) of the participant is >4 during the 4 days prior to the run-in evaluation contact. Baseline measurements will be gathered by a researcher.

Randomisation

Patients will be randomised on the day of study intervention through the CASTOR EDC application after stratification following the aetiology of pain into the OA or PPSP group. CASTOR is a web-based software designed for randomisation and data collection during clinical trials that protects the privacy of the participants, conforming to all applicable medical data privacy laws and regulations (GCP, 21 CFR Part 11, EU Annex 11, the European Data Protection Directive, ISO9001 and ISO27001/NEN7510). Patients will be assigned in a 2:2:1 ratio to receive either conventional RF intervention of the genicular nerves, cooled RF intervention of the genicular nerves or sham procedure.

Blinding

The COGENIUS study is designed as a double-blind study: the participants and the outcome assessor will be blinded to the intervention group. The intervention team (pain physician performing the RF/sham intervention and the assisting nurse) will be the only persons that are aware of the allocation group. Special attention was given to the uniformisation of the procedure during the administration of the three study interventions. Therefore, all three interventions will be performed in the same operating room, using similar monitoring and patient positioning, similar vertical drape to hinder the vision of the patient, the communication with the participant will be similar, the length of procedure and the auditory information the participant will hear, will also be similar. Patients will not be systematically unblinded. Unblinding will be possible in case of a valid safety reason or after the termination of the study at 24 months postprocedure.

The blinding of each patient enrolled in this study will be tested at 1 month after randomisation. Patients will be asked to provide their 'best guess' of the intervention

Table 1 The inclusion and exclusion criteria used in the COGENIUS trial

Inclusion criteria	Exclusion criteria
Adult patients (age ≥18 years old)	Local or systemic infection (bacteraemia)
Chronic anterior knee pain (>12 months) that is moderate to severe (defined as NRS>4 on most or all days for the index knee either constantly or with motion at time of screening and, an average NRS score reported in the patient diary >4 at the end of the run-in period)	Evidence of inflammatory arthritis or an inflammatory systemic disease responsible for knee pain
Unresponsive to conventional treatments ongoing for at least 12 months prior to inclusion	Intra-articular injections (steroids, hyaluronic acid, platelet enriched plasma, …) in the index knee during the 3 months prior to procedure
Only for knee OA patients: Radiologic confirmation of osteoarthritis of Kellgren-Lawrence grade 2 (mild), 3 (moderate) or 4 (severe)	Pregnant, nursing or planning to become pregnant
Only for patients with PPSP after TKA: a negative orthopaedic workup	Previous diagnosis of chronic widespread pain
	Patients with unstable psychosocial disorder
	Allergies to lidocaine, propofol, chlorhexidine
	Uncontrolled coagulopathy
	Uncontrolled immune suppression
	Patient is currently implanted with a neurostimulator
	Current radicular pain in index leg
	Previous conventional or cooled radiofrequency of the index knee
	Bilateral knee pain
	Patients who have a planned TKA in the near future
	Patients who are unwilling or mentally incapable to participate
	Participating in another clinical trial

NRS, Numerical Rating Scale; OA, osteoarthritis; PPSP, persistent postsurgical pain; TKA, total knee arthroplasty.

allocation and to provide the confidence level of their guess (a five-point scale ranging from 'not at all' to 'extremely'). The success of blinding will be measured using a blinding index (BI) that ranges from –1 to 1 and measures the intervention-specific proportion of unblinded subjects considering the confidence in the guess.[33 34]

Interventions

All patients will be placed in a supine position on a fluoroscopy table with the index knee flexed and will be monitored with pulse oximetry. Sedation with propofol can be administered if considered necessary so that the patient is comfortable and able to communicate and report the stimulation during the procedure adequately.

No diagnostic block is performed prior to the study intervention. The superomedial (SMG), the superolateral (SLGN) and the inferomedial (IMGN) genicular nerve will be targeted under sterile conditions using a high frequency linear ultrasound probe as depicted in figure 2.[35]

For the SMGN, the transducer is placed in a coronal orientation over the medial side of the femur at the junction between the epiphysis and diaphysis of the femur. In case of visualisation of the SM genicular artery at this level just above the bony cortex, the RF cannula will be placed directly next to this artery, otherwise the target is just anteriorly to the adductor tubercle at the posterior side of the femur. After the out-of-plane entry point is determined, the skin and soft tissues are anaesthetised with 1 mL lidocaine 2%. The cannula is inserted subcutaneously and the transducer is turned 90° into the transverse plane. The cannula is advanced anterior to posterior 'in plane' until contact is made with the bony cortex at the posterior half of the femur. An RF electrode is introduced in the cannula.

For the IMGN, the transducer is placed in a coronal orientation over the medial side of the distal knee to visualise the junction of the tibial medial epiphysis and diaphysis, the inferomedial genicular artery and the medial collateral ligament. In case the IM genicular artery is visualised below the medial collateral ligament and above the bony cortex, the RF cannula is targeted next to this artery, otherwise the physician will aim at the junction between the epiphysis and diaphysis under the medial collateral ligament. After the out-of-plane entry point of the needle is determined, the skin and soft tissues are anaesthetised with 1 mL lidocaine 2%. The cannula is inserted subcutaneously, and the transducer is turned 90°

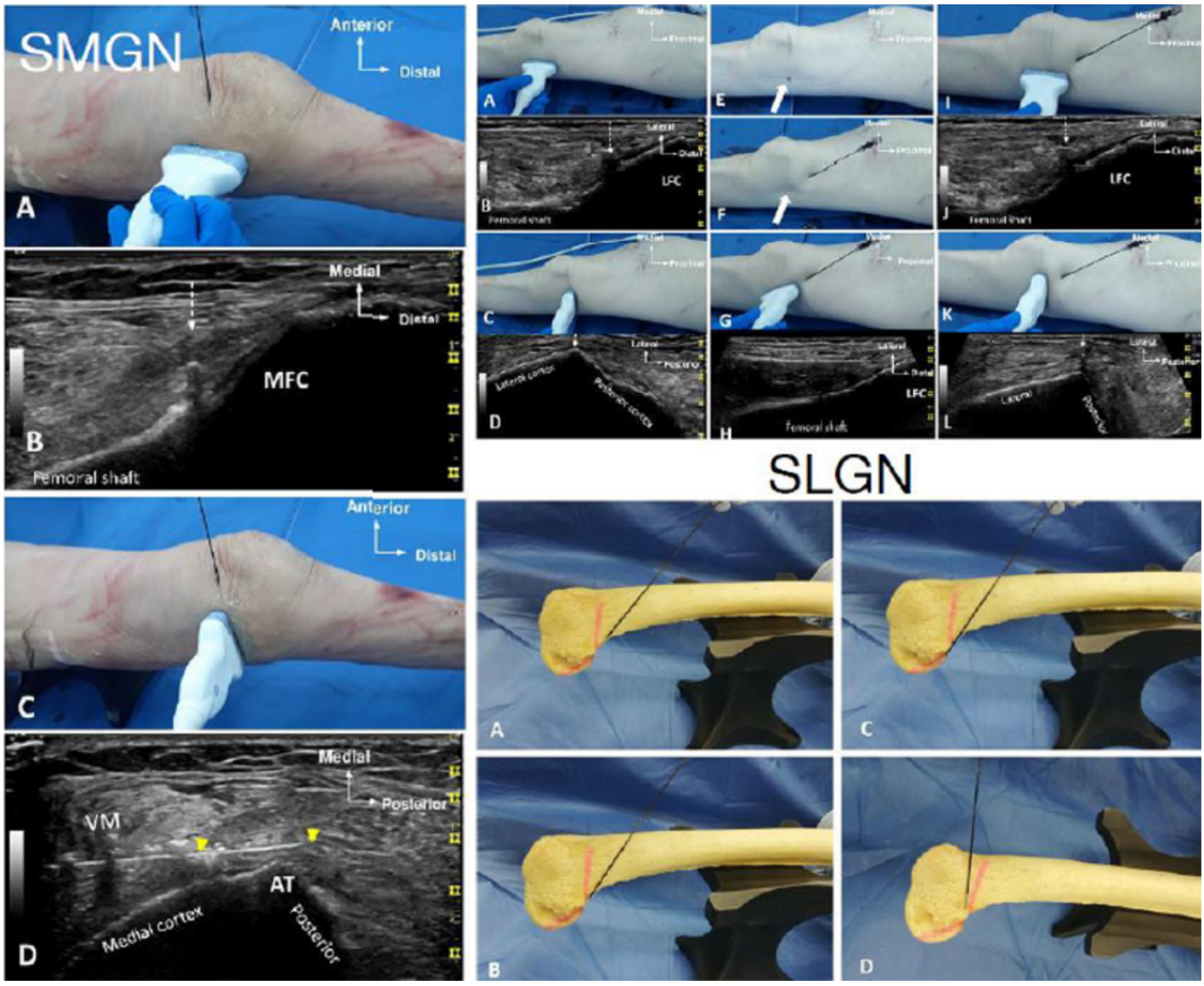

Figure 2 The ultrasound approach to target the SMGN and the SLGN. The procedure to target the IMGN is similar to the SMGN. The RF needle is marked with yellow arrows. The target point is marked with white arrows.[35] IMGN, inferomedial genicular nerve; RF, radiofrequency; SMGN, superomedial genicular nerve; SLGN, superolateral genicular nerve.

into the transverse plane. The cannula is advanced anterior to posterior 'in plane' until contact is made with the bony cortex at the centre of the tibia. An RF electrode is introduced in the cannula.

For the SLGN, the transducer is placed in a coronal orientation over the lateral side of the proximal knee at the junction between the epiphysis and diaphysis. In case the SL genicular artery is visible, the RF cannula is aimed next to the artery, otherwise the posterior side of the junction between the epiphysis and diaphysis of the femur is the target point. The transducer is centred to this target point and consecutively turned 45° into an oblique view. After the 'in plane' entry point of the needle is determined, the skin and soft tissue are anaesthetised with 1 mL lidocaine 2%. The RF cannula is inserted and advanced using an 'in plane' approach in the oblique plane until contact is made with the posterior side of the bony cortex of the femur. An RF electrode is introduced in the cannula.

After all three cannulas are positioned, their proximity to the genicular nerves is tested using sensory stimulation (50 Hz). Paraesthesia should be present at a threshold of less than 0.5 V. Additionally, motoric stimulation (2 Hz) should confirm the absence of fasciculations below 1 V. Before study treatment, the position of the cannulas is controlled using fluoroscopy. First, an AP view is made, and the needle tip should be at the junction between the diaphysis and the epiphysis in proximity of the bony cortex. Second, a lateral view is made where the needle tip should be within the two middle quarters of the tibia width for the IMGN and within the posterior half of the femur width for the SMG and SLGN. After confirmation of needle position 1 mL of lidocaine 2% is injected close to each genicular nerve with the exception of the sham procedure.

Conventional RF of the genicular nerves

A 100 mm long, 18G straight RF introducer and an electrode with a 10 mm active tip is used during conventional RF to apply 80°C at the tip during 90 s for each genicular nerve.

Cooled RF of the genicular nerves

A 100 mm long, 17G straight RF introducer and an 18 G cooled electrode with a 4 mm active tip is used during cooled RF to apply 60°C at the tip and on average 80°C in the targeted tissue during 150 s for each genicular nerve.

The sham procedure

Each genicular nerve will be similarly targeted with an 18-gauge introducer using ultrasound. Subcutaneous local anaesthetic (1 mL lidocaine 2% per entry point) will be administered before introducer. Probe placement and sensory and motor testing will be applied similar as above mentioned. The interventional team will simulate the acquisition of fluoroscopic images and also the RF treatment by using a recording of the sound of the working RF generator.

Outcome measures

The chosen primary and secondary outcomes are chosen based on the OMERACT-OARSI and IMMPACT core outcome guidelines.[36 37]

Primary outcome measures

The primary outcome is the total Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC) at 6 months postintervention.[38] The WOMAC score is derived from a self-administered OA-specific validated questionnaire on pain, stiffness and physical functioning of the knee joint and ranges between 0 and 96 points with 96 indicating the highest possible disease burden. Per stratification, the WOMAC score of each RF groups will be compared with the score of the sham group and the WOMAC score of the cooled RF will be compared with the conventional RF group.

Secondary outcome measures

The secondary outcomes of the study are as follows: (1) the WOMAC score at 1-month, 3-month, 12-month and 24-month postintervention; (2) pain intensity assessed by the mean NRS (range 0–10) of the 4 days prior to each visit; (3) the proportion of patients with a pain reduction of at least 50% assessed by the NRS compared with baseline; (4) health-related quality of life assessed by the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L); (5) physical functioning assessed by goniometry by using the CJOrtho app, 'Timed Up and Go Test' and 6 min walk test; (6) mental health status assessed by the Hospital Anxiety and Depression Scale (HADS) and Pain Catastrophising Scale (PCS); (7) Patient Global Impression of Change (PGIC); (8) patient's satisfaction assessed by 7-point Likert scale; (9) medication use measured by the Medication Quantification Scale III (MQS III); (10) opioid dependence and (11) the incidence of related adverse events (AEs).[39–45] All the secondary outcomes will be measured and analysed at 1-month, 3-month, 6-month, 12-month and 24-month post-intervention. Extra information will be gathered on the EQ-5D-5L, MQS III, opioid dependence and related AE at 9 months after intervention for the health economic analysis. We defined certain AE of interest that will be systematically questioned. There are the following: postoperative pain (transient neuritis), infection, damage to collateral tissue (nervous tissue: eg, deafferentation dysesthesia, paralysis; blood vessel: eg, bruising or haematoma; ligaments: eg, pes anserine damage; skin: for example, superficial burns), failure of technique and allergy.

Additionally, in order to perform the health economic analysis data will be gathered on healthcare resource utilisation (including AEs, additional or reinterventions to the knee, pain medication, visits to a range of medical specialists and general practitioner visits) and productivity loss resulting from work absence and/or reduced labour input due to sickness assessed by the Work Productivity and Activity Impairment (WPAI) questionnaire at baseline and at 3-month, 6-month, 9-month, 12-month and 24-month postintervention.[46 47]

The analysis of these endpoints will be performed by means of the cross-sectional difference of the endpoints at 6, 12 and 24 months following the three comparisons similar to the primary endpoint (cooled RF vs sham, conventional RF vs sham and cooled vs conventional RF) and by means of an analysis of longitudinal changes for the whole follow-up of the study.

We chose to assess the proportion of patients with a pain reduction of at least 50% assessed by the NRS compared with baseline despite the fact that the IMMPACT guidelines recommend only a threshold of 30%.[37] This decision was made since a 50% threshold is the most used threshold in the clinical setting as well as in previous studies on RF on chronic knee pain. This choice will facilitate the comparison with the current literature.

Exploratory endpoints

This trial aims additionally to define the phenotype of patients suffering from PPSP in Belgium and the Netherlands as no large regional studies have been performed in this population and to assess the proportion of patients requiring additional interventions after RF treatment. The latter includes minimally invasive interventions (IA steroid injections, IA hyaluronic acid, platelet rich plasma infiltrations, repeat RF of the genicular nerves) and surgery (primary/revision TKA and other knee related surgery) and will be measured using the variable 'time to additional interventions' recorded at each time point.

Data collection and management

Follow-up is organised with online questionnaires (used at baseline, 1-month, 3-month, 6-month, 9-month, 12-month and 24-month postintervention), telephonic consultations (at the end of the run-in phase) and in-hospital visits at baseline, 1-month, 3-month, 6-month, 12-month and 24-month postintervention as shown in

Table 2 Table of trial procedures of the COGENIUS trial (also see online supplemental file)

		Intervention phase	Follow-up phase					
Procedures	**Baseline 3 days prior to T0 and the latest on T0**	**T0**	**T1 (1MFU) 30 days post T0±3 days**	**T2 (3MFU) 90 days post T0±7 days**	**T3 (6MFU) 180 days post T0±7 days**	**T4 (9MFU) 9 months post T0±14 days**	**T5 (12MFU) 12 months post T0±14 days**	**T6 (24MFU) 24 months post T0±14 days**
Eligibility assessment	x							
Randomisation	x							
Anthropometric measurements	x							
Concomitant medication (eg, MQS III, opioid dependence)	x		x	x	x	x	x	x
Medical history	x							
NRS	x		x	x	x		x	x
Previous or additional treatment of the knee	x		x	x	x	x	x	x
DN4	x							
WOMAC, HADS and PCS	x		x	x	x		x	x
EQ-5D-5L	x		x	x	x	x	x	x
Patient's satisfaction and PGIC			x	x	x		x	x
Functional tests (goniometry, Timed Up and Go Test and 6 min walk test)	x		x	x	x		x	x
Healthcare resource use questions				x	x	x	x	x
WPAI	x		x	x	x	x	x	x
Intervention		x						
Assessment of the success of the blinding procedure			x					
Adverse events		x	x	x	x	x	x	x
Monitoring of conservative therapy	x		x	x	x		x	x

NRS values after screening will be calculated as the mean value of the 4 previous days. Radiologic imaging for assessment of Kellgren-Lawrence is necessary only for patients who will be included in the OA group.
DN4, Douleur Neuropathique 4 questionnaire; EQ-5D-L, EuroQoL-5D-5L; FU, follow-up; HADS, Hospital Anxiety and Depression Scale; MFU, month follow-up; MQS III, Medication Quantification Scale III; NRS, Numerical Rating Scale; OA, osteoarthritis; PCS, Pain Catastrophising Scale; PGIC, Patients' Global Impression of Change; T, time point; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index score; WPAI, Work Productivity and Activity Impairment questionnaire.

table 2 (and online supplemental table 1). Baseline data include demographic data (eg, age, sex, body mass index), medical history, information on the knee (eg, symptom duration, OA grade, presence of neuropathic pain assessed by the DN4), medication use, questionnaires (eg, WOMAC, HADS, PCS) and functionality tests (eg, Timed Up and Go Test, 6 min walk test). The data will be collected in an electronic case report form in CASTOR EDC in a pseudoanonymised manner and will be stored according to the current legal requirements.

Statistical plan

Sample size

The sample size was calculated to have 80% statistical power to detect a 10-point difference in the total WOMAC score between the compared groups with an estimated SD of 15 at 6 months after intervention. Ten points is reported to be the minimally clinically relevant difference in the total WOMAC score. As we plan three comparisons (cooled RF vs sham, conventional RF vs sham and cooled RF vs conventional RF), the Bonferroni correction for multiple testing was used to adjust the alpha used for testing (0.05/3=0.017) the superiority hypotheses.[48] For each knee pain aetiology (OA and PPSP separately), given the 2:2:1 randomisation ratio and after adjustment for a drop-out rate of up to 10%, we plan to include 80 patients in the conventional RF group, 80 in the cooled RF group and 40 in the sham group adding up to 400 patients in total. To compute the sample size, we used the formula for computing sample sizes to detect a between-group difference on a continuous outcome.[49] To do the computation, we used R V.4.0.2 with the package Trial Size V.1.3.

Statistical analysis

All analyses will be performed according to the intention-to-treat principle (ITT) for each group apart (OA and PPSP). Baseline characteristics will be reported stratified by group. Continuous variables will be reported as mean and SD or median and first and third quartile, depending on the nature of the distribution. Categorical variables will be reported as count and percentage.

Missing data will be imputed using multiple imputation with fully conditional specification, using predictive mean matching to draw imputations for continuous variables. However, for longitudinal analyses, the original data before imputation will be used, taking the likely mechanism of missing data into account in the linear mixed-effects regression.

For the primary endpoint, analysis of variance (ANOVA) with post hoc tests adjusted for multiple testing using the Bonferroni correction will be used. The comparison will be considered statistically significant if the $p<0.017$ (0.05/3).

The WOMAC score at 12 months and 24 months follow-up will also be analysed longitudinally as a secondary outcome using linear mixed-effects regression. Other continuous secondary outcome parameters (NRS, functional tests, EQ-5D-5L, HADS, PCS, MQS III, WPAI and healthcare resource use) will be reported using descriptive statistics and compared between groups at 6 months using ANOVA with post hoc tests, and longitudinal data using linear mixed-effects regression, similar to the primary outcome. PGIC will be dichotomised into intervention success (ie, scoring 'much improved' or 'very much improved') and compared between groups using Pearson's χ^2 test. Time to TKA in the OA group and time to additional intervention in both groups will be assessed within groups using Kaplan-Meier tables. For all secondary hypothesis testing, a conventional alpha of 0.05 will be used.

To assess the success of the double-blind procedure and thus the internal validity of this trial, we will report the BI values for all treatment arms.

All analyses will be performed in the latest version of R after collection of all the study data by a blinded statistical team assigned by the sponsor.

Health economic analysis

A health economic evaluation will be performed from a healthcare payer perspective following the Belgian guidelines, if appropriate.[50] Individual-level healthcare costs will be calculated using healthcare resource utilisation data collected during the trial. The most relevant healthcare elements include the initial intervention received, subsequent hospital visits, related AEs, additional or reinterventions to the index knee, pain medication, medical specialists and general practitioner visits. Belgian market prices or reimbursement fees will be used to value resource use. The measure of effectiveness is the quality-adjusted life-year (QALY). QALYs will be calculated using the area under the curve approach using the EQ-5D-5Lscores. A cost–utility analysis will be conducted using an ITT approach and cost-effectiveness will be expressed using an incremental cost-effectiveness ratio (ICER): the difference in costs divided by the difference in QALYs.[51] Non-parametric bootstrapping techniques are used to address the uncertainty surrounding the differences in costs and effects, and to estimate the probability of (cooled) RF intervention being cost-effective for various willingness to pay thresholds for the ICER, presented in a cost-effectiveness acceptability curve. Several one-way sensitivity analyses will be performed to assess the robustness of results. Due to the expected benefit of (cooled) RF intervention on the ability to participate in society, an additional scenario analysis will include the cost-effectiveness estimate from a societal perspective, including productivity costs.

Assessment and management of risk of trial

The risk associated with the trial interventions is estimated to be comparable to the risk of standard medical care based on the following: (1) the RF equipment device has a CE Marketing Authorisation in Europe and it is used in this trial in accordance with its indication and (2) as COGENIUS is designed as a pragmatic trial, the other study procedures do not deviate from routine clinical practice in Belgium and The Netherlands, apart from the use of more standardised functional tests and questionnaires. These, however, do not add additional safety risks to the study subjects.

Patient and public involvement

Individual patients and patient representatives from three patient organisations (Vlaamse Reumaliga, VMCP and ReumaNet vzw) who represent patients with chronic knee pain and knee OA were involved in the formulation of the research question, design of the study and protocol development. The close collaboration resulted in among others: change of the randomisation rate from 1:1:1 to 2:2:1, formulation of comprehensible informed consent forms and trial information brochures and active participation of two patient experts in the trial steering committee of the COGENIUS as patient researchers.

Status of study

The first patient was enrolled in the study on 2 June 2022. The last patient his last visit is expected in 2026.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the central Ethics Committee of the University of Antwerp (Number Project ID 3069-Edge 002190-BUN B3002022000025) and the Ethics committee of Maastricht University (Number NL80503.068.22-METC22-023) following national requirements and the separate ethics committees of each participating hospital. As such approval was consented from the following local ethics committees of the hospitals (reference number if provided): AZ Klina (N/A), UZ Leuven (S66382), AZ Maria Middelares (MMS.2023.002),

UCL Saint-LUC (N/A), AZ Delta (N/A), AZ Groeninge (AZGS2022002), Hôpital Erasme-ULB (CTC-2022-055 P2022/108), Rijnstate (N/A), AZ Turnhout (N/A), Ziekenhuis Oost-Limburg (Z-2021109), Jessa Ziekenhuis (2022/002), CHR de la Citadelle (N/A) and CHU de Liège (N/A). The protocol has been reviewed by the funder (KCE) and by high-quality independent peer-review experts contacted by the funder. On completion, the results of the study will be published in high-quality open access peer-reviewed journals and will be submitted for presentation at national and international congresses of pain and orthopaedic scientific societies. The full study report will be accessible on ClinicalTrials.gov and results will be additionally disseminated in the COGENIUS website and websites of patient organisations. Substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study.

DISCUSSION

The COGENIUS trial is designed to compare the effectiveness of conventional and cooled RF interventions versus a sham procedure in patients suffering from therapy-resistant chronic knee pain. To our knowledge, no previous powered randomised controlled trial reported this comparison in mentioned population. The design further allows the comparison of both RF treatments to each other and the evaluation of the cost-effectiveness of the RF treatments in two large populations: knee OA and PPSP after a total knee prothesis.

Beside our aim to provide novel clinical information by this pragmatic trial, we addressed several topics relevant to chronic knee pain research during the design of the protocol. First, to include a representatively large population, recruitment of patients will happen in 2 countries and 15 hospitals in total assuring a wide geographical distribution. Small sample size is often reported to be a limitation of systematic reviews on RF. Second, we stringently incorporated a multimodal approach to treat knee pain in the protocol during run-in and patient follow-up. This was done conform to guidelines on the treatment of knee pain and also clinical practice increasing the external validity of the trial.[9 11–13] The results of the trial will thus reflect the additional effect of RF treatment on top of optimal conservative care. Thirdly, the primary outcome of the COGENIUS is planned at 6 months and the total follow-up extends to 24 months. This contrasts with previously reported trials on RF of the genicular nerves where the primary endpoint is often at 3–6 months and follow-up averages around 6 months. There is a resulting controversy on the expected duration of the effect of RF due to a potential nerve regeneration.[52] We aim to provide mid-term to long-term information on the effect of RF. Lastly, there is only a single study of Desai *et al* that reports a cost-effectiveness analysis. Lack of information on the cost-effectiveness of different RF treatments compared with each other and to usual care prevents incorporation of RF in clinical decision-making algorithms and healthcare reimbursement strategies. We try to address these topics in the COGENIUS trial.

There are a few inherent limitations to the protocol of this trial. We opted to use no diagnostic block prior to the study intervention. This decision was based on the study of McCormick *et al* in which the standard prognostic block (1 mL of local anaesthetic and a 50% threshold of success) did not lead to improved outcomes. Furthermore, there are no prospective studies showing a better outcome with the use of prognostic genicular nerves blocks, multiple studies do not perform a prognostic block, and a prognostic block leads to additional patient discomfort and a potential risk of infection especially in PPSP patients post-TKA.[53–56] The use of a 80% threshold for success could lead to better patient selection in the future, however, presently no prospective studies use this criterion.[57]

Inherent to a relative new technique, there is still evolution in which the RF procedure is performed. Kim *et al* wonder whether it would be better to treat more nerves without answering the question.[22] Despite this, a comparison of Fonkoue *et al* of an RF treatment between 3 and 5 genicular nerves showed no differences.[58] The anatomical targets for the genicular nerves during the RF procedure are also regularly updated to increase the chance of treatment success. We incorporated the revised anatomic landmarks of the SMGN and SLGN in this protocol. We concluded, however, that treating three genicular nerves most accurately reflects present clinical practice.

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input and revised the manuscript. PV provided domain knowledge expertise and clinical input and revised the manuscript. KT designed the study protocol, provided support with grant application and clinical trial management and revised the manuscript. JVZ conceived the study, designed the study protocol, provided domain knowledge expertise and clinical input, revised the manuscript and is chief investigator. All authors have contributed substantially to the manuscript and agree with the content.

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