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COMPARISON OF **CO**NVENTIONAL AND COOLED RADIOFREQUENCY TREATMENT OF THE **GENI**CULAR NERVES VERS**US** SHAM PROCEDURE FOR PATIENTS WITH CHRONIC KNEE PAIN: A MULTICENTRE, DOUBLE BLIND, RANDOMISED CONTROLLED TRIAL

COGENIUS Trial

PROTOCOL AMENDMENT 02 VERSION NUMBER AND DATE

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief and co-Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC" and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:	
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Committees	Trial management group (TMG) and Trial Steering Committee (TSC)

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TRIAL SUMMARY

Trial Title	Comparison of conventional and cooled radiofrequency treatment of the genicular nerves versus sham procedure for patients with chronic knee pain: a multicentre, double blind, randomised controlled trial.
Short title	COGENIUS
Trial Design	This study is a prospective, multicentre, double blind, randomised controlled pragmatic trial with three study groups with a 2:2:1 randomisation ratio.
Trial Participants and setting	The study population of interest consists of two separate patient populations, notably patients with chronic knee pain due to therapy resistant osteoarthritis of the knee (OA) or persistent post-surgical knee pain (PPSP) after total knee arthroplasty.
Intervention(s)	There are two intervention groups: cooled and conventional radiofrequency (RF) intervention of the superolateral, superomedial and inferomedial genicular nerves.
Control	A sham procedure with placement of three needles in the subcutaneous area of the superolateral, superomedial and inferomedial genicular nerves with injection of local anaesthetic which will mimic the intervention(s) mentioned above.
Primary Endpoint	The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (range 0-96) at 6 months post-intervention. The comparison of the three groups will happen for the primary endpoint cross-sectionally at 6 months post-intervention.
Secondary Endpoints	• WOMAC score at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention • Pain intensity expressed by the Numerical Rating Scale (NRS) (0-10) at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention. The NRS score at each visit will be calculated as the mean score of the 4 days prior to each visit. • The proportion of patients with a pain reduction of at least 50% compared to baseline expressed by the numerical rating scale (NRS) (0-10). The proportion of patients will be calculated at 1-, 3-, 6-, 12- and 24-months post-intervention. • EuroQoL-5D-5L (EQ-5D-5L) at baseline and 1-, 3-, 6-, 9-, 12- and 24-months post-intervention. • Goniometry using the CJOrtho app, 'timed up and go' test and 6-minute walk test at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention. • Hospital Anxiety and Depression Scale (HADS) and Pain Catastrophizing Scale (PCS) at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention. • Patient Global Impression of Change (PGIC) at 1-, 3-, 6-, 12- and 24-months post-intervention. • Patient's satisfaction assessed by 7-point Likert scale at 1-, 3-, 6-, 12- and 24-months post-intervention.

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	• Medication Quantification Scale III (MQS III) at baseline and 1-, 3-, 6-, 9-, 12- and 24-months post-intervention. • Opioid dependence at baseline and 1-, 3-, 6-, 9-, 12- and 24-months post-intervention visit. • The incidence of related adverse events. Active capture during intervention and 1-, 3-, 6-, 9-, 12- and 24-months post-intervention to assess specific symptoms and adverse events relevant to RF intervention. • Health care resource use is collected at baseline, 3, 6, 9, 12 and 24 months post-intervention. The main elements collected are adverse events (e.g., hospitalisations), additional or re-interventions of the index knee, pain medication, medical specialist, general practitioner, and other health care providers visits. • Productivity loss assessed at baseline, 1, 3, 6, 12 and 24 months using the Work Productivity and Activity Impairment Questionnaire (WPAI). The secondary outcomes will be analysed cross-sectionally at 6-,12- and 24 -months of follow-up and longitudinally, except for adverse events and PGIC (see statistical plan).
Exploratory Endpoints	• Demographic data collected at baseline to phenotype patients suffering from PPSP. • Time to additional interventions (intraarticular (IA) steroid injections, IA hyaluronic acid, platelet rich plasma infiltrations, repeat RF of the genicular nerves or primary/revision TKA) at each time point.
Primary objective	To compare knee pain, stiffness, and function (expressed by total WOMAC score) in patients with chronic knee pain at 6 months between: • patients treated with a cooled or conventional RF intervention of the genicular nerves separately versus sham intervention. • patients treated with a cooled RF intervention of the genicular nerves versus a conventional RF intervention. The primary analysis will be done separately for the two patient populations: OA and PPSP.
Secondary objectives	To further determine the clinical effects of the cooled RF versus conventional RF versus sham procedure up to 24 months in patients with chronic knee pain due to therapy resistant knee OA and in patients with chronic knee pain due to PPSP in terms of: • pain reduction, physical functioning, medication use, and other patient reported outcomes. • side effects of performed interventions. To determine and compare health care resource use and productivity loss in the three groups (i.e., cooled RF, conventional RF, and the sham procedure)
Exploratory objectives	• To identify the phenotype of patients suffering from PPSP. • To assess time to additional interventions after RF / sham intervention.

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Planned Sample Size	200 OA and 200 PPSP randomised patients
Recruitment period	Approximately 24 months
Intervention duration	30 minutes
Follow-up duration	24 months (post-intervention)
Duration of the trial (FPI-CSR)	Approximately 57 months

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ROLE OF STUDY SPONSOR AND FUNDER

Ziekenhuis Oost Limburg autonome verzorgingsinstelling (ZOL AV) as mentioned in KEY TRIAL CONTACT shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the law of 2004.

ZOL AV shall ensure that it shall be mentioned in the protocol, the informed consent forms and in other relevant communication with the study subjects or the regulatory authorities as sponsor of the study.

ZOL AV acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the study or assume any responsibilities or liabilities in connection therewith, and **ZOL AV** shall make no representations whatsoever in this respect.

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ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The role of the TSC is to provide the overall supervision of the trial. The TSC monitors trial progress, conducts and advises on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet on average 3 times per year the first year and twice each year after that. The TSC is composed of the CI, co-CI, the trial statistician, the TC, two independent experts, a physiotherapist specialised in knee rehabilitation, a representative of other participating centres, up to 2 patients or members of the patient organisations, 1 representative of the sponsor, 1 representative of the funder. KCE shall have the right (but not the obligation) to be present at each TSC meeting.

Details of the final members of the TSC, their responsibilities, number of meetings and reporting procedures can be found in the TSC charter.

Trial management group (TMG)

The TMG includes those individuals responsible for the day-to-day management of the trial, such as the CI, co-CI, TC, statistician, and data manager.

The role of the group is to monitor all aspects of the conduct and progress of the trial, to ensure that the protocol is adhered to and to take appropriate action to safeguard the participants and the quality of the trial itself.

Data Safety Monitoring Committee (DSMC)

Given the nature of this study a DSMC 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 committees”. Monitoring of the data is important and will be performed by a clinical research monitor (Clinical Trial Unit - ZOL) and an independent safety reviewer.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
AIC	Akaike Information Criterion
AP	Antero-Posterior
ASA	American Statistical Association
ASRA	The American Society of Regional Anesthesia and Pain Medicine
BI	Blinding Index
BMI	Body Mass Index
CEAC	Cost-Effectiveness Acceptability Curve
CI	Chief Investigator
Co-CI	Co-Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DN4	Douleur Neuropathique 4 Questions
DSMC	Data Safety and Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
ESA	European Society of Anaesthesiology
EU	European Union
EuroQol-5D / EQ-5D-5L	EuroQoL- 5 Dimensions - 5-Level questionnaire
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
IA	Intraarticular
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IMA	Intermutualistisch Agentschap
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IP	Intellectual Property
ISC	Information Security Committee
ITT	Intention-to-Treat Principle
KCE	Belgian Healthcare Knowledge Centre
KL	Kellgren and Lawrence System for Classification of Osteoarthritis
MDI	Medical Device Incident
MDR	Medical Device Regulation

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MFU	Month Follow-up
MP	Monitoring Plan
MQS III	Medication Quantification Scale III
MRI	Magnetic resonance imaging
NA	Not Applicable
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OECD	Organisation for Economic Co-operation and Development
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PO	Per Os
PPSP	Persistent Post-Surgical Pain
PROMs	Patient Reported Outcome Measures
QALY	Quality-Adjusted Life Year
RCT	Randomised Control Trial
RF	Radiofrequency
RIZIV/INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut National d'Assurance Maladie-Invalidité
Rx	Radiography
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SoC	Standard of Care
SOP	Standard Operating Procedure
SORT	The Study of Osteoarthritis Real World Therapies
TC	Trial Coordinator
TKA	Total Knee Arthroplasty
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Trusted Third Party
USADE	Unanticipated Serious Adverse Device Effect
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAI	Work Productivity and Activity Impairment questionnaire
ZOL AV	Ziekenhuis Oost Limburg autonome verzorgingsinstelling

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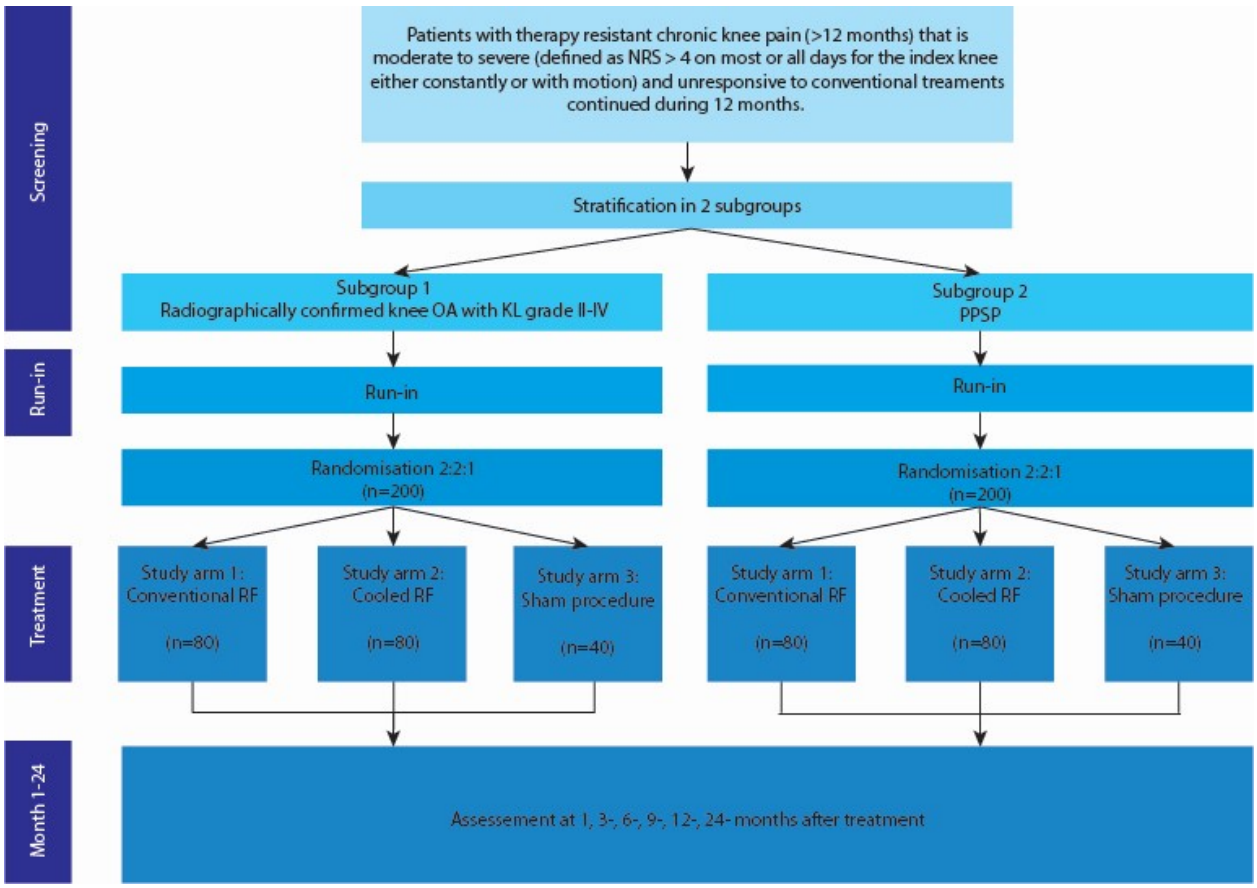
TRIAL FLOW CHART



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STUDY PROTOCOL

1. BACKGROUND

Osteoarthritis (OA) is an increasingly prevalent chronic disease and a leading cause of pain and disability.[1] Knee OA, commonly diagnosed in adults over 50 years of age, is a progressive degenerative disease that affects joint cartilage and the subchondral bone.[1,2] 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] Knee OA pain is generally localised anteromedially due to medial-compartment tibiofemoral joint OA or patellofemoral joint OA. The diagnosis and staging of knee OA are often made clinically together with appropriate imaging techniques (knee radiography or MRI). The most important risk factors linked to knee OA are age, female gender, obesity, trauma, and lifestyle factors.[5] Due to lack of disease-modifying drugs, treatment of knee OA is primary symptomatic, aimed at relieving pain and improving functionality. Conservative care of knee OA is classified as non-pharmacological care (education, land-based exercise programs, dietary weight management), pharmacological care (topical or oral non-steroidal anti-inflammatory drugs, oral paracetamol) and/or infiltrations (intra-articular corticosteroids and hyaluronic acid).[6]

Unfortunately, conservative treatment for knee OA is often insufficient or associated with side effects.[7] Around fifty percent of the population who is first diagnosed with symptomatic knee OA is estimated to eventually undergo surgical treatment in the form of a total knee arthroplasty (TKA).[8] TKA is not a guarantee of success as 20% of patients express dissatisfaction[9] and experience moderate to severe persistent postsurgical pain (PPSP) following primary TKA.[10] Diagnosis of PPSP requires pain of longer than 3-month duration and a negative orthopaedic workup.[11–13] Similar to OA, treatment of PPSP is symptomatic and limited to conservative care.

The general practitioner, the orthopaedist, the rheumatologist, rehabilitation physician, and the pain physician are frequently confronted with therapy resistant knee OA. Conservative treatments have limited efficacy and variable rates of success. Patients often rely on opioids despite their frequent adverse events and addiction. The number of TKA procedures is as a result also rapidly increasing. The lack of therapeutical options is most pronounced in the elderly patient with multiple comorbidities who cannot undergo surgery due to high perioperative risk; the young-aged knee OA patient who faces repeated surgery due to the limited lifetime of the prostheses; the patient who chooses for non-invasive treatment and the PPSP patient.

The previously sketched medical situation stresses the need for improvement in treatment strategies for OA and PPSP. Radiofrequency (RF) treatment of the genicular nerves of the knee is an alternative treatment option for OA and PPSP patients.[14–16] This 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. RF ablation of the genicular nerves is reported as a well-tolerated and safe procedure in recent systematic reviews.[17,18] Possible complications are perioperative pain, temporary increased post-operative pain, paraesthesia's, and self-limiting hematomas. Besides case reports, no serious AEs have been presently described.

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RF treatment of the genicular nerves was firstly described by Choi et al. in 2011 as an effective symptomatic treatment of therapy resistant knee OA improving pain and functionality.[19] Since this first application of RF on the genicular nerves different modalities of RF treatment have been developed. Conventional and cooled RF are two RF modalities that use continuous application of high frequency electrical current to cause a thermal lesion on the peripheral nerve tissue. Cooled RF treatment, introduced for the treatment of chronic knee pain in 2015[20–26], causes a larger lesion size compared to conventional RF by means of internal cooling of the probe.[26] Whilst a larger lesion size theoretically increases treatment efficacy by overcoming physiological variability of genicular nerve location[27], the use of cooled RF in clinical practice is limited by its high product costs. Treatment success (defined as > 50 % reduction in pain scores) is reported in 65% of the patients at twelve months after cooled RF[23–26] while conventional RF is reported to result in 59% success at 3 months after treatment.[19] A limited number of studies, including a single RCT, investigates the use of RF of the genicular nerves in PPSP patients with positive results. A comparison of the effect of the conventional and cooled modality of RF has not yet been performed in the setting of knee OA and PPSP.

The goal of this trial is to compare the effects of cooled and conventional RF of the genicular nerves separately with a sham procedure in patients with chronic knee pain due to therapy resistant OA Kellgren-Lawrence grade 2 to 4 and in patients with PPSP after TKA up to 24 months. Additionally, we plan to compare the effects of the two RF modalities (cooled RF and conventional RF) with each other in the same populations. Furthermore, we want to identify the phenotype of patients suffering from PPSP and, assess the incidence of patients requiring additional interventions after RF treatment.

2. RATIONALE

The rationale for this study is based on the further explained arguments:

- ***High prevalence and burden of knee OA and PPSP***

Knee OA and PPSP are increasingly prevalent diseases. The prevalence of knee osteoarthritis in Flanders was 2% in 1996 and in 2015 3.6%.[28] The incidence in Flanders increased also between 2006 and 2015 from 3.05‰ to 3.75‰, respectively. It is estimated that in Belgium approximately 450000 patients suffered from osteoarthritis of the knee in 2020. In the Netherlands, the prevalence was even higher, estimated to be already 4.04% in 2018.[29] This increase is mainly caused by the aging population and the increasing prevalence of obesity, a well-known risk factor, in the general population.

Due to the increasing prevalence of osteoarthritis of the knee, the incidence of a total knee replacement is also rising to 28121 procedures performed in Belgium in 2018.[30] When comparing the total knee replacement per 100000 inhabitants in 2018 with other countries from the OECD, Belgium qualifies as fifth, indicating a relatively high number of procedures performed.[31] Whilst an increase in the number of executed procedures leads inevitably to an increase in the number of patients suffering from PPSP, no data is available on the prevalence of PPSP in Belgium. International literature suggests that up to 20% of patients are dissatisfied after TKA due, among others to persistent postsurgical pain.[9]

As such, the population of interest for this study is large. Data of the COGENIUS trial will aid in the phenotyping of the patients suffering from PPSP by data collection at baseline through demographic data and patient-administered questionnaires.

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Furthermore, patients with chronic knee pain suffer from a high burden as they experience pain, stiffness and loss of function leading to psychological and sleeping disorders and a diminished quality of life.[3,4]

We verified that the research questions asked are relevant for chronic knee pain patients by contacting three patient organisations (Vlaamse Reumaliga, VMCP and ReumaNet vzw) who represent patients with osteoarthritis of the knee. The protocol, study design, outcome parameters, informed consent form, and trial information brochures were discussed and approved in meetings with the patient organisations.

- ***Limited efficacy of current OA and PPSP treatments***

The Study of Osteoarthritis Real World Therapies (SORT), a clinical prospective observational study conducted in six European countries, reported in 2015 that inadequate pain relief is a highly prevalent problem in more than half of patients with OA.[7] The patients reporting inadequate pain relief are more likely to be female and have longer disease duration, bilateral knee OA, greater opioid use, and higher prevalence of co-morbidities.[7] These data suggest that pharmacologic and non-pharmacologic therapies do not meet the needs of a large knee OA population and that patients with inadequate pain relief resort to opioids. For PPSP there is no other treatment option than pain medication with its inherent risks and revalidation. There is no study evaluating efficacy of treatment strategies in PPSP, but we know that medication has a high number needed to treat and inherent side effects.[9]

- ***Increasing evidence of efficacy of RF treatment of the genicular nerves and lack of comparative studies on different RF modalities***

The number of published articles on RF ablation as a treatment of chronic knee pain has increased exponentially in the last decade and there is increasing evidence that RF of the genicular nerves is an effective and safe procedure in knee OA. Supporting this, the updated OARSI guideline in 2019 on the treatment of osteoarthritis of the knee issued a positive recommendation on the use of radiofrequency treatment in knee OA.[6] The available body of literature on RF in PPSP is more limited, however data indicate that the efficacy is probably similar to RF in knee OA. The pathophysiological mechanisms of pain are different in OA and PPSP. Despite this, RF blocks the pain transmission pathway and acts as a universal symptomatic treatment. Due to the clinical and pathophysiological discrepancies in OA and PPSP, both groups will be investigated separately in the COGENIUS study. RF ablation of the genicular nerves is thus clinically relevant in both treatment groups as there is at the moment a lack of effective non-surgical strategies in both.

The COGENIUS study is designed to identify the most effective treatment strategy among conventional and cooled RF in knee OA and PPSP. Until present, these two treatments are compared to other non-surgical strategies but not with each other. The only direct comparisons between cooled and conventional RF of the genicular nerves are the ongoing pilot COCOGEN trial and the “COOLIEF Cooled Radiofrequency vs. Conventional Radiofrequency to Manage OA Knee Pain” trial (NCT04145011). The COCOGEN trial is the pilot study of COGENIUS and is conducted by the same research group. The NCT04145011 is an US-based industry sponsored trial developed to compare the effectiveness of cooled RF with conventional RF on knee OA. Major design differences of the COGENIUS and the NCT04145011 trial are:

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COGENIUS is a non-commercially sponsored trial; NCT04145011 is industry sponsored by AVANOS, the producer of the Cooled RF-electrode.

COGENIUS is a double-blinded study (participant and outcome assessor are blinded) while the NCT04145011 trial is single-blinded (only participant-blinded).

COGENIUS includes a sham procedure while NCT04145011 does not.

The study population in the COGENIUS includes the PPSP population while NCT04145011 focuses only on knee OA.

Due to the mentioned differences, the COGENIUS trial will add higher quality evidence on RF of the genicular nerves for knee OA and in PPSP patients. The results of NCT04145011 trial will be monitored and discussed within the TSC. Continuation of the COGENIUS trial will depend on decision made by the TSC.

- ***High economic and societal cost of chronic knee pain***

The costs associated with the treatment of chronic knee pain are large.[32,33] The highest cost is the placement of a TKA. Additionally, patients suffering from OA and PPSP are impaired in their daily activities, including (voluntary and paid) work. RF modalities have the potential to decrease costs for treatment, diagnostic procedures, outpatient clinic visits, and lost productivity in both OA and PPSP patient groups. The decrease in economic and societal costs due to RF is probably more pronounced in the OA subgroup compared to PPSP due a higher prevalence and to the high rate of surgical procedures (TKA) performed in knee OA. TKA is for example one of the most frequently performed elective surgeries worldwide and it is associated with high direct medical costs. In 2019, in Belgium 24 948 total knee replacement procedures were performed for a cost of 20 259 860 euro.[34]

The need for effective strategies for knee OA and optimisation of non-surgical treatments is stressed by a recent awareness raisingcampaign by the RIZIV/INAMI. This campaign, directed to orthopaedic surgeons and general practitioners, informs them that guidelines recommend the use of non-operative treatments such as conservative approaches or infiltrations for degenerative knee complaints in patients older than 50 years.[35] RF of the genicular nerves falls in the above mentioned non-operative category.

- ***Necessity for inclusion of a sham procedure***

The mounting evidence on the potency of the interventional placebo effect in OA is grounds for incorporation of a sham procedure in the COGENIUS trial. The OARSI Clinical Trials Recommendations on the design and conduct of clinical trials of surgical interventions for OA recommend the use of a sham procedure when ethically justified.[36] The placebo effect of interventions in osteoarthritis is estimated to be considerably higher than the placebo effect of medication.[37–39] As such, usual care is not an optimal comparison group. The power of sham surgery was clear in the comparative studies of knee arthroscopy versus sham surgery[40] and in a recent study (2020) on the placebo effect of knee injections.[41] Knee arthroscopy did not demonstrate superiority to a sham surgical procedure despite exceedingly high levels

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of patient satisfaction. Furthermore, the placebo effect of knee injections in knee OA is not only significant but also leads to long lasting functional and pain improvements.[41]

To date, conventional RF of the genicular nerves has been shown to be superior to a sham procedure in a single small sized RCT (of only 19 patients recruited in each group) on knee OA of only 3 months of follow-up.[19] No other study compares RF to a sham procedure. As such, the clinical need for (larger) adequately powered trials comparing RF to a sham procedure is unmet. The decision to include a sham procedure is fully supported by the consulted patient organisations.

- ***CONCLUSION***

The COGENIUS trial will increase evidence on the effectiveness of minimally invasive RF interventions in the highly prevalent group of individuals with chronic knee pain. The patients have a high burden with a diminished health-related quality of life. Their needs are at the moment unmet by other treatment strategies. The costs associated with chronic knee pain and its treatment are high. We want to investigate which procedure is the most effective and leads to the least health care resource use and productivity loss. In case of a positive trial, large implementation of the RF treatment has the potential to improve health-related quality of life and decrease the economic and social burden of knee OA and PPSP.

3. ASSESSMENT AND MANAGEMENT OF RISK

Patients in the three intervention groups have the opportunity to benefit from optimisation of usual care and of positive treatment effects of the RF intervention (pain relief, functional improvement, improved quality of life). Potential side effects of the RF intervention are hematoma, infection, temporary increase of pain, hyperesthesia, paraesthesia and neuralgia or paralysis, superficial burns, damage to collateral nervous tissue or soft tissue, failure of technique and allergy.[19,23] Potential side effects of the sham procedure are due to skin penetration (hematoma, infection) and allergy to the local anaesthetic used. The additional risks associated with either intervention options are expected to be very low, and we conclude that this trial can be categorised as a “Low intervention” clinical trial for the following reasons:

- The RF equipment device used for the study intervention has a CE Marketing Authorisation in Europe.
- The RF equipment device is used in accordance with the indication as mentioned in the European Marketing Authorisation.
- The additional (monitoring) study procedures do not deviate from routine clinical practice in Belgium and in the Netherlands, apart from the use of more standardised functional tests and questionnaires. These study procedures do not add additional safety risks to the study subjects.

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4. OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

4.1. Primary objective

The primary objective is to compare knee pain, stiffness, and function (expressed by the total WOMAC score) in patients with chronic knee pain due to therapy resistant knee OA and in patients with chronic knee pain due to PPSP at 6 months. The comparison will be performed between:

- Patients treated with a cooled or conventional RF intervention of the genicular nerves separately versus sham intervention.
- Patients treated with a cooled RF intervention of the genicular nerves versus a conventional RF intervention.

Our primary hypothesis is that in patients with chronic knee pain due to therapy resistant knee OA and in patients with chronic knee pain due to PPSP:

- RF intervention of the genicular nerves, whether cooled or conventional, is superior compared to a sham procedure
- A cooled RF intervention of the genicular nerves is superior compared to a conventional RF intervention of the genicular nerves

in improving the WOMAC score at six months. The primary analysis will be done separately for the two patient populations: OA and PPSP.

4.2. Secondary objectives

The secondary objectives are:

Firstly, to further determine the clinical effects of the cooled RF versus conventional RF versus sham procedure up to 24 months in patients with chronic knee pain due to therapy resistant knee OA and in patients with chronic knee pain due to PPSP in terms of:

- Pain reduction, physical functioning, medication use, and other patient reported outcomes.
- Side effects of performed interventions.

Our hypothesis for the secondary endpoints is that in patients with chronic knee pain due to therapy resistant knee OA and in patients with chronic knee pain due to PPSP:

- RF intervention of the genicular nerves, whether cooled or conventional, is superior compared to a sham procedure.
- A cooled RF intervention of the genicular nerves is superior compared to a conventional RF intervention of the genicular nerves.

Secondly, to determine health care resource utilisation and productivity loss associated with the two RF treatments and the sham procedure up to 24 months post-intervention.

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4.3. Exploratory objectives

The exploratory objectives are:

- To identify the phenotype of patients suffering from PPSP.
- To assess the incidence of patients requiring additional interventions after RF intervention.

A study investigating the longer-term effects (more than 2 years) of RF on radiographic progression in the two active intervention arms (conventional and cooled RF) compared to the sham arm in the OA population is beyond the scope of this study. A follow-up study of COGENIUS with a separate scientific research budget and protocol to address longer term efficacy, safety concerns and radiographic progression can be planned in the future.

4.4. Primary endpoint

The chosen primary and secondary outcomes follow the OMERACT-OARSI and IMMPACT core outcome guidelines.[43,44]

The primary endpoint is the WOMAC score (range 0-96) at 6 months post-intervention.

The WOMAC score is derived from a self-administered osteoarthritis-specific validated questionnaire on pain, stiffness, and physical functioning of the knee joint.[45]

This endpoint will be compared between three intervention groups. The hierarchy of the analysis will be as follows:

- A cross-sectional difference between the outcome in the RF group, whether cooled or conventional, versus the sham intervention group.
- A cross-sectional difference between the outcome in the cooled RF group versus the conventional RF group.

4.5. Secondary endpoints

The secondary endpoints together with the time points of their measurement are listed below:

- WOMAC score collected at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention.
- Pain intensity assessed by the mean numerical rating scale (NRS) (0-10) of the 4 days prior to each visit.[46] Collection of NRS will happen at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention.
- The proportion of patients with a pain reduction of at least 50% assessed by the NRS compared to baseline calculated at 1-, 3-, 6-, 12- and 24-months post-intervention*.
- Health-related quality of life assessed by the EuroQoL-5D-5L (EQ-5D-5L) collected at baseline and 1-, 3-, 6-, 9-, 12- and 24-months post-intervention.[47]
- Physical functioning [48] assessed by goniometry by using the CJOrtho app, ‘timed up and go’ test and 6-min walk test collected at baseline and 1-, 3-, 6-, 12- and 24-months post-intervention.

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- Mental health status assessed by the Hospital Anxiety and Depression Scale (HADS) [49] and Pain Catastrophizing Scale (PCS) [50] collected at baseline and at 1-, 3-, 6-, 12- and 24-months post-intervention.
- Patient Global Impression of Change (PGIC) [51] collected at 1-, 3-, 6-, 12- and 24-months post-intervention.
- Patient's satisfaction assessed by 7-point Likert scale at 1-, 3-, 6-, 12- and 24-months post-intervention.
- Medication use measured by:
    - The Medication Quantification Scale III (MQS III) collected at baseline and at 1-, 3-, 6-, 9-, 12- and 24-months post-intervention.[52]
    - Opioid dependence at 1-, 3-, 6-, 9-, 12- and 24-months post-intervention visit.
- The incidence of related adverse events. Active capture during each study contact to assess specific symptoms and adverse events related to RF intervention.
- Health care resource utilisation, including adverse events, additional or re-interventions to the index knee, pain medication, visits to a range of medical specialists, general practitioners, and other health care providers are assessed at baseline and 3, 6, 9, 12 and 24 months post-intervention.
    - Adverse events (including hospitalisations), knee interventions and pain medication are actively monitored and captured during each study contact. Three questions regarding medical specialist, general practitioner, and other health care providers visits are added to questionnaires package completed by patients at baseline, 3, 6, 9, 12 and 24 months.
- Productivity loss due to sickness assessed by the Work Productivity and Activity Impairment (WPAI) questionnaire[63] at baseline, 1, 3, 6, 9, 12 and 24 months. Productivity loss due to sickness refers to output loss resulting from work absence and/or reduced labor input due to sickness.

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 same hierarchy as the primary endpoint and by means of an analysis of longitudinal changes for the whole follow-up of the study. The adverse events and PGIC will be analysed differently (see statistical plan).

* The chosen threshold in this study is of 50% pain reduction even though IMMPACT guidelines only recommend a threshold of 30%. 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 facilitates the comparison with the current body of literature.

4.6. Exploratory endpoints

The exploratory endpoints are:

- Demographic data collected at baseline to phenotype patients suffering from PPSP.
- Time to additional interventions at each time point. Interventions will be divided in minimally invasive interventions (intra-articular (IA) steroid injections, IA hyaluronic acid, platelet rich plasma

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infiltrations, repeat RF of the genicular nerves) and surgery (primary/revision TKA and other knee related surgery) during the follow-up.

5. TRIAL DESIGN

In this three-arm, pragmatic, prospective, multicentre, double blind, randomised sham-controlled trial of approximately 4 years duration, 400 patients with chronic moderate to severe anterior knee pain (>12 months) refractory to conventional treatments will be included. Two groups of chronic knee pain patients will be enrolled depending on the aetiology of knee pain: OA and PPSP. Each patient will undergo a run-in period of 1 to 3 months depending on the previous treatments of the patient. A run-in period is added to the trial to guarantee that conservative treatment is performed in an optimal way before randomisation. In each group (OA and PPSP), non-responders to the run-in period (see section 8.7.2) will be randomly allocated to a conventional RF intervention of the genicular nerves, a cooled RF intervention of the genicular nerves or a sham procedure in a 2:2:1 ratio. Patients will not be systematically unblinded. Unblinding is only possible in the following cases: a valid medical, safety reason or after the termination of the study at 24 months post-procedure. Patients will not be actively offered a crossover option.

6. STUDY SETTING

The study is a multicentre pragmatic trial sponsored by ZOL and coordinated by the Chief investigator Prof. dr. Jan Van Zundert from the department of Anaesthesiology, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Hospital Oost-Limburg, Genk, Belgium, co-Chief investigators Prof. dr. Vincent Bonhomme from the department of Anaesthesiology and Intensive Care Medicine, CHU Liege, Liege, Belgium, dr. Thibaut Vanneste from the department of Anaesthesiology, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Hospital Oost-Limburg, Genk, Belgium and dr. Micha Sommer

Anaesthesiology, Multidisciplinary Pain Centre, MUMC+, The Netherlands.

The participating centres in Belgium and in the Netherlands are chosen because of their expertise in the subject of investigation (radiofrequency intervention of the genicular nerves) and availability of an experienced study team. Both university and non-university (peripheral) hospitals in Belgium were selected with additional attention for a balanced spread in location. All included centres will perform patient recruitment, intervention, and follow-up. The target population is encountered in both primary and secondary care: patients suffering from knee OA are treated by the general practitioner, rheumatologist, orthopaedic surgeon, rehabilitation physician, and pain physician; while patients suffering from knee PPSP are typically treated by the general practitioner, orthopaedic surgeon, rehabilitation physician, and the pain physician. Collaboration with the network and referring general practitioners of all participating centres will be ensured to maximise the recruitment potential.

The specific requirements for the recruiting centres are:

- An existing department of pain management.
- Previous experience with RF intervention of genicular nerves.
- Availability of a study nurse and experience in research studies.

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7. ELIGIBILITY CRITERIA

Adult patients with chronic, moderate to severe anterior knee pain (NRS>4) due to osteoarthritis Kellgren-Lawrence grade 2-4, or due to persistent postoperative pain after TKA will be considered eligible. A total of **400** patients is planned to be randomised in this study: 200 patients in the OA subgroup and 200 patients in the PPSP subgroup.

To be noted: Eligibility checks will be performed at every contact prior to randomisation.

7.1. Inclusion criteria

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

- Signed written informed consent must be obtained before any study assessment is performed.
- Adult patients (Age ≥ 18 years old).
- 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).
- Unresponsive (meaning insufficient pain reduction or intolerance) to conventional treatments ongoing for at least 12 months prior to inclusion. Conventional treatments must include all of the following: active physiotherapy, pharmacological treatment of pain and, in case of OA patients, intra-articular infiltration.
- Only for patients with OA: Radiologic confirmation of knee osteoarthritis of grade 2 (mild), 3 (moderate) or 4 (severe) noted within 12 months prior to the screening for the index knee according the Kellgren Lawrence criteria[54] diagnosed by an independent radiologist with experience in musculoskeletal imaging on Rx or MRI.[55] If imaging will need to be performed at screening, it is recommended to perform an MRI instead of Rx. Imaging with MRI will enable the independent radiologist to perform a better estimation of the grade of OA.
- Only for patients with PPSP after TKA: Patients with PPSP* after TKA need to have had a negative orthopaedic work-up.

***Clarification**:

PPSP is defined as pain that [11–13]:

- lasts > 3 months after surgery
- Was not present before surgery or has different characteristics or increased intensity compared to preoperative pain
- is localised in the knee
- cannot be attributed to other causes.

PPSP results mostly after TKA but could develop after any surgery of the knee. Patients will be included in this trial only if PPSP developed after a TKA.

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7.2. Exclusion criteria

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

- 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.
- Pregnant, nursing or planning to become pregnant before the study intervention. Participants who become pregnant after the study intervention during the follow-up period will not be excluded.
- Chronic widespread pain e.g., fibromyalgia.
- Patients with unstable psychosocial disorder.

  Unstable psychosocial disorder is defined as:

  - *any untreated psychiatric conditions*
  - *any psychiatric condition where the treating medication is not stable the last 3 months prior to inclusion*
  - *patients currently treated by a psychiatrist and the psychiatrist could not confirm that the psychosocial disorder is stable.*

  Patients treated by a general practitioner are considered to have a stable condition.
- Allergies to products used during the procedure (lidocaine, propofol, chlorhexidine).
- 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 neurostimulator.
- Current radicular pain in index leg.
- Previous conventional or cooled radiofrequency of the genicular nerves of the index knee. Previous RF of the index knee other than of the genicular nerves is not an exclusion criterium.
- Patients with therapy resistant bilateral knee pain defined as patients who fulfil the inclusion criteria for pain in each knee i.e., patients who experience chronic knee pain (> 12 months) in both knees that is moderate to severe (defined as NRS > 4 on most or all days either constantly or with motion) and that is unresponsive (meaning insufficient pain reduction or intolerance) to conventional treatments ongoing for at least 12 months prior to inclusion. Conventional treatments must include all of the following: active physiotherapy, pharmacological treatment of pain and, in case of OA patients, intra-articular infiltration.
- Patients who have a planned TKA in the near future defined as patients who already have agreed on a date for the TKA procedure.
- Patients who are unwilling or mentally incapable to complete the study questionnaires.

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8. TRIAL PROCEDURES

All procedures that the included patients are expected to undergo during the trial are described further; timing is indicated in the table of trial procedures (Section 8.8). Procedures are organised as either "Standard of Care (SoC)" or "Study Specific". The study specific procedures are supplementary to and not meant to substitute usual care. The aim of these procedures is to facilitate usual care.

Other interventional therapies on the index knee (including surgical interventions) are allowed for the period of the study follow-up as long as they are well documented. This is necessary for the evaluation of the secondary outcomes. Allowing patients to receive additional interventions is in agreement with the pragmatic nature of this trial and will also improve protocol compliance. Repeat RF of the genicular nerves of the index knee forms an exception to the previous statement. Repeat RF of the genicular nerves, as the intervention that is being tested in this study, is only allowed after the primary endpoint at 6 months. During the follow-up period of the study repeat RF of the genicular nerves will be discouraged in all intervention arms.

8.1. Recruitment

Every effort will be made to gather a representative sample of patients, reflecting the knee OA and knee PPSP population. Recruitment of patients will happen in usual care which is in the primary (general practitioner) and secondary care setting (rheumatologist, orthopaedic surgeon, rehabilitation physician, and pain physician).

Patients can be enrolled if they fulfil all the inclusion criteria and present none of the exclusion criteria. Patients will be recruited over an expected period of approximately 24 months.

8.1.1. Patient identification

Participant identification will happen during standard of care consultations by their treating physician (e.g., general practitioners, rheumatologists, orthopaedic surgeons, rehabilitation physician and pain physicians).

These physicians will be informed about the study by means of information leaflets and lectures explaining RF intervention of the genicular nerves and the trial.

Potential patients for a radiofrequency intervention of the genicular nerves are identified by their treating physicians and in case the patient shows interest in this intervention, they will be referred to the pain physician (PI or delegated physician) of one of the collaborating centres. During the consultation at the pain centre, the pain physician (PI or delegated physician) assesses the patient's potential eligibility for the study and, if applicable, provides all information regarding the study to the patient. If the patient is interested to participate in the study, the consent procedure (see section 8.2 Consent) and collection of baseline data will be performed during the screening visit and baseline visit.

If a potential patient is seen by the PI or delegated physician at the collaborating centres but the patient is eventually not included in the study, the patient will be anonymously listed in the pre-screening log together with the reason of exclusion. These anonymised logs will be shared with the sponsor during the study.

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Potential participants might also be recruited through publicity (posters, leaflets) which can be made publicly available in the participating centres or at the location of the referral physicians.

8.1.2. Screening

During the screening visit the patients will be assessed for eligibility. If they are eligible for the study, informed consent will be obtained, and baseline data will be collected (see section 8.7.1). The PI or delegated pain physician will afterwards prescribe the conservative treatment as part of the run-in period. This includes education, reimbursed physiotherapy, weight management, optimisation of the pharmacological therapy and self-management.

No study specific procedures are required to determine patient eligibility. All assessments are standard of care and most of the information should be available in the patient's file prior to the screening visit.

Screening and demographic data must be obtained prior to inclusion to the run-in period. Subjects not meeting one or more inclusion criteria or presenting exclusion criteria will not be randomised in the study but can be rescreened at a second time point. In this case, all the screening assessments will need to be repeated.

8.2. Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any delegated person participating in the task is duly authorised, trained, and competent according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

All PI's or delegated persons will choose patients in accordance with eligibility criteria and will not be selective, thus preventing bias.

Prior to enrolment in the study, patients will receive a comprehensive written and oral explanation of the study and the proposed intervention including the nature and objectives of the trial and the risks involved with participation. Patients will be provided with a consent document that is approved by the independent EC. Patients will be allowed sufficient time after this comprehensive explanation to consider participation in the study and their questions will be answered during the meetings with the PI or delegated study staff.

The informed consent must be signed by the PI or delegated person and by the patient before entering the study i.e., before any study-related tasks are performed. By signing the informed consent form, the patient agrees with all proposed interventions and evaluations included in the study. However, the participant is free to withdraw from the study at any time point without giving reasons. The process of obtaining informed consent should be documented in the patient source documents.

8.3. Run-in period

Once the patient is screened, all patients who meet all of the inclusion criteria and none of the exclusion criteria will undergo a run-in period of approximately 1 to 3 months with standardized conservative treatment. The purpose of the run-in period is to ensure that all participants have received optimum conservative treatment and therefore to exclude patients who are responsive to conservative treatment.

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Success of conservative treatment is defined as a mean NRS ≤ 4 during the 4 days prior to the run-in evaluation contact. Mean NRS will be measured by means of a patient pain diary which will be completed by the patient 3 times a day during the 4 days prior to the run-in evaluation contact. Patients who did not previously consult an orthopaedic surgeon will be referred for a consultation during the run-in period. This consultation is not study specific.

The run-in period includes the following:

- ***Education on Osteoarthritis or PPSP***:
  Epidemiology and risk factors, clinical presentation, diagnosis, and management of knee osteoarthritis or PPSP. Patients will be referred to other online sources of information and to patient representative groups (Appendix 6).
- ***Physiotherapy***:
  All patients will be advised to have an active lifestyle and are required to follow physiotherapy during the run-in period and the study follow-up. These will be prescribed according to a standardized scheme (e.g., for Belgium this means a maximum of 18 physiotherapy sessions per year corresponding with the reimbursed number of sessions per diagnosis per year). The physiotherapy sessions will be led by external physiotherapists who will receive a standardized physiotherapy prescription (Appendix 5) that includes the diagnosis, type, frequency, goals, and duration of the prescribed therapy.
- ***Dietary weight management*:**
  Weight loss will be advised to all patients with a Body Mass Index (BMI) > 25 kg/m². All patients with BMI ≥ 30 kg/m² will be referred to an external dietician in a standard manner and will be advised to aim a minimum of 5% weight loss.
- ***Self-efficacy and self-management programs***:
  Patients will be referred to self-help groups who organize activities about education, self-empowerment, and self-efficacy.
- ***Gait aids*** (in the form of tibiofemoral & patellofemoral knee brace) are allowed and recommended following advice of general practitioner and/or orthopaedic surgeon.
- ***Optimisation of the pharmacological treatment***:
  Optimisation of the pharmacological treatment will be performed with the medication presented in the table. The medication will be prescribed according to the following ***step-up scheme***:
  - Step 1: Topical NSAIDs & Paracetamol
  - Step 2: Oral NSAIDs
  - Step 3: Tramadol
  - Step 4: Duloxetine

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Group	***Application***	***Contra-indication***	***Specification***
Topical NSAIDs	*Transdermal local applications*	*Allergy*	*NA*
Paracetamol	*Oral*	*Allergy*	*NA*
Oral NSAIDs	*Oral*	*Gastro-intestinal comorbidity:* ● *Active gastroduodenal ulcer* ● *Gastro-intestinal bleeding or perforation during previous use of NSAIDs* ● *Active Colitis Ulcerosa or Morbus Crohn* *Kidney failure* *Allergy*	*In case of Gastro-intestinal contraindication a selective COX-2 inhibitor will be prescribed.*
COX-2 inhibitor	*Oral*	*Allergy*	*NA*
Tramadol	*Oral 2 times/ day 50 mg*	*Allergy* *Uncontrolled epilepsy* *Liver failure*	*NA*
Duloxetine	*Oral*	*Allergy* *Uncontrolled hypertension* *Kidney failure* *Liver failure*	*Indication: Non-sufficient pain control with paracetamol and NSAIDs & DN4 > 4*

The PI or delegated physician is responsible for prescription of the maximal tolerated dose for each patient. The PI or delegated physician is advised to omit any of the steps during the run-in period when the patient has previously tried one of the medications belonging to one of the mentioned drug classes without improvement or in case of medical contraindications. The patient needs to self-evaluate and step up in case of inadequate pain control. Step-up is advised after 2 weeks of testing for all medication except for Duloxetine whose effect can be evaluated only after 6 weeks of ingestion. If the patient experiences some effect from one of the tested medications, they can continue using the medication during the other steps.

All patients will be evaluated by the PI or delegated person after the run-in period. Patients who experience adequate pain control and thus fulfill the goal of the run-in period or are expected to be non-compliant to the follow-up visit will be withdrawn from the trial as screening failures. In case the response to the conservative treatment is insufficient, an appointment will be arranged with the study nurse to gather baseline data together with an appointment for the study intervention. Conservative measures initiated in the run-in period will be continued and monitored throughout the study.

8.4. Trial randomisation

As soon as the PI or delegated person registers in the source documents that the patient is still eligible after the run-in period and all baseline data are collected, the patient can be randomised. Patients should

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be randomised on the day of study intervention. Randomisation will be performed via the CASTOR EDC application.

The system will randomly assign the patient to one of the following intervention groups (2:2:1 ratio):

- Group 1: Conventional RF intervention of the genicular nerves, or
- Group 2: Cooled RF intervention of the genicular nerves, or
- Group 3: Sham procedure

The randomisation process has been set-up within each group (knee OA and knee PPSP) with variable block sizes.

Only the PI or qualified person to whom they have delegated this study task can randomise the patient in the automated web-based system of CASTOR EDC. The randomisation can only be performed by people who have been trained in using the CASTOR application.

Only the unblinded team will receive the information regarding the intervention group (cooled RF, conventional RF, or sham intervention) to which a patient is randomised. People who are blinded to the allocation of the study intervention will have no rights in CASTOR to see the specifics of the randomisation information.

8.5. Blinding

This is a double-blind study which means that the patient and outcome assessor are blinded to intervention allocation. Therefore, after randomisation, the investigator evaluating the patient (outcome assessors) and the patient will not know which intervention has been administrated.

Therefore, patients will be treated by an independent pain physician who is not involved in the assessment of the outcomes or follow-up of the patient. The intervention team (including the pain physician performing the RF/sham intervention and the nurse assisting the treating physician) will be the only individuals who are unblinded to the randomisation.

The blinding procedure will be discussed during the initiation visits at each participating site. The steps that are taken to standardize the blinding procedure for all three different interventions are described below.

Steps to standardize the intervention arms:

- All three interventions are performed in a similar context:
  - Same operation room
  - Same monitoring (oximeter)
  - Same interventional team composition: e.g., one nurse and a pain physician
  - The RF machine will be turned on and functional or the sound of RF device is mimicked.
  - A vertical drape is placed between the patient at his/her knee to hinder vision. The RF machine, the used needles and the fluoroscopy/ultrasound monitor will not be visible from the patient's perspective.

- Communication with the subject is similar:

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  - Nurse and doctor will communicate with the patient in an analogous manner following predefined script during all procedures (details see section 9).

- The procedure is similar (details see section 9):
  - Similar patient positioning
  - Periprocedural noise is similar. The RF device is turned on and functional or the sound of RF device is mimicked.
  - The local anaesthetic used for anaesthesia of the skin and soft tissue is similar (1 ml lidocaine 2% at the estimated entry points)
  - A needle of similar size is used in all interventions.
  - Sensory and motoric stimulation test will be performed in all interventions.
  - Duration of the procedure is similar. In both interventions and sham procedure, the needle will be positioned for a minimum of 150 seconds per genicular nerve.
- The unblinded source data regarding the intervention is stored by the unblinded intervention team. Only blinded information is shared in the (electronic) patient file which can be viewed by other (blinded) authorised persons at the hospital/pain clinic.

The intervention (cooled RF, conventional RF, or sham) is a study specific procedure and is accordingly refunded by the sponsor. The patient will not receive a payment request regarding this study procedure/intervention visits. This will also assure blinding of the patients.

Once a patient is assigned to one of the study interventions, they will remain in that arm and all efforts will be made to optimise the intervention trajectory. All patients that have been randomised will be kept in the intention-to-treat (ITT) analysis regardless of received intervention. In the unlikely event that this is clinically not feasible, the patient will remain in the assigned intervention arm for statistical analysis based on the ITT principle, as it represents a normal medical situation of success and failure to deliver the planned medical therapy.

The blinding of each patient enrolled in this study will be tested at the first follow-up consultation at 1 month after randomisation to provide their “best guess” of the intervention 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.[56,57]

8.6. Unblinding

Patients will not be systematically unblinded. Patients can be unblinded in case of valid medical or safety reasons e.g., in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which intervention the patient has received before the participant can be treated. Where possible, members of the sponsor research team will remain blinded. It is not mandatory but strongly encouraged to contact the chief investigator and/or co-chief before unblinding the patient’s intervention assignment.

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Unblinding steps:

1. If the treating health care professional is not a member of the unblinded intervention team, they can ask advice from the unblinded physician.
2. If the unblinded physician is not available, the unblinded dossier of the patient can be asked from the unblinded intervention team.
3. If the unblinded intervention team is not reachable, the unblinded contact person at the sponsor can be contacted. Contact details can be found in the investigator site file.

In case of premature unblinding, the reason for doing so will be documented in the medical notes and in the eCRF. This will also be documented at the end of the study in the final study report and/or statistical report. The PI/Investigation team will notify the Sponsor of the event and the reason for the unblinding in writing within one working day following the code break. The unblinded patient will be followed up afterwards for the remaining time of the study despite the unblinding. Efforts should be made to keep the patient and as many members of the research team as possible blinded.

8.7. Visit schedule

The visit schedule for this study can be divided into 4 phases:

1. **Screening phase** (screening): starting from identifying a study subject until the start of the run-in. This includes a pre-screening visit for identifying potential patients, a screening visit for obtaining informed consent and screening parameters. These visits may be performed on the same day.
2. **Run-in phase**: This includes the start of the run-in, a contact for evaluation of the run-in period for elimination of screening failures and a visit for collection of baseline parameters before randomisation. The randomisation will be performed the same day but prior to the study intervention.
3. **Intervention phase**: Performing the study intervention (1 day hospitalisation).
4. **Follow-up phase:** after the intervention, the patient will be followed up for 24 months. During this phase 5 hospital visits are planned: at 1 month follow-up (MFU) (1MFU ± 3 days), 3 (3MFU ± 7 days), 6 (6MFU ± 7 days), 12 (12MFU ± 14 days) and 24 months (24MFU ± 14 days) post-intervention. Additionally, patients will be expected to fill in questionnaires at 9 months follow-up (9MFU ± 14 days) and an assessment of the adverse events and previous or additional knee interventions.

In case of a pandemic follow the instructions of Appendix 7.

8.7.1 Screening phase

At the pre-screening visit (a SoC visit) potential patients are identified. During the screening visit eligibility is checked, informed consent is obtained, screening data is collected, and the run-in plan is discussed with the patient (see section 8.3). The list of all required assessments/information to be collected during the screening phase is presented below:

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The following information will be captured from routine clinical data (SoC) at screening visit with the researcher:

- Demographic data: age and sex
- Screening data index knee:
  - Aetiology of the index knee pain (OA or PPSP)
  - Length of symptom duration regarding the index knee
  - Severity of the chronic anterior knee pain (assessed by the patient by means of NRS on most or all days for the index knee either constantly or with motion).
  - Grade of OA (assessment by independent radiologist) in patients in the OA subgroup
  - Previous or ongoing treatments regarding the index knee (including active physiotherapy, intra-articular injections other (minimally) invasive knee treatments and/or orthopaedic workout)
- Height and weight
- Concomitant medication

The following assessment will be performed:

- DN4 (Douleur Neuropathique 4) assessment (for identification of neuropathic pain)

In addition, a consultation with the PI or delegated person will be scheduled to evaluate the run-in period. The patient will be asked to complete a patient diary during the 4 consecutive days prior to the run-in evaluation consultation (see section 8.7.2).

8.7.2 Run-in phase

The patient will need to follow the PI or delegated persons' instructions regarding the patients' run-in plan provided during the screening visit (see section 8.3). During the run-in evaluation consultation, the PI or delegated person will identify eligible patients and exclude patients that are responsive to optimal conservative care. Thereafter a baseline visit will be organised to collect the final baseline parameters and the intervention visit (1 day hospitalisation) will be scheduled. All these contacts are study specific.

The list of all required assessments/information to be collected during the run-in phase is presented below:

The following information will be captured at the run-in evaluation consultation with the researcher:

- Mean NRS of the 4 previous days measured 3 times per day. This NRS scoring will be seen as baseline data.

The following information will be captured from routine clinical data (SoC) and study specific tests at the baseline visit with the researcher:

- Medical history:

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  - Smoking history
  - Alcohol intake per week
  - Relevant medical history (Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Cancer, Endocrine, Musculoskeletal, Psychiatric disorders, Metabolic disturbances and/or other comorbidities)
- Changes in treatment of the index knee (including active physiotherapy, intra-articular injections, other (minimally) invasive knee treatments and/or orthopaedic workout)
- Concomitant medication

The following assessments will be performed at the baseline visit:

- Weight
- DN4 (Douleur Neuropathique 4) assessment (for identification of neuropathic pain)
- Functional tests:
  - Goniometry
  - Timed up and go test
  - 6-minute walk test

The following questionnaires will be completed by the patient at the latest during baseline visit:

- WOMAC
- EQ-5D-5L
- HADS
- PCS
- WPAI
- Health care resource use questions

Once the PI or delegated person has confirmed that the patient is a non-responder to the conservative treatment and all the baseline data are collected the patient can be randomised (see section 8.4).

8.7.3 Intervention phase

During the intervention phase the intervention will be performed (see section 9) and the following data will need to be collected:

- Date of the intervention
- Complications of the intervention
- Particularities occurred during intervention

After the intervention, the patient will receive a patient diary and they will be requested to complete the diary during the 4 days prior to the follow-up visits.

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All participants will also receive a standardised prescription for adequate physiotherapy with a predefined program for knee pain at the start of the study to optimise physiotherapy or restart physiotherapy (Appendix 5). Patients are encouraged to continue usual care during the study. Subjects are allowed to use other medication or undergo an intervention as long as this is documented. If required, repeat RF of the genicular nerves is only allowed after the primary endpoint at 6 months.

8.7.4 Follow-up phase

During the follow-up phase 5 hospital visits will take place. These visits will take place at 30 days (1MFU ± 3 days), 90 days (3MFU ± 7 days), 180 days (6MFU ± 7 days), 12 months (12MFU± 14 days) and 24 months (24MFU ± 14 days) after the intervention.

During these follow-up visits the following data will be collected:

- Patient Reported Outcome Measures (PROMs):
  - WOMAC
  - Mean NRS measured by patient's pain diary which was completed by the patient 3 times a day during the 4 days prior to each follow-up visit
  - EQ-5D-5L
  - HADS
  - PCS
  - Patient satisfaction measured by 7-point Likert scale
  - PGIC
  - Assessment of the success of the blinding procedure (section 8.5) (only at 1MFU)
  - Health care resource use: Medical specialist, general practitioner, and other healthcare providers visits questions (not at T1 (1MFU))
  - WPAI
- Concomitant medication
- Additional intervention(s) of the knee
- Functional tests:
  - Goniometry
  - Timed up and go test
  - 6-minute walk test
- Related Adverse Events (See section 10)
- Monitoring of conservative therapy (continued after the run-in period)

In addition, approximately 9 months after the intervention (9MFU ± 14 days) the patient will be requested to complete the following questionnaires:

- EQ-5D-5L

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- WPAI
- Health care resource use: Medical specialist, general practitioner and other healthcare providers visits questions.

During this time point also the following information will be collected:

- Concomitant medication
- Additional intervention(s) of the knee
- Related Adverse Events (See section 10)

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8.8. Table of trial procedures

Procedures	Screening Phase		Run-in Phase		Intervention Phase	Follow-up Phase					
	Pre-screening	Screening	Run-in evaluation consultation	Baseline	T0	T1 (1MFU)	T2 (3MFU)	T3 (6MFU)	T4 (9MFU)	T5 (12MFU)	T6 (24MFU)
			Approximately 1 to 3 months after screening visit	3 days prior to T0 and the latest on T0		30 days post T0 ± 3d	90 days post T0 ± 7d	180 days post T0 ± 7d	9 months post T0 ± 14d	12 months post T0 ± 14d	24 months post T0 ± 14d
Informed consent*		x									
Eligibility assessment*	x	x	x	x							
Randomisation*				x[1]							
Demographic data		x									
Anthropometric measurements		x[2]		x[3]							
Concomitant medication (e.g., MQS III*, opioid dependence)		x		x		x	x	x	x	x	x
Medical history				x							
NRS[4]		x	x			x	x	x		x	x
Radiologic imaging		x[5]									
Previous or additional treatment of the knee*		x		x		x	x	x	x	x	x
DN4		x		x							
WOMAC*, HADS*, and PCS*				x		x	x	x		x	x
EQ-5D-5L*				x		x	x	x	x	x	x

Procedures	Screening Phase		Run-in Phase		Intervention Phase	Follow-up Phase					
	Pre-screening	Screening	Run-in evaluation consultation	Baseline	T0	T1 (1MFU)	T2 (3MFU)	T3 (6MFU)	T4 (9MFU)	T5 (12MFU)	T6 (24MFU)
			Approximately 1 to 3 months after screening visit	3 days prior to T0 and the latest on T0		30 days post T0 ± 3d	90 days post T0 ± 7d	180 days post T0 ± 7d	9 months post T0 ± 14d	12 months post T0 ± 14d	24 months post T0 ± 14d
Patient's satisfaction* and PGIC*						x	x	x		x	x
Functional tests (Goniometry*, Timed up and go test*, and 6-minute walk test*)				x		x	x	x		x	x
Health care resource use questions*				x			x	x	x	x	x
WPAI*				x		x	x	x	x	x	x
Intervention (see section 9)					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	x

Study specific assessments are accompanied by an asterisk (*) while routine care assessments (SoC) are not.

1. Randomisation should be performed on the same day as the intervention
2. During Screening visit, height and weight will need to be measured and collected
3. During Baseline visit, only weight needs to be measured and collected
4. NRS values after screening will be calculated as the mean value of the 4 previous days.
5. Only for patients who will be included in the OA group

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8.9. Withdrawal criteria

All subjects will be encouraged to comply with treatment and follow up visits for the full duration of the study. However, at any time during the study and without giving reasons, subjects may withdraw from the study at their own request. The subject will not suffer any disadvantage as a result.

All patients who are randomised will be analysed using an ITT analysis. All efforts will be made to reduce the number of discontinuations as much as possible.

Discontinuation of the study after receiving study intervention (see section 9) is not always the equivalent of withdrawal of informed consent. In cases where subjects indicate they do not want to continue, investigators must determine whether this refers to unwillingness to attend the follow-up visit, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). Every effort must be made to continue to follow the subject until the end of the study.

In all cases, the reason for discontinuation (including "at the subject's request") must be recorded in the case report form (CRF) and in the subject's medical records.

If a patient is lost to follow-up, every effort will be made to obtain follow-up information and if necessary, to determine the reason for loss to follow-up. The latter will be done by means of contact with the patient's primary physician (GP), a telephone call and a letter to the subject requesting contact with the researcher for the reason for discontinuation of the study.

Withdrawn after having received the study intervention and loss to follow-up patients will not be replaced.

8.10. End of trial

The end of trial is the date of the last visit of the last patient in the trial. The sponsor will notify the participating centres and the independent Ethics Committee of the end of the clinical trial within 90 days of its completion date (last patient last visit).

9. TRIAL INTERVENTION

9.1. Name and description of intervention(s)

The COGENIUS trial involves three interventions:

- Conventional RF of the genicular nerves (superolateral, superomedial and inferomedial genicular nerves)
- Cooled RF of the genicular nerves (superolateral, superomedial and inferomedial genicular nerves)

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- Sham procedure

These procedures are performed during day hospitalisation in a multidisciplinary pain centre.

➢ ***General intervention 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.[58] In the genicular radiofrequency intervention performed in this study, we judged these factors to be in favour of not stopping anticoagulation.

During the procedure, the patient is monitored using pulse oximetry. Sedation (propofol) can be administered if needed to obtain a comfortable patient who is able to communicate and report the stimulation adequately. 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.

No diagnostic block is performed since a recent study showed no prognostic value.[59] No corticosteroids are injected to decrease the risk of complications such as systemic effects and infection.[36] 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.

➢ ***Localisation of the following genicular nerves and anaesthetic procedure:***

- <u>Superomedial genicular nerve</u>

  The transducer is placed in a coronal orientation on the medial side of the proximal knee. After identifying the femoral medial epicondyle, the transducer is displaced to the junction between the epiphysis and diaphysis of the femur and the vastus medialis superficial to it. At this level the adductor tubercle is identified with the insertion of the adductor magnus. The superomedial genicular artery may or may not be seen. 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 adductor tubercle 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 centre of the probe at the assessed probe-to-target point distance. Consecutively, the transducer is turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetised 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 posterior half of the bony cortex of the femur. A RF electrode is introduced in the cannula. Sensory stimulation (50 Hz) is applied and should produce paraesthesia 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, the transducer is repositioned until sensory threshold is reached. However, if after repositioning no sensory threshold is reached and the position of the RF cannula is considered adequate by means of imaging, RF intervention will be performed at this position. This statement is valid for all the three genicular nerves.

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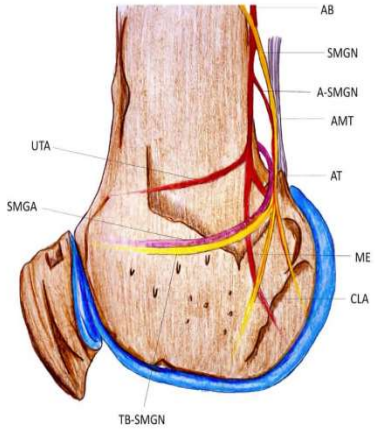

Fig. 9. Diagram of the anatomical relationships of SMGN and its terminal branches to the arteries at the superior medial aspect of the knee. The artery of the SMGN (A-SMGN) is detached from the trunk of the osteo-articular branch (AB) of the descending genicular artery, and descends with the SMGN on the adductor magnus tendon (AMT). The superior-medial genicular artery (from popliteal artery), runs alongside the transverse terminal branch of the SMGN (TB-SMGN) at the level of medial epicondyle. The upper transverse artery (UTA) runs at junction of medial femoral epiphysis and diaphysis, without a nerve branch. SMGN, superior-medial genicular nerve; AT, adductor tubercle; ME, medial femoral epicondyle; CLA, central longitudinal artery.

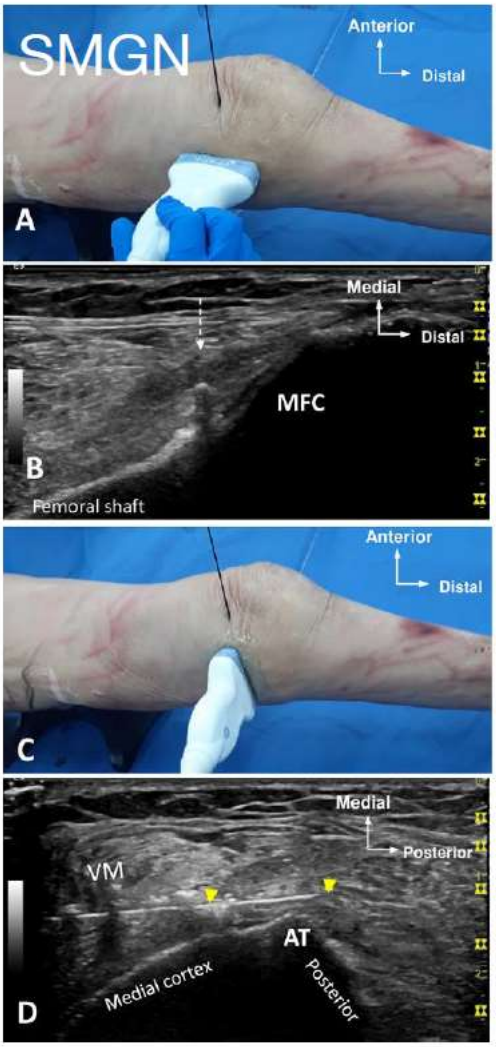

Fig. Ultrasound probe position and corresponding images for genicular radiofrequency intervention.

- Inferomedial genicular nerve

The transducer is placed in a coronal orientation on 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. 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 centre of the probe at the assessed probe-to-target point distance. Consecutively, the transducer is turned 90° into the transverse plane at this point. The skin and soft tissue are anesthetised 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 centre of the tibia. A RF electrode is introduced in the cannula.

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Sensory stimulation (50 Hz) is applied and should produce paraesthesia at a threshold of less than 0.5 V. The absence of fasciculations below 1 V is observed after motor stimulation at 2 Hz, confirming sufficient distance to relevant motor branches. If no sensory stimulation threshold is obtained at this position, the transducer is repositioned until sensory threshold is reached.

- Superolateral genicular nerve

The transducer is placed in a coronal orientation on the lateral side of the proximal knee. After identifying the femoral lateral epicondyle, the transducer is displaced proximally to image the junction between the epiphysis and diaphysis of the femur and the vastus lateralis superficial to it. The superolateral genicular artery may or may not be seen between the deep fascia of the muscle and the femur at this level. If the superolateral genicular artery is visualised just above the bony cortex, the target point is next to this artery. If the artery is not visualised, the posterior side of the junction between the epiphysis and diaphysis is the target point. The transducer is centred to this target point and consecutively turned 45° into an oblique view. The skin and soft tissue are anesthetised with 1 ml lidocaine 2% at the estimated entry point. The cannula is advanced using an anterior to posterior '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. Sensory stimulation (50 Hz) is applied and should produce paraesthesia 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.

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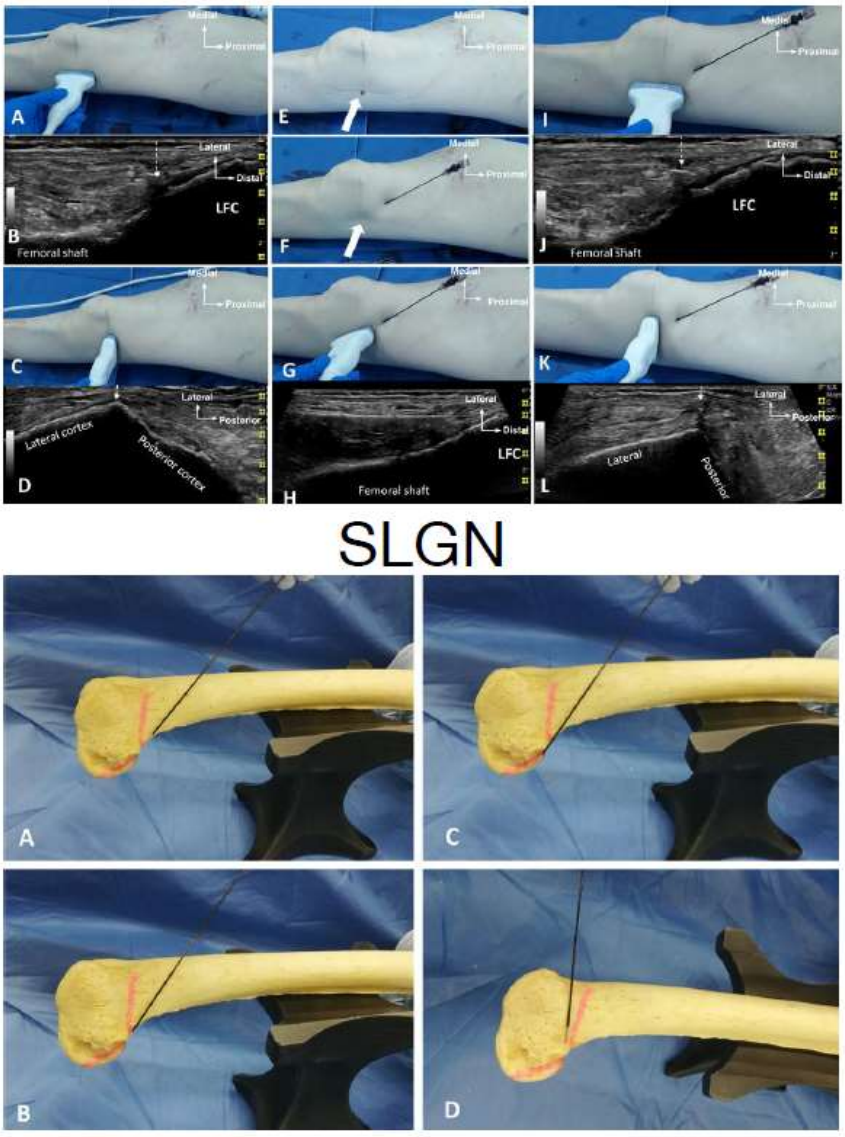

Fig. Ultrasound probe position and corresponding images for genicular radiofrequency intervention.

If all three target nerves are 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 tibia width for the inferomedial genicular nerve and within the posterior half of the femur width for the superomedial and superolateral genicular nerve.

- ***Sham procedure***

For each nerve, the ultrasound and fluoroscopy are placed in a similar way as described above for the RF intervention. Subcutaneous local anaesthetic (1mL lidocaine 2% per entry point) administration and introducer and probe placement are also similar. Sensory and motor testing will also be performed in a similar manner. The generator will also be turned on for 150 seconds per nerve with the only difference

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being that the generator is not connected with the probe (the sound of the generator is mimicked) and that there is no injection of local anaesthetics prior to turning the generator on.

- ***Intervention procedure details:***

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 intervention.

In the **conventional radiofrequency** group an intervention of 80°C at the tip is applied during 90 seconds at each nerve. The probe stays in place for 150 seconds at each nerve so that the time needed for each procedure is similar.

In the **cooled radiofrequency** group an intervention of 60°C measured at the tip and on average 80°C in the targeted tissue is applied for 150 seconds using the Cooled RF system at each nerve.

In the **sham** group a 18G introducer and probe will be placed but no RF intervention will be applied. The generator will be turned on without connection to the probe for 150 seconds and the sound of the generator will be mimicked with a recording. The position of the needle will not be checked by fluoroscopy; however, the intervention team will position the fluoroscopy arm and mention the acquisition of the fluoroscopic image to the patient. This way no unnecessary radiation is used.

After the procedure, the patient is transferred to the recovery. After 30 minutes without any events, the patient is discharged. Home medication is continued postoperative. The patient is informed about potential transient increase in pain due to neuritis and about the alarm symptoms (fever, swelling, bleeding and motor weakness). The patient will be instructed to contact his PI or delegated physician in case they experience any of the alarm symptoms.

A sensory loss is a possible AE of RF but as its incidence is very low (estimated to be less than 10%-internal unpublished data) it is unlikely to threaten blinding.

- ***Intervention blinding procedure details:***

Information on the performed procedure will be maintained in the unblinded patient record file to ensure continued blinding. The routine medical record will state that patient received a ‘study intervention of the genicular nerves (COGENIUS trial) with references to the patient number’.

Standardised script and instructions for the RF procedure in the three intervention arms:

1. The nurse receives the patient and confirms the patient identity, allergies, indication and side of procedure. Patient will be asked to position him/herself in the operating table.
2. Nurse connects pulse oximeter to the patient to start patient’s monitoring.
3. Nurse positions the structure blocking the patients’ vision between the patient and their knee.
4. The ultrasound and fluoroscopy, RF generator, RF introducers/probes and the physician performing the intervention are positioned behind the blocking structure.
5. Nurse disinfects the knee.

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6. Pain physician uses an ultrasound machine to identify the position of each genicular nerve and injects subcutaneous local anaesthetic after notifying the patient. After 2 minutes, the physician notifies the patient of the insertion of the probe and positions this in proximity of the nerves.
7. After positioning, the patient is asked on the sensory and motor stimulation. The interventionist asks the patient the following:
8. Sensory stimulation: '*We will apply an electrical current to assess the proximity to the genicular nerves. Please confirm if you feel any subtle change in perception in your knee. The electrical current could cause a sensation of tingling, pain or pressure.'*
9. If a correction of the position is necessary following sensory testing, the patient is asked the previous question again. During the sham procedure no electrical current will be applied.
10. Motor stimulation: *'We will apply an electrical current to assess the proximity to the motor nerves. Please confirm if you feel any muscle contractions.'*
11. After stimulation, the position of the needle is checked radiographically in the two RF intervention groups. In the sham procedure the fluoroscopy arm is also positioned to acquire an image of the index knee, however no radiation is given. The digital fluoroscopy screen is positioned in a manner that it is not visible from the patient's perspective to assure blinding.
12. Afterwards, local anaesthetic is injected in the form of 1ml of lidocaine 2% in each genicular nerve with exception to the sham procedure.
13. The RF procedure is started in both cooled and conventional RF groups by starting the RF program on the RF machine. In the sham group the RF machine will be turned on but will not be connected to the patient and the sound of the working generator will be mimicked with a recording. The pain physician reports intervention of each of the three nerves after a minimum procedure of 150 seconds per genicular nerve.
14. After intervention, the three incision points will be covered with a band aid. Pulse oximeter will be removed, and the patient will be directed to the recovery room.

9.2. Legal status of the intervention

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 the investigator site file.

9.3. Product Insert

- ***Cooled RF device***

The following is a summary description of the used study device. For additional information, please refer to the cooled RF system "Instructions for Use" which is filed in the investigator site file.

The cooled RF 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'):

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- 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.

➢ ***Conventional RF device***

The following is a summary description of the used control device. For additional information, please refer to the 'Instructions for Use' which is filed in the investigator site file.

The conventional RF device is composed of two primary components and is used in conjunction with the same pain management generator, connector cables and dispersive electrodes (also known as grounding pads) (Halyard) as in the study group.

- Radiofrequency introducer (sterile, single use, 100 mm, 18 gauge, straight): it is to be used with the probes only. The radiofrequency introducer provides a path for the probe to the targeted nervous tissue.
- Radiofrequency probe (sterile, single use, 18 gauge): 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.

➢ ***Sham intervention***

The sham procedure is performed with the 18-gauge introducer as in the conventional RF intervention group.

9.4. Device storage and supply

The probe, introducer, and tube kit for RF are ethylene oxide sterilised 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, which are filed in the investigator site file, are included in each kit.

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All material to perform the cooled, conventional RF and sham procedure will be supplied by the sponsor free of charge for the hospital and patient.

The accountability of the delivered and used material will need to be managed by the hospital study team. Detailed information regarding the accountability of the material will need to be documented on the study specific accountability form in the investigator site file.

The study material lidocaine 2% is available in normal hospital stock.

9.5. Dosage modifications or Intervention modifications

No intervention modification is allowed in the trial.

9.6. Rescue medication

Patients will be advised to continue their current analgesic medication after the trial intervention. If these fail to sufficiently target the pain, the following steps will be taken:

1. Optimisation of dose and frequency of current analgesic medication
2. Association of Tramadol (Tradonal Retard form) in its maximum necessary dose, if tolerated by the patient:
   Step-up scheme:
   Step 1: 50 mg 2 times/day PO, in the morning and evening
   Step 2: 100 mg 2 times/day PO, in the morning and evening
   Step 3: 150 mg 2 times/day PO, in the morning and evening
   Step 4: 200 mg 2 times/day PO, in the morning and evening
   Patients should evaluate the pain and step up after 3 days of each step.

In case of neuropathic pain (DN4 > 4):

Step-up scheme:

Step 1: Lidocaine patch if localised neuropathic pain

Dose & frequency:	Cutaneous application 1 time/day during 12h in the painful area
Contra-indication:	Allergy

Step 2: Amitriptyline

Dose & frequency:	1 time/day 10 mg PO in the evening during the first week Weekly increase with 10 mg until clinical effect or a max. dose of 50 mg/day
Contra-indication:	Long QT syndrome Allergy

Step 3: Pregabaline

Dose & frequency:	1 time/day 75 mg PO in the evening during the first 3 days Increase in intervals of 3 days with 75 mg until clinical effect or a max. dose of 300 mg/day
Contra-indication:	Allergy

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10. SAFETY RECORDING AND REPORTING

10.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users, or other persons whether or not related to the investigational medical device. For patients, this definition includes events related to the investigational device and the procedures. For users or other persons, this definition is restricted to events related to investigational medical device(s).
Serious Adverse Event (SAE)	A serious adverse event is any adverse event that led to any of the following: ● Death ● Serious deterioration in the health of the subject, that resulted in any of the following: ○ life-threatening illness or injury, ○ permanent impairment of a body structure or a body function, ○ hospitalisation or prolongation of patient hospitalisation, ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, ○ chronic disease ● Foetal distress, foetal death or a congenital physical or mental impairment or birth defect (MDR Article 2(58)).
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2 This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	A Serious Adverse Device Effect of which the nature or severity is not consistent with the applicable product information (e.g., IFU as compiled by the manufacturer). Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected MDIs. NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report.
Medical Device Incident (MDI)	Any malfunction or deterioration in the characteristics and/or performance of a device (i.e., any device deficiency), as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

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10.2. Recording of safety findings in function of the available evidence

10.2.1. Adverse Events (AE), Adverse Device Effect (ADE) and Serious Adverse Events (SAE), Medical Device Incident (MDI)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational intervention. 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 from the time the intervention is started until the end of the last study visit according to the following procedure.

All adverse events reported spontaneously by the subject or observed by the investigator, or his staff will be recorded in the source documentation. Only adverse events and serious adverse events related to the intervention will need to be reported in the eCRF.

Therefore, for each AE, the PI or delegated physician will assess the causality/relationship to the received intervention according to the following criteria:

Relatedness	**Definition**
Unlikely	The AE does not follow a reasonable sequence from the intervention or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
Possible	The association of the AE with the intervention is unknown; other aetiologies are also possible.
Probable	A reasonable temporal sequence of the AE with the intervention exists and based upon the medical professional's clinical experience, the association of the AE with the intervention seems likely.
Definite	A causal relationship exists between the intervention 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.

If an adverse event is assessed as a possible, probable, or definite, the event is an **adverse device effect (ADE)** and will need to be reported to the sponsor via the eCRF.

ADEs of interest are chosen based on the AEs previously mentioned in other clinical trials on RF of the genicular nerves and on other possible theoretical AEs of the RF intervention.

ADEs of interest are the following:

- Postoperative pain (transient neuritis),
- Infection,
- Damage to collateral tissue:
    - nervous tissue: e.g., deafferentation dysesthesia, paralysis
    - blood vessel: e.g., bruising or hematoma
    - ligaments: e.g., pes anserine damage
    - skin: e.g., superficial burns

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- Failure of technique defined as the clinical setting where the pain physician is unable to perform the procedure (e.g., due to technical issues, patient cooperation)

- Allergy

Lidocaine, the local anaesthetic, is used within its approved label. Local injection of lidocaine could result in an allergic reaction.

If these anticipated adverse events are considered serious (see definition SAE section 10.1) they should be reported as an anticipated serious adverse device effect (ASADE) unless the severity of the event was considered to be unanticipated (USADE).

The list of anticipated Adverse Events can be found in the instruction for use of the RF system used to treat the patient.

Serious adverse device effects are adverse device effects which comply with the definition of SADE as mentioned in section 10.1 and will need **to be reported** by the PI or delegated person to the sponsor **within 24 hours of becoming aware of the event via the eCRF**.

For each SADE, the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e., relatedness to trial intervention), in the opinion of the investigator
- whether the event would be considered anticipated or unanticipated.

Any change of condition or other follow-up information should be reported to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

A ***medical device incident*** (MDI) as mentioned in section 10.1 will need to be reported by the PI or delegated person to the sponsor within 24 hours of becoming aware of the incident via the eCRF. The sponsor will take contact with the site to obtain additional information in order to report the incident to the company producing the device.

10.2.2. Regulatory safety reporting timelines

Sites will be instructed to follow their normal routine processes for adverse event reporting. However, the possible, probable, or definite related SAEs (SADEs) will be specifically monitored. The sponsor will report the SADEs to the EC, within 7 days of first knowledge for SADEs 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 SADEs will

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be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

The Unanticipated Serious Adverse Device Effect (USADE) will be reported following the timelines of a possible, probable, or definite related SAE (SADE).

The submission process of these safety events will be performed according to the national requirements *(e.g., 'ToetsingOnline' in the Netherlands)*.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of ADE and SADE which are required to continue being reported according to the protocol for regulatory purposes. The patient informed consent contains a section explaining this to the participant.

10.3. Responsibilities

Principal Investigator (PI) of each participating centre:

1. Checking for adverse events when participants attend for intervention / follow-up.
2. Using medical judgement in assigning seriousness, causality, and expectedness.
3. Ensuring that all SADE (including USADEs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
4. Ensuring that ADEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / Co-Chief Investigator/ delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness of all reported SADEs.
4. Immediate review of all SADEs.

Sponsor:

1. Central data collection and verification of adverse events according to the trial protocol.
2. Reporting safety information to the CI/Co-CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit.
3. Reporting safety information to the independent oversight committees identified for the trial.
4. Reporting of ADE and SADE (including USADEs) to the EC within required timelines.
5. Notifying Investigators of USADEs that occur within the trial.
6. The unblinding of a participant for the purpose of USADEs by unblinded responsible person.

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7. Suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the EC 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 EC.

Trial Steering Committee (TSC):

In accordance with the charter for the TSC, periodically reviewing safety data.

Independent Safety reviewer:

1. Reviewing safety information presented yearly by means of the safety report.
2. Advising the Sponsor on suspension of the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety.

10.4. Notification of deaths

Only deaths that are assessed to be caused by the intervention will need be reported to the sponsor immediately (for more details see section 10.2.2).

10.5. Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Co-CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the EC of the measures taken and the circumstances giving rise to those measures.

10.6. The type and duration of the follow-up of subjects after adverse events

All AEs will be followed by the investigator 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.

Any USADE will need to be reported to the Sponsor irrespective of how long after intervention the reaction has occurred.

11. STATISTICS AND DATA ANALYSIS

11.1. Sample size calculation

The outcome on which the sample size calculation is based is the total WOMAC score at the 6-month follow-up moment. The sample size was determined to be able to have sufficient statistical power (i.e., 80%) to detect a minimally clinically relevant difference between groups of 10 points, with an estimated standard deviation of 15.[60] As we will make three comparisons (cooled RF separately or conventional RF separately versus sham, and cooled RF compared to conventional RF), we have used the Bonferroni correction for multiple testing to adjust the alpha used for testing (0.05/3 = 0.017) our superiority

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hypotheses. For each of the two studies (OA and PPSP separately), given the 1:2:2 randomisation ratio, we would need to include 40 patients in the control group, and 80 in each of the intervention (conventional and cooled RF) groups, after adjustment for a drop-out rate of up to 10%. This means that in total, 400 patients will be included.

The calculation has been performed in R, version 4.0.4, using the TrialSize package, version 1.3, based on the formula to test for differences in means from Chow SC et al. Sample Size Calculation in Clinical Research. New York: Marcel Dekker, 2003.

11.2. Planned recruitment rate

Patients will be recruited by approximately 20 sites within a period of approximately 24 months. The recruitment rate will start slow due to the site initiation activities at each centre, which are performed in parallel during the first recruitment months. A feasibility study has been performed identifying centres who are experienced in performing the study intervention and in conducting research.

Once the sites are up and running, we expect on average of 20 inclusions / month to reach an average inclusion of 240 inclusions/year. Taking a buffer into account, this should allow us to finish enrolment of the patient population within 24 months. Each site is on average estimated to see 2 potential patients per month of which 1 is eligible for the study.

Also, with the publication of three-monthly research letters to the participating sites and announcement through posters/leaflets of the COGENIUS-study in the outpatient departments, the inclusion process might be enhanced.

11.3. Statistical analysis plan

All analyses will be performed according to the intention-to-treat principle (ITT), regardless of intervention received, and will be performed for both groups (OA and PPSP group). Hence, even if patients randomised to the sham group eventually receive either of the interventions due to continuing debilitating pain, they will be analysed as sham patients. In case of substantial cross-over from the sham group, an exploratory per protocol analysis will be performed in addition to the main ITT analysis. For null hypothesis testing between groups (i.e., cooled and conventional RF separately versus sham, and both compared to each other) the alpha for testing will be 0.05/3 = 0.0167. For all other null-hypothesis testing, a conventional alpha of 0.05 will be used, but the focus will be on the clinical relevance of effect sizes, as per guidelines by the American Statistical Association (ASA) Statement on p-Values. All analyses will be performed in R, using the latest version supported at the time of analyses. To support transparency and reproducibility, all R syntaxes will be published in a version-controlled repository on GitHub. The analysis of all endpoints, including the primary endpoint, will be performed after collection of all the study data.

11.3.1. Summary of baseline data and flow of patients

The flow of patients will be described using a CONSORT-statement flow diagram.

Baseline characteristics will be reported per intervention group. Continuous variables will be reported as mean and standard deviation (SD) or median and first and third quartile, depending on the nature of the

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distribution. The distribution will be assessed using histograms and QQ-plots. Categorical variables will be reported as count and percentage. No null-hypothesis testing will be performed on between-group differences at baseline.

11.3.2. Primary outcome analysis

The primary outcome, the total WOMAC score at 6 months post intervention, will be reported as mean and SD or median and first and third quartile, depending on the nature of the distribution. Mean between-group differences will be reported including their 95% confidence intervals. Analysis of variance (ANOVA) with post-hoc tests adjusted for multiple testing using the Bonferroni correction will be used to test the null-hypotheses that between-group differences are zero. This entails both differences between RF interventions and sham, as well as between both RF interventions. Conclusions on efficacy of the effect of intervention on the WOMAC at 6 months will be based on the abovementioned analysis.

11.3.3. Secondary outcome analysis

In addition to cross-sectional analysis of the primary endpoint WOMAC score at six months, we will analyse cross-sectional the WOMAC score at 12 and 24 months. Also, longitudinal analyses using all follow-up moments will be performed to assess differences in trajectories of WOMAC scores over time. To do so, we will use linear mixed-effects regression with a random intercept on patient identification number, and a random slope with time, with an unstructured variance-covariance matrix. Autocorrelation will be accounted for using a continuous first-order autoregressive model or left unstructured, depending on the model with the lowest Akaike Information Criterion (AIC). Heteroscedasticity and normal distribution of the residuals will be assessed. Results will be presented as regression coefficients and 95% confidence intervals.

Continuous secondary outcome parameters (Numerical Rating Scale, functional tests, EQ-5D-5L, Hospital Anxiety and Depression subscales, Pain Catastrophizing Scale, MQS III, WPAI and Health care 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; patient global impression of change will be dichotomised into intervention success (i.e., scoring “Much improved” or “Very much improved”) and compared between groups using Pearson’s chi-square test. In case of expected cell-counts of less than 5, we will use Fisher’s Exact test. Time to total knee arthroplasty in the OA group and time to additional intervention in both subgroups will be assessed within groups using Kaplan-Meier tables. Differences between groups will be tested using Cox proportional-hazards regression and presented as hazard ratio including 95% confidence interval. The proportional hazards assumption will be tested by computing the scaled Schoenfeld residuals and estimating their association with time. The analysis of economic endpoints is described in section 11.4. Although all secondary outcomes are secondary to the primary outcome, the following are the principal secondary outcomes: WOMAC, pain intensity and EQ-5D.

All the primary and secondary outcomes are chosen following the OMERACT-OARSI and IMMPACT core outcome guidelines.

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We will compute and report blinding index (BI) values for all treatment arms. The BI can range between -1 (guessing the opposite of what one received) and 1 (complete lack of blinding). A BI of 0 would indicate perfect blinding.

11.3.4. Procedure(s) to account for missing or spurious data

Missing data will be described as count and percentage of missing values per outcome variable, and the count and percentage of incomplete patient records. In case of over 10% of incomplete records, data will be imputed (drop-out for up to 10% has been accounted for in the sample size calculation, but intermittent missing data may be present for patients not dropping out). Data imputation will be performed to allow the use of data of all participants for the primary endpoint at 6 months follow-up. 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. In the case of imputation, we will use multiple imputation with fully conditional specification. The values to be imputed will be drawn using predictive mean matching. The number of imputations will be set to the percentage of incomplete patients, as per imputation guidelines. The imputation model will consist of variables to be imputed, variables that are likely associated with the missing data mechanism, and variables that are associated with the incomplete variables. Data will be imputed using the *mice* package in R, the version being the latest one available at the time of analyses.

Discontinuation of the study after receiving study intervention (see section 8.9) is not always the equivalent of withdrawal of informed consent. In cases where subjects indicate they do not want to "continue", investigators must determine whether this refers to unwillingness to attend the follow-up visit, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). Every effort will be made to continue to follow the subject until the end of the study.

In all cases, the reason for discontinuation (including "at the subject's request") will be recorded in the case report form (CRF) and in the subject's medical records.

If a patient is lost to follow-up, every effort will be made to obtain follow-up information and if necessary, to determine the reason for loss to follow-up. This last will be done by means of contact with the patient's primary physician (GP), a telephone call and a letter to the subject requesting contact with the researcher for the reason of discontinuation with the study.

11.4. Data collection for economic evaluation

One of the goals of the KCE Trials program is to improve the efficiency of the health care system.

Therefore, parallel to the clinical trial, utilisation of the most relevant health care resources associated with OA and PPSP and the interventions are collected. Accordingly, it will be feasible to perform an economic evaluation if deemed relevant. Such an economic evaluation will adhere to the KCE guidelines for health economic evaluations.[42] Therefore, the reference case analysis is conducted from the health care payer

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perspective and with a time horizon that captures the main expected differences in health and cost outcomes.

Individual level health care costs can be calculated using health care resource utilisation data collected during the trial. The most relevant health care elements include the initial intervention received, subsequent hospital visits, related adverse events, additional or re-interventions to the index knee, pain medication, medical specialists, general practitioner, and other healthcare providers visits. All health care resource use is already collected as part of the clinical trial, except for visits to a medical specialist, a general practitioner, and other healthcare providers. The patient is asked to report the number of these visits as part of the package of questionnaires they complete at baseline, 3, 6, 9, 12 and 24 months post intervention. Use of pain medication is collected via the MQS III that is completed at each visit (see section 4.5), supplemented by theoretical calculations for in-between time periods. Belgian market prices or reimbursement fees, using validated sources, are used to value resource use.[42] In addition, productivity loss will be collected using the WPAI. If the economic evaluation is conducted in collaboration with KCE as part of an HTA procedure, data linkage with the IMA database may be used to identify the relevant health care resource use and cost data. 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-5L scores.

A cost-utility analysis will be conducted with an intention-to-treat approach and cost-effectiveness is expressed using incremental cost-effectiveness ratios (ICERs): the (incremental) cost per QALY.[62]

Non-parametric bootstrapping with 5000 replicates of the joint distribution of costs and QALYs will 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 (CEAC). 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.

12. DATA HANDLING

12.1. Data collection tools and source document identification

It is the responsibility of the Principal Investigator at each site to maintain adequate and accurate source data, source documentation and CRFs to record all observations and other data pertinent to the clinical investigation in a timely manner.

Patient's personal data, which are included in the sponsor database shall be treated in compliance with all applicable laws and regulations. The data collected will be pseudo-anonymised and the data will only be used for the purpose(s) of this trial.

- ***Source Data***

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ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

- ***Source Documents***

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

- ***Case report forms***

A case report form (CRF) is a form on which individual patient data required by the trial protocol are recorded.

All data relating to the trial must be recorded in the eCRF prepared by the Sponsor. Data reported in the eCRF should be in English, consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated in the eCRF. All missing and ambiguous data will be queried.

The study data will be transcribed by study personnel from the source documents onto an eCRF, within 5 working days of the subject's visit.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subjects' source documentation.

Every effort should be made to ensure that all subjective assessments to be recorded in the eCRF are performed by the same individual who made the initial assessment.

The Principal Investigator or delegated person must verify that all data entries in the eCRF are accurate and correct. All eCRF entries, corrections, and alterations must be made by the Investigator or other authorised study-site personnel. In case of a query, the Investigator or an authorised member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

COGENIUS uses an eCRF to collect the data which will be used to perform statistical analysis for the trial. The CRF has been constructed to ensure:

- adequate data collection
- proper audit trails will be kept to demonstrate the validity of the trial (both during and after the trial)
- that only the data required by the protocol are captured in the CRF

An annotated CRF is developed with coding convention as will be used in the database.

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At the end of the trial a copy of the CRF of each enrolled patient will be provided to the Principal Investigator for archiving.

The principal investigator is responsible to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

- ***CRFs as Source Documents***

During the study, the patient will be asked to complete several questionnaires. The clinical study team can propose to the patient to complete these questionnaires on paper or electronically. If the patient decides to complete the questionnaires on paper, the paper will contain source data and this data will be transferred by the PI or delegated person to the eCRF. If the patient decides to complete the questionnaires electronically, the PI or delegated person will provide these questionnaires via CASTOR to the patient prior to a study visit. During the study visit the electronic questionnaire will be checked for completeness by the PI or delegated person. If required, the patient can complete/update the questionnaire during the study visit. In this case the CRF will contain the source data.

At the end of the study the PI will receive a copy of the CRF including this source data (if applicable) in order to be archived by the PI according to the current legal requirements.

12.2. Data handling and record keeping

All collected study data will be recorded and stored in the CRF created with the CASTOR© software. To protect the privacy of the participants, all collected data will be encoded. Following the creation of a new study record in the eCRF, a study specific patient code will be created. The code will consist of a code specific for the site of recruitment (i.e., 01, 02, etc.), the abbreviation of the study (COG), and an incremental 3-digit number per centre (starting from 001 in order of inclusion). Examples of study codes could be 01-COG-023 or 02-COG-008.

CASTOR© complies with 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.

All other data collected that is not/cannot be stored in the eCRF (i.e., paper notes, signed ICFs etc.) are stored in the local investigator site file, which is stored behind a locked environment which is only accessible by the local PI or delegated study person.

Once the PI and delegated member(s) of the investigational staff have been trained, they will receive the link of the eCRF together with a log-in account and password. Detailed information regarding the eCRF is provided in the CRF completion guidelines.

All handling of data will be in agreement with the 'EU General Data Protection Regulation' and the implementing law of Belgium and the Netherlands

The Principal Investigator will be responsible for data entry and the quality of the data at his/her hospital.

The sponsor will be responsible for the data analysis.

Detailed information regarding data handling and record keeping is provided in the Data Management Plan.

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12.3. Access to Data

Only the local PI and local delegated study person have access to the key linking the individual patient to the study patient code. At no point will the key leave the local study site. Access to the decoded data can be necessary for controlling and monitoring purposes.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the national (e.g., in the Netherlands: Inspectie Gezondheidszorg en Jeugd (IGJ), in Belgium: Federal agency for medicines and health products (FAMHP)) and international regulatory authorities to permit trial-related monitoring, audits, and inspections. No data will be shared with countries outside of the EU.

12.4. Archiving

The encoded study data will be archived for research purpose in relation to publications related to this study.
Archiving will be authorised by the Sponsor following the submission of the clinical study report.

It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation (e.g., GCP certificates, training logs, delegation logs, etc.) and source records (e.g., signed Informed Consent Forms, patients' hospital notes, etc.) at their site are securely retained as long as required by the national regulations (i.e., 10 years for Belgium and 15 years for the Netherlands) following termination of the trial.

The sponsor will be responsible for archiving the Trial Master File (including the CRF documents and trial database) as long as required by the national regulations (i.e., 10 years for Belgium and 15 years for the Netherlands) following termination of the trial.

Therefore, all essential documents will be archived for a minimum period after completion of trial as required by the applicable legislation.

Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data.

13. MONITORING, AUDIT & INSPECTION

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorised entities such as but not limited to the Sponsor or its designees and competent regulatory or health authorities. As such eCRFs, source records and other Trial related documentation (e.g., the investigator site file, pharmacy records, etc.) must be kept current, complete, and accurate at all times.

Monitoring

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner

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that assures data integrity. Therefore, Source Data will be compared with the data recorded in the eCRF. Remote and on-site monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff) according to the monitoring plan. The Investigator/Participating Site will permit direct access to the Trial data and corresponding Source Data and to any other Trial related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy are described in the Trial specific Monitoring Plan (MP).

The Trial Monitoring Plan has been developed and agreed by the TMG based on the trial risk assessment which will be done by exploring the trial dataset or performing site visits.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Regulatory Review & reports

This clinical study will need to be assessed and approved by a central ethics committee (EC) in Belgium and in the Netherlands following the national requirements, before the study can start, and patients can be enrolled.

Substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study.

All correspondence with the EC will be retained in the Trial Master File/Investigator Site File.

An annual progress report will be submitted to the EC within 30 days of the anniversary date.

It is the Chief Investigator's responsibility to produce the annual reports as required and he will notify the EC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the EC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the EC.

More information for the Dutch centers can be found in Appendix 8.

14.2. Peer review

The protocol has been reviewed by KCE (the funder).

In addition, COGENIUS has undergone a high-quality peer review by experts who have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

14.3. Public and Patient Involvement

Three patient organisations (Vlaamse Reumaliga, VMCP and ReumaNet vzw) who represent patients with chronic knee pain and osteoarthritis of the knee were closely involved in the formulation of the research question, design of the study and protocol development. Four chronic knee pain patients, two from Flanders and two from Wallonia, who are not a member of a patient organisation were contacted and engaged in the

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study design. These four patients will be further involved in proofreading of the informed consent form and trial information brochures.

Furthermore, two patient experts schooled from the Patient Expertise Centrum will be part of the TSC as patient researchers to monitor and supervise the evolution of the study, the analysis and preparation of the study reports. Finally, the close collaboration of the research group together with the individual patients and the three patient organisations will aid with the dissemination of the results of the study. These last will be published among others in the online platforms of the patient organisations and the website of the COGENIUS study.

14.4. Regulatory Compliance

The trial will not commence until approval is obtained from the independent Ethics Committee. The protocol and trial conduct shall be governed and construed in accordance with the principles of the Declaration of Helsinki as revised most recently in Brazil, 2013.

In Belgium the trial will be in accordance with the law of May 7th, 2004, regarding experiments on the human and the Belgian law of December 22nd, 2020, concerning medical devices and any relevant amendments/guidelines.

In the Netherlands the trial will comply with the Dutch law (Wet Medisch-wetenschappelijk Onderzoek met Mensen (WMO) and any relevant amendments/guidelines.

14.5. Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

- Prospective, planned deviations or waivers to the protocol are not allowed and must not be used (e.g., it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol)
- Accidental protocol deviations can happen at any time. They must be adequately documented and explained on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The sponsor and the Chief Investigator will be notified immediately of any case where the above definition applies during the trial conduct phase.

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The sponsor of the clinical trial will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial within 7 days of becoming aware of that breach.

14.7. Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Regulation (EU) 2016/679 of April 27, 2016 of the European Parliament and the Council Concerning the protection of individuals with regard to the processing of personal data and the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation), the European Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and, as of the 5th of September 2018 the Law of 30 July 2018 related to the protection of natural persons with regard to the processing of personal data, the Law of 22 August 2002 related to the rights of patients, including their respective Royal Decrees), with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

Therefore:

- personal information will be collected, kept secure, and maintained at the participating centers in a way that is conform all regulation concerning privacy.
- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis with a list of persons who have access to data, and all this conform the regulation concerning privacy.
- the confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators.
- the data will be stored as long as required by the national regulations (i.e., 10 years for Belgium and 15 years for the Netherlands) .
- The data custodian is the sponsor.

14.8. Financial and other competing interests for the chief investigator, co-Chief investigator, PIs at each site and committee members for the overall trial management

The chief investigator, co-chief investigator, all principal investigators of current participating sites and committee members have no financial or other competing interests. Principal investigators of future participating sites will be asked for competing interests and if needed this section will be updated.

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14.9. Indemnity

The Sponsor will ensure appropriate insurance to meet the potential legal liability of the Sponsor(s) for harm to participants arising from the management of the research.

The Sponsor will ensure appropriate insurance for legal liability of the Sponsor(s) or employer(s) for harm to participants arising from the design of the research.

Before the start of the trial, approval regarding the insurance taken out by the sponsor will be sought from the EC.

The participating sites will ensure appropriate insurance to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

More detailed information for the Dutch centers can be found in Appendix 8.

14.10. Access to the Study Data by KCE and similar institutes in the EU

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

A distinction is to be made by access by KCE (and similar institutes in Europe) and access by other parties.

Access to Study Data by KCE and similar institutes in the EU is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/fr/open-calls and then click on the last call open.

In case, the patient National Number will be used to link with IMA data:

After the completion of the study the Sponsor will transfer the pseudonymised study data set to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g., IMA data by a trusted third party (TTP, eHealth platform) using the patient national number.

The patient information and consent include wording that the national number will be recorded on site by the investigator for later data linkage but will not be included in trial database available to the sponsor or any other third party. The patient information and consent will also include that in case the patient is randomised, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data. To this end, KCE will receive the link between the study number and the national number under pseudonymised form. KCE will never be able to use the link without authorisation of the ISC and the intervention of the TTP. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the patient that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by KCE. The processing of personal data for this analysis is necessary for the performance of a task carried out in the public interest, as specified in the law defining KCE's missions and tasks. To the extent the personal data is related to health, the processing is necessary for scientific or statistic purposes, as specified in the law defining KCE's missions and tasks. For all processing related to the analysis of effectiveness and cost-effectiveness of the intervention, KCE is the controller.

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KCE and Sponsor have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.

“Background” means any intellectual property (IP), data, materials, information owned or controlled by the Sponsor or a Site and required to run this Study. Sponsor will identify such Background including the legal restrictions of which Sponsor, or Sites are aware that may affect the use of the Background for the purpose of the Study, or the rights granted to KCE under this Agreement.

The Study Data consist of this protocol, including amendments, the electronic forms for data capture, including the annotations and guidance for use, the electronic database of the pseudonymised clinical and non-clinical data collected using data capture, including the log of changes from data entry to database lock, study reports based on these pseudonymised data, and any data or reports generated at a later stage, e.g., based on exploratory analyses or stored samples.

“Foreground” means any Study Data, and any tangible biological, chemical, and physical material and inventions, that are generated, acquired, discovered, conceived, developed, created, exemplified, or derived as a result of carrying out the Clinical Study, whatever its form or nature, whether it can be protected or not, as well as any Foreground IP. Sponsor acknowledges that the main purpose of the research performed under this Agreement is to generate results that will serve the general public interests, and specifically the interests of the patients and public healthcare decision making bodies, and, therefore, undertakes not to exploit the Foreground in any way that is or could be detrimental to such interests.

The Sponsor owns the Study Data but provides KCE with a copy of the pseudonymised database after database lock as well as a royalty-free unrestricted license to use the Study Data for non-commercial public health related purposes as detailed in the Agreement between KCE and the sponsor. If judged appropriate, KCE will introduce the request to the competent chamber of the Information Security Committee and arrange for the data linkage. For the sake of clarity, the linked data are not part of the Study Data. However, KCE will discuss with the Sponsor the results of the analyses and the reporting of the linked data.

14.11. Access to the final trial dataset by other parties

After the main publication, a request by a third person to share the study data for scientifically valid reason will be handled according to the Data Sharing Policy of the sponsor.

15. DISSEMINATION POLICY

15.1. Dissemination policy

This section should be read in conjunction with the research agreement, which supersedes the protocol.

Upon completion of the trial,

- the data arising from the trial will be owned by the sponsor;
- the data will be analysed and tabulated, and a Final Study Report prepared;

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- the full study report can be accessed online as well as on ClinicalTrials.gov;
- Participating investigators will have rights to publish any of the trial data upon approval of the steering committee;
- the publication containing the primary study results should be finalised within 6 months of the statistical analysis. There are no time limits or review requirements on the additional publications;
- funding by KCE will be acknowledged within the publications;
- the participants of the trial will be notified by a letter containing the outcome of the trial by provision of the publication and/or via a specifically designed newsletter;
- the participants might specifically request results from their PI upon completion of the trial, which might be provided once the results have been published;
- it is foreseen that at the latest at publication, a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications will be deposited (preferably open access). The research data needed to validate the results presented in the scientific publications will be deposited.

Therefore, upon completion, the study will also be submitted for presentation at national and international congresses of pain and orthopaedic scientific societies.

The primary study results of the COGENIUS study will be reported fully and made publicly available when the research has been completed. All researchers shall ensure that the outcome of the research is prepared as a research paper for publication in a suitable peer-reviewed, preferably open-access, journal. The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/).

In conclusion, it is felt that a positive endpoint might lead to improving health-related quality of life in patients with chronic knee pain in a cost-effective manner by reaching a large population of patients and healthcare practitioners because of:

1. Publication in top ranked medical journal
2. Presentation of study results in national and international meetings
3. Adoption in guidelines
4. Internationally recognised expert study team

15.2. Authorship eligibility guidelines and any intended use of professional writers

For COGENIUS, the TSC will manage study publications with the goal of publishing findings from the data. Membership in the TSC does not guarantee authorship.

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org).

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Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria. Authors, including KCE representatives, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfil the authorship conditions stated above to be listed as authors, and all contributors who fulfil the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “COGENIUS Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated. Based on the recruitment, site investigators might also be part of the Authorship.

A methods paper describing the COGENIUS study, as well as the publication containing the primary study results will be drafted by the Chief and co-Chief Investigator and submitted for publication after approval of the members of the steering committee.

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17. APPENDICES

Appendix 1. RISK ASSESSMENT OF THE TRIAL INTERVENTION(S)

Risks associated with trial interventions

X A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

COGENIUS is a pragmatic trial which follows as much as possible the standard care treatment of the patients with chronic knee pain due to therapy resistant osteoarthritis of the knee (OA) or persistent post-surgical knee pain (PPSP). Furthermore, the RF equipment device used for the study intervention has a CE Marketing Authorisation in Europe. The RF equipment device is used in accordance with the indication as mentioned in the European Marketing Authorisation. And finally, the additional 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. But these study procedures do not add additional safety risks to the study subjects. Accordingly, the added risk for the study subject related to the study protocol assessments compared to the standard of care would be minor.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Conventional RF-Cooled RF – Sham intervention	Knee is incorrectly treated	Mitigation	1	- Only investigators who have experience in RF genicularis will be selected for the study. - Investigators will be well trained by the central study physicians regarding the intervention prior to the enrolment of the first patient
Conventional RF-Cooled RF – Sham intervention	Incorrectly reporting of adverse events	Mitigation	Between intervention and 2 year FU visit for each treated patient	- Investigators will inform the patient to contact the investigator immediately in case of a possible related adverse event. - Investigators are instructed to actively ask the patient regarding possible adverse events at the start of each FU visits. - Detailed guideline regarding the safety reporting is documented in the protocol. - Sites will be visited on a regulator time points

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				(according to the monitoring plan) by the monitor to perform SDV and check for protocol compliance.
Conventional RF-Cooled RF – Sham intervention	Intervention is unblinded prior to 24 month FU visit	Mitigation	Between intervention and 12 month FU visit for each treated patient	- Blinded procedures used in the Pilot study (COCOGEN) were re-assessed and improved before they were implemented in the COGENIUS study. - General blinding procedure are documented in the protocol. - All costs related to the intervention will be reimbursed by the sponsor.

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g., DMC, independent data review, etc.)

- When an SAE related to the intervention (SADE) is reported via the eCRF, the sponsor will receive a notification. Accordingly, the sponsor can immediately review the event and contact the site if more information is needed and report the event to the EC following the legal requirements.
- 100% review of the adverse events data entered in the eCRF will be reviewed by the data manager and queried where needed.
- Periodically a safety listing will be provided to the CI, co-chief and independent safety reviewer or delegated physician regarding all reported adverse events in the eCRF for medical safety review.
- Annual safety reporting will be performed to the involved ECs.
- In case new safety information regarding the intervention becomes available, information will be communicated to all participating centres and the protocol will be amended (if needed).
- Sites will be monitored following the risk-based monitoring plan regarding their protocol compliance (including safety reporting requirements).
- Substantial safety deviations and safety data will be reported to the TSC.

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Appendix 2. AUTHORISATION OF PARTICIPATING SITES

- ***Required documentation***

Prior to submitting the trial to the Ethics Committee, the Principal Investigator (PI) is required to sign a protocol signature page confirming his/her agreement to conduct the trial in accordance with this document and all the instructions and procedures found in this protocol.

Detailed information regarding the mandatory documentation which are required before the trial can start at the participating sites can be found in the Manual of Operations.

- ***Procedure for initiating/opening a new site***

Once all start-up documentation (see Manual of Operations) from the participating site is available at the sponsor and the study material is available at the participating site, the sponsor will send confirmation by e-mail to the PI that the study can start. Only upon receipt of this site activation confirmation the site can screen/enrol patients.

- ***Principal Investigator responsibilities***

The PI is the responsible leader of the investigational team of the participating site. The PI is responsible that he/she and his/her investigational team conducts the trial according to the instructions and procedures documented in this protocol. Full list of PI's legal responsibilities is listed in the Clinical Trial Agreement.

The PI has the primary responsibility to protect the rights and welfare of the patient in the trial. The PI's primary responsibilities also include the following:

- *Delegation of Responsibilities*

  PI must personally perform or delegate to qualified sub-investigator or investigational staff all the necessary tasks to carry out this trial. Even when specific tasks are delegated, the PI remains ultimately responsible for proper conduct of the trial and fulfilment of all associated obligations.

- *Oversight of Investigational Team*

  The PI must provide members of the investigational team with sufficient oversight, training and information to facilitate appropriate safety procedures and protocol adherence. In addition, the EC must be informed if a PI is no longer able to fulfil his or her duties for any reason including, but not limited to, traveling for a prolonged period.

- *Evaluation of Adequacy of Resources*

  PIs must ensure that adequate resources (facilities, equipment, supplies, and personnel) exist to conduct the research, protect subjects, and ensure the integrity of the research.

- *Document Retention*

  The PI must ensure adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate and complete. PI must ensure that this source data is reported to the sponsor in the CRF and in the required reports according to the timelines defined in this protocol.

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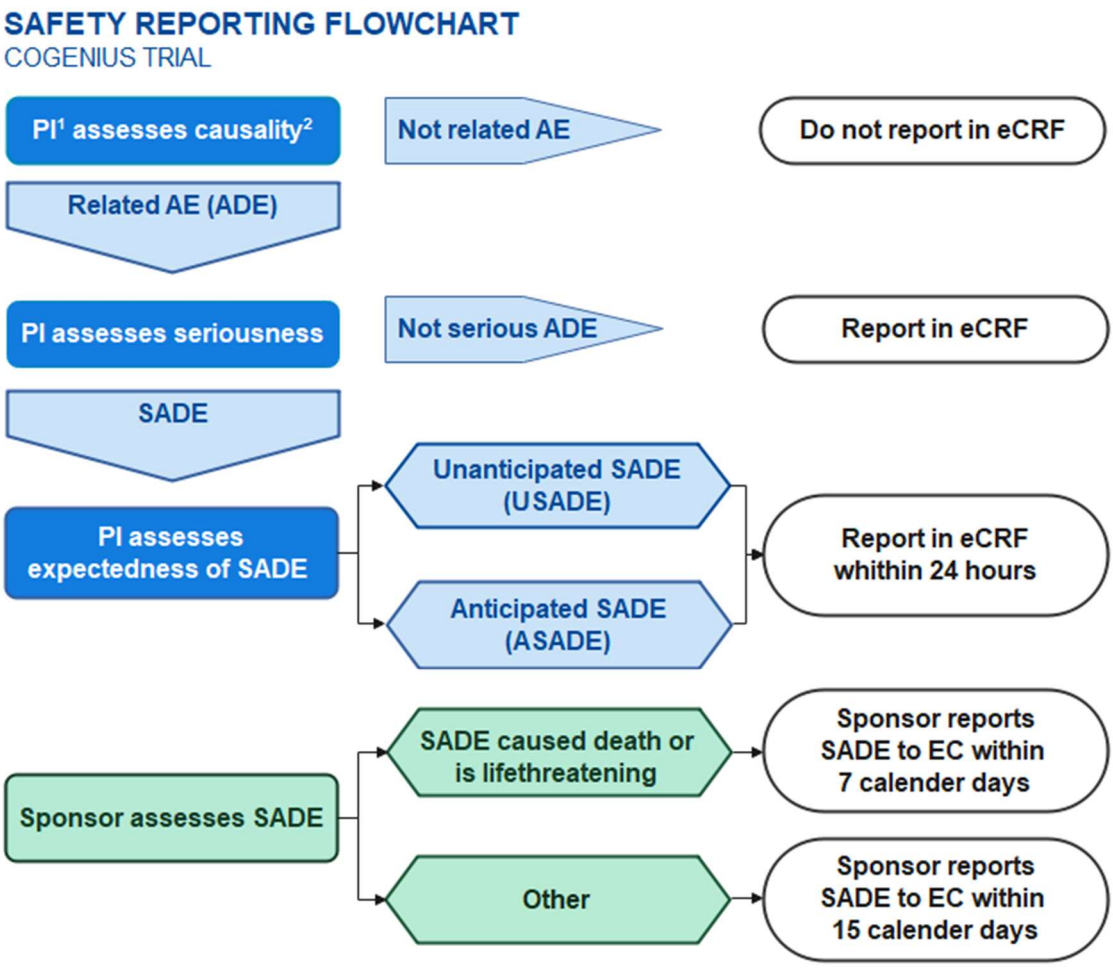
Appendix 3. SAFETY REPORTING FLOW CHART



Adverse Event (AE):
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.

Adverse Device Event (ADE):
Any AE considered related to the investigational intervention.

Serious Adverse Device Event (SADE):

- Results in death
- is life-threatening
- results in permanent impairment
- results in hospitalisation or prolongation of hospitalisation,
- results in chronic disease
- results in foetal distress or death or a birth defect

Anticipated SADE (ASADE):
Any adverse event which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report as anticipated.

PI should describe nature, severity, degree of causality and treatment of all ADE in the eCRF.

Footnotes:
[1] PI or delegated physician
[2] Causality should be assessed as:

- Not related (unreasonable/ unlikely sequence of events or explained by other variables)
- Related (possible, probably or definite causality of the adverse event with the investigational medical device)

Abbreviations: Chief investigator (CI); Ethics Committee(EC); electronic Case Report Form (eCFR); PI (Principal inventigator).

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Appendix 4. AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	14 April 2022	TMG	- Clarification of an inclusion criteria. Clarification that a patient will be eligible only if at the end of the run-in period the average NRS score is > 4 as completed in the patient diary. (section 7.1 – inclusion criteria number 3) - Correction of an exclusion criteria. The wording 'for the index knee' were mentioned while the criteria concerns both knees. The wording 'for the index knee" has been deleted. (section 7.3 – exclusion criteria number 14) - Clarification regarding the time point of collection of screening/baseline parameters (section 8.7 and 8.8) - During the study all medications that the subject is taking on predefined time points will be collected and not only the pain medication (section 8.7 and 8.8) - Updates in section 8.7 and 8.8 so the information will be consistent with the table in section 8.8 and text in section 8.7 respectively. - Upon agreement with scientific team it has been decided not to report periprocedural pain as an event of special interest. (section 10.2.1) - Reported ADEs and SADEs will not be coded using the Medical Dictionary (MedDRA) (section 10.3) - This trial is categorised as a medical device trial. Following the European regulation on IMD (2017/45 – Annex XV, chapter 3) and Belgian law of 22 December 2020 (Art.75) , study data should only be kept for 10 years. (section 12.4)
2	3.0	15 July 2022	TMG	- Adding an additional co-chief investigators (Dr Thibaut Vanneste and Dr Micha Sommer) - Clarification of the role of the pain physician versus researcher as requested by the METC. Updates in section 8.1 and 8.3. - Additional clarification of the consent collection process in section 8.2 - Information regarding providing each patient a leaflet in section 8.3 (appendix 6) has been removed following the performed initiation visits. The centers informed that they have their own documentation or

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				instruction channels to educate and inform their patients regarding their condition and the RF treatment. - Pre-screening and screening visits can be performed on the same day. Text has been updated in section 8.7 accordingly. - Correction made regarding practical conduct of the study intervention in section 9.1 Localisation of the following genicular nerves and anaesthetic procedure - Superolateral genicular nerve: The following sentence has been update: '*Second, a lateral view is made where the needle tip should be within the 2 middle quarters of the ~~femur~~* ***tibia*** *width for the inferomedial genicular nerve and within the posterior half of the femur width for the superomedial and superolateral genicular nerve.* - Additional instructions were added regarding the reporting of safety event tools in section 10.2. - The code used in the eCRF was added in section 12.2 - Additional instructions regarding who will have access to the study data at each participating centre has been added in section 12.3
3	4.0	12 Sep 2022	TMG	- Visit window of 9MFU was corrected from ± 7 days to ± 14 days in section 8.7. - Distinction was made between Belgian and Dutch administrative aspects in the following sections: 12.2, 12.3, 12.4, 14.4, 14.7. Appendix 8 was added as well. - Data will not be shared outside of the EU was added to section 12.3 - The purpose of archiving data was added to section 12.4 - "in case of contradictory statements" was deleted in section 15.1.
4	4.1	19 Oct 2022	TMG	Upon request of the Dutch Central Ethical committee (METC azM/UM) sections 14.1 and 14.4 were updated to clarify that the study is performed according to the national regulation in both countries.
5	5.0	04 Sep 2023	TMG	- Dr. Griet vander Velpen was replaced by Dr. Martijn Grieten - Address change - Evi Theunissen is replaced by Katrien Tartaglia

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				- Clarification on bilateral knee pain, repeat RF, and previous RF - Extended use and addition of one question to health care use questionnaire - Note that OA patients must have had an IA infiltration

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Appendix 5. STANDARDISED PRESCRIPTION FOR PHYSIOTHERAPY

Kinesitherapeutisch voorschrift COGENIUS studie

Betreffende: Naam Achternaam
Geboortedatum
Patiëntennummer

Geachte mevrouw,

Geachte heer,

U heeft de diagnose van primaire osteoartrose van de knie of persisterende post chirurgische pijn na een totale knie prothese gekregen en u bent geïncludeerd als proefpersoon in de COGENIUS studie. Dit is een vergelijkende studie tussen drie studiegroepen:

- Conventionele radiofrequente behandeling van de geniculaire zenuwen
- Cooled radiofrequente behandeling van de geniculaire zenuwen
- Sham procedure

Het is belangrijk dat voor u deze behandeling krijgt, de klassieke behandeling wordt geoptimaliseerd. Deze klassieke behandeling omvat onder andere oefentherapie. Verder is het aangeraden dat u deze oefentherapie ook combineert met een gezonde leefstijl (gewichtsreductie), zelfmanagement en het hanteren van een juist balans tussen belasting en belastbaarheid om zo uw dagdagelijks functioneren te optimaliseren.

Met behulp van dit voorschrift lichten wij u en uw kinesist in over de belangrijkste elementen van de aangeraden kinesitherapeutische behandelingen. Deze revalidatie kan u helpen om beter te functioneren en minder pijn te ervaren. U mag deze brief presenteren aan uw kinesist. Het volgen van kinesitherapie is een vereiste voor deelname aan de studie.

Het onderzoeksteam

COGENIUS studie

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Kinesitherapeutisch voorschrift COGENIUS studie

Betreffende: Naam Achternaam
Geboortedatum
Patiëntennummer

Diagnose: □ Gonartrose
□ Persisterende post chirurgische pijn na een totale knie prothese

Aantal sessies: 18

Frequentie van sessies: Maand 1: 1X per week
Maand 2 & 3: 1X per twee weken
Na de 3de maand: 1X per maand

De principes van de behandeling van primaire gonartrose en persisterende post chirurgische pijn zijn de volgende:

- Het behouden van actieve en passieve range of motion (ROM)
- Tonificatie van de quadriceps spier
- Proprioceptieve stabilisatie oefeningen

Volgende oefeningen worden aangeraden:

- Mobiliserende oefeningen, flexie/extensie van de knie, eventueel na manuele mobilisatie
- Looptraining met accent op gangpatroon
- Spierkracht oefeningen (bijvoorbeeld isometrisch/concentrisch)
- Stabiliteitsoefeningen op gelijke en ongelijke ondergrond.
- Stabiliteitsoefeningen op het aangetaste been
- Conditie training zoals fietsen
- Eventueel sport-specifieke training

De oefentherapie wordt best aangepast aan de noden van de individuele patiënt. Het is aangeraden om deze oefentherapie te combineren met een gezonde leefstijl (gewichtsreductie), zelfmanagement en de juist balans tussen belasting en belastbaarheid.

Stempel + Handtekening

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Prescription kiné — étude COGENIUS

Concerne: Nom Prénom
Date de naissance
Numéro administratif

Madame, Monsieur,

Vous souffrez de douleurs secondaires à une arthrose du genou ou de douleurs persistantes après la pose d'une prothèse totale de genou. Vous avez été inclus dans l'étude COGENIUS, qui est une étude comparative entre trois groupes :

- Radiofréquence conventionnelle des nerfs géniculés.
- Radiofréquence refroidie des nerfs géniculés.
- Procédure placebo.

Avant de pouvoir envisager cette intervention, il est important que le traitement conservateur soit le plus optimal possible. Il comporte entre autre une prise en charge kinésithérapeutique. En outre, nous vous conseillons de la combiner à un mode de vie sain (perte de poids) et à l'apprentissage de techniques d'autogestion, le tout en respectant un équilibre entre le niveau d'exercice et votre condition physique.

Le but de cette prescription est d'informer votre kinésithérapeute des éléments les plus importants de la prise en charge. Cette prise en charge peut vous permettre de mieux fonctionner et réduire l'intensité de votre douleur. Vous pouvez présenter cette lettre à votre kinésithérapeute. Attention, suivre les séances de kinésithérapie est une condition indispensable à votre participation à l'étude.

L'équipe d'investigateurs,
Étude COGENIUS

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Prescription kiné — étude COGENIUS

Concerne: Nom Prénom
Date de naissance
Numéro administratif

Diagnostic : □ Gonarthrose
□ Douleur persistante après prothèse de genou

Nombre de séances : 18

Fréquence : Premier mois : 1x par semaine
Deuxième et troisième mois : 1x toutes les deux semaines
Après le troisième mois : 1x par mois

Les principes de prise en charge des douleurs secondaires à une gonarthrose ou après une prothèse totale de genou sont les suivants :

- Maintien de l'amplitude de mouvement passive et active
- Tonification du muscle quadriceps
- Exercices de stabilisation proprioceptive

Les exercices suivants sont recommandés :

- Mobilisation, flexion/extension du genou, éventuellement après mobilisation manuelle
- Entrainement à la marche, en prêtant une attention particulière à la démarche
- Tonification musculaire (par exemple isométriques/concentriques)
- Exercices de stabilité, sur sol égal et inégal
- Exercices de stabilité sur la jambe atteinte
- Conditionnement à l'effort, par exemple sur vélo
- Éventuellement, exercices spécifiques à un sport

La prise en charge kinésithérapeutique doit être adaptée aux besoins individuels de chaque patient. Il est conseillé de la combiner à un mode de vie sain (perte de poids) et un apprentissage de techniques d'autogestion, tout en respectant l'équilibre entre niveau d'exercice et condition physique.

Cachet et signature

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Appendix 6. INFORMATION ON OSTEOARTHRITIS AND PERSISTENT POST-SURGICAL PAIN

Patients can be referred to:

- Other online sources of information (e.g., Patient education: Osteoarthritis (The Basics and Beyond the basics))
- Patient representative groups (e.g., Reumanet)

Patients will be advised to follow self-efficacy and self-management programs organized by the patient self-help groups (e.g., Reumanet).

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Appendix 7. PANDEMIC MEASURES

Under a pandemic situation all sites should perform a risk assessment for the continuation or discontinuation of study recruitment under the actual conditions at the local study site, considering the local guidance for research and patient care as well as governmental requirements.

In general, every study site shall evaluate whether the safety requirements can be met under pandemic conditions. The recruitment of new patients should be evaluated depending on the local situation and governmental and other regulatory requirements. It is of highest importance to ensure the patient's safety at any time.

Should on-site visits be allowed by the local study site and local government, they should be performed as along as the patient and health staff is not endangered and the recommended hygiene measures are consequently respected.

If these requirements and/or the local governmental measures cannot be fulfilled or if the patient declines on-site visits, the on-site visits should be replaced by telephone visits. The functional test (Goniometry, Timed up and go test and 6-minute walk test) cannot be performed during a telephone contact should be performed at a hospital visit as soon as possible within study visit window.

During the pandemic, the Safety reporting must be ensured.

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Appendix 8. ADMINISTRATIVE ASPECTS (ONLY APPLICABLE FOR THE DUTCH CENTERS)

Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). 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.

Temporary halt and (prematurely) end of study report

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

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

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

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

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.

Regulation statement

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

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Certificaat betreffende voltooiing

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Certificaatpagina's: 9
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Stempel met envelop-id plaatsen: Ingeschakeld
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Paraaf: 0

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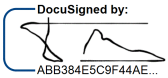
Opdrachtgever van envelop:
Clinical Trial Unit
Synaps Park 1
Genk, 3600
ctu@zol.be
IP-adres: 193.191.133.1

Records bijhouden

Status: Original
07 september 2023 | 13:39

Houder: Clinical Trial Unit
ctu@zol.be

Locatie: DocuSign

Ondertekenaargebeurtenissen	Handtekening	Tijdstempel
Dr. Tom Arts Tom.arts@zol.be Tom Arts, Voorzitter Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  ABB384E5C9F44AE... Aanneming van de handtekening Ondertekend op apparaat IP-adres gebruiken: 84.199.42.115	Verzonden: 07 september 2023 | 13:55 Bekeken: 07 september 2023 | 14:39 Ondertekend: 07 september 2023 | 14:39

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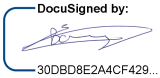
Erwin Bormans erwin.bormans@zol.be Algemeen Directeur Ziekenhuis Oost Limburg Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  30DBD8E2A4CF429... Aanneming van de handtekening Afbeelding geüploade handtekening IP-adres gebruiken: 193.168.148.1	Verzonden: 07 september 2023 | 13:55 Bekeken: 07 september 2023 | 14:30 Ondertekend: 07 september 2023 | 14:30

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Martijn Grieten Martijn.Grieten@zol.be md Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  96C5F1AD2AA8476... Aanneming van de handtekening Afbeelding geüploade handtekening IP-adres gebruiken: 193.168.148.1	Verzonden: 07 september 2023 | 13:55 Bekeken: 08 september 2023 | 17:44 Ondertekend: 08 september 2023 | 17:45

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Ondertekenaargebeurtenissen	Handtekening	Tijdstempel
Jan Van Zundert Jan.VanZundert@zol.be Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  2944175F685C426... Aanneming van de handtekening Vooraf geselecteerde stijl IP-adres gebruiken: 193.168.148.1	Verzonden: 07 september 2023 | 13:55 Bekeken: 11 september 2023 | 12:44 Ondertekend: 11 september 2023 | 12:45

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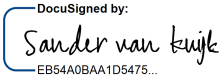
Sander van Kuijk sander.van.kuijk@mumc.nl Associate professor of Clinical Epidemiology Maastricht UMC+ Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  EB54A0BAA1D5475... Aanneming van de handtekening Vooraf geselecteerde stijl IP-adres gebruiken: 145.29.254.35	Verzonden: 11 september 2023 | 12:45 Bekeken: 11 september 2023 | 13:03 Ondertekend: 11 september 2023 | 13:03

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Nelle Stocquart Nelle.Stocquart@kce.fgov.be KCE Trials Study lead Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	DocuSigned by:  E0F5B054B4F94B6... Aanneming van de handtekening Vooraf geselecteerde stijl IP-adres gebruiken: 193.191.212.97	Verzonden: 11 september 2023 | 13:03 Bekeken: 12 september 2023 | 09:53 Ondertekend: 12 september 2023 | 09:54

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Gebeurtenissen voor persoonlijke ondertekenaar	Handtekening	Tijdstempel

Verzendingsgebeurtenissen voor bewerker	Status	Tijdstempel

Verzendingsgebeurtenissen voor vertegenwoordiger	Status	Tijdstempel

Verzendingsgebeurtenissen voor tussenpersoon	Status	Tijdstempel

Gecertificeerde verzendingsgebeurtenissen	Status	Tijdstempel

Carbon copy-gebeurtenissen	Status	Tijdstempel
Charlotte Claes charlotte.claes@zol.be Beveiligingsniveau: E-mailadres, Accountverificatie (geen)	**Gekopieerd**	Verzonden: 07 september 2023 | 13:55 Bekeken: 11 september 2023 | 10:58

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Getuige evenementen	Handtekening	Tijdstempel

Notarisgebeurtenissen	Handtekening	Tijdstempel

Gebeurtenissen voor envelopsamenvatting	Status	Tijdstempels
Envelop verzonden	Gehasht/gecodeerd	07 september 2023 | 13:55
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Ondertekening voltooid	Beveiliging gecontroleerd	12 september 2023 | 09:54
Voltooid	Beveiliging gecontroleerd	12 september 2023 | 09:54

Betalingsgebeurtenissen	Status	Tijdstempels

Elektronische document- en handtekeninginformatie

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