Supplementary information file

SPIRIT checklist
#2b Trial registration: data set, #3 Protocol version, #5b Roles and responsibilities: sponsor contact information

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05407610
Date of registration in primary registry	6 June, 2020
Protocol version	4.1 19/10/2022
Secondary identifying numbers	- COGENIUS - Ethics Committee of University of Antwerp (Number Project ID 3069 - Edge 002190 - BUN B3002022000025) - Ethics committee of Maastricht University (Number NL80503.068.22 - METC22-023) - Sponsor number Z-2021109 - KCE trial number KCE20-1255
Source(s) of monetary or material support	Belgian Health Care Knowledge Centre (KCE) Administrative Centre Botanique, Doorbuilding, Boulevard du Jardin Botanique 55, B-1000 Brussels, Belgium Trials@kce.fgov.be +32 (0)22 87 33 88
Primary sponsor	Ziekenhuis Oost Limburg AV Schiepse bos 6, 3600 Genk, Belgium Main contact person: Evi Theunissen Evi.theunissen@zol.be +32 (0)89 32 71 92
Contact for public queries	Katrien Tartaglia ctu@zol.be +32 (0)89 21 20 87
Contact for scientific queries	Katrien Tartaglia ctu@zol.be +32 (0)89 21 20 87
Public title	COMPARISON OF CONVENTIONAL AND COOLED RADIOFREQUENCY TREATMENT OF THE GENICULAR NERVES VERSUS SHAM PROCEDURE FOR PATIENTS WITH CHRONIC KNEE PAIN: PROTOCOL FOR A MULTICENTRE, DOUBLE BLIND, RANDOMISED CONTROLLED TRIAL.
Scientific title	COMPARISON OF CONVENTIONAL AND COOLED RADIOFREQUENCY TREATMENT OF THE GENICULAR NERVES VERSUS SHAM PROCEDURE FOR PATIENTS WITH CHRONIC KNEE PAIN: PROTOCOL FOR A MULTICENTRE, DOUBLE BLIND, RANDOMISED CONTROLLED TRIAL.
Countries of	Belgium

Data category	Information
recruitment	The Netherlands
Health condition(s) or problem(s) studied	Chronic knee pain due to therapy resistant osteoarthritis of the knee or persistent post-surgical knee pain after total knee arthroplasty.
Intervention(s)	Active comparator: cooled and conventional radiofrequency (RF) intervention of the superolateral, superomedial and inferomedial genicular nerves.
	Placebo comparator: 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.
Key inclusion and exclusion criteria	- Signed written informed consent - Adult patients (Age ≥ 18 years old) - Chronic anterior knee pain (> 12 months) that is moderate to severe - Unresponsive to conventional treatments ongoing for at least 12 months prior to inclusion. - Only for patients with OA: Radiologic confirmation of knee osteoarthritis of grade 2 (mild), 3 (moderate) or 4 (severe)
	- 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 - Patients with unstable psychosocial disorder - 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 index knee - Patients with bilateral knee pain - Patients who have a planned TKA in the near future - Patients who are unwilling or mentally incapable to complete the study questionnaires
Study type	Interventional
	Allocation: randomized intervention model. Participants will be randomly allocated to a conventional RF intervention, a cooled RF intervention or a sham procedure following a 2:2:1 ratio.

Data category	Information
	Parallel assignment masking: double blind (subject, caregiver, investigator, outcomes assessor)
	Primary purpose: To compare knee pain, stiffness, and function (expressed by total WOMAC score) in patients with chronic knee pain at 6 months.
Date of first enrolment	June 2022
Target sample size	400
Recruitment status	Recruiting
Primary outcome(s)	The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (range 0-96) at 6 months post-intervention.
Key secondary outcomes	- WOMAC score - Pain intensity expressed by the Numerical Rating Scale (NRS) (0-10) and the proportion of patients with a pain reduction of at least 50% compared to baseline - EuroQoL-5D-5L - Goniometry - Timed up and go test - 6- minute walk test - Hospital Anxiety and Depression Scale - Pain Catastrophizing Scale - Patient Global Impression of Patient's satisfaction assessed by 7-point Likert scale - Medication Quantification Scale III - Opioid dependence - Incidence of related adverse events - Health care resource use - Productivity loss using the Work Productivity and Activity Impairment Questionnaire

#5c Roles and responsibilities: sponsor and funder

Ziekenhuis Oost Limburg autonome verzorgingsinstelling (ZOL AV) 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.

#5d Roles and responsibilities: committees

1.Principal Investigator (PI) of each participating centre:

- Checking for adverse events when participants attend for intervention / follow-up.
- Using medical judgement in assigning seriousness, causality, and expectedness.
- Ensuring that all Serious Adverse Device Effect (SADE) (including unexpected SADEs) 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.

- Ensuring that Adverse Device Effects are recorded and reported to the Sponsor in line with the requirements of the protocol.

2. Chief Investigator (CI) / Co-Chief Investigator/ delegate:
   - Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
   - Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment.
   - Using medical judgement in assigning expectedness of all reported SADEs.
   - Immediate review of all SADEs.
3. Sponsor:
   - Central data collection and verification of adverse events according to the trial protocol.
   - Reporting safety information to the CI/Co-CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit.
   - Reporting safety information to the independent oversight committees identified for the trial.
   - Reporting of ADE and SADE (including USADEs) to the Ethics Commission (EC) within required timelines.
   - Notifying Investigators of USADEs that occur within the trial.
   - The unblinding of a participant for the purpose of USADEs by unblinded responsible person.
   - 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.
4. Trial Steering Committee (TSC):
   - To provide the overall supervision of the trial.
   - To monitor trial progress, conduct and advise on scientific credibility.
   - To carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.
   - To oversee the performance of the study and discuss important topics in relation thereto.
   - Periodically reviewing safety data.
5. Independent Safety reviewer:
   - Reviewing safety information presented yearly by means of the safety report.
   - Advising the Sponsor on suspension of the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety.

#11b Interventions: modifications

As the radiofrequent treatment is performed only once, there are no criteria for discontinuing or modifying the intervention. All patients will receive the allocated interventions. During the follow-up, patients will not be actively offered a crossover option. However, if indicated and at participant's request, a repeat conventional RF could be performed after the primary endpoint at 6 months.

#15 Recruitment

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 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.

#16a Allocation: sequence generation

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.

#16c Allocation: implementation

During the consultation at the pain centre, the pain physician (Principal investigator of the COGENIUS trial (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. The PI or delegated physician will enrol the patient in the trial and assign them to the intervention using the randomization procedure in the automated web-based system of CASTOR EDC.

#18b Data collection plan: retention

At any time during the study and without giving reasons, subjects may withdraw from the study at their own request. All efforts will be made to reduce the number of discontinuations as much as possible. Discontinuation of the study after receiving study intervention 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) and collect the most possible data.

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, a telephone call and a letter to the subject requesting contact with the researcher for the reason for discontinuation of the study. The reason for loss to follow-up and date of loss to follow-up will be the only additional data that will be collected.

Patients that receive an intervention that deviates from the protocol will be followed up throughout the trial per protocol.

#19 Data management

All data relating to the trial must be recorded in the eCRF prepared by the Sponsor. Data reported in the electronic the case report form (eCRF) will be in English, consistent with the source data or the discrepancies should be explained. 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.

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.

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. 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.
During the study, the patient will be asked to complete several 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.

Data handling and record keeping
All collected study data will be recorded and stored in the electronic the case report form (eCRF) 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.
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.

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 to 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.

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.

#21a data monitoring committee
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 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 Trial Management Group based on the trial risk assessment which will be done by exploring the trial dataset or performing site visits.

#21b data monitoring interim analysis + #23 auditing
There will be no interim analysis.
The role of the TSC is to provide the overall supervision of the trial. The trial steering committee (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 trial steering committee (TSC) will meet on average 3 times per year the first year and twice each year after that. The TSC is composed of the chief investigator, co-chief investigator, the trial statistician, the trial coordinator, 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.

<u>Trial management group (TMG)</u>
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 theprotocol is adhered to and to take appropriate action to safeguard the participants and the quality of the trial itself.

<u>Data Safety Monitoring Committee (DSMC)</u>
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.

#27 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 withregard 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 privacythe 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 coinvestigators 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.