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# Ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain: a study protocol for a randomized controlled trial

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## ABSTRACT

### Introduction

The goals for the management of patients with osteoarthritis (OA) of the knee are to control pain and to minimize disability. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain and function after ultrasound-guided pulsed radiofrequency of the genicular nerves.

### Methods and Analysis

This study is a randomized, double-blind, placebo-controlled trial, parallel design. One hundred and fifty eight out-patients with osteoarthritis of the knee will be recruited from Mallorca, Spain. Participants will be randomly allocated into two groups: Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) and Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF). The primary outcome will be the observed changes from baseline pain intensity based on visual analogue scale (VAS).The possible changes in the secondary efficacy variables from the baseline as assessed by: the Goldberg Anxiety and Depression Scale (GADS), pain medication use, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC subscales), and VAS pain intensity, also to be included in the study. These variables will be assessed at baseline, 1 month, 3 months, 6 months and 1 year after study commencement.

## Discussion

The findings from this study will help to determine whether ultrasound-guided pulsed radiofrequency of the genicular nerves is effective for chronic knee pain management and if this technique can deliver results for the improvement of pain relief, stiffness and disability.

## Ethics and Dissemination

The protocol was approved by the Research Ethic Committee of the Balearic Islands (IB 3223/16 PI). The results will be disseminated in peer-reviewed journals and at scientific conferences.

**Trial registration:** ClinicalTrials.gov NCT02915120. Not yet recruitment.

## Keywords

Knee pain, osteoarthritis, genicular nerve, ultrasonography, pulsed radiofrequency

## Strengths and limitations of this study

- This study is a randomized, double-blind, placebo-controlled trial, parallel design with large sample size, a long-term follow-up and checklists for gathering information about adverse effects.
- Central randomisation and blinded assessment will be used.
- This is a single-centre clinical trial.
- The study design would favour patients that could responded to the treatment (double diagnostic nerve blocks positive to the inclusion) and exclude patients that experienced placebo effects or could be resistant to the treatment (double diagnostic nerve blocks negative to the inclusion)
- Loss of participants at follow-up is possible, especially for non-responders. Trial enrolment and duration may have to be extended to ensure availability of data for analysis.

## INTRODUCTION

Osteoarthritis (OA) of the knee is one of the main causes of disability. Population-based studies revealed that symptomatic knee OA is present in 20–30% of the elderly population aged >65 years, and its prevalence is increasing due in part to the aging of the population [1]. According to the study of prevalence of rheumatic diseases in the Spanish population (EPISER study) symptomatic knee OA prevalence is estimated at 10.2% (14% of women and 5,7% of men) in Spain. The prevalence of radiographic osteoarthritis is increased from 60% among those aged 65 to 80% among those over 75 years of age [2].

The goals of management of patients are to control pain and to minimize disability. Evidence-based guidelines from National Institute of Health and Clinical Excellence (NICE) [3] and Osteoarthritis Research International (OARSI) [4] suggest that the treatment should be multidisciplinary. Optimal management requires a combination of non-pharmacological (changes in lifestyle, pacing of activities, weight reduction, regular aerobic exercise, acupuncture, muscle strengthening and range of motion exercises) and pharmacological modalities when additional treatment is required. Total knee arthroplasty (TKA) should be considered for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy. However, there are some fragile patients who are at high risk during surgery and other patients who are not willing to undergo surgery. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. Recently, genicular nerve ablation with conventional radiofrequency (CRF) has been used in the

management of osteoarthritis related knee pain [5]. The tissue is heated grossly by electrical energy dissipation, and it is the tissue heating that leads to localized destruction of the neural tissue and consequent interruption of neural signaling. A variation of conventional radiofrequency, pulsed radiofrequency (PRF) is often effective without raising the average target tissue temperature above 42°C, which has been traditionally been thought to be below the irreversible tissue destruction threshold (i.e., the heat-lesion threshold) of 45°C to 50°C. [6]. Radiofrequency treatments on the knee joint have the potential to reduce pain from osteoarthritis [7]. The use of ultrasound-guided genicular nerve block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks, and the visualization of neurovascular bundles and identification of the nerves are the most important ones, beyond the advantage of no ionizing radiation [8].The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of PRF on periarticular nerves have not been studied.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks.

## METHODS AND ANALYSIS

### Study aims:

Patients that receive ultrasound-guided pulsed radiofrequency of the genicular nerves will have a measured basal pain perception that is 30 mm less or >30% [9] on VAS pain intensity after pulsed radiofrequency treatment, compared to non-treated patients.

### Study design and setting

This study proposes a randomized, double-blind, placebo-controlled, pre and post-test, parallel design clinical trial; which conforms to the Standard Protocol Items for Randomized Trials recommendations (SPIRIT) [10], Consolidated Standards of Reporting Trials (CONSORT) guidelines [11] (Figure 1) and OARSI Clinical Trials Recommendations [12].

Approximately between 3000-4000 patients visit the Pain Unit at Son Llàtzer University Hospital each year, of which 5% are diagnosed with chronic knee pain. This means that in our clinic 150–200 patients with chronic knee pain are treated each year. To increase the amount of eligible patients for our trial, hospitals and general practitioners in our region we will be approached to help recruit potential participants. The eligibility of prospective participants will be determined by a researcher who is not involved in the assessment or treatment of the participants.

## Inclusion criteria

Eligibility requirements will include the following: patients of either sex with primary osteoarthritis of one or both knees fulfilling diagnostic criteria for osteoarthritis knee laid down by American College of Rheumatology [13], Kellgren-Lawrence (radiologic criterion) score of at least 2 with chronic knee pain with pain intensity of at least 4 out 10 on the VAS on most or all days for more than 3 months, resistant to conventional therapy including NSAIDs, opioids, muscle relaxants, oral steroids, physical therapy, and intra-articular injection. In patients with bilateral knee OA the most painful side will be studied.

## Exclusion Criteria

Patients with any of the following will be excluded from the study: patients with secondary osteoarthritis of knees (i.e., rheumatoid arthritis or gouty arthritis); any knee treatment with steroids, methotrexate, or azathioprine; previous radiofrequency ablation treatment for similar symptoms; intra-articular knee corticosteroid or hyaluronic acid injection in the past 3 months:; active systemic or local infections at the site of proposed needle and electrode placement; coagulopathy or other bleeding disorder; cognitive deficit; unstable medical or psychiatric illness; or previous knee joint replacement surgery

The use of analgesic medicine will be allowed at any time during the study.

## Randomization

Each eligible patient will be randomly twice (the randomizer will be otherwise uninvolved in the study):

1. *Double diagnostic block*. Patients will be assigned to one of two groups: "physiological saline first block" or "2% lidocaine first block". A random number list generated by SPSS statistical software version 18.0 (IBM Corporation, Armonk, NY, USA) (balanced for each six cases per study branch) will be used for the allocation to each group. Researchers from the statistical center will send the randomized list in a numbered, sealed, and opaque envelope to the researcher responsible for participant recruitment and group assignment.
2. *Radiofrequency group*. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures. A computer generated randomization list will allocate patients in a 1:1 ratio to Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF) or Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) groups. Randomization is stratified by OA severity using Kellgren-Lawrence grade (2 and 3 vs. 4) using random blocks of size 2, 4 and 6

## Concealment of allocation

The patient codes of the double-blind study will be placed in numbered, sealed, and opaque envelopes. Researchers, personnel performing the interviews,

statisticians, and participants will be blinded to patient allocation. The sequence generation will be prepared by a statistician and the envelopes will be prepared by an external investigator not involved in the trial.

**Blinding**

All clinical assessments will be conducted by an assessor blinded to treatment allocation. Any occurrence of unblinding of the assessor will be recorded with its reason and reported along with the trial's results. The researcher executing and supervising the treatments will be blinded to the group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

**Interventions**

Study procedures are as follows (figure 1).

Trial objectives will be explained, and any questions or doubts with respect to the study will be resolved to all eligible participants. Patients will be informed that they will be receiving a new technique based on radiofrequency for knee pain treatment, and that they will be allocated to either active or sham treatment(with a strict 50 % probability), one will be followed treatment with real pulsed radiofrequency and the other will be followed treatment with sham pulsed radiofrequency. The necessity of a double diagnostic block for testing the benefits for the radiofrequency treatment will be informed. Long term benefits of treatment will be informed to control patients' expectations and to reduce drop outs. Each participant will sign the written informed consent form before undergoing any

examination or study procedure and will then be assigned a unique sequentially-numbered study identifier according to the order in which he or she is enrolled in the trial.

| | Visits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1st Baseline visit | 2nd 1st Diagnostic Block | 3rd 1st Block Assessment | 4th 2nd Diagnostic Block | 5th 2nd Block Assessment | 6th Radiofrequency | 7 th Follow up 1st month | 8 th Follow up 3rd month ** | 9 th Follow up 6th month | 10 th Follow up 12th month |
| *(Schedule since baseline visit)* | *(1st day)* | *(10th day)* | *(Phone call)* | *(20th day)* | *(Phone call)* | *(30th day)* | *(2nd month)* | *(4th month)* | *(7th month)* | *(13th month)* |
| **Enrolment** | | | | | | | | | | |
| Patient's evaluation and collection of the relevant data | √ | | | | | | | | | |
| Inclusion/Exclusion criteria | √ | | √ | | √ | | | | | |
| Explanation of the objectives of the procedure and how it works | √ | | √ | | √ | | | | | |
| Informed consent | √ | | | | | | | | | |
| Randomization, blinding and allocation | | √* | | | | √ | | | | |
| **Interventions** | | | | | | | | | | |
| Double Diagnostic Block | | √ | | √ | | | | | | |
| Genicular Nerve Pulsed Radiofrequency Real (Real GENPRF) | | | | | | √ | | | | |
| Genicular Nerve Pulsed Radiofrequency Sham (Sham Real GENPRF) | | | | | | √ | | | | |
| **Assessments** | | | | | | | | | | |
| Visual analogue scale (VAS) pain intensity | √ | | √ | | √ | √ | √ | √ | √ | √ |
| McMaster Universities Osteoarthritis Index (WOMAC) | √ | | | | | | √ | √ | √ | √ |
| Medication use | √ | | | | | | √ | √ | √ | √ |
| Goldberg Anxiety and Depression scales | √ | | | | | | √ | √ | √ | √ |
| Adverse event | | | √ | | √ | √ | √ | √ | √ | √ |
| Outcome assessment | | | | | | | | | | √ |
| Reasons of drop-outs or withdrawals | | | | | | | √ | √ | √ | √ |
| Satisfaction and expectations Survey | | | | | | | | | | √ |

** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded. ** 3rd month follow-up VAS pain intensity ≥ baseline assessment, modifies analgesic treatments.*

**Table 1. Schedule of enrolment, interventions, and assessments.**

**Baseline visit (1st visit)**

Once eligibility has been confirmed "and informed consent obtained a baseline assessment will be undertaken. At the baseline assessment appointment the researcher will further explain the study, and answer any questions. After clinical and radiologic assessment, comorbidities, age, gender, body mass index,, duration of knee OA symptoms, medication use, previous treatment and surgery for knee OA will be obtained at baseline.Neuropathic Pain Diagnostic Questionnaire (DN4), the Spanish version validated by Perez et al. [14], will estimate the probability of neuropathic pain (recent studies suggest that neuropathic mechanisms involved in joint pain [15]).

- Overall average knee pain intensity over the last month will be assessed by a continuous scale comprised of a horizontal line, anchored by "no pain" (score of 0) and "worst imaginable pain" (score of 100 [100-mm scale]). (VAS pain intensity score)
- Self-reported knee pain and difficulty with physical function will be measured using WOMAC Index (the Spanish version validated by Escobar et al. [16]
- Analgesic medicine use will be obtained with a questionnaire elaborated according to the EUROHIS (European Health Interview Survey) recommendations [17]. Subjects will be asked (1) about the prescription medicine their general practitioner may have prescribed for them ("Have you taken any pain medicine prescribed by your general practitioner?") as well as any medication not prescribed by their general practitioner ("Have

you taken any pain medicine not prescribed by your general practitioner") and (2) whether or not their prescribed and non-prescribed pain medication use has increased or decreased.

- Levels of depression and anxiety will be measured with the Goldberg Anxiety and Depression Scale. The Spanish version validated by Montón et al. will be used [18].

**1º Diagnostic Block visit (2nd visit2)**

Between 7 or 10 days since baseline visit, the eligible patients will be randomized, using a computer generated randomization schedule, to undergo diagnostic genicular nerve block with local anaesthetic or physiological saline (Table 2). Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. To find the genicular nerves exact location, the genicular arteries are used as landmarks because they share the same trajectories as the genicular nerves. Other important landmarks are the femoral and tibial cortical surfaces because of their close topographic relation to the genicular neurovascular bundles. Genicular nerves consist of the superior lateral (SL), middle, superior medial (SM), inferior lateral (IL), inferior medial (IM), and recurrent tibial genicular nerve. The targets included the SL, SM and IM genicular nerves which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. The IL genicular nerve did not targeted due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula. A 10-cm long, 21-gauge needle (Stimuplex, B. Braun Medical, Bethlehem, PA) connected to nerve stimulador (0,5 mA, 0,1 ms, 2Hz), will

be advanced towards the target nerve. When needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced to assure no motor response present at < 0,2 mA. Then 2 ml of 2% lidocaine or physiological saline will be injected, in adequate spread, in the desired tissue plane, with an injection resistence normal. The procedure will be repeated at each targeted site.

**1º Block Assessment (3rd visit)**

In the evening of the same day a researcher will call the patient to assess the VAS pain intensity. Responses will be recorded as positive if the participants experience a decrease in numeric pain scores of at least 50% during 2-3 hours with 2% lidocaine or no response with physiological saline. Patients with a positive response will be made a new appointment in a week. Patients with a negative response will be excluded.

**2º Diagnostic Block visit (4th visit)**

Between 15 or 20 days since baseline visit, patients with a positive response in the first diagnostic block will be performed a second diagnostic block with physiological saline if they received 2% lidocaine in the first block or 2% lidocaine if they received physiological saline. This second diagnostic block will be undergone the same procedure.

**2º Block Assessment (5th visit)**

In the evening of the same day a researcher will call the patient to assess the VAS pain intensity. Responses will be recorded as positive if the participants experience a decrease in numeric pain scores of at least 50% during 2-3 hours

with 2% lidocaine or no response with physiological saline. Patients with a negative response will be excluded. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures.

**Radiofrequency visit (6th visit)**

One month since the baseline visit the patient will be reviewed. First of all the interviewers will repeat the assessments for pain level. Patients with a significant reduction in VAS scores from baseline levels (reductions on VAS scale of at least 30mm or 30% to be moderately clinically meaningful [9]), will be excluded in the Pulsed Radiofrequency procedures.

Patients included will be again randomly assigned to receive Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF group, n=79) or Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF group, n=79) using another computer generated randomization schedule. The randomization sequence will be concealed throughout the study from both the study patients and the investigator who will be an independent physician from the Outpatient Pain Clinic.

Real radiofrequency group

Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. Skin and soft tissues will be anesthetized with 1 mL 2% lidocaine. Before needle insertion, the patient's inferomedial (IM), superomedial (SM), and superolateral (SL) GN branches will be identified under ultrasound guidance. RF

needles and probes will be advanced to each of the target nerves under ultrasound guidance. A 10 cm 22-gauge RF cannula with a 10 mm active tip radiofrequency (Model SL-S1010-22, NeuroTherm, Inc.) will be employed for the technique. A 50 Hz-frequency sensorial stimulation will be applied with a threshold of < 0.6 V to identify the nerve position. During the sensorial stimulation, the patients will be asked if they feel tingling, pain, or discomfort inside the knee. The RF probe will be maintained in place until one of those feelings is elicited. In order to avoid inactivating motor nerves, the nerve will be tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 1,2 V at 2 Hz. with an impedance value between 300-700 Ω". Lidocaine (1 mL of 2%) will be injected before activation of the RF generator (Neurotherm NT1000 radiofrequency generator (NeuroTherm Inc., Croydon Surrey, United Kingdom). The RF electrode will be then inserted through the cannula, and RF lesions will be generated by applying pulsed RF treatment (current of 2 Hz at 40 volts with 20 msec active and 480 msec silent periods)to the IM, SM and SL, GN branches for 8 minutes each GN branch, whereby the temperature was below 42◦C [19].

Sham radiofrequency group

Control patients will undergo the same procedure. The sensorial and motor stimulations will be applied too. The RF electrode will be then inserted through the cannula, and RF lesions will be simulated without applying pulsed RF treatment to the IM, SM and SL, GN branches for 8 minutes each GN branch and the temperature of the electrode tip was not raised.

**1st, 3rd and 6th month visit since RF (7th, 8th and 9th visit).**

Two, four and seven months since baseline the assessments for pain level, analgesic consumption, WOMAC scale, adverse events and the GADS, will be repeated. The interviewers will also note radiofrequency related adverse effects or complications observed either by the participants or by the interviewers.

The type of treatment that the patient believes he or she is receiving (blinding test) will be asked in the 1st appointment after RF (7th visit). . If 3rd month follow-up, since RF, VAS pain intensity ≥ baseline assessment, the analgesic treatments will be modified.

**12th month visit since RF (10th visit)**

Thirteen months since baseline, at study completion, questions related to patient satisfaction with the treatment received, and their expectations for improvement will be included in the questionnaires.

**Outcomes**

The primary outcome will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks.

Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in functional capacity and stiffness (WOMAC subscales), and VAS scores measured at 1 month, 3 months, 6 months, and 1 year after study commencement.

## Adverse events

Any adverse events will be monitored and reported by researchers at each visit since double diagnostic block. All expected and unexpected adverse events potentially related to the study will be monitored, and their progress will be recorded until resolution. The physicians will decide whether trial participation should be discontinued or not based on these reports.

## Sample size

A total of 142 patients will be necessary (71 subjects for each treatment group) to detect differences of at least 30 mm or >30% in the pain perception assessment according to VAS pain intensity (scale of 0 to 100 mm). Accepted values will be for an alpha risk of 0.05 and beta risk of less than 0.2 in a bilateral contrast as well as a value of 2,5 for the standard deviation (size effect of 0.75) [9]. It is assumed that 20 % of the trial patients will be lost to attrition. Patients will be included in the study by case-consecutive, non-probability sampling after responding to a recruitment visit to the Pain Clinic; then if they sign an informed consent form, they will be placed randomly into one of the treatment groups [20].

## Statistical analysis

*Analysis population*

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.

Data will be presented as mean (standard deviation), median (interquartile range) or number (%). Inter-group comparisons at baseline will be analyzed using independent samples t-test or Mann–Whitney U test for continuous variables and chi square or Fisher's exact test for categorical variables. Intra-group differences (between baseline and 3-month; between baseline and 1-year) will be evaluated using paired samples t-test or Wilkoxon signed rank paired test for continuous variables and McNemar test for dichotomized variables. Inter-group comparisons at 3-months and at 1-year will be assessed using analysis of covariance and Fisher's exact test after adjusting changes in categorical and continuous variables for baseline values. Point-biseral (dichotomic data) and Pearson/Spearman (continuous data) correlations coefficients will be computed to assess the relationship between each possible predictor variables at baseline and VAS change at 3-months and at 1-year. Multiple linear regression models will be used to identify baseline predictors of VAS reduction at 3-months and at 1-year. Analysis will be performed using stepwise and backward method for all models. A two-tailed p value < 0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

**Interim analyses**

An interim-analysis will be performed on the primary endpoint when 100% of patients have been randomised and have completed the 3 months follow-up. The interim-analysis will be performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the Research Ethic Committee of the Balearic Islands (RECIB). The RECIB will have unblinded access to all data.

## Data collection, management and monitoring

The data will be collected by means of a case report form (CRF) specially designed for the study written by the researchers and outcome assessors and then will be entered into electronic database hosted at the Son Llàtzer University Hospital on the research computer server. Any paper study records will be kept in locked storage cabinets. All electronic participant study records will be stored in the password-protected computer study database, accessible to the researchers only.

Entry and coding of clinical data and data management and reporting will be conducted by the clinical data manager. In accordance with European Legislation, all the documentation should be retained for at least 25 years after completion or discontinuation of the trial, as per the new Clinical Trials Regulation (CTR) EU Nº 536/2016.

This study will be monitored by the Research Ethic Committee of the Balearic Islands. During the study period, the clinical research associate will monitor written informed consent documents, recruitment status, protocol compliance and overall trial progress, data quality, timeliness of data collection, treatment administration, and other relevant trial aspects and processes.

## Discussion

The effect of genicular nerve ultrasound guidance pulsed RF treatment OA knee pain, selected after repeated diagnostic blocks, will be investigated in this study. Effectiveness indicators should be the relief of pain, stiffness and functional disability of the knee and a reduction in medication use.

RF is a type of alternate current that creates heating the target tissues by providing friction between the molecules; thus a thermal lesion is formed by the heat generated from this current [21]. RF has been used to treat a variety of pain conditions such as trigeminal neuralgia, cervicogenic headaches and spinal pain [22-24].

Choi et al described fluoroscopically guided conventional RF neurotomy of the sensory nerves (genicular nerves) supplying the knee joint. The findings of the study showed that there was a significant improvement in pain and satisfaction in the RF treatment group [5]. The genicular nerves are sensory branches of the tibial, common peroneal, and obturator nerves. They provide innervation to the capsule of the knee joint, as well as to the intraarticular and extraarticular ligaments [25].

A recent anatomic studies in cadavers on innervation of the knee [8,26] supports the methodology used by Choi et al [5] who targeted IM, SM, and nerves on the SL aspect of the knee joint accompanying genicular vessels because of their proximity to bony structures (junction of the metaphyseal and epiphyseal parts of the femur and tibia). The IL genicular nerve did not targeted due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula.

Use of prognostic nerve blocks at the site of pain generators has generated debate in the interventional pain community [27]. Pain arising from the knee joint is often complex. Nerve blocks with local anesthetics are frequently used to confirm a joint as the primary pain generator, in predicting the success of RF treatments.

Controlled blocks are recommended because of a 25–41% false positive response when using only single blocks [28]. It is logical to suggest that ablative RF treatments should be preceded by nerve blocks with local anesthetics to better prognosticate the likelihood of success and to allow patients to experience temporarily a partly denervated knee joint, but there is no evidence based algorithm established which provides a means of properly selecting which patients would benefit from genicular nerve radiofrequency. The general consensus is to start by diagnostic blocks.

A variation of conventional radiofrequency, pulsed radiofrequency (PRF) produces pulses with amplitude of45 V and duration of 20 ms; a silent phase of 480 ms follows each pulse allows time for heat elimination. In this way, when pulses radiate the tissues, the RF generator modifies parameters of the subsequent pulses until the temperature falls within the limit of 42 C: the signal amplitude (volt) or the pulse duration are often modified. PRF also appears to be a relatively safe procedure. Unlike CRF, which is associated with neuritis-like reactions, motor deficits, and the risk of deafferentation pain, PRF seems to have few side effects.

The use of ultrasound-guided genicular nerve block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks, and the visualization of neurovascular bundles and identification of the nerves are the most important ones, beyond the advantage of no ionizing radiation [8]. Pulsed RF has been performed in the above mentioned conventional RF applications, in peripheral joints, and in other neuropathic syndromes. Pulsed RF appears to have

genuine biological effects in cell morphology, synaptic transmission, and pain signalling, which are likely to be temperature independent [29-31].

The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of pulsed RF on periarticular nerves have not been studied but the publications on pulsed RF treatments of major nerves for knee pain reported significant analgesic benefit at 10 days to 6 months following the interventions [20, 32-33].

To the best of our knowledge, the study of Kesikburun et al [34], a preliminary report, is the first study of ultrasound-guided genicular nerve pulsed RF treatment in patients with osteoarthritis related knee pain. The number of participants was limited, the lack of a control group (no double-blind controlled study) and the fact that long-term effect of pulsed RF treatment was not evaluated, are limiting factors of this study.

To conclude clinical recommendations for ultrasound-guided pulsed RF as a treatment for severe knee OA should not be written until high quality (randomized controlled) clinical studies confirm the results and address the safety aspects. In this article, we combine all of the methodological suggestions, attempting to minimize the biases that may result from study design: the number of patients recruited is sufficient to achieve the significant differences, treatment number, long-term treatment, blinding method (from recruitment), patient perception assessment of the type of technique used before and after treatment, the objective and subjective assessment of the technique, and sham without applying pulsed RF treatment.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks (2% lidocaine and physiological saline solution).

## Trial status

The trial is currently in the recruitment phase. Participant recruitment is expected to start in March 2017 and to end in December 2017.

## Ethics and dissemination

All of the participants will be recruited through voluntary participation, and written informed consent forms from all trial participants will be obtained by researchers in accordance with the Declaration of Helsinki [35]. Trial participation may be terminated during the trial at any time through voluntary refusal to continue or in cases of significant clinical adverse event as judged by the researchers. Participants suffering from trial-related problems or adverse events may be administered medical treatment for compensation. Any amendments to the study protocols will be publicly available via the US National Institutes Health Clinical Trials Registry, Clinical Trials.gov. (Trial number: NCT02915120). Data management procedures will be conducted by JM and BH. Access to the final trial dataset will comply with the conditions of the ethics committee approval and will be at the discretion of the lead CI, JM. The results will be disseminated in peer-reviewed journals, at scientific conferences and all participants in the RCT will receive a report outlining the study findings at the conclusion of the trial.

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## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

JM is leading the trial coordination and helped to conceive the project, develop the protocol, and write the first and final drafts of the manuscript. PV helped to design the protocol. BM will head participant recruitment. BH will recruit and screen the participants and perform data entry. JLA helped to write the first and final drafts of the manuscript. All authors participated in the trial design, provided feedback on drafts of this article, and read and approved the final manuscript.

## Data sharing statement

No later than 3 years after the study will have ended a completely deidentified data set will deliver to an appropriate data archive for sharing purposes

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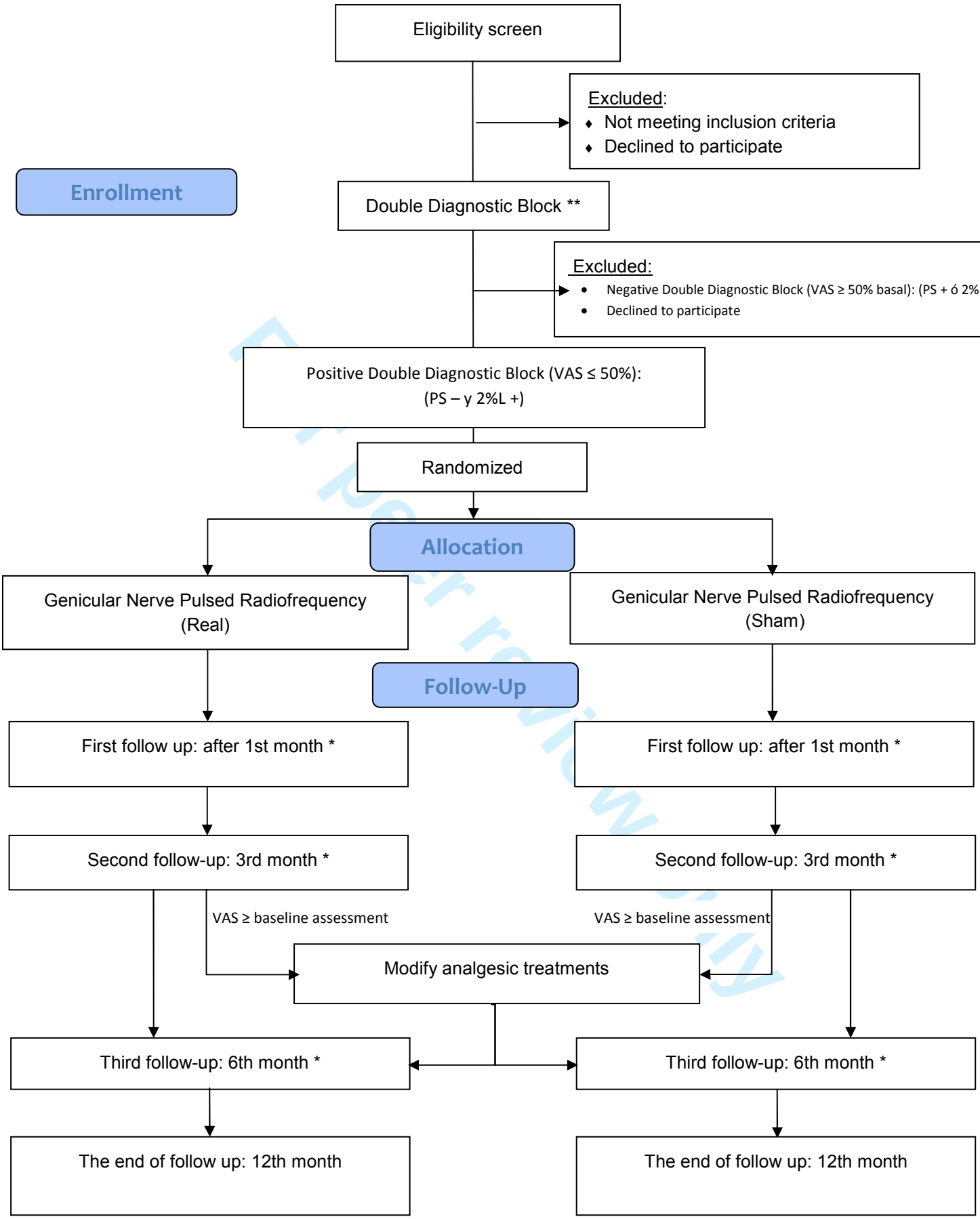
**Figure 1.**Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. * Visual analogue scale pain intensity, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. 3rd month follow-up VAS ≥ baseline assessment modifies analgesic treatments. ** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded.

**Figure 2.**Flow chart showing progression in Diagnostic nerve blocks.




Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. * Visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. VAS, Visual analogue scale. 3rd month follow-up VAS ≥ baseline assessment, modifies analgesic treatments. ** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded.

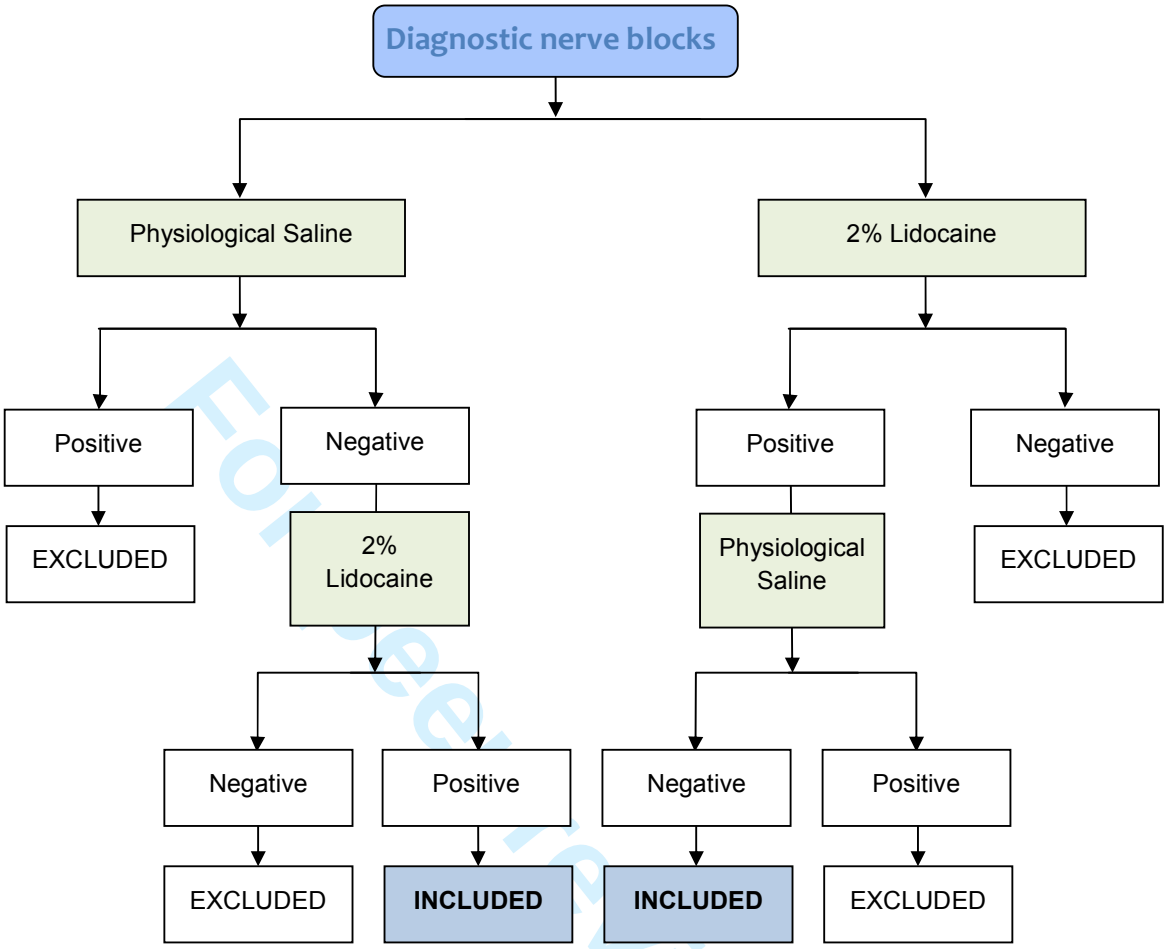



**Figure 2**. Flow chart showing progression in Diagnostic nerve blocks.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | End of this file |
| Protocol version | 3 | Date and version identifier | 3 |
| Funding | 4 | Sources and types of financial, material, and other support | 24 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 25 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 24 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 24 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-6 |
| | 6b | Explanation for choice of comparators | 6 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non inferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 15-16 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 18 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 8 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12-13, 17 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 11 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 18 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8-9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7-9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 10 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12-13 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7, 24 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 19-20 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 18-19 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 18-19 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 19 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 21 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 20 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 19 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 21 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 3 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 25 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 10 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 19-20 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 26 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 24 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 24 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 24 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 25 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 26 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | 10 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

| | |
|---|---|
| **Register:** | NTC |
| **Last refreshed on:** | January 24, 2017 |
| **Main ID:** | NCT02915120 |
| **Date of registration:** | September 23, 2016 |
| **Primary sponsor:** | Son Llatzer University Hospital |
| **Public title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Scientific title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Date of first enrolment:** | March 2017 |
| **Target sample size:** | 158 |
| **Recruitment status:** | Not yet recruiting |
| **URL:** | https://clinicaltrials.gov/ct2/show/record/NCT02915120 |
| **Study type:** | Interventional |
| **Study design:** | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double Blind (Subject, Investigator, Outcomes Assessor)<br>Primary Purpose: Supportive Care |
| **Phase:** | Not applicable |

BMJ Open

# A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain



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| Primary Subject Heading: | Rehabilitation medicine |
| Secondary Subject Heading: | Anaesthesia, Research methods |
| Keywords: | Knee pain, osteoarthritis, genicular nerve, ULTRASONOGRAPHY, pulsed radiofrequency |
| | |

# A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain

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## ABSTRACT

### Introduction

The goals for the management of patients with osteoarthritis (OA) of the knee are to control pain and to minimize disability. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound guided pulsed radiofrequency treatment of the genicular nerves in patients with chronic painful knee osteoarthritis.

### Methods and Analysis

This study is a randomized, double-blind, placebo-controlled trial, parallel design. One hundred and forty-two out-patients with osteoarthritis of the knee will be recruited from Mallorca, Spain. Participants will be randomly allocated into two groups: Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) and Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF). The primary outcome measures will be the observed changes from baseline pain intensity based on visual analogue scale (VAS). The possible changes in the secondary efficacy variables from the baseline as assessed by: The Goldberg Anxiety and Depression Scale (GADS), pain medication use, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC subscales), and VAS pain intensity, also to be included in the study. These variables will be assessed at baseline, 1 month, 3 months, 6 months and 1 year after study commencement.

## Discussion

The findings from this study will help to determine whether ultrasound-guided pulsed radiofrequency of the genicular nerves is effective for chronic knee pain management and if this technique can deliver results for the improvement of pain relief, stiffness and disability.

## Ethics and Dissemination

The protocol was approved by the Research Ethic Committee of the Balearic Islands (IB 3223/16 PI). The results will be disseminated in peer-reviewed journals and at scientific conferences.

**Trial registration:** ClinicalTrials.gov NCT02915120. Recruiting.



## Keywords

Knee pain, osteoarthritis, genicular nerve, ultrasonography, pulsed radiofrequency

## Strengths and limitations of this study

- This study is a randomized, double-blind, placebo-controlled trial, parallel design with large sample size, a long-term follow-up and checklists for gathering information about adverse effects.
- Central randomisation and blinded assessment will be used.
- This is a single-centre clinical trial.
- The study design would favour patients that could responded to the treatment (double diagnostic nerve blocks positive to the inclusion) and exclude patients that experienced placebo effects or could be resistant to the treatment (double diagnostic nerve blocks negative to the inclusion)
- Loss of participants at follow-up is possible, especially for non-responders. Trial enrolment and duration may have to be extended to ensure availability of data for analysis.

## INTRODUCTION

Osteoarthritis (OA) of the knee is one of the main causes of disability. Population-based studies revealed that symptomatic knee OA is present in 20–30% of the elderly population aged >65 years, and its prevalence is increasing due in part to the aging of the population [1]. According to the study of prevalence of rheumatic diseases in the Spanish population (EPISER study) symptomatic knee OA prevalence is estimated at 10.2% (14% of women and 5,7% of men) in Spain. The prevalence of radiographic osteoarthritis is increased from 60% among those aged 65 to 80% among those over 75 years of age [2].

The goals of management of patients are to control pain and to minimize disability. Evidence-based guidelines from National Institute of Health and Clinical Excellence (NICE) [3] and Osteoarthritis Research International (OARSI) [4] suggest that the treatment should be multidisciplinary. Optimal management requires a combination of non-pharmacological (changes in lifestyle, pacing of activities, weight reduction, regular aerobic exercise, acupuncture, muscle strengthening and range of motion exercises) and pharmacological modalities when additional treatment is required. Total knee arthroplasty (TKA) should be considered for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy. However, there are some fragile patients who are at high risk during surgery and other patients who are not willing to undergo surgery. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. Recently, genicular nerve ablation with conventional radiofrequency (CRF) has been used in the

management of osteoarthritis related knee pain [5]. The tissue is heated grossly by electrical energy dissipation, and it is the tissue heating that leads to localized destruction of the neural tissue and consequent interruption of neural signaling. A variation of conventional radiofrequency, pulsed radiofrequency (PRF) is often effective without raising the average target tissue temperature above 42°C, which has been traditionally been thought to be below the irreversible tissue destruction threshold (i.e., the heat-lesion threshold) of 45°C to 50°C. [6]. Radiofrequency treatments on the knee joint have the potential to reduce pain from osteoarthritis [7]. The use of ultrasound-guided genicular nerve block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks, and the visualization of neurovascular bundles and identification of the nerves are the most important ones, beyond the advantage of no ionizing radiation [8].The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of PRF on periarticular nerves have not been studied.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks.

**Aims**

The primary outcome will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks. Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of

the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in functional capacity and stiffness (WOMAC subscales), and VAS scores measured at 1 month, 3 months, 6 months, and 1 year after study commencement.

**Hypothesis:**

The primary hypothesis is that ultrasound-guided pulsed radiofrequency of the genicular nerves will mitigate pain and improve function as compared to placebo.

## METHODS AND ANALYSIS

### Study design and setting

This study proposes a randomized, double-blind, placebo-controlled, pre and post-test, parallel design clinical trial; which conforms to the Standard Protocol Items for Randomized Trials recommendations (SPIRIT) [9], Consolidated Standards of Reporting Trials (CONSORT) guidelines [10] (Figure 1) and OARSI Clinical Trials Recommendations [11].

Approximately between 3000-4000 patients visit the Pain Unit at Son Llàtzer University Hospital each year, of which 5% are diagnosed with chronic knee pain. This means that in our clinic 150–200 patients with chronic knee pain are treated each year. To increase the amount of eligible patients for our trial, hospitals and general practitioners in our region we will be approached to help recruit potential participants. The eligibility of prospective participants will be determined by a researcher who is not involved in the assessment or treatment of the participants.

## Inclusion criteria

Eligibility requirements will include the following: patients of either sex with primary osteoarthritis of one or both knees fulfilling diagnostic criteria for osteoarthritis knee laid down by American College of Rheumatology [12], Kellgren-Lawrence (radiologic criterion) score of at least 2 with chronic knee pain with pain intensity of at least 4 out 10 on the VAS on most or all days for more than 3 months, resistant to conventional therapy including NSAIDs, opioids, muscle relaxants, oral steroids, physical therapy, and intra-articular injection. In patients with bilateral knee OA the most painful side will be studied.

## Exclusion Criteria

Patients with any of the following will be excluded from the study: patients with secondary osteoarthritis of knees (i.e., rheumatoid arthritis or gouty arthritis); any knee treatment with steroids, methotrexate, or azathioprine; previous radiofrequency ablation treatment for similar symptoms; intra-articular knee corticosteroid or hyaluronic acid injection in the past 3 months:; active systemic or local infections at the site of proposed needle and electrode placement; coagulopathy or other bleeding disorder; cognitive deficit; unstable medical or psychiatric illness; or previous knee joint replacement surgery

The use of analgesic medicine will be allowed at any time during the study.

## Randomization

Each eligible patient will be randomly twice (the randomizer will be otherwise uninvolved in the study):

1. *Double diagnostic block*. Patients will be assigned to one of two groups: "physiological saline first block" or "2% lidocaine first block". A random number list generated by SPSS statistical software version 18.0 (IBM Corporation, Armonk, NY, USA) (balanced for each six cases per study branch) will be used for the allocation to each group. Researchers from the statistical center will send the randomized list in a numbered, sealed, and opaque envelope to the researcher responsible for participant recruitment and group assignment: starting with a sham and ending with a positive versus starting with a positive and ending with a sham.
2. *Radiofrequency group*. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures. A computer generated randomization list will allocate patients in a 1:1 ratio to Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF) or Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) groups. Randomization is stratified by OA severity using Kellgren-Lawrence grade (2 and 3 vs. 4) using random blocks of size 2, 4 and 6

### Concealment of allocation

The patient codes of the double-blind study will be placed in numbered, sealed, and opaque envelopes. Researchers, personnel performing the interviews, statisticians, and participants will be blinded to patient allocation. The sequence generation will be prepared by a statistician and the envelopes will be prepared by an external investigator not involved in the trial.

### Blinding

All clinical assessments will be conducted by an assessor blinded to treatment allocation. Any occurrence of unblinding of the assessor will be recorded with its reason and reported along with the trial's results. The researcher executing and supervising the treatments will be blinded to the group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

### Interventions

Study procedures are as follows (table 1).

Trial objectives will be explained, and any questions or doubts with respect to the study will be resolved to all eligible participants. Patients will be informed that they will be receiving a new technique based on radiofrequency for knee pain treatment, and that they will be allocated to either active or sham treatment (with a strict 50 % probability), one will be followed treatment with real pulsed radiofrequency and the other will be followed treatment with sham pulsed radiofrequency. The necessity of a double diagnostic block for testing the benefits

for the radiofrequency treatment will be informed. Long term benefits of treatment will be informed to control patients' expectations and to reduce drop outs. Each participant will sign the written informed consent form before undergoing any examination or study procedure and will then be assigned a unique sequentially-numbered study identifier according to the order in which he or she is enrolled in the trial.

| | Visits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1st | 2nd | 3rd | 4th | 5th | 6th | 7 th | 8 th | 9 th | 10 th |
| | *Baseline visit* | *1st Diagnostic Block* | *1st Block Assessment* | *2nd Diagnostic Block* | *2nd Block Assessment* | *Radiofrequency* | *Follow up 1st month* | *Follow up 3rd month *** | *Follow up 6th month* | *Follow up 12th month* |
| *(Schedule since baseline visit)* | *(1st day)* | *(10th day)* | *(Phone call)* | *(20th day)* | *(Phone call)* | *(30th day)* | *(2nd month)* | *(4th month)* | *(7th month)* | *(13th month)* |
| **Enrolment** | | | | | | | | | | |
| Patient's evaluation and collection of the relevant data | √ | | | | | | | | | |
| Inclusion/Exclusion criteria | √ | | √ | | √ | | | | | |
| Explanation of the objectives of the procedure and how it works | √ | | √ | | √ | | | | | |
| Informed consent | √ | | | | | | | | | |
| Randomization, blinding and allocation | | √* | | | | √† | | | | |
| **Interventions** | | | | | | | | | | |
| Double Diagnostic Block | | √ | | √ | | | | | | |
| Genicular Nerve Pulsed Radiofrequency Real (Real GENPRF) | | | | | | √ | | | | |
| Genicular Nerve Pulsed Radiofrequency Sham (Sham Real GENPRF) | | | | | | √ | | | | |
| **Assessments** | | | | | | | | | | |
| Visual analogue scale (VAS) pain intensity | √ | | √ | | √ | √ | √ | √ | √ | √ |
| McMaster Universities Osteoarthritis Index (WOMAC) | √ | | | | | | √ | √ | √ | √ |
| Medication use | √ | | | | | | √ | √ | √ | √ |
| Goldberg Anxiety and Depression scales | √ | | | | | | √ | √ | √ | √ |
| Adverse event | | | √ | | √ | √ | √ | √ | √ | √ |
| Outcome assessment | | | | | | | | | | √ |
| Reasons of drop-outs or withdrawals | | | | | | | √ | √ | √ | √ |
| Satisfaction and expectations Survey | | | | | | | | | | √ |

** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded. † Patients with a significant reduction in VAS scores from baseline levels (reductions on VAS scale ≥ 30%), will be excluded in the Pulsed Radiofrequency procedures. ** 3rd month follow-up VAS pain intensity ≥ baseline assessment, modifies analgesic treatments.*

**Table 1. Schedule of enrolment, interventions, and assessments.**

**Baseline visit (1st visit)**

Once eligibility has been confirmed "and informed consent obtained a baseline assessment will be undertaken. At the baseline assessment appointment, the researcher will further explain the study, and answer any questions. After clinical and radiologic assessment, comorbidities, age, gender, body mass index, duration of knee OA symptoms, medication use, previous treatment and surgery for knee OA will be obtained at baseline. Neuropathic Pain Diagnostic Questionnaire (DN4), the Spanish version validated by Perez et al. [13], will estimate the probability of neuropathic pain (recent studies suggest that neuropathic mechanisms involved in joint pain [14]).

- Overall average knee pain intensity over the last month will be assessed by a continuous scale comprised of a horizontal line, anchored by "no pain" (score of 0) and "worst imaginable pain" (score of 100 [100-mm scale]). (VAS pain intensity score)
- Self-reported knee pain and difficulty with physical function will be measured using WOMAC Index (the Spanish version validated by Escobar et al. [15]
- Analgesic medicine use will be obtained with a questionnaire elaborated according to the EUROHIS (European Health Interview Survey) recommendations [16]. Subjects will be asked (1) about the prescription medicine their general practitioner may have prescribed for them ("Have you taken any pain medicine prescribed by your general practitioner?") as well as any medication not prescribed by their general practitioner ("Have

you taken any pain medicine not prescribed by your general practitioner") and (2) whether or not their prescribed and non-prescribed pain medication use has increased or decreased.

- Levels of depression and anxiety will be measured with the Goldberg Anxiety and Depression Scale. The Spanish version validated by Montón et al. will be used [17].

**1º Diagnostic Block visit (2nd visit2)**

Between 7 or 10 days since baseline visit, the eligible patients will be randomized, using a computer generated randomization schedule, to undergo diagnostic genicular nerve block with local anaesthetic or physiological saline (figure 2). Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. To find the genicular nerves exact location, the genicular arteries are used as landmarks because they share the same trajectories as the genicular nerves. Other important landmarks are the femoral and tibial cortical surfaces because of their close topographic relation to the genicular neurovascular bundles (figure 3). Genicular nerves consist of the superior lateral (SL), middle, superior medial (SM), inferior lateral (IL), inferior medial (IM), and recurrent tibial genicular nerve. The targets included the SL, SM and IM genicular nerves which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. The IL genicular nerve did not target due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula. A 10-cm long, 21-gauge needle (Stimuplex, B. Braun Medical, Bethlehem, PA) connected to nerve stimulador (0,5

mA, 0,1 ms, 2Hz), will be advanced towards the target nerve. When needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced to assure no motor response present at < 0,2 mA. Then 2 ml of 2% lidocaine or physiological saline will be injected, in adequate spread, in the desired tissue plane, with an injection resistence normal. The procedure will be repeated at each targeted site.

**1º Block Assessment (3rd visit)**

In the evening of the same day a researcher will call the patient to assess the VAS pain intensity. Responses will be recorded as positive if the participants experience a decrease in numeric pain scores of at least 80% during 2-3 hours with 2% lidocaine or no response with physiological saline. Patients with a positive response will be made a new appointment in a week. Patients with a negative response will be excluded.

**2º Diagnostic Block visit (4th visit)**

Between 15 or 20 days since baseline visit, patients with a positive response in the first diagnostic block will be performed a second diagnostic block with physiological saline if they received 2% lidocaine in the first block or 2% lidocaine if they received physiological saline. This second diagnostic block will be undergone the same procedure.

**2º Block Assessment (5th visit)**

In the evening of the same day a researcher will call the patient to assess the VAS pain intensity. Responses will be recorded as positive if the participants

experience a decrease in numeric pain scores of at least 80% during 2-3 hours with 2% lidocaine or no response with physiological saline. Patients with a negative response will be excluded. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures.

**Radiofrequency visit (6th visit)**

One month since the baseline visit the patient will be reviewed. First of all, the interviewers will repeat the assessments for pain level. Patients with a significant reduction in VAS scores from baseline levels (reductions on VAS scale of at least 30mm or 30% to be moderately clinically meaningful [18]), will be excluded in the Pulsed Radiofrequency procedures.

Patients included will be again randomly assigned to receive Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF group, n=71) or Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF group, n=71) using another computer generated randomization schedule. The randomization sequence will be concealed throughout the study from both the study patients and the investigator who will be an independent physician from the Outpatient Pain Clinic.

Real radiofrequency group

Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. Skin and soft tissues will be anesthetized with 1 mL 2% lidocaine. Before needle insertion, the patient's inferomedial (IM), superomedial (SM), and

superolateral (SL) GN branches will be identified under ultrasound guidance. RF needles and probes will be advanced to each of the target nerves under ultrasound guidance. A 10 cm 22-gauge RF cannula with a 10 mm active tip radiofrequency (Model SL-S1010-22, NeuroTherm, Inc.) will be employed for the technique. A 50 Hz-frequency sensorial stimulation will be applied with a threshold of < 0.5 mA to identify the nerve position, the current intensity (mA) will be reduced at < 0,2 mA. During the sensorial stimulation, the patients will be asked if they feel tingling, pain, or discomfort inside the knee. The RF probe will be maintained in place until one of those feelings is elicited. In order to avoid inactivating motor nerves, the nerve will be tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 0,5 mA at 2 Hz. with an impedance value between 300-700 Ω", when needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced at < 0,2 mA. Lidocaine (1 mL of 2%) will be injected before activation of the RF generator (Neurotherm NT1000 radiofrequency generator (NeuroTherm Inc., Croydon Surrey, United Kingdom). The RF electrode will be then inserted through the cannula, and RF lesions will be generated by applying pulsed RF treatment (current of 2 Hz at 40 volts with 20 msec active and 480 msec silent periods) to the IM, SM and SL, GN branches for 8 minutes each GN branch, whereby the temperature was below 42◦C [19].

Sham radiofrequency group

Control patients will undergo the same procedure. The sensorial and motor stimulations will be applied too. The RF electrode will be then inserted through the cannula, and RF lesions will be simulated without applying pulsed RF treatment to

the IM, SM and SL, GN branches for 8 minutes each GN branch and the temperature of the electrode tip was not raised.

**1st, 3rd and 6th month visit since RF (7th, 8th and 9th visit).**

Two, four and seven months since baseline the assessments for pain level, analgesic consumption, WOMAC scale, adverse events and the GADS, will be repeated. The interviewers will also note radiofrequency related adverse effects or complications observed either by the participants or by the interviewers.

The type of treatment that the patient believes he or she is receiving (blinding test) will be asked in the 1st appointment after RF (7th visit). If 3rd month follow-up, since RF, VAS pain intensity ≥ baseline assessment, the analgesic treatments will be modified.

**12th month visit since RF (10th visit)**

Thirteen months since baseline, at study completion, questions related to patient satisfaction with the treatment received, and their expectations for improvement will be included in the questionnaires.

**Outcomes**

The primary outcome measures will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks.

Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in

functional capacity and stiffness (WOMAC subscales), and VAS scores measured at 1 month, 3 months, 6 months, and 1 year after study commencement.

**Adverse events**

Any adverse events will be monitored and reported by researchers at each visit since double diagnostic block. All expected and unexpected adverse events potentially related to the study will be monitored, and their progress will be recorded until resolution. The physicians will decide whether trial participation should be discontinued or not based on these reports.

**Sample size**

A total of 142 patients will be necessary (71 subjects for each treatment group) to detect differences between groups of at least 30 mm or >30% in the pain perception assessment according to VAS pain intensity (scale of 0 to 100 mm). Accepted values will be for an alpha risk of 0.05 and beta risk of less than 0.2 in a bilateral contrast as well as a value of 2,5 for the standard deviation (size effect of 0.75) [18]. It is assumed that 20 % of the trial patients will be lost to attrition. Patients will be included in the study by case-consecutive, non-probability sampling after responding to a recruitment visit to the Pain Clinic; then if they sign an informed consent form, they will be placed randomly into one of the treatment groups [20].

## Statistical analysis

*Analysis population*

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.

Data will be presented as mean (standard deviation), median (interquartile range) or number (%). Inter-group comparisons at baseline will be analyzed using independent samples t-test or Mann–Whitney U test for continuous variables and chi square or Fisher's exact test for categorical variables. Intra-group differences (between baseline and 3-month; between baseline and 1-year) will be evaluated using paired samples t-test or Wilkoxon signed rank paired test for continuous variables and McNemar test for dichotomized variables. Inter-group comparisons at 3-months and at 1-year will be assessed using analysis of covariance and Fisher's exact test after adjusting changes in categorical and continuous variables for baseline values. Point-biseral (dichotomic data) and Pearson/Spearman (continuous data) correlations coefficients will be computed to assess the relationship between each possible predictor variables at baseline and VAS change at 3-months and at 1-year. Multiple linear regression models will be used to identify baseline predictors of VAS reduction at 3-months and at 1-year. Analysis will be performed using stepwise and backward method for all models.

An interim-analysis will be performed on the primary endpoint when 100% of patients have been randomised and have completed the 3 months' follow-up. The interim-analysis will be performed by an independent statistician, blinded for the

treatment allocation. The statistician will report to the Research Ethic Committee of the Balearic Islands (RECIB). The RECIB will have unblinded access to all data.

A two-tailed p value < 0.0294 will be considered statistically significant after adjusting according Pocock's method [21] for interim analysis. Statistical analyses will be performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

**Data collection, management and monitoring**

The data will be collected by means of a case report form (CRF) specially designed for the study written by the researchers and outcome assessors and then will be entered into electronic database hosted at the Son Llàtzer University Hospital on the research computer server. Any paper study records will be kept in locked storage cabinets. All electronic participant study records will be stored in the password-protected computer study database, accessible to the researchers only.

Entry and coding of clinical data and data management and reporting will be conducted by the clinical data manager. In accordance with European Legislation, all the documentation should be retained for at least 25 years after completion or discontinuation of the trial, as per the new Clinical Trials Regulation (CTR) EU Nº 536/2016.

This study will be monitored by the Research Ethic Committee of the Balearic Islands. During the study period, the clinical research associate will monitor written informed consent documents, recruitment status, protocol compliance and overall trial progress, data quality, timeliness of data collection, treatment administration, and other relevant trial aspects and processes.

## Discussion

The effect of genicular nerve ultrasound guidance pulsed RF treatment OA knee pain, selected after repeated diagnostic blocks, will be investigated in this study. Effectiveness indicators should be the relief of pain, stiffness and functional disability of the knee and a reduction in medication use.

RF is a type of alternate current that creates heating the target tissues by providing friction between the molecules; thus a thermal lesion is formed by the heat generated from this current [22]. RF has been used to treat a variety of pain conditions such as trigeminal neuralgia, cervicogenic headaches and spinal pain [23-25].

Choi et al described fluoroscopically guided conventional RF neurotomy of the sensory nerves (genicular nerves) supplying the knee joint. The findings of the study showed that there was a significant improvement in pain and satisfaction in the RF treatment group [5]. The genicular nerves are sensory branches of the tibial, common peroneal, and obturator nerves. They provide innervation to the capsule of the knee joint, as well as to the intraarticular and extraarticular ligaments [26].

A recent anatomic studies in cadavers on innervation of the knee [8,27] supports the methodology used by Choi et al [5] who targeted IM, SM, and nerves on the SL aspect of the knee joint accompanying genicular vessels because of their proximity to bony structures (junction of the metaphyseal and epiphyseal parts of the femur and tibia). The IL genicular nerve did not target due to concerns about inadvertent

injury to the common peroneal nerve that lies in close proximity at the neck of the fibula.

Use of prognostic nerve blocks at the site of pain generators has generated debate in the interventional pain community [28]. Pain arising from the knee joint is often complex. Nerve blocks with local anesthetics are frequently used to confirm a joint as the primary pain generator, in predicting the success of RF treatments. A threshold of 80% reduction in pain after diagnostic genicular nerve block with 2% lidocaine is used. This protocol is more stringent than that which has been previously reported by Choi et al. 80% or greater relief from diagnostic blocks is associated with high accuracy in predicting treatment success [29].

Controlled blocks are recommended because of a 25–41% false positive response when using only single blocks [30]. It is logical to suggest that ablative RF treatments should be preceded by nerve blocks with local anesthetics to better prognosticate the likelihood of success and to allow patients to experience temporarily a partly denervated knee joint, but there is no evidence based algorithm established which provides a means of properly selecting which patients would benefit from genicular nerve radiofrequency. The general consensus is to start by diagnostic blocks.

A variation of conventional radiofrequency, pulsed radiofrequency (PRF) is the technique whereby radio frequency oscillations are gated at a rate of pulses per second (cycles per second, defined as a hertz (Hz)). Current of 2 Hz means two cycles per second (with 20 msec active and 480 msec silent periods per cycle). PRF uses radiofrequency current in short (20 ms), high-voltage bursts (with amplitude

of 45 V); the "silent" phase (480 ms) of PRF allows time for heat elimination, generally keeping the target tissue below 42°: the signal amplitude (volt) or the pulse duration are often modified. PRF also appears to be a relatively safe procedure. Unlike CRF, which is associated with neuritis-like reactions, motor deficits, and the risk of deafferentation pain, PRF seems to have few side effects.

The use of ultrasound-guided genicular nerve block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks, and the visualization of neurovascular bundles and identification of the nerves are the most important ones, beyond the advantage of no ionizing radiation [8]. Pulsed RF has been performed in the above mentioned conventional RF applications, in peripheral joints, and in other neuropathic syndromes. Pulsed RF appears to have genuine biological effects in cell morphology, synaptic transmission, and pain signalling, which are likely to be temperature independent [31-33].

The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of pulsed RF on periarticular nerves have not been studied but the publications on pulsed RF treatments of major nerves for knee pain reported significant analgesic benefit at 10 days to 6 months following the interventions [20, 34-35].

To the best of our knowledge, the study of Kesikburun et al [36], a preliminary report, is the first study of ultrasound-guided genicular nerve pulsed RF treatment in patients with osteoarthritis related knee pain. The number of participants was limited, the lack of a control group (no double-blind controlled study) and the fact

that long-term effect of pulsed RF treatment was not evaluated, are limiting factors of this study.

To conclude clinical recommendations for ultrasound-guided pulsed RF as a treatment for severe knee OA should not be written until high quality (randomized controlled) clinical studies confirm the results and address the safety aspects. In this article, we combine all of the methodological suggestions, attempting to minimize the biases that may result from study design: the number of patients recruited is sufficient to achieve the significant differences, treatment number, long-term treatment, blinding method (from recruitment), patient perception assessment of the type of technique used before and after treatment, the objective and subjective assessment of the technique, and sham without applying pulsed RF treatment.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks (2% lidocaine and physiological saline solution).

## Trial status

The trial is currently in the recruitment phase. Participant recruitment is started in March 2017 and expected to end in December 2017.

## Ethics and dissemination

All of the participants will be recruited through voluntary participation, and written informed consent forms from all trial participants will be obtained by researchers in accordance with the Declaration of Helsinki [37]. Trial participation may be terminated during the trial at any time through voluntary refusal to continue or in cases of significant clinical adverse event as judged by the researchers. Participants suffering from trial-related problems or adverse events may be administered medical treatment for compensation. Any amendments to the study protocols will be publicly available via the US National Institutes Health Clinical Trials Registry, Clinical Trials.gov. (Trial number: NCT02915120). Data management procedures will be conducted by JM and BH. Access to the final trial dataset will comply with the conditions of the ethics committee approval and will be at the discretion of the lead CI, JM. The results will be disseminated in peer-reviewed journals, at scientific conferences and all participants in the RCT will receive a report outlining the study findings at the conclusion of the trial.

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## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

JM is leading the trial coordination and helped to conceive the project, develop the protocol, and write the first and final drafts of the manuscript. PV helped to design the protocol. BM will head participant recruitment. BH will recruit and screen the participants and perform data entry. JLA helped to write the first and final drafts of the manuscript. All authors participated in the trial design, provided feedback on drafts of this article, and read and approved the final manuscript.

## Data sharing statement

No later than 3 years after the study will have ended a completely deidentified data set will deliver to an appropriate data archive for sharing purposes

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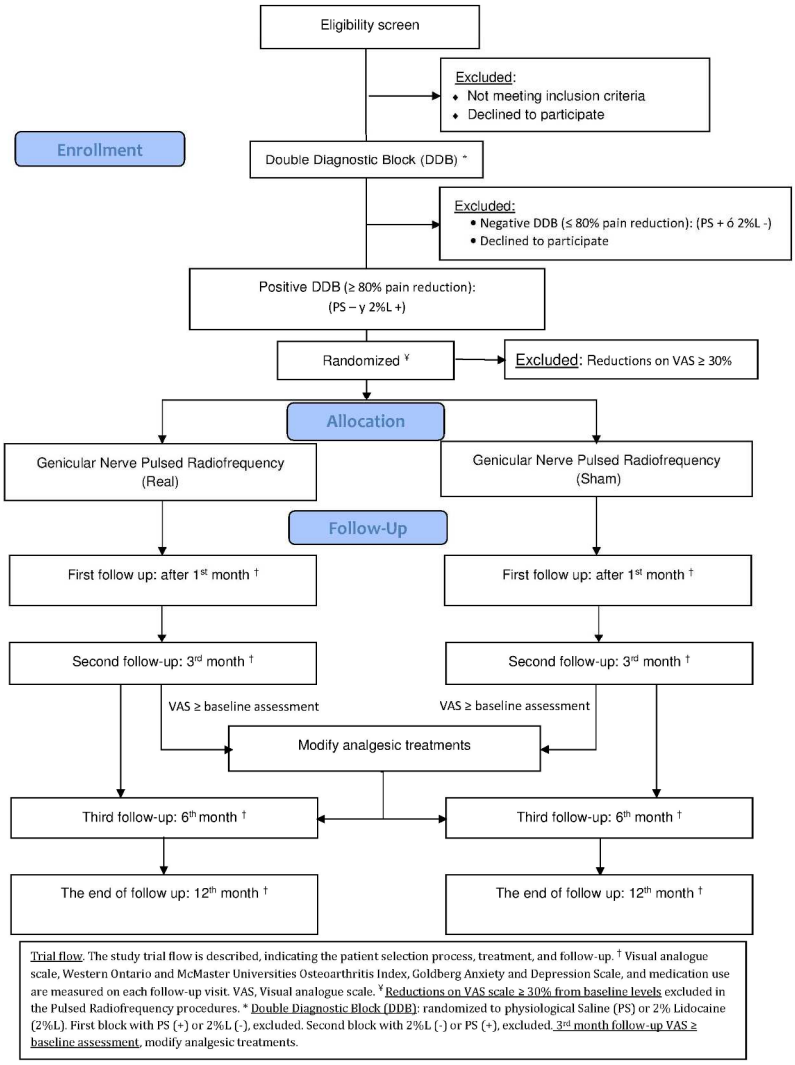
**Figure 1.** Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. * Visual analogue scale pain intensity, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. 3rd month follow-up VAS ≥ baseline assessment modifies analgesic treatments. ** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded.

**Figure 2.** Flow chart showing progression in Diagnostic nerve blocks.

**Figure 3**. Genicular nerves location.




Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. † Visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. VAS, Visual analogue scale. ¥ Reductions on VAS scale ≥ 30% from baseline levels excluded in the Pulsed Radiofrequency procedures. * Double Diagnostic Block (DDB): randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded. 3rd month follow-up VAS ≥ baseline assessment, modify analgesic treatments.

Trial flow

209x297mm (300 x 300 DPI)

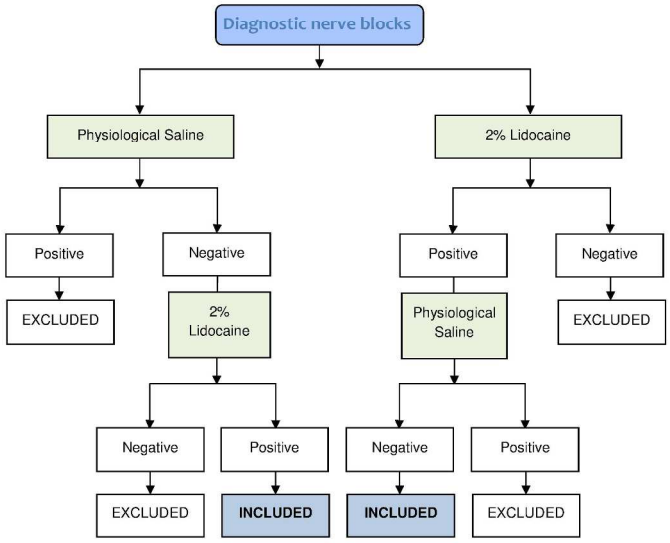
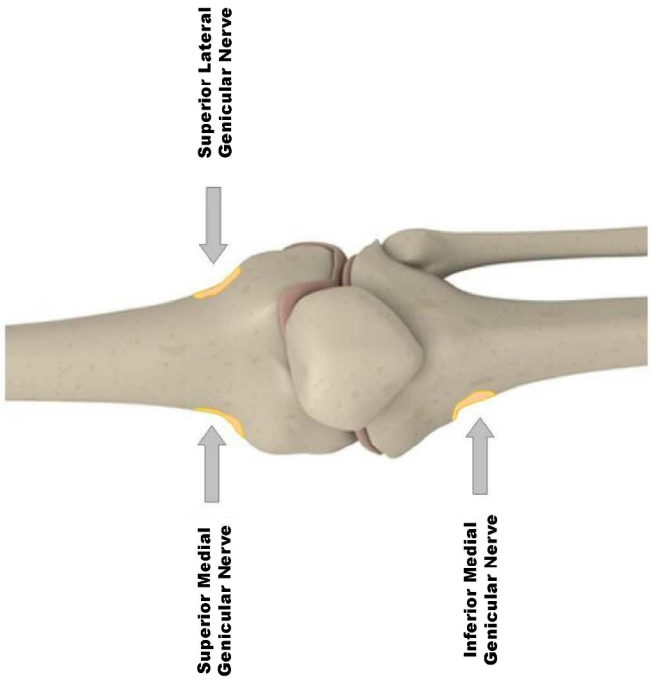



**Figure 2**. Flow chart showing progression in Diagnostic nerve blocks.

Diagnostic block

209x297mm (300 x 300 DPI)




Genicular nerves location

209x297mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | End of this file |
| Protocol version | 3 | Date and version identifier | 3 |
| Funding | 4 | Sources and types of financial, material, and other support | 24 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 25 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 24 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 24 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-6 |
| | 6b | Explanation for choice of comparators | 6 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non inferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 15-16 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 18 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 8 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12-13, 17 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 11 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 18 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8-9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7-9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 10 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12-13 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7, 24 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 19-20 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 18-19 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 18-19 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 19 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 21 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 20 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 19 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 21 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 3 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 26 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 11 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 21-22 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 26 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 27 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 25 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 25 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 26 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 27 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | 11 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

| | |
|---|---|
| **Register:** | NTC |
| **Last refreshed on:** | January 24, 2017 |
| **Main ID:** | NCT02915120 |
| **Date of registration:** | September 23, 2016 |
| **Primary sponsor:** | Son Llatzer University Hospital |
| **Public title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Scientific title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Date of first enrolment:** | March 2017 |
| **Target sample size:** | 142 |
| **Recruitment status:** | Recruiting |
| **URL:** | https://clinicaltrials.gov/ct2/show/record/NCT02915120 |
| **Study type:** | Interventional |
| **Study design:** | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double Blind (Subject, Investigator, Outcomes Assessor)<br>Primary Purpose: Supportive Care |
| **Phase:** | Not applicable |

BMJ Open

# A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain



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|---|---|
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| Secondary Subject Heading: | Anaesthesia, Research methods |
| Keywords: | Knee pain, osteoarthritis, genicular nerve, ULTRASONOGRAPHY, pulsed radiofrequency |
| | |

# A study protocol for a randomized controlled trial of ultrasound-guided pulsed radiofrequency of the genicular nerves in the treatment of patients with osteoarthritis knee pain

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**Word Count: 4667**

## ABSTRACT

### Introduction

The goals for the management of patients with osteoarthritis (OA) of the knee are to control pain and to minimize disability. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. The purpose of this article is to present a refined protocol to determine if there is long-term improvement in pain and function after ultrasound guided pulsed radiofrequency treatment of the genicular nerves in patients with chronic painful knee osteoarthritis.

### Methods and Analysis

This study is a randomized, double-blind, placebo-controlled trial, parallel design. One hundred and forty-two out-patients with osteoarthritis of the knee will be recruited from Mallorca, Spain. Participants will be randomly allocated into two groups: Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) and Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF). The primary outcome measures will be the observed changes from baseline pain intensity based on visual analogue scale (VAS). The possible changes in the secondary efficacy variables from the baseline as assessed by: The Goldberg Anxiety and Depression Scale (GADS), pain medication use, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC subscales), and VAS pain intensity, also to be included in the study. These variables will be assessed at baseline, 1 month, 3 months, 6 months and 1 year after treatment.

## Ethics and Dissemination

The protocol was approved by the Research Ethic Committee of the Balearic Islands (IB 3223/16 PI). The results will be disseminated in peer-reviewed journals and at scientific conferences.

**Trial registration:** ClinicalTrials.gov NCT02915120. Recruiting.

**Keywords**

Knee pain, osteoarthritis, genicular nerve, ultrasonography, pulsed radiofrequency

## Strengths and limitations of this study

- This study is a randomized, double-blind, placebo-controlled trial, parallel design with large sample size, a long-term follow-up and checklists for gathering information about adverse effects.
- Central randomisation and blinded assessment will be used.
- This is a single-centre clinical trial.
- The study design favours patients that respond to the treatment (double diagnostic nerve blocks positive to the inclusion) and exclude patients that experience placebo effects or can be resistant to the treatment (double diagnostic nerve blocks negative to the inclusion)
- Loss of participants at follow-up is possible, especially for non-responders. Trial enrolment and duration may have to be extended to ensure availability of data for analysis.

## INTRODUCTION

Osteoarthritis (OA) of the knee is one of the main causes of disability. Population-based studies revealed that symptomatic knee OA is present in 20–30% of the elderly population aged >65 years, and its prevalence is increasing due in part to the aging of the population [1]. According to the study of prevalence of rheumatic diseases in the Spanish population (EPISER study) symptomatic knee OA prevalence is estimated at 10.2% (14% of women and 5,7% of men) in Spain. The prevalence of radiographic osteoarthritis is increased from 60% among those aged 65 to 80% among those over 75 years of age [2].

The goals of management of patients are to control pain and to minimize disability. Evidence-based guidelines from National Institute of Health and Clinical Excellence (NICE) [3] and Osteoarthritis Research International (OARSI) [4] suggest that the treatment should be multidisciplinary. Optimal management requires a combination of non-pharmacological (changes in lifestyle, pacing of activities, weight reduction, regular aerobic exercise, acupuncture, muscle strengthening and range of motion exercises) and pharmacological modalities when additional treatment is required. Total knee arthroplasty (TKA) should be considered for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy. However, there are some fragile patients who are at high risk during surgery and other patients who are not willing to undergo surgery. Because the number of patients will increase as the population ages, alternative approaches to alleviate their joint pain other than conventional treatments are necessary. Recently, genicular nerve ablation with conventional radiofrequency (CRF) has been used in the

management of osteoarthritis related knee pain [5]. The tissue is heated grossly by electrical energy dissipation, and it is the tissue heating that leads to localized destruction of the neural tissue and consequent interruption of neural signaling. A variation of conventional radiofrequency, pulsed radiofrequency (PRF) is often effective without raising the average target tissue temperature above 42°C, which has been traditionally been thought to be below the irreversible tissue destruction threshold (i.e., the heat-lesion threshold) of 45°C to 50°C. [6]. Radiofrequency treatments on the knee joint have the potential to reduce pain from osteoarthritis [7].

As opposed to the traditional approach under fluoroscopy, ultrasound allowed the visualization of neurovascular bundles, soft tissue structures and, presumably, more accurate nerve identification [8].

The recommendations for PRF as a treatment of patients with OA knee pain are debated until randomized controlled trials with long-term follow-up confirm the results of current studies.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks.

**Aims**

The primary outcome will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks. Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of

the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in functional capacity and stiffness (WOMAC subscales), and VAS pain scores measured at 1 month, 3 months, 6 months, and 1 year after treatment.

**Hypothesis:**

The primary hypothesis is that ultrasound-guided pulsed radiofrequency of the genicular nerves will mitigate pain and improve function as compared to placebo.

## METHODS AND ANALYSIS

### Study design and setting

This study proposes a randomized, double-blind, placebo-controlled, pre and post-test, parallel design clinical trial; which conforms to the Standard Protocol Items for Randomized Trials recommendations (SPIRIT) [9], Consolidated Standards of Reporting Trials (CONSORT) guidelines [10] (Figure 1) and OARSI Clinical Trials Recommendations [11].

Approximately between 3000-4000 patients visit the Pain Unit at Son Llàtzer University Hospital each year, of which 5% are diagnosed with chronic knee pain. This means that in our clinic 150–200 patients with chronic knee pain are treated each year. To increase the amount of eligible patients for our trial, hospitals and general practitioners in our region we will be approached to help recruit potential participants. The eligibility of prospective participants will be determined by a researcher who is not involved in the assessment or treatment of the participants.

## Inclusion criteria

Eligibility requirements will include the following: patients of either sex with primary osteoarthritis of one or both knees fulfilling diagnostic criteria for osteoarthritis knee laid down by American College of Rheumatology [12], Kellgren-Lawrence (radiologic criterion) score of at least 2 with chronic knee pain with pain intensity of at least 4 out 10 on the VAS on most or all days for more than 3 months, resistant to conventional therapy including NSAIDs, opioids, muscle relaxants, oral steroids, physical therapy, and intra-articular injection. In patients with bilateral knee OA the most painful side will be studied.

## Exclusion Criteria

Patients with any of the following will be excluded from the study: patients with secondary osteoarthritis of knees (i.e., rheumatoid arthritis or gouty arthritis); any knee treatment with steroids, methotrexate, or azathioprine; previous radiofrequency ablation treatment for similar symptoms; intra-articular knee corticosteroid or hyaluronic acid injection in the past 3 months:; active systemic or local infections at the site of proposed needle and electrode placement; coagulopathy or other bleeding disorder; cognitive deficit; unstable medical or psychiatric illness; or previous knee joint replacement surgery

The use of analgesic medicine will be allowed at any time during the study.

## Randomization

Each eligible patient will be randomized twice (the randomizer will be otherwise uninvolved in the study):

1. *Double diagnostic block*. Patients will be assigned to one of two groups: "physiological saline first block" or "2% lidocaine first block". A random number list generated by SPSS statistical software version 18.0 (IBM Corporation, Armonk, NY, USA) (balanced for each six cases per study branch) will be used for the allocation to each group. Researchers from the statistical center will send the randomized list in a numbered, sealed, and opaque envelope to the researcher responsible for participant recruitment and group assignment: starting with a sham and ending with a positive versus starting with a positive and ending with a sham.
2. *Radiofrequency group*. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures. A computer generated randomization list will allocate patients in a 1:1 ratio to Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF) or Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF) groups. Randomization is stratified by OA severity using Kellgren-Lawrence grade (2 and 3 vs. 4) using random blocks of size 2, 4 and 6

### Concealment of allocation

The patient codes of the double-blind study will be placed in numbered, sealed, and opaque envelopes. Researchers, personnel performing the interviews, statisticians, and participants will be blinded to patient allocation. The sequence generation will be prepared by a statistician and the envelopes will be prepared by an external investigator not involved in the trial.

### Blinding

All clinical assessments will be conducted by an assessor blinded to treatment allocation. Any occurrence of unblinding of the assessor will be recorded with its reason and reported along with the trial's results. The researcher executing and supervising the treatments will be blinded to the group allocation. Group allocation will be immediately unblinded if deemed necessary by the chief investigator in the case of serious adverse events potentially related to the study.

### Interventions

Study procedures are as follows (table 1).

Trial objectives will be explained, and any questions or doubts with respect to the study will be resolved to all eligible participants. Patients will be informed that they will be receiving a new technique based on radiofrequency for knee pain treatment, and that they will be allocated to either active or sham treatment (with a strict 50 % probability), one will be followed treatment with real pulsed radiofrequency and the other will be followed treatment with sham pulsed radiofrequency. The necessity of a double diagnostic block for testing the benefits

for the radiofrequency treatment will be informed. Long term benefits of treatment will be informed to control patients' expectations and to reduce drop outs. A researcher who is not involved in the assessment or treatment will obtain informed consent from the participants before undergoing any examination or study procedure and will then be assigned a unique sequentially-numbered study identifier according to the order in which he or she is enrolled in the trial.

| | Visits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **1st** *Baseline visit* | **2nd** *1st Diagnostic Block* | **3rd** *1st Block Assessment* | **4th** *2nd Diagnostic Block* | **5th** *2nd Block Assessment* | **6th** *Radiofrequency* | **7 th** *Follow up 1st month* | **8 th** *Follow up 3rd month *** | **9 th** *Follow up 6th month* | **10 th** *Follow up 12th month* |
| *(Schedule since baseline visit)* | *(1st day)* | *(10th day)* | *(Phone call)* | *(20th day)* | *(Phone call)* | *(30th day)* | *(2nd month)* | *(4th month)* | *(7th month)* | *(13th month)* |
| **Enrolment** | | | | | | | | | | |
| Patient's evaluation and collection of the relevant data | √ | | | | | | | | | |
| Inclusion/Exclusion criteria | √ | | √ | | √ | | | | | |
| Explanation of the objectives of the procedure and how it works | √ | | √ | | √ | | | | | |
| Informed consent | √ | | | | | | | | | |
| Randomization, blinding and allocation | | √* | | | | √† | | | | |
| **Interventions** | | | | | | | | | | |
| Double Diagnostic Block | | √ | | √ | | | | | | |
| Genicular Nerve Pulsed Radiofrequency Real (Real GENPRF) | | | | | | √ | | | | |
| Genicular Nerve Pulsed Radiofrequency Sham (Sham Real GENPRF) | | | | | | √ | | | | |
| **Assessments** | | | | | | | | | | |
| Visual analogue scale (VAS) pain intensity | √ | | √ | | √ | √ | √ | √ | √ | √ |
| McMaster Universities Osteoarthritis Index (WOMAC) | √ | | | | | | √ | √ | √ | √ |
| Medication use | √ | | | | | | √ | √ | √ | √ |
| Goldberg Anxiety and Depression scales | √ | | | | | | √ | √ | √ | √ |
| Adverse event | | | √ | | √ | √ | √ | √ | √ | √ |
| Outcome assessment | | | | | | | | | | √ |
| Reasons of drop-outs or withdrawals | | | | | | | √ | √ | √ | √ |
| Satisfaction and expectations Survey | | | | | | | | | | √ |

** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded. † Patients with a significant reduction in VAS pain scores from baseline levels (reductions on VAS scale ≥ 30%), will be excluded in the Pulsed Radiofrequency procedures. ** 3rd month follow-up VAS pain intensity ≥ baseline assessment, modifies analgesic treatments.*

**Table 1. Schedule of enrolment, interventions, and assessments.**

**Baseline visit (1st visit)**

Once eligibility has been confirmed and informed consent obtained a baseline assessment will be undertaken. At the baseline assessment appointment, the researcher will further explain the study, and answer any questions. After clinical and radiologic assessment, comorbidities, age, gender, body mass index, duration of knee OA symptoms, medication use, previous treatment and surgery for knee OA will be obtained at baseline. Neuropathic Pain Diagnostic Questionnaire (DN4), the Spanish version validated by Perez et al. [13], will estimate the probability of neuropathic pain (recent studies suggest that neuropathic mechanisms involved in joint pain [14]).

- Overall average knee pain intensity over the last month will be assessed by a continuous scale comprised of a horizontal line, anchored by "no pain" (score of 0) and "worst imaginable pain" (score of 100 [100-mm scale]). (VAS pain intensity score)
- Self-reported knee pain and difficulty with physical function will be measured using WOMAC Index (the Spanish version validated by Escobar et al. [15]
- Analgesic medicine use will be obtained with a questionnaire elaborated according to the EUROHIS (European Health Interview Survey) recommendations [16]. Subjects will be asked (1) about the prescription medicine their general practitioner may have prescribed for them ("Have you taken any pain medicine prescribed by your general practitioner?") as well as any medication not prescribed by their general practitioner ("Have

you taken any pain medicine not prescribed by your general practitioner") and (2) whether or not their prescribed and non-prescribed pain medication use has increased or decreased.

- Levels of depression and anxiety will be measured with the Goldberg Anxiety and Depression Scale. The Spanish version validated by Montón et al. will be used [17].

**1º Diagnostic Block visit (2nd visit2)**

Between 7 or 10 days since baseline visit, the eligible patients will be randomized, using a computer generated randomization schedule, to undergo diagnostic genicular nerve block with local anaesthetic or physiological saline (figure 2). Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. To find the genicular nerves exact location, the genicular arteries are used as landmarks because they share the same trajectories as the genicular nerves. Other important landmarks are the femoral and tibial cortical surfaces because of their close topographic relation to the genicular neurovascular bundles (figure 3). Genicular nerves consist of the superior lateral (SL), middle, superior medial (SM), inferior lateral (IL), inferior medial (IM), and recurrent tibial genicular nerve. The targets include the SL, SM and IM genicular nerves which pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. The IL genicular nerve is not target due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula. A 10-cm long, 21-gauge needle (Stimuplex, B. Braun Medical, Bethlehem, PA) connected to nerve stimulador (0,5 mA, 0,1 ms,

2Hz), will be advanced towards the target nerve. When needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced to assure no motor response present at < 0,2 mA. Then 2 ml of 2% lidocaine or physiological saline will be injected, in adequate spread, in the desired tissue plane, with an injection resistence normal. The procedure will be repeated at each targeted site.

**1º Block Assessment (3rd visit)**

A researcher calls the patient to assess the VAS pain intensity between 2 and 3 hours after procedure. Responses will be recorded as positive if the participants experience a decrease in numeric pain scores of at least 80% with 2% lidocaine or no response with physiological saline. Patients with a positive response will be given a new appointment in a week. Patients with a negative response will be excluded.

**2º Diagnostic Block visit (4th visit)**

Between 15 or 20 days since baseline visit, patients with a positive response in the first diagnostic block will be made a second diagnostic block with physiological saline if they received 2% lidocaine in the first block or 2% lidocaine if they received physiological saline. This second diagnostic block will be undergone the same procedure.

**2º Block Assessment (5th visit)**

Same assessment protocol as after the first diagnostic block. Patients with a double positive response will be included in the Pulsed Radiofrequency procedures.

**Radiofrequency visit (6th visit)**

One month since the baseline visit the patient will be reviewed. First of all, the interviewers will repeat the assessments for pain level. Patients with a significant reduction in VAS pain scores from baseline levels (reductions on VAS scale of at least 30% reduction to be moderately clinically meaningful [18]), will be excluded in the Pulsed Radiofrequency procedures.

Patients included will be again randomly assigned to receive Ultrasound-Guided Sham Genicular Nerve Pulsed Radiofrequency without active treatment (Sham GENPRF group, n=71) or Ultrasound-Guided Real Genicular Nerve Pulsed Radiofrequency (Real GENPRF group, n=71) using another computer generated randomization schedule. The randomization sequence will be concealed throughout the study from both the study patients and the investigator who will be an independent physician from the Outpatient Pain Clinic.

Real radiofrequency group

Under sterile conditions and appropriate monitoring, the patient will be placed in a supine position on a table and the knee slightly flexed with a pillow under the popliteal fossa. Skin and soft tissues will be anesthetized with 1 mL 2% lidocaine. Before needle insertion, the patient's inferomedial (IM), superomedial (SM), and superolateral (SL) GN branches will be identified under ultrasound guidance. RF needles and probes will be advanced to each of the target nerves under ultrasound guidance. A 10 cm 22-gauge RF cannula with a 10 mm active tip radiofrequency (Model SL-S1010-22, NeuroTherm, Inc.) will be employed for the technique. A 50 Hz-frequency sensorial stimulation will be applied with a threshold of < 0.5 mA to

identify the nerve position, the current intensity (mA) will be reduced at < 0,2 mA. During the sensorial stimulation, the patients will be asked if they feel tingling, pain, or discomfort inside the knee. The RF probe will be maintained in place until one of those feelings is elicited. In order to avoid inactivating motor nerves, the nerve will be tested for the absence of fasciculation in the corresponding area of the lower extremity on stimulation of 0,5 mA at 2 Hz. with an impedance value between 300-700 Ω, when needle is judged to be adequately placed by ultrasound, the current intensity (mA) will be reduced at < 0,2 mA. Lidocaine (1 mL of 2%) will be injected before activation of the RF generator (Neurotherm NT1000 radiofrequency generator (NeuroTherm Inc., Croydon Surrey, United Kingdom). The RF electrode will be then inserted through the cannula, and RF lesions will be generated by applying pulsed RF treatment (current of 2 Hz at 40 volts with 20 msec active and 480 msec silent periods) to the IM, SM and SL, GN branches for 8 minutes each GN branch, whereby the temperature was below 42◦C [19].

Sham radiofrequency group

Control patients will undergo the same procedure. The sensorial and motor stimulations will be applied too. The RF electrode will be then inserted through the cannula, and RF lesions will be simulated without applying pulsed RF treatment to the IM, SM and SL, GN branches for 8 minutes each GN branch and the temperature of the electrode tip was not raised.

**1st, 3rd and 6th month visit since RF (7th, 8th and 9th visit).**

Two, four and seven months since baseline the assessments for pain level, analgesic consumption, WOMAC scale, adverse events and the GADS, will be

repeated. The interviewers will also note radiofrequency related adverse effects or complications observed either by the participants or by the interviewers.

The type of treatment that the patient believes he or she is receiving (blinding test) will be asked in the 1st appointment after RF (7th visit). If 3rd month follow-up, since RF, VAS pain intensity ≥ baseline assessment, the analgesic treatments will be modified.

**12th month visit since RF (10th visit)**

Thirteen months since baseline, at study completion, questions related to patient satisfaction with the treatment received, and their expectations for improvement will also be included in the questionnaires.

**Outcomes**

The primary outcome measures will be the change from the baseline of the VAS for pain at the completion of treatment at 12 weeks.

Secondary variables to be considered are the following: the change in the secondary efficacy variables from the baseline of the scores for the Goldberg Anxiety and Depression Scale (GADS), changes in pain medication use, changes in functional capacity and stiffness (WOMAC subscales), and VAS pain scores measured at 1 month, 3 months, 6 months, and 1 year after treatment.

**Adverse events**

Any adverse events will be monitored and reported by researchers at each visit since double diagnostic block. All expected and unexpected adverse events

potentially related to the study will be monitored, and their progress will be recorded until resolution. The physicians will decide whether trial participation should be discontinued or not based on these reports.

**Sample size**

A total of 142 patients will be necessary (71 subjects for each treatment group) to detect differences between groups of at least 30% in the pain perception assessment according to VAS pain intensity (scale of 0 to 100 mm). Accepted values will be for an alpha risk of 0.05 and beta risk of less than 0.2 in a bilateral contrast as well as a value of 2,5 for the standard deviation (size effect of 0.75) [18]. It is assumed that 20 % of the trial patients will be lost to attrition. Patients will be included in the study by case-consecutive, non-probability sampling after responding to a recruitment visit to the Pain Clinic; then if they sign an informed consent form, they will be allocated randomly into one of the treatment groups [20].

**Statistical analysis**

*Analysis population*

The primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.

Data will be presented as mean (standard deviation), median (interquartile range) or number (%). Inter-group comparisons at baseline will be analyzed using independent samples t-test or Mann–Whitney U test for continuous variables and

chi square or Fisher's exact test for categorical variables. Intra-group differences (between baseline and 3-month; between baseline and 1-year) will be evaluated using paired samples t-test or Wilkoxon signed rank paired test for continuous variables and McNemar test for dichotomized variables. Inter-group comparisons at 3-months and at 1-year will be assessed using analysis of covariance and Fisher's exact test after adjusting changes in categorical and continuous variables for baseline values. Point-biseral (dichotomic data) and Pearson/Spearman (continuous data) correlations coefficients will be computed to assess the relationship between each possible predictor variables at baseline and VAS change at 3-months and at 1-year. Multiple linear regression models will be used to identify baseline predictors of VAS reduction at 3-months and at 1-year. Analysis will be performed using stepwise and backward method for all models.

An interim-analysis will be performed on the primary endpoint when 100% of patients have been randomised and have completed the 3 months' follow-up. The interim-analysis will be performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the Research Ethic Committee of the Balearic Islands (RECIB). The RECIB will have unblinded access to all data.

A two-tailed p value < 0.0294 will be considered statistically significant after adjusting according Pocock's method [21] for interim analysis. Statistical analyses will be performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

**Data collection, management and monitoring**

The data will be collected by means of a case report form (CRF) specially designed for the study written by the researchers and outcome assessors and then will be

entered into electronic database hosted at the Son Llàtzer University Hospital on the research computer server. Any paper study records will be kept in locked storage cabinets. All electronic participant study records will be stored in the password-protected computer study database, accessible to the researchers only.

Entry and coding of clinical data and data management and reporting will be conducted by the clinical data manager. In accordance with European Legislation, all the documentation should be retained for at least 25 years after completion or discontinuation of the trial, as per the new Clinical Trials Regulation (CTR) EU Nº 536/2016.

This study will be monitored by the Research Ethic Committee of the Balearic Islands. During the study period, the clinical research associate will monitor written informed consent documents, recruitment status, protocol compliance and overall trial progress, data quality, timeliness of data collection, treatment administration, and other relevant trial aspects and processes.

**Discussion**

The effect of genicular nerve ultrasound guidance pulsed RF treatment OA knee pain, selected after repeated diagnostic blocks, will be investigated in this study. Effectiveness indicators should be the relief of pain, stiffness and functional disability of the knee and a reduction in medication use.

RF is a type of alternate current that creates heating the target tissues by providing friction between the molecules; thus a thermal lesion is formed by the heat generated from this current [22]. RF has been used to treat a variety of pain

conditions such as trigeminal neuralgia, cervicogenic headaches and spinal pain [23-25].

Choi et al described fluoroscopically guided conventional RF neurotomy of the sensory nerves (genicular nerves) supplying the knee joint. The findings of the study showed that there was a significant improvement in pain and satisfaction in the RF treatment group [5]. The genicular nerves are sensory branches of the tibial, common peroneal, and obturator nerves. They provide innervation to the capsule of the knee joint, as well as to the intraarticular and extraarticular ligaments [26].

A recent anatomic studies in cadavers on innervation of the knee [8,27] supports the methodology used by Choi et al [5] who targeted IM, SM, and nerves on the SL aspect of the knee joint accompanying genicular vessels because of their proximity to bony structures (junction of the metaphyseal and epiphyseal parts of the femur and tibia). The IL genicular nerve is not target due to concerns about inadvertent injury to the common peroneal nerve that lies in close proximity at the neck of the fibula.

Use of prognostic nerve blocks at the site of pain generators has generated debate in the interventional pain community [28]. Pain arising from the knee joint is often complex. Nerve blocks with local anesthetics are frequently used to confirm a joint as the primary pain generator, in predicting the success of RF treatments. A threshold of 80% reduction in pain after diagnostic genicular nerve block with 2% lidocaine is used. This protocol is more stringent than that which has been

previously reported by Choi et al. 80% or greater relief from diagnostic blocks is associated with high accuracy in predicting treatment success [29].

Controlled blocks are recommended because of a 25–41% false positive response when using only single blocks [30]. It is logical to suggest that ablative RF treatments should be preceded by nerve blocks with local anesthetics to better prognosticate the likelihood of success and to allow patients to experience temporarily a partly denervated knee joint, but there is no evidence based algorithm established which provides a means of properly selecting which patients would benefit from genicular nerve radiofrequency. The general consensus is to start by diagnostic blocks.

A variation of conventional radiofrequency, pulsed radiofrequency (PRF) is the technique whereby radio frequency oscillations are gated at a rate of pulses per second (cycles per second, defined as a hertz (Hz)). Current of 2 Hz means two cycles per second (with 20 msec active and 480 msec silent periods per cycle). PRF uses radiofrequency current in short (20 ms), high-voltage bursts (with amplitude of 45 V); the "silent" phase (480 ms) of PRF allows time for heat elimination, generally keeping the target tissue below 42°: the signal amplitude (volt) or the pulse duration are often modified. PRF also appears to be a relatively safe procedure. Unlike CRF, which is associated with neuritis-like reactions, motor deficits, and the risk of deafferentation pain, PRF seems to have few side effects.

The use of ultrasound-guided genicular nerve block offers advantages over fluoroscopically guided techniques: the excellent soft tissue imaging, which enables the use of soft tissue structure as landmarks other than bony landmarks,

and the visualization of neurovascular bundles and identification of the nerves are the most important ones, beyond the advantage of no ionizing radiation [8].

Pulsed RF has been performed in the above mentioned conventional RF applications, in peripheral joints, and in other neuropathic syndromes. Pulsed RF appears to have genuine biological effects in cell morphology, synaptic transmission, and pain signalling, which are likely to be temperature independent [31-33].

The use of PRF to treat mechanical pain is controversial because there are no controlled clinical trials demonstrating efficacy. The long-term effects of pulsed RF on periarticular nerves have not been studied but the publications on pulsed RF treatments of major nerves for knee pain reported significant analgesic benefit at 10 days to 6 months following the interventions [20, 34-35].

To the best of our knowledge, the study of Kesikburun et al [36], a preliminary report, is the first study of ultrasound-guided genicular nerve pulsed RF treatment in patients with osteoarthritis related knee pain. The number of participants was limited, the lack of a control group (no double-blind controlled study) and the fact that long-term effect of pulsed RF treatment was not evaluated, are limiting factors of this study.

To conclude clinical recommendations for ultrasound-guided pulsed RF as a treatment for severe knee OA should not be written until high quality (randomized controlled) clinical studies confirm the results and address the safety aspects. In this article, we combine all of the methodological suggestions, attempting to minimize the biases that may result from study design: the number of patients

recruited is sufficient to achieve the significant differences, treatment number, long-term treatment, blinding method (from recruitment), patient perception assessment of the type of technique used before and after treatment, the objective and subjective assessment of the technique, and sham without applying pulsed RF treatment.

The purpose of this study is to determine if patients with chronic painful knee osteoarthritis experience meaningful and long-term improvement in pain, function, and analgesic use after ultrasound-guided pulsed radiofrequency of the genicular nerves following a double diagnostic genicular nerve blocks (2% lidocaine and physiological saline solution).

## Trial status

The trial is currently in the recruitment phase. Participant recruitment is started in March 2017 and expected to end in December 2017.

## Ethics and dissemination

All of the participants will be recruited through voluntary participation, and written informed consent forms from all trial participants will be obtained by researchers in accordance with the Declaration of Helsinki [37]. Trial participation may be terminated during the trial at any time through voluntary refusal to continue or in cases of significant clinical adverse event as judged by the researchers. Participants suffering from trial-related problems or adverse events may be administered medical treatment for compensation. Any amendments to the study protocols will be publicly available via the US National Institutes Health Clinical Trials Registry, Clinical Trials.gov. (Trial number: NCT02915120). Data

management procedures will be conducted by JM and BH. Access to the final trial dataset will comply with the conditions of the ethics committee approval and will be at the discretion of the lead CI, JM. The results will be disseminated in peer-reviewed journals, at scientific conferences and all participants in the RCT will receive a report outlining the study findings at the conclusion of the trial.

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**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

JM is leading the trial coordination and helped to conceive the project, develop the protocol, and write the first and final drafts of the manuscript. PV helped to design the protocol. BM will head participant recruitment. BH will recruit and screen the participants and perform data entry. JLA helped to write the first and final drafts of

the manuscript. All authors participated in the trial design, provided feedback on drafts of this article, and read and approved the final manuscript.

**Data sharing statement**

No later than 3 years after the study will have ended a completely deidentified data set will deliver to an appropriate data archive for sharing purposes

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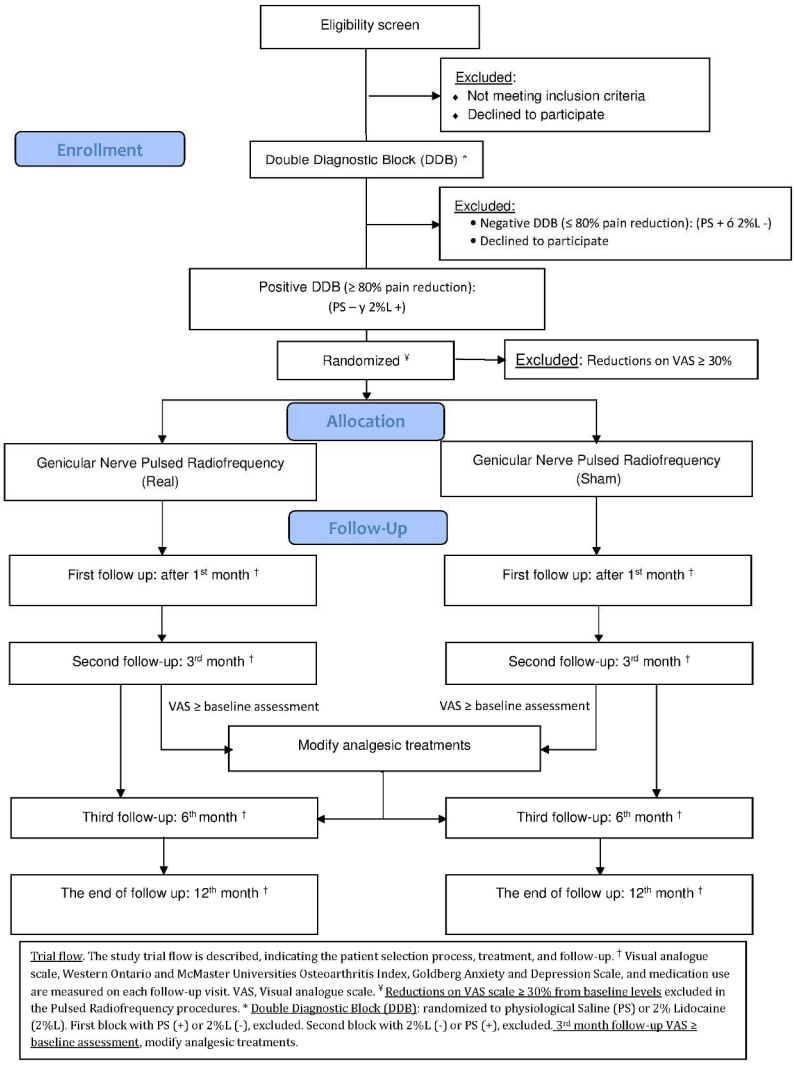
**Figure 1.** Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. * Visual analogue scale pain intensity, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. 3rd month follow-up VAS ≥ baseline assessment modifies analgesic treatments. ** Double Diagnostic Block: randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded.

**Figure 2.** Flow chart showing progression in Diagnostic nerve blocks.

**Figure 3**. Genicular nerves location.




Trial flow. The study trial flow is described, indicating the patient selection process, treatment, and follow-up. † Visual analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, Goldberg Anxiety and Depression Scale, and medication use are measured on each follow-up visit. VAS, Visual analogue scale. ¥ Reductions on VAS scale ≥ 30% from baseline levels excluded in the Pulsed Radiofrequency procedures. * Double Diagnostic Block (DDB): randomized to physiological Saline (PS) or 2% Lidocaine (2%L). First block with PS (+) or 2%L (-), excluded. Second block with 2%L (-) or PS (+), excluded. 3rd month follow-up VAS ≥ baseline assessment, modify analgesic treatments.

Trial flow

209x297mm (300 x 300 DPI)

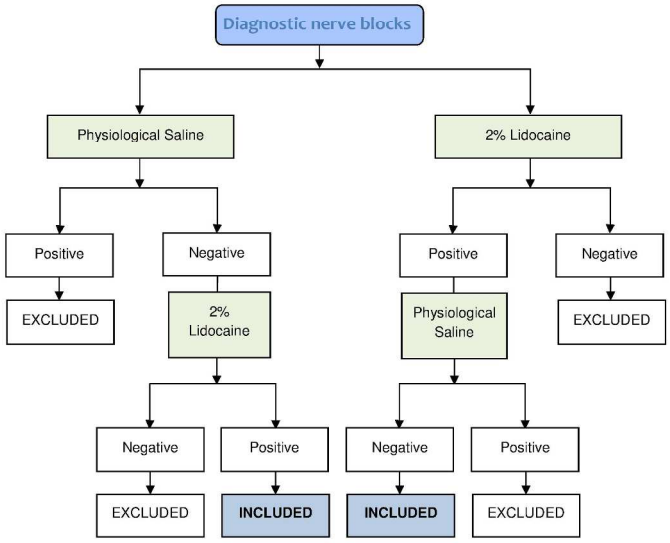
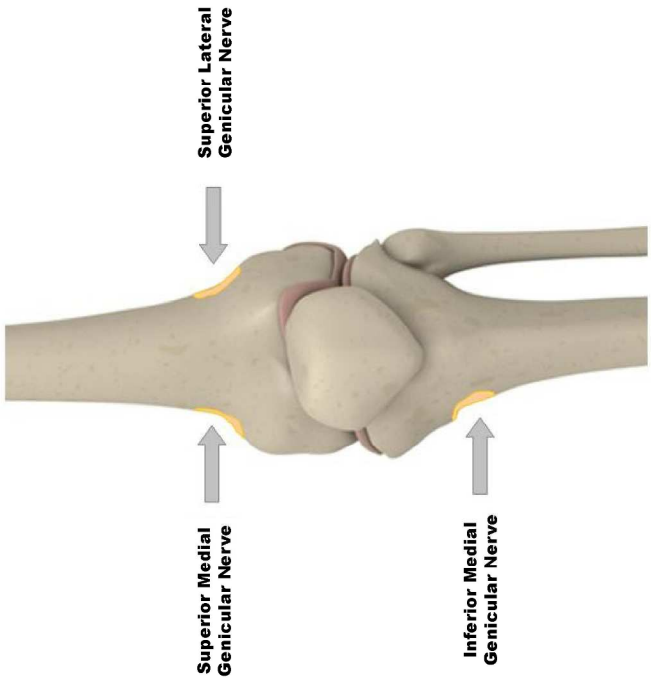



**Figure 2**. Flow chart showing progression in Diagnostic nerve blocks.

Diagnostic block

209x297mm (300 x 300 DPI)




Genicular nerves location

209x297mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | End of this file |
| Protocol version | 3 | Date and version identifier | NA |
| Funding | 4 | Sources and types of financial, material, and other support | 26 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 26 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 25-26 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-6 |
| | 6b | Explanation for choice of comparators | 7 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non inferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 16-17 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 16 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 11 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 8 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6-7,18, 20 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 12 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 19 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9-10 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 10 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9-11 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 10 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 10 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13-14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7, 17-18 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 20-21 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 19-20 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 19-20 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 19 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 21 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 20 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 18-19 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 21 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 3 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 25-26 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 11 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 20-21 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 26 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 21 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 25 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 26-27 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 26-27 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 27 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | File attachment |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

| | |
|---|---|
| **Register:** | NTC |
| **Last refreshed on:** | January 24, 2017 |
| **Main ID:** | NCT02915120 |
| **Date of registration:** | September 23, 2016 |
| **Primary sponsor:** | Son Llatzer University Hospital |
| **Public title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Scientific title:** | Ultrasound-Guided Pulsed Radiofrequency Of The Genicular Nerves In The Treatment Of Patients With Osteoarthritis Knee Pain: Randomized, Double-Blind, Placebo Controled Trial |
| **Date of first enrolment:** | March 2017 |
| **Target sample size:** | 142 |
| **Recruitment status:** | Recruiting |
| **URL:** | https://clinicaltrials.gov/ct2/show/record/NCT02915120 |
| **Study type:** | Interventional |
| **Study design:** | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double Blind (Subject, Investigator, Outcomes Assessor)<br>Primary Purpose: Supportive Care |
| **Phase:** | Not applicable |