# Prospective, Open Label Trial to Assess Tolerability of Lumbar Sympathetic Chain Stimulation in patients with Nociceptive pain due to Knee OsteoArthritis or Endometriosis

**Investigator**

Dr Ganesan Baranidharan
Consultant in Pain Medicine and Anaesthesia
Pain Management Service, B Floor, Brotherton Wing, LGI, Leeds, UK

**Funder**

ABVF BV
Stationsplein 45, A4.004
3013AK, Rotterdam, the Netherlands

**Research Team Members**

Dr Beatrice Bretherton-Liu
Research Fellow
Pain Management Service, D Floor, Martin Wing, LGI.

Ms Emma Binns
Research Nurse
Pain Management Service, D Floor, Martin Wing, LGI.

Mrs Lisa Speight
Research Nurse
Pain Management Service, D Floor, Martin Wing, LGI.

Miss Monica Laria Suarez
Clinical Trials Assistant
Pain Management Service, D Floor, Martin Wing, LGI

Mr Adam Ley
Clinical Trials Assistant
Pain Management Service, D Floor, Martin Wing, LGI

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**Sponsor**

ABVF BV

| **Participant Identification Center** | **Leeds Community Healthcare NHS Trust (Musculoskeletal Service Clinical and Community Pain Clinics)** |
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# CLINICAL AGREEMENT SIGNATURE

I have read and understand the clinical investigation plan (CIP) below. In my capacity as Investigator, my duties include making sure of the safety of the study participants enrolled by supervising them and providing ABVF BV with complete and timely information. This information will be provided as outlined in this clinical investigation plan. All the information relating to this study will be held in strict confidence and these confidentiality requirements apply to all staff at this study site or involved with this study. I agree to maintain the procedures required to perform this study in accordance with Good Clinical Practice principles and to abide by the terms of this clinical investigation plan.

| | | | |
|---|---|---|---|
| CIP REFERENCE NUMBER | ABVF-002 | DATE | 22NOV2024 |
| CIP TITLE | Prospective, Open Label Trial to Assess Tolerability of Lumbar Sympathetic Chain Stimulation in patients with Nociceptive pain due to Knee OsteoArthritis or Endometriosis | | |

Site Principal Investigator Signature Date

Name and Title Print Institution

| | |
|---|---|
| CONTACT INFORMATION | Dr Ganesan Baranidharan<br>Post: Consultant in Anaesthesia and Pain Management<br>Qualifications: MBBS (India), FRCA, Diploma in Anaesthesia, FFPMRCA<br>The Leeds Teaching Hospitals NHS Trust<br>B Floor, Brotherton Wing, LGI<br>Leeds<br>Post Code LS1 3EX<br>Work E-mail: g.baranidharan@nhs.net<br>Work Telephone: 01133922075 |

## Study Summary

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|---|---|
| **TITLE** | Prospective, Open Label Trial to Assess Tolerability of Lumbar Sympathetic Chain Stimulation in patients with Nociceptive pain due to Knee OsteoArthritis or Endometriosis |
| **SHORT TITLE** | Lumbar Sympathetic Chain (LSC) Stimulation for Nociceptive Pain |
| **STUDY DESIGN** | Single centre, prospective, open label pilot study |
| **STUDY OBJECTIVES** | To evaluate the safety and tolerability of lumbar sympathetic chain (LSC) stimulation as a treatment for refractory pain in patients with knee osteoarthritis (OA) and pelvic pain secondary to endometriosis. |
| **NUMBER OF SUBJECTS** | It is anticipated that up to 20 participants will be implanted. |
| **STATISTICAL METHODOLOGY AND ANALYSIS** | As this is a pilot study, the focus of the statistical analyses will be primarily descriptive. This will entail generating descriptive statistics (mean ± standard deviation [SD], median, minimum, maximum and interquartile range) for outcome measures at the study visits.<br>The frequency and nature of reported adverse events and/or relevant adverse events will form the basis of the safety evaluation of the study. |
| **STUDY POPULATION** | Two groups of participants will be recruited: 1) Male or non-pregnant female aged 30-75 years with chronic moderate to severe knee pain due to OA. 2) Pre-menopausal women aged 18 to 50 years old with chronic moderate to severe pelvic pain secondary to endometriosis. A maximum of 20 subjects will be enrolled in the study. |
| **DURATION OF INVESTIGATION** | 18 months (12month study recruitment with 6 month follow up) |
| **PARTICIPANT DURATION** | Participants will be involved in the study for approximately 8-9 months (~2-3 months for screening, baseline and implant with 6 month follow up post-activation of the device) |
| **STUDY PROCEDURES AND FOLLOW_UP** | Visit 1: Consent, Screening and Baseline<br>Visit 2: Stimulation information session (as soon as possible, no window) |

| | |
|---|---|
| | Visit 3: Surgical implantation (as soon as possible, no window)<br>Visit 4: Wound check and activation visit – approximately 21 days post-implantation<br>Visit 5: Weekly video/telephone check-ins (for 3 weeks)<br>Visit 6: 30-day post-activation follow up visit<br>Visit 7: 60-day post-activation follow up visit<br>Visit 8: 90-day post-activation follow up visit<br>Visit 9: 120-day post-activation video/telephone check-in<br>Visit 10: 150-day post-activation video/telephone check-in<br>Visit 11: 180-day post-activation follow up visit and End of Study |

## List of Abbreviations:

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ASADE | Anticipated Serious Adverse Device Event |
| BRS | Baroreflex Sensitivity |
| CGIC | Clinician Global Impression of Change |
| CNS | Clinical Nurse Specialist |
| CRA | Clinical Trial Associate |
| CRF | Case Report Form |
| EQ-5D-5L | EuroQol- 5 Dimension questionnaire |
| EC | Ethics Committee |
| FSH | Follicle-Stimulating Hormone |
| GP | General Practitioner |
| HRV | Heart Rate Variability |
| ICH/GCP | International Conference on Harmonisation (ICH)/WHO Good Clinical Practice standards |
| LSC | Lumbar Sympathetic Chain |
| MDT | Multi-Disciplinary Team |
| MHRA | Medicines and Healthcare Products Regulation Agency |
| NHS | National Health Service |
| NRS | Numeric Rating Scale |
| OA | Osteoarthritis |
| PGIC | Participants Global Impression of Change |
| PNS | Peripheral Nerve Stimulation |
| PRVP | Persistent Refractory Visceral Pain |
| REC | Research Ethics Committee |
| ROM | Range of motion (knee) |
| SAE | Serious Adverse Event |
| SADE | Serious Adverse Device Effect |
| SDV | Source Data Verification |
| SKNA | Skin Sympathetic Nerve Activity |
| UK | United Kingdom |
| UADE | Unanticipated Adverse Device Event |

# 1 Introduction

This document is a research protocol, and the described study will be conducted in compliance with the protocol, The Research Governance Framework, ICH/GCP, Directive2001/20/EC and associated regulatory (MHRA) regulations, and all applicable Leeds Teaching Hospitals NHS Trust research requirements.

This is a single centre, prospective, open label pilot study to evaluate the impact of lumbar sympathetic chain (LSC) stimulation for the treatment of pain due to refractory nociception. A sample of up to 20 participants will be implanted after obtaining informed consent and being successfully screened. A commercially available (CE-Marked) neurostimulator will be implanted near the LSC for persistent pain secondary to knee osteoarthritis or pelvic pain secondary to endometriosis. These patients will have been managed under the orthopaedic, gynaecology, pain management services, or referred by Patient Identification Centers (PIC)and deemed suitable for an investigational therapy using LSC stimulation. Participants will attend the pain clinic at the hospital for a baseline visit where screening for study suitability will be undertaken. If suitable for the study, the patient will be booked into a stimulation information session, followed by the relevant treatment session to have LSC neurostimulator leads implanted. During the implantation visit, recruited patients will be implanted with sympathetic chain leads and implantable pulse generator system on lumbar sympathetic nerves at the L1-L4 level unilaterally or bilaterally, depending on patient needs as determined by the implanting physician.

Following implantation, participants will return to the pain clinic for a standard care post-operative assessment. Participants will then attend the research clinic for an activation visit, where the device will be switched on and set up. During this visit and upon verification of acute safety, participants will be sent home with a set of test stimulation parameters to try for the remainder of the study. Participants will have video check-ins to make sure the stimulation is appropriate, and to ask about their pain. If video is not an option for participants, check-ins can be done by telephone. Subsequently, participants will be assessed at in-person clinic visits or video/telephone check-ins on a monthly basis for the remainder of the 6-month study.

## 1.1 Background

Nociceptive pain is pain perceived by the subject due to an increase in nerve signalling from diseased tissue. In most of the conditions that cause nociceptive pain, increased neural proliferation is seen in the pathological tissue. Examples of such nociceptive pain syndromes include knee pain due to osteoarthritis and pelvic pain due to endometriosis. These nociceptive

pain syndromes are associated with significant burden, reduced mobility, negative impacts on quality of life and depression in some cases [1–4].

Knee osteoarthritis affects an estimated 300 million people worldwide with a higher incidence in women than men (2:1) [5]. In the UK, the average age for diagnosis is 51 years of age, and the median age for knee replacement is 69 years [6]. As a result, patients spend close to a decade or more managing chronic nociceptive pain with non-steroidal anti-inflammatory drugs (NSAIDs), local hyaluronic acid injections and chronic opioids. Despite these treatments, the pain returns over time and progressively worsens.

Endometriosis is estimated to affect 10-15% of women of reproductive age [7,8]. Pelvic pain due to endometriosis can be debilitating. It can begin during late teens and progressively worsen despite treatment. Current treatments include analgesics, cyclic oral contractive pills and surgical treatments. The long-term efficacy of these treatments is unclear [8,9].

The reason for refractory pain in these nociceptive pain syndromes is due to central sensitization mechanisms that are mediated via sympathetic afferents, spinal transmission to higher brain regions in the thalamus. LSCs are part of the paravertebral sympathetic chain that contain (a) post-ganglionic vasodilator and vasoconstrictor fibres that drive changes in blood flow in the legs and feet that occur during local-, reflex- and centrally-mediated commands [10,11,20–29,12,30–39,13,40,14–19] and (b) spinally-projecting dorsal root ganglia (DRG) afferents that promote active neurogenic vasodilation within the contralateral limb [10,11,20–29,12,30–39,13,40,14–19] and increases in minute ventilation via ascending pathways that directly or indirectly reach the Nucleus Tractus Solitaris region of the brain stem (unpublished findings). This therefore suggests there may be clear biomarkers of target engagement that can be measured.

On the assumption that LSCs in humans contain nociceptive DRG afferents, a number of studies explored the possible benefits of disrupting LSCs (i.e., chemical or surgical denervation) in pain syndromes [41–46]. However, although lumbar sympathectomy offered transient pain relief in a limited number of patients, there is little high-quality evidence to suggest that surgical or chemical sympathectomy is associated with improvements in nociceptive pain syndromes [47] and could cause haemodynamic issues pointing to involvement of sympathetic afferents [47–50].

The analgesic effect of LSC stimulation has been validated in humans [51]. Indeed, patients with drug-refractory, idiopathic loin pain haematuria syndrome were implanted with a temporary spinal

cord lead for 14 days to assess improvements. For patients who reported reductions in pain with the temporary stimulation, they went on to receive a permanent spinal cord implant (lead and implantable pulse generator). During the temporary stimulation, immediate improvements in pain scores were seen and in three of the four patients who received a permanent implant, this efficacy continued. One patient had significant pain relief with the temporary stimulation with the effect lasting even after stimulation cessation. As a result, this patient opted out of a permanent lead.

Taken together, these data suggest that LSC stimulation might offer a promising approach to treat nociceptive pain, for which all existing neuromodulation approaches are indicated for use.

# 2 Study Objectives

## 2.1 Primary Objective

To evaluate the safety and tolerability of LSC stimulation in patients with nociceptive pain syndrome due to knee osteoarthritis (OA) or endometriosis.

# 3 Study Design

## 3.1 General Design

The study is a single centre, prospective, pilot trial to assess the safety and tolerability of LSC stimulation for nociceptive pain syndromes associated with knee osteoarthritis and endometriosis. Upon initial patient baseline assessment for inclusion and following completion of the participant questionnaires (pain and health-related quality of life questionnaires (HRQoL)), medication assessment, measures of autonomic function and blood draws to assess follicle-stimulating hormone (FSH) levels, autonomic function and safety, participants will receive a LSC stimulation information session, followed by surgical implantation of a CE-marked implantable peripheral nerve stimulation (PNS) neurostimulation system (see Section 3.3 for more information). As part of the baseline screening for the endometriosis arm of the study, participants will be required to provide NRS pain scores for their pelvic pain during their menstrual cycle.

Participants will be followed for post-operative checks and adverse event assessment. Participants will attend a device activation visit, where they will undergo stimulation programming, have their wound assessed and be asked about adverse events.

Participants will then have video/telephone check-ins with a member of the research team at pre-specified time points to enquire about pain scores, adverse events and to collect diary information.

Throughout the study, participants will complete a diary in which they will document details of the stimulation program they utilized, such as stimulation duration and NRS score (0-10) before and after stimulation. Menstrual cycle also will be captured for participants with endometriosis. If participants require further programming, they will be invited to attend a reprogramming visit in the hospital (please see below).

Following device activation, participants will repeat the questionnaires (pain and HRQoL) completed at the baseline, medication changes will be ascertained, and the same autonomic measures and blood draws will be performed as during the baseline visit. To provide an indication of overall improvement, participants will also be asked to complete the patient global impression of change (PGIC) and the clinician will complete the clinician global impression of change (CGIC). The stimulation will be assessed and recorded, and adverse events will be assessed by specific questioning and recorded.

Please see Section 5: Study Procedures for more information.

## 3.2 Study Endpoint

The study endpoints for this trial are as follows:

Patients with knee OA:

- Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale at 30, 60, 90 and 180 days. The WOMAC is a self-administered, disease-specific questionnaire which assesses clinically important, participant-relevant symptoms for pain, stiffness, and physical function in participants with OA. The WOMAC pain subscale is a 5-item questionnaire that assesses the amount of pain experienced due to OA of an index joint (knee or hip) during the past 48 hours. It is calculated as the mean of scores from 5 questions, which may not be a whole (integer) number. Scores for each question on the WOMAC Pain subscale are scored on a five-point scale ranging from 0 (no pain) to 4 (extreme pain), where higher scores indicate higher pain.
- Change from baseline in WOMAC Physical Function Subscale at 30, 60, 90 and 180 days. Physical function refers to the patient's ability to move around and perform usual activities of daily living. The WOMAC physical function subscale is a 17-item questionnaire used to assess the degree of difficulty experienced due to OA in an index joint (knee or hip) during the past 48 hours. It is calculated as mean of the

scores from 17 individual questions, which may not be a whole (integer) number. Scores for each question on the WOMAC physical function subscale are scored on a five-point scale ranging from 0 (no difficulty) to 4 (extreme difficulty), where higher scores indicated extreme difficulty/worse physical function.

- Change from baseline in Knee Injury and Osteo Arthritis Outcome Score (KOOS) at 30, 60, 90 and 180 days.
- Change from baseline in the following tests: knee range of motion (ROM), knee swelling, and ambulation ability at 30, 60, 90 and 180 days. (These outcomes may be captured retroactively if the referring physician has captured these data as part of their standard of care,)

Patients with pelvic pain secondary to endometriosis:

- Change from baseline in the Endopain 4D Questionnaire [52] at 30, 60, 90 and 180 days. The Endopain 4D Questionnaire comprises 20 items that assess patient reported pain symptoms in women treated for endometriosis including dysmenorrhoea, non-menstrual pelvic pain, intense pain, worsening pain, pain before period, stabbing pain, lower back pain, leg/hip pain, disabling pain, pain affecting mobility, dyspareunia, interruption of sexual intercourse, painful bowel movements, bowel spasms, diarrhoea/constipation, pain when urinating, bladder pain, sciatica and right shoulder pain.

All patients:

- Change from baseline in pain at 30, 60, 90 and 180 days using NRS.
- Change from baseline in HRQoL at 30, 60, 90 and 180 days using the EQ-5D-5L.
- Proportion of participants reporting an improvement in EQ-5D-5L index score (≥0.200) at 30, 60, 90 and 180 days months using the EQ-5D-5L Health questionnaire.
- Change in baseline in autonomic function as assessed with heart rate variability (HRV), baroreflex sensitivity (BRS) and skin sympathetic nerve activity (SKNA) at 30, 60, 90 and 180 days.
- Change in blood draw measures to assess cortisol, metanephrine levels and c-reactive protein (CRP) at 30, 60, 90 and 180 days.
- Patient and clinician global impression of change (PGIC, CGIC) at 30, 60, 90 and 180 days.
- Change in medication at 30, 60, 90 and 180 days.

- Complications/adverse events.

## 3.3 Device Description

Any CE-Marked, commercially available neurostimulation system that is indicated for peripheral nerve stimulation, in the treatment of pain, shall be employed. For example, The Medtronic PNS Intellis system may be utilized. The Medtronic PNS Intellis system is CE-Marked and is indicated as follows: *Neurostimulation for Peripheral Nerve Stimulation (PNS) using percutaneous leads - A Medtronic PNS neurostimulation system is indicated for PNS as an aid in the management of chronic, intractable pain of the posterior trunk.*

The system will include an implantable pulse generator (IPG), which contains a medical-grade battery, and electronics designed to deliver electrical stimulation to nerve tissue. The stimulation pulses may be delivered via two implanted, 8-contact leads placed near the peripheral nerve(s). Specifically, during this study, the leads will be placed unilaterally or bilaterally at the Lumbar Sympathetic Chain ganglia, at a vertebral level ranging from L1 to L4.

# 4 Methods

## 4.1 Subject Selection and Withdrawal

### Inclusion Criteria

Patients will be recruited to the study if he/she meets the following inclusion criteria:
Inclusion criteria for both knee and pelvic pain:

1. Agree to maintain a stable dose of analgesics thirty days prior to enrolment.
2. Willing to hold their usual analgesic medication constant throughout the study.
3. Able and willing to comply with the follow-up schedule and protocol.
4. Previously tried and failed at least one conservative treatment for chronic pain including but not limited to pharmacological therapy, physical therapy and interventional pain procedures for persistent pain.
5. Been deemed suitable for the study by the pain MDT.
6. Willing to provide informed consent.
7. Maximum daily dose of 90 mg-morphine equivalents. If the patients are taking more than this dose, they will be offered a referral to an opioid reduction clinic to achieve the target opioid dose, and the baseline opioid will be taken as the dose on referral.
8. In the investigator’s opinion, the patient is a suitable candidate for LSC stimulation.

9. Participants diagnosed with persistent refractory pelvic pain secondary to endometriosis for at least 6 months **OR** knee pain secondary to OA for at least 6 months.
10. Subject able to distinguish between primary pain (knee or pelvis) from other sources of pain.

Inclusion criteria for knee pain secondary to osteoarthritis:

1. Male or non-pregnant female aged 30-75 years with chronic moderate to severe knee pain due to OA (Baseline pain diary scores of ≥ 6 of 10 on NRS for knee pain).
2. If female and of child-bearing age, willing to use contraception throughout the trial.

Inclusion criteria for pelvic pain secondary to endometriosis:

1. Pre-menopausal women aged 18 to 50 years old.
2. If of child-bearing age, willing to use contraception throughout the trial.
3. Recurrent symptoms suggestive of superficial peritoneal endometriosis (ASRM stage 1 or 2) identified during laparoscopy, confirmed via biopsy and performed within the last 5 years, who prefer not to undergo repeat surgery. **OR** Symptoms suggestive of ovarian endometrioma seen on ultrasound or MRI with cyst ≤ 3 cm in diameter.
4. If on hormonal therapies, they must be on a stable dose for at least 90 days prior to implant and agree to maintain a stable dose throughout the study.
5. Baseline pain diary scores of ≥ 6 of 10 on NRS for pelvic pain.
6. Participants are able to distinguish among chronic pain due to the following: endometriosis, irritable bowel syndrome (IBS), and painful bladder syndrome (PBS).

## Exclusion Criteria

Participants will not be recruited to the study if they meet any of the following exclusion criteria:
Exclusion criteria for both knee and pelvic pain:

1. Female participants of childbearing potential who are pregnant/nursing or plan to become pregnant during the course of the trial.
2. Escalating or changing pain condition within the past month as evidenced by investigator examination.
3. Has a psychiatric or psychological condition that would interfere with participation in the study.
4. Have a history of major depression, severe anxiety or post-traumatic stress disorder within 2 years of screening or a history of other major psychiatric disorders.
5. Chemical sympathectomy treatment within the past 6 months.

6. Currently has an active implantable device such as pacemaker, spinal cord stimulator or intrathecal drug delivery system.
7. In the investigator's opinion has an active infection.
8. Participated in another clinical investigation within 30 days.
9. Medical co-morbidities that preclude surgical intervention.
10. Patient is incapable of understanding or responding to the study questionnaires.
11. Patient is incapable of understanding or operating the patient programmer handset.
12. Patient has a BMI > 45kg/$m^2$ with obesity related comorbidity.
13. Participant has a current or previous condition, which will probably require MRI investigation sometime in the following 2 years.
14. Participant has another predominant persistent painful condition other than persistent refractory pelvic pain or knee pain.
15. History of alcohol/IV drug abuse in the last three years.
16. History or symptoms of autoimmune disorders, cancer within the last 5 years except for cutaneous basal cell or squamous cell cancer resolved by excision, allergic reaction to monoclonal antibodies or IgG-fusion proteins, Hepatitis B, C or HIV, drug abuse, fibromyalgia, clinically significant cardiac disease, diabetes mellitus requiring oral treatment or insulin, clinically significant neurological disease or clinically significant psychiatric disorders.
17. Any anxiolytic beta blocker dosage, exceeding 40 mg/day. Dosage must be stable for at least 3 months prior to enrolment.
18. Known postural hypotension, bradycardia or cardiac arrhythmia.
19. History of refractory hypotension or vasovagal syncope.
20. Severe DASS-21 scores of ≥21 for depression, ≥15 for anxiety or ≥26 for stress.
21. Within the past 6 months have tried interventional pain procedures for persistent pain.

Exclusion criteria pelvic pain secondary to endometriosis:

1. Diagnosis of Irritable Bowel Syndrome (IBS) diagnosed by a qualified physician using the ROME 4 criteria, with the IBS identified as a predominant pain generator.
2. Diagnosis of Painful Bladder Syndrome (PBS) as determined by O'Leary-Sant questionnaire with PBS identified as a predominant pain generator.

Exclusion Criteria - Knee Pain

1. Hip pain is greater than or equal to knee pain.

## 4.2 Subject Recruitment

Participants will be approached and recruited from the orthopaedic, gynaecology and chronic pain clinic departments at Leeds Teaching Hospitals NHS Trust. Potential participants will also be approached through Leeds Community Healthcare NHS Trust Musculoskeletal service clinics and Community Pain Service clinics, and invited to contact the LTHT research team if interested in study participation. Only patients who have appropriately diagnosed knee osteoarthritis or pelvic pain secondary to endometriosis, who have failed conservative treatments and are suitable candidates for LSC stimulation will be invited to give consent. Patients will be given oral information about the trial as well as the tri-fold brochures, one-page fliers, invitation letter and patient information sheet for the study. The tri-fold brochures and one-page fliers may also be available in patient waiting areas, as well as throughout the hospital. The investigator(s) will be responsible for obtaining valid informed consent once the potential participant has had adequate time to consider the information and ask questions. Informed consent will be obtained prior to any trial related procedures.

If the patient is willing to participate in the study, he/she must read, understand and sign the informed consent form. The investigator will also sign the consent form at the same time. Two further copies of the consent form will be made. The original copy of the signed consent form will be kept in the Investigator Site File at the investigational site. A copy will be kept in the patient's medical notes and a further copy given to the participant.

Each participant will be allocated a unique identification number upon entering the study. A recruitment log will be kept in the Investigator Site File. Participation in the study will be recorded in the participant's medical notes, with a copy of the informed consent, and a letter to the participant's GP.

## 4.3 Withdrawal of Subjects

### 4.3.1 When and How to Withdraw Subjects

Participants can leave the study at any time for any reason without affecting their future management. The responsible investigator can also withdraw a participant from the study at any time if he/she deems the participant not suitable for any reason. The reasons for withdrawal may include, but not limited to the following: if continuing participation in their opinion is detrimental for the participant's well-being; if there is a clinical need for commencement of beta-blocker exceeding 40mg/day, or statin medication; in instances of protocol violations and non-compliance; in case of a severe or serious adverse event haematological, blood chemistry and urine laboratory

tests or other special examinations. All participants discontinued from the study due to an unanticipated adverse event directly related to the device or procedure will be treated until the event resolves.

Participants who have withdrawn from the study following the LSC stimulator implantation will not be replaced. Participants who withdraw from the study prior to the LSC stimulator implant will be replaced.

## 4.4 Study Termination

Each participant will participate for a maximum of 12 months. This allows for standard care preoperative assessments to be completed between baseline and visit 2 (approximately 4 months) and the postoperative follow up period of six months. End of study will be classed when the last participant completes the last visit. At the end of the study, participants will be given the option of explant or to continue with the therapy. If participants opt to continue with the therapy, they will transfer over to standard peripheral nerve stimulator after-care and follow-up as per standard NHS guidelines.

## 4.5 Prior and Concomitant Therapy

Details of participants' concomitant medical therapy will be obtained during the screening process and the baseline visit, using hospital records if appropriate. It is likely that this patient cohort will be using various medications for pain relief both before and during the study. This will be recorded at baseline and the follow-up visits (tracked throughout the study). Those currently taking anxiolytic beta-blockers, exceeding 40 mg/day, will be excluded from the study. If there is a clinical need for these participants to commence these medications at any point during the study process, they will be withdrawn from the study to enable this. Participants taking statins will not be excluded from the study if they are already established on this medication. However, they will be withdrawn from the study if there is a clinical need to commence or change dose of statin therapy between the study visits.

## 4.6 Stopping Rules

The Sponsor reserves the right to stop the investigation at any stage, with appropriate written notice to the investigator according to applicable regulations. Possible reasons for early termination of the investigation by the Sponsor, either at local, national or international level, may include, but are not limited to:

- The therapy fails to perform as intended. Data will be analysed on an ongoing basis during the study to evaluate the safety and potential therapeutic benefits of LSC stimulation.
- Occurrence of USADE which pose a risk to future participants.
- Sponsor's decision, e.g., based upon significant delays in enrolment.
- Request from Regulatory bodies.
- Request of EC(s).

The investigator may also discontinue participation in the clinical investigation with appropriate written notice to the Sponsor. Should either of these events occur, the investigator shall return all documents to the Sponsor; provide a written statement as to why the premature termination has taken place and notify the EC and the MHRA (if applicable). Follow-up for all enrolled participants will be as per routine clinical care. The site shall be closed appropriately by the Sponsor.

### 4.7 Treatment in the Case of Premature Study Termination

In case the investigation is prematurely terminated, participants will return to the pain clinic's routine follow-up schedule. The device programming will be left at the physician's discretion and no further study-related activities will be performed.

## 5 Study Procedures

The data for the study will be collected according to the following schedule:
Visit 1: Consent, screening and baseline
Visit 2: Stimulation information session (as soon as possible, no window). MRI screening for LSC depth assessment.
Visit 3: Surgical implantation (as soon as possible, no window)
Visit 4: Wound check and activation visit – approximately 21 days post-implantation
Visit 5 (a, b, c): Weekly video/telephone check-ins (for 3 weeks)
Visit 6: 30-day post-activation follow up visit
Visit 7: 60-day post-activation follow up visit
Visit 8: 90-day post-activation follow up visit
Visit 9: 120-day post-activation video/telephone check-in
Visit 10: 150-day post-activation video/telephone check-in
Visit 11: 180-day post-activation follow up visit and End of Study

## Table 1: Data Collection

| Procedure/datapoint | Visit 1: Consent/ screening/ baseline | Visit 2: LSC stimulation information session | Visit 3: Surgical implant | Visit 4: Wound Check/ Activation visit | Visit 5 (a, b, c): Weekly video/telephone check-ins (for 3 weeks) | Visit 6, 7, 8: 30-, 60-, 90-day office visit | Visit 9, 10: 120-, 150-day video/telephone check-in | Visit 11: 180-day office visit/EOS |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | |
| Inclusion/exclusion criteria check | X | | | | | | | |
| Gender, year of birth | X | | | | | | | |
| Weight & height, blood pressure & pulse rate | X | | | | | | | |
| Diagnosis and duration of current pain condition | X | | | | | | | |
| Relevant medical history | X | | | | | | | |
| MRI of low back and pelvis | X | | | | | | | |
| Surgical implantation | | | X | | | | | |
| Wound assessment | | | X | X | | | | |
| Stimulation assessment | | | X | X | X | X | | X |
| X-ray | | | X | (X) | | (X) | | (X) |
| Assessment of vasodilation | | | | (X) | | (X) | | (X) |

(x) = Optional

**Table 2: Outcome Assessments**

| Outcomes | Visit 1: Consent/ screening/ baseline | Visit 2: LSC stimulation information session | Visit 3: Surgical implant | Visit 4: Wound Check/ Activation visit | Visit 5(a,b,c): Weekly telephone check-ins (for 3 weeks) | Visit 6, 7, 8: 30-, 60-, 90-day office visit | Visit 9, 10: 120-, 150-day telephone check-in | Visit 11: 180-day office visit/EOS |
|---|---|---|---|---|---|---|---|---|
| WOMAC | X | | | | | X | | X |
| KOOS | X | | | | | X | | X |
| ROM, swelling, ambulation | X | | | | | X | | X |
| Endopain 4D | X | | | | | X | | X |
| EQ-5D-5L | X | | | | | X | | X |
| O'Leary-Sant questionnaire | X | | | | | | | X |
| DASS-21 | X | | | | | | | |
| NRS pain scores | X | | | | X | X | X | X |
| Autonomic measures | | | | (X) | | (X) | | (X) |
| Upper Arm Cuff BP Measurement | | | | (X) | | (X) | | (X) |
| Blood sample | X | | | | | X | | X |
| Medication | X | | X | | | X | | X |
| Baseline screening diary for endometriosis participants | X (dispensed) | X (collected) | | | | | | |
| Baseline screening diary for knee OA participants | X (dispensed) | X (collected) | | | | | | ⁎ |
| Duration of implant procedure | | | X | | | | | |
| Implant information | | | X | | | | | |
| Programming data | | | X | | | | | |
| Intra-operative complications | | | X | | | | | |
| Length of hospital stay | | | X | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Daily stimulation and pain diary | | | | x (dispensed) | x (collected & dispensed) | x (collected & dispensed) | x (collected & dispensed) | x (collected) |
| Patient global impression of change (PGIC) | | | | | | X | | x |
| Clinician global impression of change (CGIC) | | | | | | X | | x |
| Adverse event assessment | X | x | x | x | x | X | x | x |

(X) = Optional

## 5.1 Screening and Enrolment

Screening will occur once a potential participant has been identified as a suitable study participant. This may be either during the pain management outpatient clinic or through orthopaedic and gynaecology referrals. Potential participants will be assessed on their suitability for this study using the inclusion/exclusion criteria. If potentially eligible, they will be given the invitation letter and patient information sheet. If they are keen to proceed, they will be sent an appointment for informed consent and baseline measurements. Potential participants will be asked if they would be content for the researcher to call them after a week if no reply has been received, to ascertain if they wish to participate, have further time to think, or wish to decline the study invitation.

For potential participants identified through Leeds Community Healthcare Service (LCH) clinics, study information will be sent to them from LCH by SMS / letter along with an invitation to contact the research study team if they are interested in participating in the study. For patients making contact with the research study team, suitability will be assessed using the inclusion/ exclusion criteria. If they are keen to proceed, they will be sent an appointment for informed consent and baseline measurements.

Potential participants who appear to be eligible based upon inclusion/exclusion criteria, will be consented. After consent, participants will be handed a baseline diary to complete at home. The site study coordinators will review the completed baseline diary for final screening and inclusion. Once all inclusion/exclusion criteria have been met and screening is complete, participants will be considered enrolled and will be scheduled for device implantation. Participants who fail to meet the study requirements or decline the stimulator implant, will be considered screen failures and will be exited from the study. During the implant procedure, the leads will be placed near the LSC under fluoroscopic guidance and then activated temporarily in the operating theatre, and participants will be asked to report the tolerability of stimulation. If the participant finds the stimulation uncomfortable or intolerable, the leads will be removed and the participant will be exited from the study, and replacement participants will be added to the study with the goal of a total of 20 implanted participants.

## 5.2 Study visits

### Visit 1: Consent, screening and baseline

At the baseline visit, informed consent will be taken prior to any trial investigations. At this visit after signing the consent form, participants will be assessed on their suitability for this study using the inclusion/exclusion criteria. The following assessments/data will then be conducted/collected:

- Gender, year of birth.
- Weight & height, blood pressure & pulse rate.
- Diagnosis and duration of current pain condition.
- Relevant medical history.
- For endometriosis participants only, menstrual cycle history will be recorded including date of last menstrual period, frequency, duration of flow and menstrual cycle length.
- Participant completed questionnaires: WOMAC and KOOS. ROM, swelling and ambulation for participants with knee OA.
- Endopain 4D Questionnaire for participants with pelvic pain due to endometriosis, and the EQ-5D-5L for all participants.
- O'Leary-Sant questionnaire for endometriosis participants to check for painful bladder syndrome.
- Depression, Anxiety and Stress Scale - 21 Items (DASS-21) will be administered.
- NRS pain scores (in office for the week prior to the visit, based upon recall).
- Blood draws: for baseline cortisol, metanephrines, CRP. This blood can be drawn anytime following consent but prior to the procedure to implant the stimulator (i.e., this baseline reading is not constrained to Visit 1).
- For endometriosis participants only: blood draw for FSH level (required only if investigator deems testing necessary to rule out menopause).
- Current analgesic medication.
- Concomitant medication.
- A baseline diary will be dispensed capturing both menstrual cycle and pelvic pain for the endometriosis participants and will be completed following informed consent. This will capture NRS pain scores twice per day, once in the morning and once in the afternoon or evening. Participants will start the diary immediately and complete it for a total of 40 consecutive days.

- A baseline diary will be dispensed and will capture NRS pain scores twice per day, once in the morning and once in the afternoon or evening, in knee pain participants following informed consent. The baseline diary will be completed for 7 days.

### Visit 2: LSC Stimulation Information session (as soon as possible, no window)

Participants will be invited to attend a dedicated information session on LSC stimulation with a Pain Clinical Nurse Specialist (CNS) or clinician. The CNS will be part of the research team for this trial, responsible for the delivery of the information session and programming of the implants post operatively. The information session includes preparing for surgery, the surgical procedure, the equipment, post-operative recovery and lifestyle activities such as avoiding heavy lifting to prevent damage to the internal leads (standard clinical practice). Participants will be informed that during implantation of the stimulator, the investigator will insert the device leads to the target area and then turn on the device to its full level with the aim of mapping the painful area to provide maximum coverage. The device will then be switched off whilst the other components of the device are implanted. Once the operative procedure has been completed, the leads will be tested again by the same method. The participants will be informed that the procedure is conducted as a day case and the machine will remain switched off initially. They will return to the Pain Clinic for the post-operative wound check and device activation in approximately 3 weeks. When discussing what the therapy feels like when active, the CNS will explain that participants will be provided with different programs during the device activation. Participants will be told that they will be required to turn stimulation on multiple (2 to 6) times per day at home, and that they will complete a patient diary. Following this, participants will be able to choose which stimulation parameters(s) they prefer. Participants will turn in their completed baseline diary at this visit. If their diary is not yet complete, they can turn it in any time prior to the date of implantation. An MRI of the low back and pelvis may be scheduled/completed prior to the implant procedure to ensure that the patient body habitus will allow proper placement of the implanted leads. MRI will be required at PIs discretion.

### Visit 3: Surgical implantation (as soon as possible, no window)

The participant will attend as a day-case for implant of the LSC stimulator. During the implant procedure, the investigator will place the leads at the target area and commence mapping the painful area. If the investigator is unable to insert the leads or mapping is not effective, the participant will be classed as a failed trial and will not proceed to full implant (Cohort C). Participants who are successfully implanted will be discharged from the day unit when they are fit to do so with an outpatient appointment to attend the pain clinic for a post-operative assessment

at day 21 (± 7 days). During the surgical implantation visit, the following data will be collected for all participants:

- Duration of implant procedure (skin to skin, total theatre time, fluoroscopy irradiation time).
- Implant information: failed trial/full implant.
- Programming data.
- An x-ray will be taken during the implant procedure to confirm the electrode locations.
- Intra-operative complications (if present).
- Length of hospital stay.
- Changes to medication (if applicable).
- Assessment of any adverse events.

### Visit 4: Wound check and activation visit 21 (± 7 post-implant) days post-implant

All participants will be reviewed post-operatively in outpatients by the CNS and research team at day 21 (± 7 days). During this visit, the post-operative wound will be examined, and adverse events will be assessed by specific questioning.

All participants will attend an activation visit at 21 (± 7) days post-implant.

- Perform electrode impedance and threshold measurements and record results.
- Program IPG.
- Assessment of vasodilation using Laser Doppler flowmetry. (Optional)
- Train the participant on use of the Remote Control, and document assessment of participant's ability to self-administer therapy. Instruct participant on timetable of therapy delivery (i.e., few times (2-6 times) a day starting the next day).
- Train the participant in the procedure to deliver stimulation, including time of day and participant in a seated position.
- Participants will take home a diary for capturing the following: date, program, stimulation time on, stimulation time off, stimulation duration, NRS score (0-10) before and after stimulation, and menstrual cycle in the endometriosis group.
- Optional x-ray if necessary to check for possible lead migration.
- Optional: Measures of autonomic function: HRV, BRS and SKNA for 10 minutes whilst participants are at rest semi-supine on an examination couch. All measures of autonomic function will be derived using LabChart software.

- HRV: HRV is an indirect method of measuring autonomic nervous system activity, with contributions from both the sympathetic and parasympathetic nervous systems. The high-frequency (HF) component is thought to reflect vagal control of heart rate. Although the physiological understanding of the low-frequency (LF) component is disputed, current interpretation regards it as potentially reflecting baroreflex function [53,54]. From HF and LF power, it is possible to calculate the ratio of LF to HF power (LF/HF ratio), where a decrease may reflect a shift away from sympathetic predominance [55]. To derive HRV, heart rate will be monitored and recorded using a three-lead electrocardiogram (ECG). This requires placing electrode pads on the chest and abdominal walls. This may require shaving part of the chest for male participants. As HRV components can be disrupted by low respiration rates, respiration will be monitored and recorded using a transducer belt (Pneumotrace) placed around the chest to ensure respiration rates do not drop below 10 breaths/minute.
- BRS: Alterations of the baroreceptor-heart rate reflex (known as baroreflex sensitivity [BRS]) can be analysed by measuring the spontaneous oscillations of systolic arterial pressure and the interval between consecutive R waves on the ECG (known as the RR interval) [56]. To derive BRS, blood pressure will be continuously recorded from the finger using an inflatable finger cuff.
- SKNA: NeuECG is the simultaneous non-invasive recording of ECG and SKNA, and is thought to reflect a direct recording of sympathetic nerve activity [57]. The electrical activity measured from the skin surface comes from a combination of the heart, muscle and nerve structures. By applying high-pass or band pass filtering, the SKNA can be isolated and measured [57]. SKNA will be recorded by connecting the remaining two leads from the ECG to electrode pads on the chest and abdomen, this may require shaving part of the chest for male participants.

- Optional upper arm cuff blood pressure measurement.

## Visit 5 (a, b, c): Weekly video/telephone check-ins (for 3 weeks post-activation)

Whilst trialling the stimulation at home, all participants will complete a patient diary which will require them to provide the following details: date, program, stimulation time on, stimulation time off, duration, NRS score (0-10) before and after stimulation and menstrual cycle in the endometriosis group. The diaries can be emailed or posted directly to the research team prior to Visit 6. For the 3 weeks immediately following activation, all participants will have a video appointment every week with the research team, for pain scores (NRS), adverse event

assessment and documentation and to ensure the device is working properly and that the participants are following the stimulation protocol. If video is not an option for participants, the weekly check-ins can be done by telephone. If participants require further programming, they will be invited to attend a reprogramming visit in the hospital (please see below).

### Visit 6: 30-day post-activation follow-up visit (± 7 days)

All participants will return to the pain clinic for assessment. Participants with knee OA will be asked to complete the WOMAC, KOOS, ROM, swelling, ambulation, NRS, EQ-5D-5L and PGIC questionnaires. Participants with pelvic pain secondary to endometriosis will be asked to complete the Endopain 4D Questionnaire, EQ-5D-5L, NRS and PGIC questionnaires. A patient diary, requiring the following details: date, program, stimulation time on, stimulation time off, duration, NRS score (0-10) before and after stimulation and menstrual cycle in the endometriosis group will be collected and dispensed for return on Visit 7. Participants will undergo optional physiological measures of HRV, BRS and SKNA and a blood draw (for cortisol, metanephrines and CRP), and optional vasodilation assessment using Laser Doppler flowmetry. Also, assessment of any adverse events and changes to medication will be recorded. The clinician will complete the CGIC questionnaire. Readout from IPG of therapy delivery times and duration will be recorded and stimulation configuration and amplitude will be adjusted as appropriate. There may be an optional x-ray if necessary to check for possible lead migration. Optional upper arm cuff blood pressure measurement.

### Visit 7: 60-day post-activation follow-up visit (± 15 days)

All participants will return to the pain clinic for assessment. Participants with knee OA will be asked to complete the WOMAC, KOOS, ROM, swelling, ambulation, NRS, EQ-5D-5L and PGIC questionnaires. Participants with pelvic pain secondary to endometriosis will be asked to complete the Endopain 4D Questionnaire, EQ-5D-5L, NRS and PGIC questionnaires. A patient diary, requiring the following details: date, program, stimulation time on, stimulation time off, duration, NRS score (0-10) before and after stimulation and menstrual cycle in the endometriosis group will be collected and dispensed for return on Visit 8. Participants will undergo optional physiological measures of HRV, BRS and SKNA and a blood draw (for cortisol, metanephrines and CRP), and optional vasodilation assessment using Laser Doppler flowmetry. Also, assessment of any adverse events and changes to medication will be recorded. The clinician will complete the CGIC questionnaire. Readout from IPG of therapy delivery times and duration will be recorded and stimulation configuration and amplitude will be adjusted as appropriate. There may be an optional

x-ray if necessary to check for possible lead migration. Optional upper arm cuff blood pressure measurement.

### Visit 8: 90-day post-activation follow-up visit (± 15 days)

All participants will return to the pain clinic for assessment. Participants with knee OA will be asked to complete the WOMAC, KOOS, ROM, swelling, ambulation, NRS, EQ-5D-5L and PGIC questionnaires. Participants with pelvic pain secondary to endometriosis will be asked to complete the Endopain 4D Questionnaire, NRS, EQ-5D-5L and PGIC questionnaires. Participants will undergo optional physiological measures of HRV, BRS and SKNA and a blood draw (for cortisol, metanephrines and CRP), and optional vasodilation assessment using Laser Doppler flowmetry. Also, assessment of any adverse events and changes to medication will be recorded. The clinician will complete the CGIC questionnaire. Readout from IPG of therapy delivery times and duration will be recorded and stimulation configuration and amplitude will be adjusted as appropriate. There may be an optional x-ray if necessary to check for possible lead migration. A patient diary, requiring the following details: date, program, stimulation time on, stimulation time off, duration, NRS score (0-10) before and after stimulation and menstrual cycle in the endometriosis group will be collected and dispensed for return on Visit 9. Optional upper arm cuff blood pressure measurement.

### Visit 9: 120-day post-activation follow-up visit (± 15 days)

All participants will have a video appointment with the research team for pain scores (NRS), adverse event assessment and documentation and to ensure the device is working properly and that the participants are following the stimulation protocol. The diaries will be emailed or posted directly to the research team. If video is not an option for participants, this visit can be done by telephone. If participants require further programming, they will be invited to attend a reprogramming visit in the hospital.

### Visit 10: 150-day post-activation follow-up visit (± 15 days)

All participants will have a video appointment with the research team, for pain scores (NRS), adverse event assessment and documentation and to ensure the device is working properly and that the participants are following the stimulation protocol. The diaries will be emailed or posted directly to the research team. If video is not an option for participants, this visit can be done by telephone. If participants require further programming, they will be invited to attend a reprogramming visit in the hospital.

### Visit 11: 180-day post-activation follow-up visit plus End of Study (± 15 days)

All participants will return to the pain clinic for assessment. Participants with knee OA will be asked to complete the WOMAC, KOOS, ROM, swelling, ambulation, NRS, EQ-5D-5L and PGIC questionnaires. Participants with pelvic pain secondary to endometriosis will be asked to complete the Endopain 4D Questionnaire, O'Leary Sant, NRS, EQ-5D-5L and PGIC questionnaires. Participants will undergo optional physiological measures of HRV, BRS and SKNA and a blood draw (for cortisol, metanephrines and CRP), and optional vasodilation assessment using Laser Doppler flowmetry. Also, assessment of any adverse events and changes to medication will be recorded. The clinician will complete the CGIC questionnaire. Readout from IPG of therapy delivery times and duration will be recorded and stimulation configuration and amplitude will be adjusted as appropriate. Participants will hand in a completed diary for capturing the following: date, program, stimulation time on, stimulation time off, stimulation duration, NRS score (0-10) before and after stimulation, and menstrual cycle in the endometriosis group. There may be an optional x-ray if necessary to check for possible lead migration. At the end of the study, participants will be given the option of explant or to continue with the therapy. If participants opt to continue with the therapy, they will transfer over to standard peripheral nerve stimulator after-care and follow-up as per standard NHS guidelines. Optional upper arm cuff blood pressure measurement.

A sponsor representative will be present in the operating theatre to observe and take notes during the implant procedure. A sponsor representative will also be present during the majority of office visits and video/telephone calls to take notes, to assist with programming under the direction of the clinician, and to ensure that the device is functioning properly. Verbal consent for the sponsor representative to be present in the operating theatre, office visits, video/telephone check-ins and any study-related contact will be sought from the participant by the research team prior to the sponsor representative joining or contacting the patient. To ensure patient well-being and safety, fully anonymised source data will be photocopied and provided to the sponsor. No personally identifiable data will be in the source data photocopied. The research team will be involved in the programming with the sponsor.

## 5.3 Unscheduled visits

If any participants require an unscheduled clinic review regarding the LSC stimulation, then the following data will be collected:

- Reason for review.
- Assessment of any adverse events.

- Changes to medication.
- New stimulation parameters setting.
- Optional assessment vasodilation using Laser Doppler flowmetry
- Optional x-ray if necessary to check for possible lead migration.
- The following are optional at unscheduled follow-up visits:

  Participants with knee OA will be asked to complete the WOMAC, KOOS, ROM, swelling, ambulation, NRS, EQ-5D-5L and PGIC questionnaires. Participants with pelvic pain secondary to endometriosis will be asked to complete the Endopain 4D Questionnaire, NRS, EQ-5D-5L and PGIC questionnaires. Participants will undergo optional physiological measures of HRV, BRS and SKNA and a blood draw (for cortisol, metanephrines and CRP). Also, assessment of any adverse events and changes to medication will be recorded. The clinician will complete the CGIC questionnaire. Readout from IPG of therapy delivery times and duration will be recorded and stimulation configuration and amplitude will be adjusted as appropriate. A patient diary, requiring the following details: date, program, stimulation time on, stimulation time off, duration, NRS score (0-10) before and after stimulation and menstrual cycle in the endometriosis group will be collected and dispensed for return on the next visit. Optional upper arm cuff blood pressure measurement.

## 6 Risks/benefits involved

Study participants will receive implantation of an existing FDA-approved and CE-marked device used for peripheral nerve stimulation, to assess the benefits of stimulating the LSC in reducing pain.

There are risks associated with the implant procedure which might include:

- Bleeding, which may lead to bruising and rare cases may require further surgery (1 in 300 cases).
- The electrode near the spine may move or not work and so participants may need further surgery over the life of the device, which is expected to be between thirty and thirty-five years. Whilst our experience of using the device for this length of time is very low, best estimate is 1 in 10 cases will require further surgery.
- Infection: system may need to be removed to prevent the spread of infection, even if the system was helping to reduce pain (3 in 100 cases).

- There is a risk of allergy to the implant material, such as nickel (1 in 1000 cases).
- Risk of nerve damage (1 in 3000 cases).
- Hardware malfunction/battery failure of the system (3 in 100 cases).
- Potential inability to undergo MRI scan due to the implantable pulse generator.

If the therapy does not reduce pain, the device may be removed safely through a minor surgical procedure.

For participants in this study, they will have a peripheral nerve stimulator inserted using x-ray guidance. X-rays are a type of ionising radiation which are used to form images of the body and to guide the doctor during the insertion of the peripheral nerve stimulator. Participants may also have some x-rays after the procedure, to check that the peripheral nerve stimulator is in the right place. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study may increase the chances of this happening to participants to 50.02%. The maximum number of x-rays (lumbar spine, AP + Lateral) participants will receive in this study is 3.

If the subjects decide to take part in this research study, there is a potential opportunity to temporarily reduce their long-standing chronic pain. The information gathered in this study will add to the understanding of treatment options for patients suffering from similar chronic pain in the future. The sponsor is undertaking this research to ensure the future device is much smaller and easier to use. So, participation in this study will also help with optimising this future device, which in turn will improve outcomes for many others living with this type of pain in the future.

# 7 Statistical Plan

## 7.1 Sample Size Determination

As this is a pilot study, a sample size of up to 20 participants in total who have been successfully implanted with a LSC stimulator will be required. This sample size will allow us to carefully examine the safety profile of LSC stimulation in these two nociceptive pain populations, as well as generate the initial data required to determine next steps with the research.

## 7.2 Statistical Methods

This is a feasibility study that aims to explore the safety and tolerability of LSC stimulation in knee OA and pelvic pain secondary to endometriosis. To that end, the focus of the statistical analyses will be primarily descriptive. This will entail generating descriptive statistics (mean ± standard deviation [SD], median, minimum, maximum and interquartile range) for all measures during each visit.

To aid with designing future research, particularly relating to sample size calculations, repeated measure ANOVAs (or Friedman tests for non-normally distributed data) will explore differences in pain, HRQoL, autonomic measures and blood draws between the face-to-face visits.

# 8 Safety and Adverse Events

The frequency and nature of reported adverse events and/or relevant adverse events will form the basis of the safety evaluation of the study.

## 8.1 Definition of Adverse Events (AE)

An adverse event is defined as ‘any untoward medical occurrence in a patient’. This definition does not imply that there is a relationship between the adverse event and the device under investigation. An adverse event can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease temporarily associated with the use of the investigational device, whether or not related to the investigational device.

At each contact with the participant, the researcher will seek information on adverse events by specific questioning and by examination if appropriate. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate Adverse Event Report form. The severity of these adverse events will thereby be graded by the investigator on a 3-point scale as defined below:

- Mild: discomfort noticed but no disruption of normal daily activity
- Moderate: discomfort sufficient to reduce or affect normal daily activity
- Severe: inability to work or perform daily activity

The duration of the event will be classified by the investigator on a 3-item scale as defined below:

- Single occasion: single event with limited duration
- Intermittent: several episodes of an event, each of limited duration
- Persistent: event, which remained indefinitely

For each adverse event the relation to the procedure and device will be rated (definite, probable, possible, unknown or definitely not) as judged by the investigator as well as eventual actions taken will be recorded. The reporting period for adverse events will be from entry to the study to 30 days post trial withdrawal or completion.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

## 8.2 Definition of Serious Adverse Event (SAE)

All SAE's must be reported on a Serious Adverse Events form and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event. Serious adverse events that are still on-going at the end of the study period will be followed up to determine the final outcome.
A serious adverse event is defined as an adverse event that:

a. Led to a death
b. Led to a serious deterioration in the health of the patient that
    - resulted in life threatening illness or injury
    - resulted in a permanent impairment of a body structure or a body function
    - required in-patient hospitalisation or prolongation or existing hospitalisation
    - resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect

Events which will not be reported as SAEs for the purposes of this study:

- Hospital admission for scheduled elective surgery
- Accident and Emergency visits where the patient is not actually admitted to the hospital (however, they may be reported at the Investigator's discretion).

All SAE's will be reported to the REC. If the event is deemed life threatening or fatal the report will be made within 7 days of the sponsor becoming aware, with any additional information reported within 8 days of sending the first report. All other events will be reported within 15 days of the sponsor becoming aware of the event.

### 8.3 Adverse Device Effect (ADE)

An ‘adverse device effect’ is defined as ‘any untoward and unintended response to a medical device’. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of user error.

### 8.4 Serious Adverse Device Effect

A ‘serious adverse device effect’ is defined as ‘an adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

### 8.5 Unanticipated Adverse Device Effect (UADE) & Anticipated Serious Adverse Device Effect (ASADE)

An ‘unanticipated adverse device effect’ is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current ‘Instructions for Use’

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the ‘Instructions for Use’. All UADE’s and ASADE’s will be reported to the REC and regulatory authorities (as required) in the same process as reporting SAE’s. If the event is deemed life threatening or fatal the report will be made within 7 days of the sponsor becoming aware, with any additional information reported within 8 days of sending the first report. All other events will be reported within 15 days of the sponsor becoming aware of the event.

## 9 Data Handling and Record Keeping

### 9.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Calldicott Guardian, The Research Governance Framework for Health and Social Care and Ethics Committee Approval.

Participants will be identified by their initials, date of birth and study number only. This information will be made available to study monitors/auditors/inspectors from regulatory authorities as well as

those involved in the care of the patient. All investigators will maintain confidentiality as outlined in the Data Protection Act (1998).

## 9.2 Source Documents

Participant records and other source data must be kept for the maximum period of time permitted by the hospital but not less than 15 years. The data retained in the hospital medical records for each patient should contain the following information:

- study number, brief description or title of study date that the subject gave written consent
- all visit dates
- all adverse events
- all concomitant medications

On-site monitoring will also include source document verification (SDV). SDV is the procedure whereby the data contained in the case report forms (CRFs) are compared with the primary source data (e.g., participant notes, original recordings from automated instruments, X-ray films, ECG tracings, laboratory results) contained in the subject records held at the investigational site, and thereby verified as accurate.

The Investigator must be aware that:

- SDV is a part of the normal monitoring process.
- SDV will be carried out by direct comparison of entries made in the CRF with appropriate source data. Direct access to source data requires that the subject gives written, documented consent to allow access to the source data.
- The following information will be verified from source documents for all subjects:
- Subject identity – date of birth, sex, initials and subject number
- Primary efficacy variable or data from which it is derived (if possible)
- Diagnosis of the condition under investigation and other selected eligibility criteria
- Details of adverse events and serious adverse events.

## 9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for this study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct the error, draw a single straight line

through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE ERRORS by any method. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. Never use correction fluid. The Investigator must review all entries for completeness and correctness.

The Investigator is responsible for the quality of the data recorded in the case report form. The data recorded should be a complete and an accurate account of the subject's record collected during the study.

## 9.4 Records Retention

The Investigator will retain essential documents until 15 years post study in accordance with local policy. The items will be stored in a clearly labelled storage box stating study name, funder/sponsor details, storage and destruction date.

Records to be retained by the Investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- Investigator agreement.
- Signed and dated informed consent documents.
- Application(s) to ethics committee/ institutional review board Ethics committee
- Ethics committee composition.
- Regulatory authorisation (if appropriate)
- Curriculum vitae of the Investigator and personnel to whom he/she has delegated some of his/her responsibilities as an Investigator.
- All clinical laboratory normal ranges in place during the study (if appropriate).
- Clinical laboratory accreditation certificate or certification of established QC and/or external QA or other validations (if appropriate).
- Details of study material/supplies shipment dates, batch numbers, method of shipping etc. (if applicable).
- Monitoring log.
- Case report forms.
- Serious adverse event reports.
- X-ray or Fluoroscopic images of the lead implant location.

# 10 Study Monitoring, Auditing, and Inspecting

## 10.1 Study Monitoring Plan

The investigator will permit study-related monitoring, audits and inspections by the Ethics Committee, the Sponsor and the study allocated Clinical Research Associate (CRA). The CRA will monitor this trial in accordance with the study protocol and in line with the responsibilities set out in the Research Governance Framework and Directive 2001/20/EC.

# 11 Ethical Considerations

This study will be conducted according to the standards of International Conference on Harmonization Good Clinical Practice Guideline, declaration of Helsinki, Research Ethics Committee regulations, EU Clinical Trial Directive (if applicable) and any applicable government regulations and Local NHS Trust Research Office policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Research Ethics Committee (REC) for approval of the study conduct. The decision of the REC concerning the conduct of the study will be made in writing to the investigator.

All patients eligible for participating in this study will be provided with an information sheet describing the elements of this study and sufficient information to make an informed decision about their participation in this study. Participants will complete and sign a consent form to indicate that they are giving valid consent to participate. This Information Sheet and Consent form will be submitted with the protocol for review and approval by the REC for the study.

# 12 Study Finances

## 12.1 Funding Source

This study is funded by ABVF BV.

## 12.2 Sponsorship:

This study is sponsored by ABVF BV.

## 12.3 Indemnity for the performance of the study

NHS indemnity via The Leeds Teaching Hospitals NHS Trust

## 13 Publication Plan

Data will be evaluated on an ongoing basis throughout the study. The results may be presented as a poster, abstract or publication in an appropriate scientific conference or medical journal. At the conclusion of the study, a full clinical study report will be completed and submitted to the sponsor, REC and funder. The findings from the completed study may be published in suitable scientific medical journals. In addition, the publication of the trial information on clinicaltrials.gov website was deferred for a year, to enable intellectual property capture. A request to this end, was approved by the EC, but it has now expired..

All information and data generated in association with this study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the Sponsor.

## 14 References

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