Multicentre, Double Blind, Randomised Sham-Controlled Trial of 10kHz High-Frequency Spinal Cord Stimulation for Chronic Neuropathic Low Back Pain (MODULATE-LBP): A Trial Protocol

Adnan Al-Kaisy
Guy's and Saint Thomas' NHS Foundation Trust
Jonathan Royds (roydsj@gmail.com)
Guy's and Saint Thomas' NHS Foundation Trust https://orcid.org/0000-0003-0756-2690
Stefano Palmisani
Guy's and Saint Thomas' NHS Foundation Trust
David Pang
Guy's and Saint Thomas' NHS Foundation Trust
Samuel Wesley
Guy's and Saint Thomas' NHS Foundation Trust
Rod S Taylor
University of Exeter
Andrew Cook
University of Southampton
Sam Eldabe
South Tees Hospitals NHS Foundation Trust
Lance McCracken
Uppsala Universitet
Rui Duarte
University of Liverpool
Jeremy Fairbank
University of Oxford

Study protocol

Keywords: Spinal Cord Stimulation, Neuropathic Pain, Chronic Neuropathic Low Back pain, Neuromodulation

Posted Date: October 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.12200/v2

Version of Record: A version of this preprint was published on January 28th, 2020. See the published version at https://doi.org/10.1186/s13063-019-3831-4.

Abstract

Introduction Chronic neuropathic low back pain (CNLBP) is a debilitating condition in which established medical treatments seldom alleviate symptoms. There is evidence demonstrating high frequency 10kHz spinal cord stimulation (SCS) reduces pain and improves health-related quality of life in patients with Failed Back Surgery Syndrome (FBSS) but there is limited evidence in CNLBP without prior surgery. The aim of this multicentre randomised trial is to assess the clinical and cost-effectiveness of 10kHz SCS for this population. Methods This is a multicentre double-blind randomised sham-controlled trial with a parallel economic evaluation. A total of 96 patients with CNLBP who have not had spinal surgery will be implanted with an epidural lead and a sham lead outside the epidural space without a screening trial. Patients will be randomised 1:1 to 10kHz SCS plus usual care (intervention group) or sham 10kHz SCS plus usual care (control group) after full implant. The SCS devices will be programmed identically using a cathodal cascade. Participants will use their handheld programmer to alter the intensity of the stimulation as per routine practice. Primary outcome will be a 7 day daily pain diary. Secondary outcomes include the Oswestry Disability Index, complications, EQ-5D-5L, and health and social care costs. Outcomes will be assessed at baseline (pre-randomisation) and at 1 month, 3 months and 6 months after device activation. The primary analyses will compare primary and secondary outcomes between groups at 6-months adjusting for baseline outcome scores. Incremental cost per quality adjusted life year (QALY) will be calculated at 6-months and over the patient lifetime. Discussion The outcomes of this trial will inform clinical practice and healthcare policy on the role of high frequency 10kHz SCS for patients with CNLBP without prior surgery.

Introduction

The prevalence of chronic low back pain worldwide is estimated to range between 12%-28% of adults (1-4). This leads to prolonged disability and time lost from work for those affected (5). Within this group an estimated 12-15% suffer from chronic neuropathic lower back pain (CNLBP), have relatively greater pain severity, and account for more of the costs of this condition (6, 7). Neuropathic pain is defined as a lesion or disease of the somatosensory system. Commonly used therapies for low back pain are largely ineffective for CNLBP(8).

The National Institute for Health and Care Excellence (NICE) recommends spinal cord stimulation (SCS) for refractory neuropathic pain. SCS is routinely used for people with predominantly neuropathic radicular pain typically resulting from, or persisting after spinal surgery (so-called failed back surgery syndrome [FBSS]) (9, 10). SCS has demonstrated cost effectiveness for this indication(11). However, due to a lack of existing evidence and the difficulty of obtaining paraesthesia over the lower back, SCS has not been commonly used for treating patients with back pain without previous spinal surgery (10, 12).

High frequency 10kHz-SCS (Nevro, Redwood, CA, USA) is a recent advance in SCS technology. The current is delivered at a frequency of 10kHz, as opposed to the 40 to 60Hz generated by conventional SCS (13). The key advantage of a higher frequency current is apparent superiority to conventional SCS in

targeting residual low back pain following back surgery(14). Moreover, it does not generate any stimulation related sensations, so called “paraesthesia’s” that can become intolerable (14, 15). An advantage in this absence of paraesthesia is that 10kHz-SCS provides the opportunity for sham controlled and double blind studies in the field of SCS without the need for device modifications.

Our group has conducted an uncontrolled, multicentre, single arm study in which 72 patients with significant low back pain with or without leg pain were implanted with a 10kHz-SCS (16). This was a mixed cohort of patients with and without prior spinal surgery. At 24 months, the mean reported Visual Analogue Scale (VAS) score for back pain was 3.3 (SD 0.3) in 65 patients, compared with 8.4 (SD 0.1) at baseline (pre-implant) and 2.7 (SD 0.3) at 6 months(16). A total of 60% of all patients were responders (>50% reduction in back pain) at 24 months(16). VAS is a psychometric response scale to measure pain severity between 0-10cm with 10cm indicating the worst imaginable pain experienced(17). Similar improvements were observed in leg pain, disability, sleep and marked reductions in medication intake (16).

In a more recent multicentre randomised controlled trial (RCT), 10kHz-SCS therapy demonstrated superiority to conventional tonic SCS in the treatment of FBSS. A total of 198 subjects with both back and leg pain were randomised to 10 KHz-SCS or conventional SCS. 10kHz-SCS decreased back pain intensity by 67% compared to 44% in the conventional SCS arm(18). This decrease was sustained at 24 months (19).

The above mentioned studies focused on neuropathic back pain in the context of patients with previous spinal surgery. However, a small subset of patients without prior spine surgery that received 10kHz-SCS therapy in these studies also experienced pain relief and functional improvements, comparable to those of patients with FBSS (14, 18)

We hypothesised that patients with CNLBP with no prior spine surgery would benefit from 10kHz-SCS. To evaluate this hypothesis, we initially designed and conducted an open label uncontrolled pilot study in 21 patients with CNLBP and no prior spine surgery. 10kHz-SCS therapy significantly reduced VAS back pain intensity by an average of 5.59 (SD 1.80) at 12 months in medically refractory low back pain patients with no past history of spine surgery. 90% of the implanted patients were classified as responders (i.e. VAS back pain reduction >50%) at 12 months. We also observed a significant increase in physical function scores and health-related quality of life at one year post 10kHz- SCS implant. Mean pain intensity was reduced by 73% and disability measured by the Oswestry Disability Index (ODI) was reduced by 48%. Opioid medication intake decreased by 64% and mean EQ-5D quality of life scores improved from 0.16 to 0.47. Remarkably 75% of patients were able to return to employment (20). This improvement was sustained at 3 years follow up (21).

To date 10kHz-SCS has not been formally tested against a sham therapy in order to isolate specific therapeutic effects from those induced by placebo (22). It is very possible that some of the benefit reported may be nonspecific treatment effects (enhanced by a surgical procedure) or result from reporting bias in either the patient or assessor (22). We have therefore specifically designed this fully powered,

double blind, randomised, sham controlled trial of 10kHz-SCS to address this major methodological limitation of previous studies.

Objectives:

Hypothesis: The addition of 10kHz-SCS to usual medical care ('intervention group') will provide superior back pain relief, compared to sham stimulation plus usual medical care ('control group') for CNLBP.

Aim: The overarching aim of this study is to demonstrate the efficacy, safety and cost-effectiveness of 10kHz-SCS in the treatment of CNLBP with no prior surgery.

Trial Design

This is a multicentre, randomised, double-blind, superiority, sham-controlled trial with parallel economic evaluation. Patients will be individually allocated to activated 10kHz-SCS plus usual care (intervention) or sham 10kHz-SCS plus usual care (control) and followed up to 6 months. A summary of the study consort diagram is illustrated in Figure 1.

Methods

This protocol has been prepared and reported in accord with the Defining Standard Protocol Items for Clinical Trials (SPIRIT) statement(23).

Study Setting

Participants will be recruited from two neuromodulation centres: Guy's & St. Thomas NHS Foundation Trust, London, UK and South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK.

Patient and Public Involvement

We organised three Patient and Public Involvement and Engagement (PPIE) meetings to discuss research design elements that would be acceptable to patients for a condition that has been resistant to conventional medical management. On the 8th April 2016 a PPIE event was held at the biannual scientific meeting of UK spine societies (BritSpine). At this event 7 patients and 22 professionals attended a session to provide feedback and advice on this application. On 24th July 2015 Guy's & St Thomas' Hospital hosted a PPIE meeting of participants from our pilot study(16). Eleven patients and their relatives attended. In addition another 10 patients attended a subsequent meeting on the 11th November 2016. The outline of the proposed study was presented during both meetings, patients were asked whether they would enrol into the study and to give their general thoughts on the study methods. Two experienced facilitators from the local Research and Design Service (RDS) fielded questions including recruitment, comparison treatments, blinding, outcome measures and methods, and dissemination of results. Feedback was collected via assessment sheets, reviewed, and incorporated into the study design.

Patient and public engagement meetings occur annually through the duration of the study, with an additional dissemination meeting in the final year.

During the PPIE Meetings a number of points were raised:

1. The overall response to these meetings have been thoroughly positive, patients have expressed their enthusiasm for this trial and willingness to attend future meetings.
2. Patients described longstanding chronic pain, inadequate treatments and the need for long lasting therapy without using medications.
3. Patients expressed a willingness to join the trial and to be allocated 50/50 to an active or inactive treatment, provided assurances were given about device activation at the end of the study
4. Patients accepted inclusion of a sham arm but we abandoned our original plan to crossover at 6 months and extend the trial to 12 months. This was felt to be unfair for patients who were allocated active therapy that was then withdrawn.
5. A 6 months blinded period was accepted as a reasonable balance between patient and research needs but 12 months was too long.
6. Emphasis from patients on measures related to their broader experiences such as physical function, disability and goal orientated outcomes rather than just pain.
7. Patient travel reimbursement maximum raised from £30 per visit to £50 per visit as £30 was deemed inefficient for patients travelling from outside of London.
8. Throughout these meetings, the patients have appointed a PPIE representative, Mr Dean Walker. Dean was a subject in our pilot study, joined the research team before this application was first drafted and agreed to be a co-applicant. He has attended all our PPIE events, has participated fully as a member of the applicant team, and will remain on the research team until completion of the study.

Eligibility Criteria

The intended study population is subjects with CNLBP without prior surgery. Participants will be assessed for eligibility using the study-specific inclusion/exclusion criteria during the Screening visit.

Inclusion criteria

1. 18 years old at the time of consent
2. Willing and able to sign and date informed consent form
3. Capable of independently comprehending and consenting to the requirements of the study
4. Willing and able to comply with all study procedures, study visits, and be able available for the duration of the study
5. Diagnosed with Low back Pain with VAS pain scores ≥60 out of 100mm for at least 12 consecutive months

6. Low back pain of greater intensity than any leg pain
7. Presence of clear component of neuropathic pain based on a PainDETECT Questionnaire score of ≥19(24)
8. Degenerative disc disease confirmed by imaging or internal disc degeneration as confirmed by discography
9. Stable dose (no new, discontinued or changes) of all prescribed pain medications for at least 4 weeks prior to screening and willing to maintain or only decrease the dose of all prescribed pain medications through Trial Assessment 2.
10. Has tried appropriate conventional medical management for their pain

Exclusion criteria

1. Presence of an active neurostimulator implanted device, whether turned on or off
2. Previous spinal surgery
3. Current signs of a systemic infection
4. Pregnant or lactating, inadequate birth control, or the possibility of pregnancy during the study
5. Current diagnosis of a progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, rapidly progressive diabetic peripheral neuropathy, brain or spinal cord tumour, or severe/critical central or foraminal spinal stenosis
6. Mechanical spine instability detected by a clinician (validation by flexion/extension films of lumbar spine within the past 12 months showing 4 mm or more translational movement or excessive angular movement manifested by >5 degrees segmental angular movement) e.g. any forms of spondylolisthesis
7. A medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator
8. Evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcome as determined by the Investigator
9. Significant drug-related behavioural issues (eg. alcohol dependency, illegal substance abuse)
10. Using greater than 120mg morphine equivalents of opioids daily
11. Structural abnormalities of the spine that may prevent electrode implantation
12. Co-existing disorder of the nervous system that may affect study measurements e.g. polyneuropathy
13. Diagnosed with Fibromyalgia or other generalised pain syndromes
14. Active malignancy or diagnosis of cancer and not in remission for at least 1 year prior to screening
15. Participating or planning to participate in another clinical trial

16. Patient is in close contact with other people involved with the study, such that there is a high risk that the patient may be unblinded.

Interventions:

Removal of 'temporary trial' phase from design

A trial of stimulation is often performed in standard care to eliminate non-responders prior to full implant. This temporary trial of stimulation is performed by implanting the leads and connecting them via a temporary extension to an external battery that the patient can wear for up to two weeks. This is a recommendation of current NICE guidelines and the manufacturer's device manual.

RCT evidence does not support the role of temporary screening trials of stimulation in predicting long term outcomes of the therapy(25). There exists positive evidence of harm from temporary screening trails including higher infection rates as well as potential elimination of long term responders(26). In our preliminary study on 10kHz stimulation for patients with low back pain without prior surgery we noted a trial success rate of 95%(20). This high success rate was credited to more stringent patient selection, based on characterisation of pain mechanisms, and other clearly defined inclusion criteria. By removing the trial phase we reduce the number of procedures that patients undergo from two to one.

Therefore, we assert that a pre-implantation trial of 10kHz-SCS in this population offers little clinical value, and instead increases costs , harms and, in the context of the present trial, reduces the scientific value of this research.

Identification and Description of the Investigational Device

The Senza^{TM} System is a totally implantable SCS system that is intended to aid in the management of chronic intractable pain and received an European Union (EU) CE Mark in May 2010.

The Senza System consists of a rechargeable implantable pulse generator (IPG) with 16 output channels. The IPG is implanted in a subcutaneous pocket and is capable of stimulating the spinal cord nerves when used with one or two 8-contact percutaneous leads. The IPG is controlled by a Patient Remote and/or a clinician Programmer.
Lead(s): The percutaneous lead has 8 contacts.
Extension(s): An extension may be used during the permanent implant procedure, to connect the lead to the IPG.
IPG: The IPG is a rechargeable stimulator with 16 output terminals. Each of the 16 outputs can be programmed as a cathode or an anode. The IPG is powered by a 3.6 V nominal lithium-ion rechargeable battery. It is capable of stimulating the spinal cord nerves through the electrodes of the leads connected to any combination of the output terminals, using one programmable current source.
Patient remote control: The patient remote control is a handheld battery operated unit that the subject can use to turn stimulation on and off and to change stimulation programs/settings.

Charger: This charger is used to transcutaneously charge the IPG battery. It is a portable device powered by a rechargeable battery and can be held in one hand.
Clinician programmer: The clinician programmer is an off-the-shelf laptop installed with proprietary software to allow the programming of the IPG and subject remote control.
Lead anchors: Lead anchors may be used to secure the leads to the fascia, possibly preventing lead migration and/or lead strain.

We will be using cascade programming in both groups, this involves 4 pairs of electrode groups and each of them is switched on for 5 seconds before moving on to the next (Figure 3). Therefore in 20 seconds the whole lead has been activated and the cycle repeats. The rationale is that this avoids overstimulation, mitigates against small degrees of lead migration and removes any need for reprogramming. During the study, as both groups are programmed identically and reprogramming is not expected, it reduces the risk of unblinding and subsequent bias.

Device Implantation

Under standard operating theatre practice, all participants will be implanted with the following equipment: 10kHz Senza IPG, two octopolar (8 contact) leads.

The first of the 2 leads will enter the epidural space through a lumbar or lower thoracic epidural puncture. The lead will be advanced cranially in the epidural space to reach a final position where contacts 4 and 5 span the T9/10 disc space on Anterior-Posterior fluoroscopy in the anatomical midline as per our pilot experiment (Figure 3). A lateral image will be obtained to ensure the lead is placed posteriorly in the epidural space.

Once satisfactory epidural lead placement is confirmed it will be anchored to the deep fascia or supraspinous ligament and a strain relief loop made. The active epidural lead will be tunnelled to a subcutaneous pocket for the battery using an extension if necessary. This subcutaneous pocket is made in the gluteal region via a small skin incision and blunt subcutaneous dissection. It should be large enough to accommodate the IPG, extensions and sham lead. This active lead (AL) will be used to provide therapy to the intervention group. AL will be connected to the first or top port of the IPG in all subjects and a second sham lead (SL) inserted subcutaneously and attached to the second port of the IPG (Figure 4). Impedances to check electrical integrity of the system will be performed at this time. Information will be given about wound care and the device will remain ‘off’ until their next visit. Removal of sutures (if necessary) will be done at the implanting site.

It may be possible that the SCS will need removal or revision. Reasons include: Patient withdrawal from study, Infection, Hardware failure, Lead migration, SCS related pain, allergy or other adverse reaction to device and requirement for MRI scan

If this occurs, the subject will have consent to a further surgical procedure and the process of surgery is similar to that of implantation. With removal, all hardware will be removed and with revision the changes

necessary to the SCS components will be determined by which component is unsatisfactory. Risk of these surgeries is similar to that of implantation and there is a small risk that some of the components may not be safely removed.

All such procedures will be done by the study implanter.

Outcomes:

Primary Outcome:

To compare the effects of stimulation delivered on the mean VAS back pain scores from the 7 days of diary data the week prior to and 6-months following post-randomisation between intervention and control.

Secondary Outcomes:

- To compare secondary outcomes of disability, depression, health-related quality of life, patients' global impression of change, sensation maps and medication usage between intervention and control at 1, 3, and 6 months post-randomisation.
- To compare the cost-effectiveness of 10kHz-SCS between intervention and control at six months post-randomisation.
- To compare complications and adverse events at 6-months post-randomisation between intervention and control.

Participant timeline:

Screening Visit

The schedule of events is listed in Figure 2. Subjects will be given a copy of the patient information sheet and informed consent form and will be provided sufficient time to read and understand the document and the opportunity to ask questions. Subjects will be informed of their right to withdraw from the study at any time without prejudice.

The screening visit will commence after each subject has been enrolled. During the Screening visit the following will be collected: eligibility assessment, subject demographics, medical history, pain map, pain severity on a 0-100mm (VAS), PainDETECT questionnaire, pregnancy test from all female subjects of child-bearing potential, and pain medication usage.
If a subject reports a PainDETECT score lower than 19, they will be discontinued from the study. During the Screening visit, subjects will be provided with a multi-day diary. Subjects will record their VAS back and leg pain scores for 7 days prior to the baseline visit.

Baseline Visit

During the Baseline visit, subjects will be asked to complete the following questionnaires after being provided detailed instructions: Oswestry Disability Index (ODI v2.1a), Patient Health Questionnaire (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), EQ5D-5L, pain medication usage, work status and work absence. If a subject reports a mean VAS back pain score lower than 60mm on their multi-day pain diary, they should be discontinued from the study.

Randomisation and Device Activation

The randomisation and device activation visit will take place between 2 and 4 weeks post implant, pending proper wound healing.

Firstly, the following will be performed by blinded study personnel:

- Assess subjects to determine whether they have experienced any adverse events and complete event Case Report Form (CRF) as applicable.
- Take new x-ray images to record the lead locations.
- Provide subjects with a multi-day diary and instruct them to record their VAS pain scores daily for 7 days prior to 1 month follow up.
- Program the subject' device and lead according to their allocated group, whilst the lead is different, the programming parameters used are identical and can be found in Figure 3.

At this point the patient enters the 'follow up' phase of the study, with visits at 1, 3 and 6 months. These visit frequencies mirror our standard of care routine clinical practice.

During these visits, all subjects will be asked to complete the following questionnaires in addition to bringing their multi-day pain diary:

- Pain severity on a 0-100mm (VAS)
- Pain Map
- Oswestry Disability Index (ODI v2.1a)
- Patient Health Questionnaire 9 (PHQ-9)
- Pittsburgh Sleep Quality Index (PSQI)
- EQ5D-5L
- Pain medication usage
- Patient Global Impression of Change (PGIC)
- Subject Satisfaction
- Sensation Map

Any adverse events are monitored and documented in the CRF. An X-ray may be taken if there are any concerns about lead migration.

To check fidelity of blinding, participants and assessors will be asked to guess their treatment allocation at the end of the study. We will monitor potential outcome assessor blinding by asking them to guess each patient's allocation at the end of each follow up assessment. After the trial is completed we will compare actual and anticipated treatment allocations.

After 6 month follow up:

After the 6 month visit all patients will be managed in the standard pain management service, outside the trial.

Medication Usage

All medications prescribed for the treatment of pain will be recorded during the Screening visit. Only subjects who are on a stable dose of all prescribed pain medications for at least 4 weeks prior to screening and willing to maintain or decrease the dose of all prescribed pain medications are eligible for participation in this study. Any changes to subject's pain medications while they are enrolled in the study will be recorded.
The addition of pain medications for the relief of surgical discomfort after implant procedures is allowed. Pain medications prescribed for short-term post-operative pain management are not considered an increase in pain medications if the medication is ceased and the medication end date is prior to the date of randomisation.
All medications used to treat adverse events (regardless of their reason prescribed) will be documented as interventions on the Event CRF.

Sample size

For our primary outcome of pain severity VAS (0-100mm), Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) propose a minimally important clinical difference (MICD) of 20mm(27). To detect this MICD and based on a back/leg pain VAS standard deviation of 25mm as seen in previous conventional and 10Khz-SCS RCTs, at 90% power and 5% alpha, and a worst case attrition rate of 30% at 6-months follow up. We will require a total of 96 participants (48 per centre) recruited per group.

Recruitment:

Recruitment will be through outpatients in the 2 centres. The study will be presented in national and international meetings to target pain physicians, spinal surgeons, neurosurgeons and physiotherapists. Advertising will be conducted through newspapers and magazines to enhance recruitment. Road shows were organised targeting spine surgeons, neurosurgeons and pain physicians.

Assignment of intervention:

Allocation: Sequence generation:

Patients will be randomised using a validated and password-protected trial website, designed and supported by UK CRC registered Exeter Clinical trials unit (CTU).

Allocation Concealment:

Patients will be allocated 1:1 to intervention or control stratified by centre using web-based computer generated random allocation sequence to ensure concealment. This website will be password protected and managed by Exeter CTU.

Blinding:

Patients, investigators, outcome assessors and analysts will all be blinded. Only two study nurses at each site will be unblinded to the treatment received by the participants.

Data Collection/Management:

Data analyses will be conducted and reported in accord with CONSORT (Consolidated Standards Of Reporting Trials) guidelines for non-drug trials(28). Participant flow will be summarised using a flow diagram, reporting recruitment and drop outs and baseline patient characteristics and outcome scores reported and compared by group. The primary analysis for both primary and secondary outcomes will take an intention to treat approach based on a between group comparison of intervention and control participants with complete data at 6-months, adjusting for baseline outcome score and centre. In a secondary analysis we will extend the primary analysis model with a repeated measures comparison of groups at all follow up points. We comprehensively examine patterns and reasons of missing outcome data and undertake appropriate imputation models to assess the impact of missingness on primary analysis models. Results with reported as between group mean differences and 95% confidence intervals. Safety outcomes will be reported descriptively by group. No correction of p-values for multiplicity of testing will be undertaken. However, the primary outcome analysis will be performed before all others analyses and the P-values of all subsequent analyses interpreted in the context of multiple testing. No interim analyses is planned.

Economic Evaluation Methods

The economic evaluation aims to estimate the cost-effectiveness of 10kHz-SCS plus usual medical care when compared to sham stimulation plus usual medical care. Healthcare resource utilisation e.g. management of adverse events, interventions, investigations, medication, inpatient hospitalisations, Emergency Department and other health care related visits, plus out of pocket costs and absences from work will be collected for each patient during the study follow-up period. Resources required for the implantation intervention will be recorded within the trial.

Items of resource use will be costed using national averages obtained from national sources (such as the Personal Social Services Research Unit, the British National Formulary and National Health Service (NHS) reference cost databases). Cost components will be combined to derive total patient level costs for the NHS. In addition, non-NHS costs such as productivity loss due to absence from work or patient out of pocket expenses will also be quantified to provide a full picture of how the strategies being compared will affect the financial burden imposed by the condition on both the NHS and the patients.

Generic health-related quality-of-life (HRQoL) data will be collected using the EQ-5D-5L instrument. Both resource utilisation (costs) and EQ-5D-5L will be collected at each follow-up visit. A within-trial cost consequence analysis will be carried out to estimate mean resource utilisation, costs, EQ-5D scores and total quality-adjusted life-years (QALYs) in each group, together with relevant measures of sampling uncertainty. QALYs will be calculated using the area under the curve approach, with regression-based adjustment for baseline EQ-5D score.

The economic evaluation will take the form of a cost-utility analysis, to calculate the cost per additional QALY gained. Base-case analyses will be conducted from the NHS perspective, with additional analyses from the societal perspective. Deterministic and probabilistic sensitivity analysis will be undertaken to explore the robustness of the results to plausible variations in key assumptions and variations in the analytical methods used. Cost-effectiveness acceptability curves will be constructed to show the probability that the intervention is cost-effective at specific thresholds of cost per QALY gained. The analyst will be blinded to group allocation.

Statistical Methods:

The trial statistician will be blinded to group allocation and will undertake analyses using STATA. A detailed statistical analysis plan (SAP) will be prepared that will be presented to the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) for their review ahead of any analysis being undertaken.

Data Monitoring:

A joint Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will provide supervision for the trial, providing advice to the Chief and Co-investigators [Trial Management group (TMG)] on all aspects of the trial conduct and affording protection for patients by ensuring the trial is conducted according to the Medical Research Council (MRC) Guidelines for Good Clinical Practice in Clinical Trials. The TSC/DMC will be chaired by an academic clinician independent of the trial plus three other members plus the chief investigator, trial manager, statistician and health economist.

Harms:

Foreseeable adverse events and anticipated adverse device effects

We expect the risk of serious adverse events to be rare and our results from the previous 10kHz stimulation trial showed the risk of adverse events to be:

- Battery pocket pain 8%
- Wound infection 3%
- Electrode migration 5 %
- Lead Fracture or malfunction 6%
- Headache from dural puncture 1%
- Nerve injury <1%
- Spinal cord haematoma and abscess <1%
- Unwanted, perceived stimulation <1%

Pocket pain is usually self-limiting within 6 months and electrode migration is mitigated using a cascade stimulation programming. Wound infection will necessitate removal of the device. There may be instances where the system will require revision or removal. The reasons for this include infection, hardware displacement, pain or discomfort from the device, or device failure. The risks are similar to those mentioned above.

All adverse events will be recorded and reported in accordance with Good Clinical Practice.

Device Revision or Removal

It may be possible that the SCS will need removal or revision. Reasons include: patient withdrawal from study, infection, hardware failure, lead migration, SCS related pain, allergy or other adverse reaction to device, requirement for MRI scan.

If this occurs, the subject will have consent to a further surgical procedure and the process of surgery is similar to that of implantation. With removal, all hardware will be removed and with revision the changes necessary to the SCS components will be determined by which component is unsatisfactory. Risk of these surgeries is similar to that of implantation and there is a small risk that some of the components may not be safely removed. All such procedures will be done by the study implanter. Any adverse events are monitored and documented in the CRF.

Auditing:

The TSC will meet three times in the first year; twice in the second year and three times during the third year. The DMC will meet twice in the first year and annually thereafter.

If the Chief and Co-investigators are unable to resolve any concern satisfactorily, personal investigators, and all others associated with the study, may write through the Trial Office to the chairperson of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or about any other matters thought relevant. Interim analyses of recruitment rate, safety and outcome data will be

supplied, in strict confidence, to the committee along with any other analyses that the committee may request.

Ethics and Dissemination:

Declaration of Helsinki, International Standards and national regulations

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO 14155 and all other applicable device and UK regulations.

Central ethical approval was provided by London- Camberwell St Giles Research Ethics Committee for both centres, part of the NHS Health Research Authority. REC reference: 18/LO/1031, IRAS project ID: 232729. We will not begin recruiting at other centres in the trial until local ethical approval has been obtained. Informed written consent will be obtained prior to trial participation.

Protocol amendments:

Any protocol amendments will be discussed and approved within the TMG and presented inform the TSC/DMC.

Consent:

The principal investigator or qualified designee will document the informed consent process, including the date of consent and name of the person conducting the consent process in the subject's medical record. Subjects will be considered enrolled in the study once they have signed the informed consent form. On the consent form, participants will be asked if they agree to use of their data by responsible and designated individuals in the Foundation trust and regulatory authorities, the Exeter CTU and other collaborators. Participants will also be asked for permission about being contacted about future research projects, where relevant. This trial does not involve collecting biological specimens for storage.

Confidentiality:

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification. Subjects will be assigned a trial identification number by the study site sequentially upon enrolment into the study. The study site will maintain a master Subject Identification Log.

Dissemination

The results of this trial will be reported and presented at national and international meetings. The outcomes will be published in high-quality, peer reviewed journals to make the results available to other physicians and scientists. Further long-term outcomes will be reported to potentially validate the longevity of the therapy.

Discussion

The results of this study will demonstrate if the application of 10Khz-SCS in patients with CNLBP is a suitable alternative to conventional medical therapy. Multiple large scale trials involving the use of SCS thus far have been industry sponsored without the use of a placebo group. Many studies have chosen not to use a placebo arm with a high probability of unblinding due to the nature of SCS. The methods used in this trial attempt to ensure unblinding does not take place. The sham lead positioned outside the epidural space ensures energy consumption without neurostimulation, requiring the patient to recharge the device. None of these patients will have had exposure to SCS prior to the trial so the experience of the therapy will be novel. As this is the first trial to apply these concepts the results will act as a pillar to future trials evaluating the efficacy of SCS in other pathologies.

Trial Status: The current protocol version is V1.2 dated 18/12/18. The start date of the study was on 14th of August 2018 and is currently recruiting patients. Recruitment is expected to be completed by the 1st December 2020. The estimated primary completion date is 1st July 2021.

Abbreviations

AL; Active lead, CE; Conformité Européene, CRF; Case Report Form, CNLBP; Chronic Neuropathic Low Back Pain, CONSORT; Consolidated Standards of Reporting Trials, CTU; Clinical Trials Unit, EU; European Union, DMC; Data Monitoring Committee, EQ-5D; European Quality of Life Score, FBSS; Failed Back Surgery Syndrome, IPG; Implantable Pulse Generator, LBP; Low Back Pain, MICD; Minimally Important Clinical Difference, MRC; Medical Research Council, MRI; Magnetic Resonance Imaging, NHS; National Health Service, NICE; National Institute of Clinical Excellence, ODI; Oswestry Disability Index, PPIE; Patient and Public Involvement and Engagement, PGIC; Patients Global Impression of Change, PHQ; Patient Health Questionnaire, PSQI; Pittsburgh Sleep Quality Index, QALY; Quality Adjusted Life Years, RDS; Research and Design Service, RCT; Randomised Controlled Trial, SAP; statistical analysis plan, SCS; spinal cord stimulation, SD; standard deviation, SL; Sham Lead, TMG; Trial Management Group, TSC; Trial Steering Committee, VAS; Visual Analogue Score

Declarations

Acknowledgements: Not applicable

Ethics approval and consent to participate:

Ethical approval was provided by London- Camberwell St Giles Research Ethics Committee, part of the NHS Health Research Authority. REC reference: 18/LO/1031, IRAS project ID: 232729. Informed consent

will be obtained prior to trial participation.

Consent for publication:

Not Applicable

Availability of data and material:

The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

Competing interests:

AK has received receipt of honoraria from Nevro and is a stock shareholder in Micron Devices. DP has received travel expenses from Medtronic and Nevro outside the submitted work. SP reports grants and non-financial support from Saluda Medical, personal fees and non-financial support from Nevro outside the submitted work. RT is a paid consultant for Medtronic and Nevro. RD has received consultancy fees from Medtronic and Boston Scientific. SE, AC, LM, JR, and SW have no conflict of interest.

Funding:

This study is funded by the Research for Patient Benefit programme of the National Institute of Health and Research (NIHR) in the UK, project number: PB-PG-0816-20036. The funder does not have a role in the trial design , data collection, analysis or interpretation.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a subject is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. Guy’s and St Thomas’ NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

Authors’ Contributions:

AK, SP, DP, SW, RST, AC, SE, LM, RD and JF all contributed to trial design and securing trial funding. AK, JR, SP, DP, SE are involved in recruitment, performing the intervention and follow up. SW will perform data collection and analysis. RST will be responsible for the statistical analysis and RD will be responsible for the health economic analysis. All authors contributed to preparation of this protocol manuscript and have read and approved.

References

1. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73(6):968-74.
2. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, et al. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). Pain. 2012;153(1):27-32.
3. Forster M, Mahn F, Gockel U, Brosz M, Freynhagen R, Tolle TR, et al. Axial low back pain: one painful area–many perceptions and mechanisms. PLoS One. 2013;8(7):e68273.
4. Mafi JN, McCarthy EP, Davis RB, Landon BE. Worsening trends in the management and treatment of back pain. JAMA Intern Med. 2013;173(17):1573-81.
5. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. BMC public health. 2013;13:1229.
6. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. Spine (Phila Pa 1976). 2013;38(1):75-82.
7. Schmidt CO, Schweikert B, Wenig CM, Schmidt U, Gockel U, Freynhagen R, et al. Modelling the prevalence and cost of back pain with neuropathic components in the general population. Eur J Pain. 2009;13(10):1030-5.
8. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. The Lancet. 2018;391(10137):2368-83.
9. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007;132(1-2):179-88.
10. Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation. 2014;17(6):515-50; discussion 50.
11. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain. 2010;26(6):463-9.
12. Deer T, Pope J, Hayek S, Narouze S, Patil P, Foreman R, et al. Neurostimulation for the treatment of axial back pain: a review of mechanisms, techniques, outcomes, and future advances. Neuromodulation. 2014;17 Suppl 2:52-68.
13. Tiede J, Brown L, Gekht G, Vallejo R, Yearwood T, Morgan D. Novel spinal cord stimulation parameters in patients with predominant back pain. Neuromodulation. 2013;16(4):370-5.
14. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation. 2013;16(1):59-65; discussion -6.

15. Ahmed S, Yearwood T, De Ridder D, Vanneste S. Burst and high frequency stimulation: underlying mechanism of action. Expert Rev Med Devices. 2018;15(1):61-70.
16. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med. 2014;15(3):347-54.
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S240-52.
18. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015;123(4):851-60.
19. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery. 2016;79(5):667-77.
20. Al-Kaisy A, Palmisani S, Smith TE, Pang D, Lam K, Burgoyne W, et al. 10 kHz High-Frequency Spinal Cord Stimulation for Chronic Axial Low Back Pain in Patients With No History of Spinal Surgery: A Preliminary, Prospective, Open Label and Proof-of-Concept Study. Neuromodulation. 2017;20(1):63-70.
21. Al-Kaisy A, Palmisani S, Smith TE, Carganillo R, Houghton R, Pang D, et al. Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36 Months. Pain Med. 2018;19(6):1219-26.
22. Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain. 2008;138(3):479-83.
23. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
24. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22(10):1911-20.
25. Weinand ME, Madhusudan H, Davis B, Melgar M. Acute vs. Prolonged Screening for Spinal Cord Stimulation in Chronic Pain. Neuromodulation. 2003;6(1):15-9.
26. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. Pain Medicine. 2015;17(2):325-36.
27. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
28. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ.

2010;340:c869.

Figures

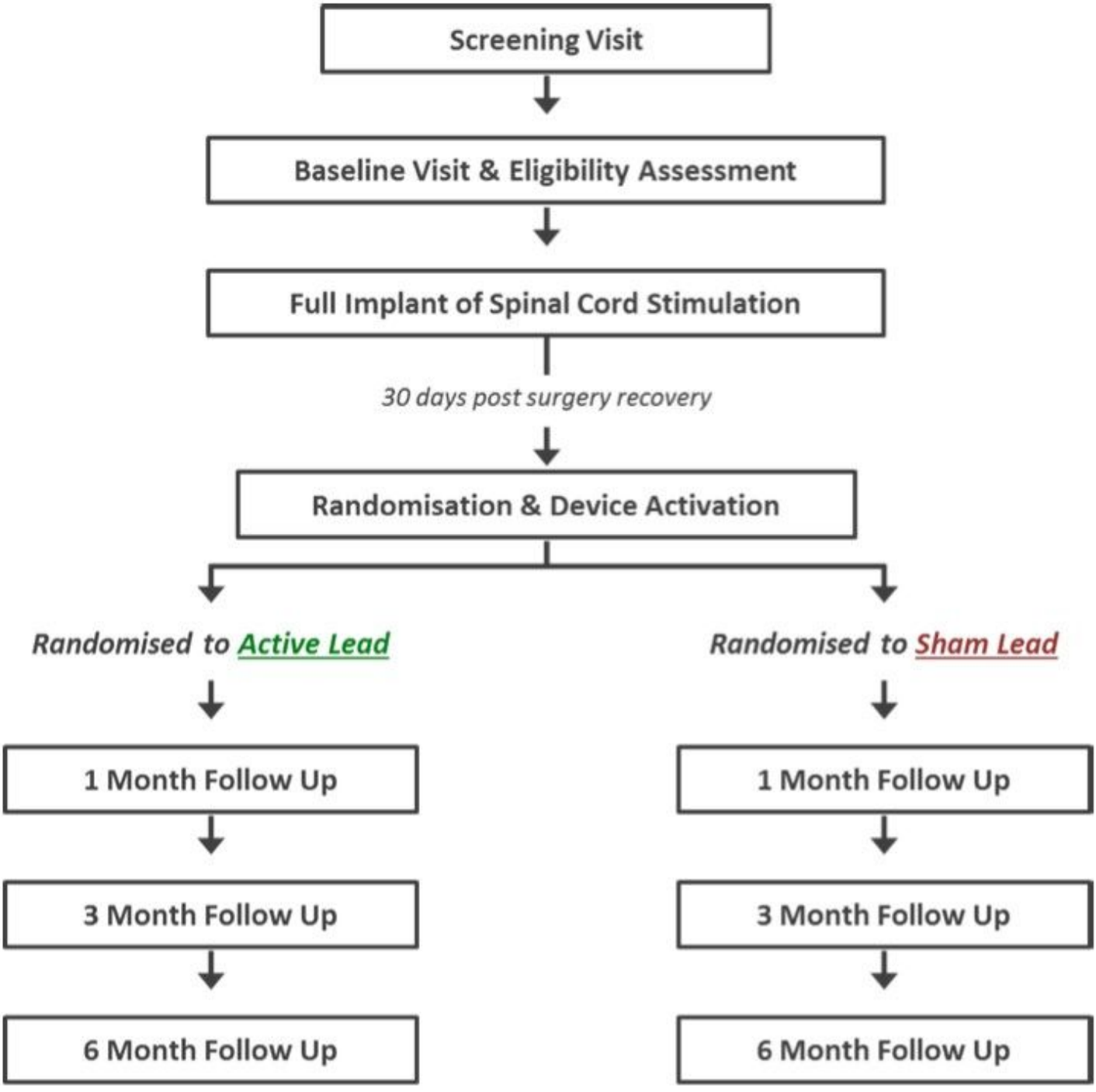

Figure 1

Consort Diagram of MODULATE-LBP trial

		Screening	Baseline	Implant	Device Activation	Month 1	Month 3	Month 6	Discontinuation	Unscheduled Visit
	Window	*Day -90*	*Day -83 to Day -60*	*Day -60 to Day -30*	*Day 0*	*Day 30 (±7d)*	*Day 90 (±14d)*	*Day 180 (±14d)*	-	-
	Informed Consent	x								
	Eligibility Assessment	x								
	Demographics	x								
	Medical History	x								
Patient Questionnaires	Pain Map	x				x	x	x		
	Pain VAS	x				x	x	x		
	PainDETECT Questionnaire	x								
	PHQ-9 Questionnaire		x			x	x	x		
	PSQI Questionnaire		x			x	x	x		
	Oswestry Disability Index (v2.1a)		x			x	x	x		
	EQ-5D Questionnaire		x			x	x	x		
	Work status, work absence & out of pocket expenses		x				x	x		
	Healthcare Utilisation						x	x		
	Patients Global Impression of Change					x	x	x	x	
	7 Day Subject VAS Pain Diary	dispense	collect[1] dispense		dispense	collect dispense	collect dispense	collect dispense	collect	
	Subject satisfaction and recommendation to others					x	x	x	x	
	Sensation Map		x			x	x	x		x
	Treatment Allocation Questionnaire							x		
Investigations	MRI, lumbar	x[2]								
	X-ray, lumbar[4]	x[2]		x[6]	x	x[5]	x[5]	x	x[5]	
	Urine Pregnancy test	X								
	Fluoroscopy			x						
	Subject videotaping[3]	[x]	[x]					[x]		
	Device Programming				x			[x]	[x]	[x]
	Download Device Data				x	x	x	x	x	x
	Pain medication usage	x	x	x	x	x	x	x	x	x
	Adverse event monitoring	x	x	x	x	x	x	x	x	x

Figure 2

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram

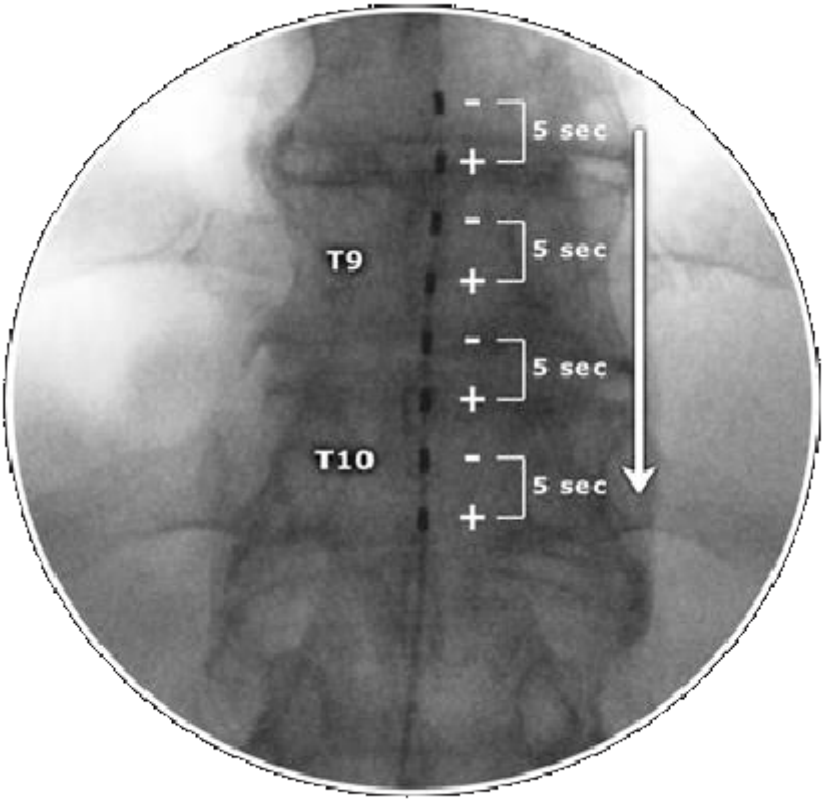

Figure 3

Anterior-Posterior X-ray position of desired lead location and diagrammatic illustration of “cascade”

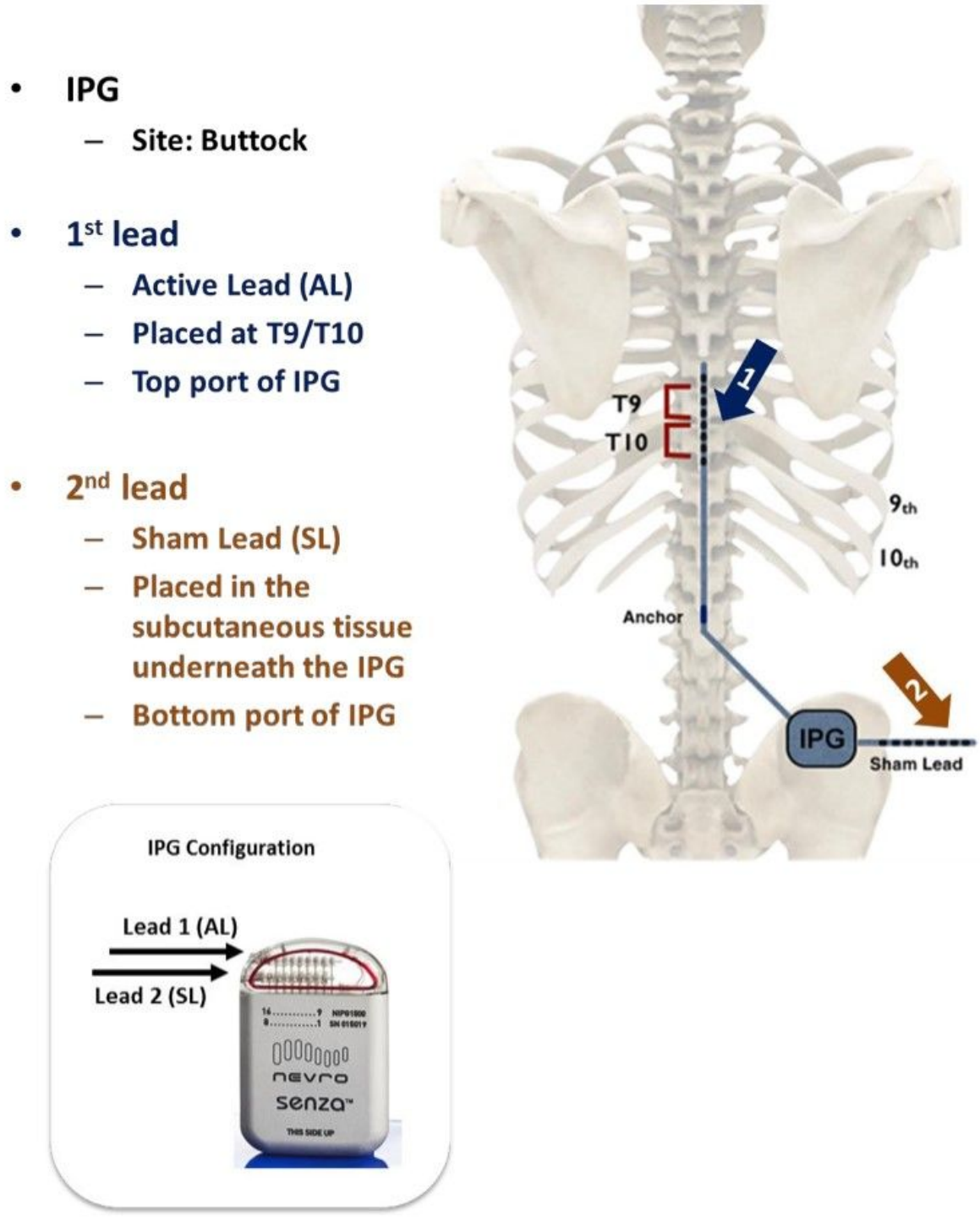

Figure 4

Position of Epidural lead (1), Sham lead (2) and Implantable Pulse Generator

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITFillablechecklistModulateTrials.pdf