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16 # Original protocol

17 **(from February 13th 2018)**

Spinal cord burst stimulation in patients with failed back surgery syndrome: A randomized double-blind sham-controlled crossover trial

Sasha Gulati MD PhD (1,2), Sozaburo Hara MD (1), Sven M. Carlsen MD PhD (3,4), Ole Solheim MD PhD (1,2), Jan V. Jørgensen MD (1), Kristin Taraldsen PhD (2), Tomm B. Müller MD PhD (1), Øystein P. Nygaard MD PhD (1,2), Mattis A. Madsbu MS (1,2), Astrid Brautaset MD (5), Erling A. Tronvik MD PhD (2,6), Eirik Amundal MD (5,6), Agnete M. Gulati MD (2,8), Asgeir S. Jakola MD PhD (9), Tore K. Solberg MD PhD (10), Petter Borchgrevink MD PhD (5), and Øyvind Salvesen MSc PhD (11)

1. Department of Neurosurgery, St. Olavs University Hospital 2. Department of Neuromedicine and Movement Science, NTNU 3. Department of Endocrinology, St. Olavs University Hospital 4. Department of Clinical and Molecular Medicine, NTNU 5. Norwegian Advisory Unit on Complex Symptom Disorders, St. Olavs University Hospital 6. Department of Neurology, St. Olavs University Hospital 7. Department of Anesthesia, St. Olavs University Hospital 8. Department of Rheumatology, St. Olavs University Hospital 9. Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden 10. Departement of Neurosurgery and Norwegian Spine Registry, University of Hospital of North Norway 11. Department of Public Health and Nursing, NTNU

1. Relevance relative to the call for proposals

Funding is sought for one ph.d. student for a period of 3 years within the framework of the project. The study is in compliance with the strategic documents of *the Central Norway Regional Health Authority*, *St. Olavs Hospital* and *the Department of Neuromedicine and Movment Science (INB)*, NTNU. This trial focuses on patient-related clinical research, medical technology, patient safety and cost-effectiveness. Management of chronic back pain seems to interest not only medical researchers and decision makers but also the general public and receives constant media attention. The trial is highly relevant to society and may benefit large groups of patients on both a national and international level. Funding of a ph.d. student is important to maintain our status as a leading international research group on degenerative spinal disorders.

2. Background and status of knowledge

The Global Burden of Disease study tracks the prevalence of deaths and diseases worldwide and uses a metric called "Disability Adjusted Life Years" (DALYs).[1] DALYs combine the number of years of life a person loses if they die prematurely with the amount of time they spend living with a disability. Think of it as time patients did not spend living their #bestlife – because of illness or death. In developed countries, the number one cause of these DALYs is not surprising: ischemic heart disease. However, the number two condition is perhaps a bit surprising: plain, old-fashioned, ever-present, back pain. In fact, low back pain is the leading cause of activity limitation and work absence throughout much of the world, and it is an enormous economic burden on the whole society ranging from individuals, families, communities, industry and all the way to governments.[2] Back pain affects people of all ages[3,4] and although the natural course often is favorable, more than 5,000 patients undergo spine surgery annually in Norway alone. The most common reasons for low back surgery are persisting or intolerable pain due to sciatica and narrowing of the spinal canal (i.e. spinal stenosis).[5,6] Unfortunately, 10-40% of patients who undergo spine surgery experience persisting or worsening of pain and disability.[7] Spinal cord stimulation (SCS) is a commonly established therapy to treat chronic neuropathic pain of various etiologies (Figure 1). One of the most common indications for SCS is failed back surgery syndrome (FBSS), a persistent or recurrent complex chronic pain syndrome with mixed neuropathic/radicular and nociceptive (e.g., mechanical, inflammatory) elements following spine surgery.[8] In traditional SCS therapies, the objective has been to replace the pain sensation with paresthesia that requires mapping of stimulation to the region of pain. The anticipation is that the electrical current alters pain processing by masking the sensation of pain with a comfortable tingling or paresthesia. Although patients mostly cope with paresthesia, a significant proportion reports that the sensation is unpleasant, particularly with positional changes. The stimulation is provided either through electrodes that are placed through a small skin incision into the epidural space or through a surgical paddle lead that is delivered via a laminotomy or laminectomy. Patients typically undergo a testing period of neuromodulation with an externalized power source and if this test proves to be positive and compelling, they subsequently have a subcutaneously implantable pulse generator ("pacemaker") for long-term therapy.

The field of neuromodulation for the treatment of pain has developed rapidly since the seminal paper on the electrical inhibition of pain by stimulation of the dorsal column more than 50 years ago.[9] As is often the case in surgery, the widespread use of SCS has not been backed by solid evidence. The existing SCS literature is dominated a large number of case series reports and only a limited number of high quality, industry-independent, large prospective, consecutively recruited, randomized, or controlled comparative trials.[10-16] The absence of placebo-controlled trials has long been an important point of criticism of the stimulation literature. Due to the to the nature of the interventions with the sensation of paresthesia, studies with placebo control have not been considered possible. However, recent advances in SCS allow paresthesia-free stimulation.[17] Burst stimulation, utilizes complex programming to deliver high-frequency stimuli of a 40 Hz burst mode with 5 spikes at 500 Hz per spike delivered in a constant current mode. Using this methodology, it has been suggested that burst SCS may provide paresthesia-free stimulation resulting in better pain relief of low back and leg pain when compared to traditional tonic stimulation.[18] Moreover, this programming mode also allows comparison with placebo stimulation since the stimulation is often undetected by the patient. In the literature, SCS is reported as a safe procedure due to its reversible and minimally invasive characteristics.[19] Although catastrophic complications are possible (i.e. neurological injury, epidural hematoma), they are extremely rare. However, the incidence of minor complications of SCS (i.e. lead fracture, lead migration, infection, discomfort at implant site, implantable pulse generator seroma, dural puncture) is reported at around 30%-40%. These minor complications tend to occur within 12 months of implantation and are readily reversible and generally resolved. Although SCS is an established treatment, questions concerning treatment effects and cost-effectiveness remain unanswered, especially for burst SCS.

The aim of this randomized double-blind sham-controlled crossover trial is to evaluate the efficacy of burst SCS in patients with FBSS.

3. Topics and objectives

3.1 Primary outcome measure

The primary outcome is difference in change from baseline on the Oswestry disability index (ODI), version 2.0, between active burst stimulation and placebo stimulation periods.[20,21] The ODI questionnaire quantifies disability for degenerative conditions of the lumbar spine and covers intensity of pain, ability to lift, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. For each topic there are six statements describing potential scenarios, and patients select the one that most closely resembles their situation. The index is scored from 0 to 100. Zero means no disability and 100 reflects maximum disability.

3.2 Secondary outcome measures

- Changes in generic health-related quality of life measured with the Euro-Qol-5D
- Back pain and leg pain measured using numerical rating scales (NRS)
- Brief Pain Inventory (Short form)
- Level of physical activity
- Cost-effectiveness
- Use of analgesics

Figure 1. The concept of burst spinal cord stimulation

1. Pain signals travel up the spinal cord to the brain.
2. A generator, similar to a cardiac pacemaker, sends pulses to a thin wire called a lead.
3. The lead delivers these pulses to nerves along the spinal cord.
4. The pulses modify the pain signals as they travel to different parts of the brain.
5. The pulses can change the perception of pain - providing potential relief from physical pain as well as the suffering associated with pain.

4. Methods and materials

4.1 Study population, ethics, trial registration and user involvement

The study will be conducted at St. Olavs University Hospital. SCS procedures have been performed at the Department of Neurosurgery for thirty years, and 30-40 patients undergo the procedure annually. The Norwegian Back Pain Association (*Ryggforeningen*) will be provided the opportunity to review the study protocol and give feedback concerning study design and outcome measures. An application for ethical approval will be submitted to The Regional Committee for Medical Research in Central-Norway. The study will be registered in Clinicaltrials.gov.

4.1 Inclusion criteria

1. Patients ≥18 years who have undergone ≥1 back surgeries and later developed FBSS, defined as chronic, intractable pain of the trunk and/or limbs that has remained refractory to non-surgical treatment for ≥6 months.
2. Minimum pain intensity of 5/10 on the NRS at baseline.
3. Successful two-week SCS testing period with tonic stimulation (≥30% reduction in NRS from baseline). This means patients will experience paresthesia during the SCS trial period.
4. Mandatory assessment at the Norwegian Advisory Unit on Complex Symptom Disorders, St. Olavs University Hospital.

4.2 Exclusion criteria

1. Coexisting conditions that would increase procedural risk (e.g., sepsis, coagulopathy).
2. History of laminectomy or posterior fusion at the thoracolumbar junction, where percutaneous electrode end tips are routinely placed.
3. Abnormal pain behavior and/or unresolved psychiatric illness.
4. Unresolved issues of secondary gain or inappropriate medication use.

4.3 Follow-up during the study

During the 12 months following implantation the patients will undergo four three-month long periods with either burst SCS or no stimulation (sham) in a randomized order. All patients will undergo two periods of SCS and sham stimulation. The outcome measures will be collected prior to the test period and at the end of each of the four treatment periods.

4.4 “Pentablinding” of the study

The patients will be blinded to the actual treatment allocation during the different study periods (first blinding). The surgeons and all study personnel involved in handling the patients and collecting the study data (except those who perform the actual setting of the device) will be blinded to the actual treatment allocation (second blinding). All study personnel evaluation end points measures will be blinded to the actual treatment (third blinding). All the tables and figures to be presented from the study will be settled before any data from the study is evaluated in order to avoid selective presentation of findings according to

statistical results (fourth blinding). The statistician performing the statistical procedures on the outcome of the study will be blinded. The data will only show treatment allocation as treatment A and treatment B. Then the tables and figures are filled in (fifth blinding). In order to minimize the possibility of incidental unblinding the main outcome measure will be evaluated first, the secondary endpoints and lastly adverse effects. All statistical analyses will be predefined before commencement of the study. Only after all this has been performed and the procedures documented at the Unit for Applied Clinical Research (NTNU), the codes will be broken. The only remaining procedure will then be to substitute treatment A and B in the tables and figures with active and placebo. This ambitious procedure will secure maximum possible blinding of the study, integrity of the study and make the study results trustworthy.

4.5 Sample size calculation

For the sample size calculation, the outcome variable is defined as the difference between each participant's mean ODI scores under "treatment A" and "treatment B". Assuming that the population mean and the standard deviation for the differences are 10 and 18, respectively, a one sample t-test of the differences at the 5% significance level needs 34 study participants to achieve 90% power.

5. Description of the research group

This study unites several groups at INB (NTNU) and St. Olavs Hospital, as well as both national and international collaborators. Most of the researchers involved have extensive research experience, longstanding collaborations, and have published in top tier journals together. The project leader, professor Gulati, has already supervised several master and ph.d. students. There is a need for a ph.d. student and this student will join an established and productive research group with a friendly and constructive working environment.

6. Activity plan, publishing and plan for implementation

The study will commence when funding and ethical approval has been obtained, hopefully in September 2018. Data collection should be completed by March 2021, and data analyses, interpretation of results and writing of the manuscript will be completed by March 2022. This study will give rise to at least one scholarly publication that will be published in a high-ranking international peer-reviewed journal. Results will also be presented at both national and international scientific meetings and conferences. Further, we will focus on popular science dissemination through local and national media channels and social media channels.

7. Budget

Funding is sought for one ph.d. student. Payroll expenses for other members of the group are covered by their current employers. The Department of Neurosurgery will cover all expenses for inpatient treatment and SCS implant costs. Funding will later be sought for one research nurse.

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Summary of changes to the protocol

1. In the original inclusion criteria (Section 4.1 in the protocol) we stated that all study participants had to undergo a mandatory assessment at the Norwegian Advisory Unit on Complex Symptom Disorders, St. Olavs University Hospital. Due to logistical issues this was changed to a mandatory assessment at the Multidisciplinary outpatient clinic for back, neck, and shoulder rehabilitation, St. Olavs University Hospital. This change was also made to the registration in Clinicaltrials.gov. Brief Pain Inventory and use of analgesics were specified as secondary outcomes in the protocol, but were omitted before trial registration and commencement. The reason for omitting the Brief Pain Inventory was that pain is extensively covered by the other self-reported outcomes. The reason for omitting use of analgesics was that we did not want to overburden study participants with data registration, several analgesics (ie., acetaminophen, ibuprofen) are available over-the-counter without a prescription, and inappropriate medication use was an exclusion criterion.

Original statistical analysis plan

1. Statistical Analysis Plan

The Statistical Analysis Plan of May 10th 2022 has not been changed and is final:

Administrative information:

Sponsor name	St. Olavs Hospital
Sponsor address	Nevroklinikken, 7006 Trondheim, Norway
REC no.	2018/475
Trial title	Spinal cord burst stimulation for chronic radicular neuropathic pain following lumbar spine surgery: A randomized double-blind sham- controlled crossover trial
Trial registration number	NCT03546738

SAP and protocol version

SAP version and date	This SAP is version 1, dated May 10th 2022
Protocol version	This document was written based on information contained in the study protocol version 1.0, dated January 18th 2018

SAP revision history

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
1.0	1.0	NA	First edition of SAP	May 10th 2022

2. Signature page

Principal/coordinating investigator:

Consultant neurosurgeon Sozaburo Hara, MD
Department of Neurosurgery
St. Olavs Hospital
7006 Trondheim, Norway

Signature — 10.05.2022 Date (dd/mm/yyyy)

Trial statistician:

Associate professor Øyvind O. Salvesen, MSc PhD
Norwegian University of Science and Technology
7006 Trondheim, Norway

Signature — 10.05.2022 Date (dd/mm/yyyy)

Main supervisor:

Consultant neurosurgeon and professor Sasha Gulati, MD PhD
Department of Neurosurgery
St. Olavs Hospital
7006 Trondheim, Norway

Signature — 10.05.2022 Date (dd/mm/yyyy)

275 3. Abbreviations

SCS	Spinal cord stimulation
ODI	Oswestry disability index
NRS	Numerical rating scale
EQ-5D	EuroQol 5D
PROMs	Patient reported outcome measures
FAS	Full analysis set
PPS	Per protocol set
CCS	Complete case set

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4. Introduction

4.1 Background and rationale

Spinal cord stimulation (SCS) is a widely applied therapy to treat chronic neuropathic pain, and one of the most common indications is persisting radicular neuropathic pain following lumbar spine surgery. In traditional SCS therapies, the objective has been to replace the pain sensation with paresthesia. The anticipation is that the electrical current alters pain processing by masking the sensation of pain with a comfortable tingling or paresthesia. Although patients mostly cope with paresthesia, a significant proportion reports that the sensation is unpleasant.

'Burst' SCS utilizes complex programming to deliver high-frequency stimuli. This SCS technique seems to provide paresthesia-free stimulation, resulting in better pain relief of low back and leg pain then traditional tonic stimulation.

The widespread use of SCS has not been backed by solid evidence. The absence of placebo-controlled trials has long been an important point of criticism, but due to the nature of the intervention with sensation of paresthesia, studies with placebo control have so far not been considered possible. When 'burst' SCS is used the stimulation is often unnoticed by the patient, allowing comparison with placebo stimulation.

The aim of this randomized double-blind sham-controlled crossover trial is to evaluate the efficacy of 'burst' spinal cord stimulation for chronic radicular pain following spine surgery.

4.2 Trial objectives

4.2.1 Primary objective

The primary aim is to evaluate the efficacy of burst spinal cord stimulation versus sham/placebo for chronic radicular pain following spine surgery measured by the Oswestry disability index (ODI).

4.2.2 Secondary objectives

The secondary objectives are to assess if there are any differences between active burst stimulation and sham/placebo with regards to:

Changes in health-related quality of life measured with the Euro-Qol-5D (EQ-5D)

Back pain and leg pain measured using numerical rating scales (NRS)

Daily physical activity measured by use of a body-worn accelerometer (activPALs from PAL Technologies Ltd., Glasgow, United Kingdom) attached by a waterproof tape to the midpoint of the patients' anterior right thigh

If the mean difference in ODI change between active stimulation and placebo exceeds the predefined minimal clinically important difference of 10 points, a cost-effectiveness analysis will be performed (health care providers' cost per gained quality-adjusted life year)

Secondary objectives also include complications and surgical revisions of the implanted SCS systems. At the end of each treatment period study participants were asked whether they believe they received active burst stimulation or not.

5. Trial methods

5.1 Trial design

This is a single center randomized controlled crossover study performed at St. Olavs Hospital, Trondheim, Norway. Both specialist health care services and general practitioners in Norway can refer patients for assessment of study eligibility. Initial assessment of study eligibility was performed at the Multidisciplinary outpatient clinic for back, neck and shoulder rehabilitation, St. Olavs Hospital. The surgical procedures and postoperative follow-up will be performed at the Department of Neurosurgery, St. Olavs Hospital.

5.2 Randomization

During the 12 months following spinal cord stimulator implantation the study participants will undergo four three-month long periods with either burst SCS or no stimulation (sham) in a randomized order. All patients had two periods of SCS and two with sham stimulation. The outcome measures were collected prior to the test period and at the end of each of the four treatment periods.

5.3 Sample size

For the sample size calculation, the outcome variable was defined as the difference between each participant's mean ODI scores under "treatment A" and "treatment B". Assuming that the population mean and the standard deviation for the differences are 10 and 18, respectively, a one sample t-test of the differences at the 5% significance level needs 34 study participants to achieve 90% power. Due to expected loss to follow-up of 10-20% and breakthrough of paresthesia during burst stimulation in 20-30% of patients we aimed at including a total of 50 study participants.

5.4 Statistical framework

5.4.1 Hypothesis test

First, a test of overall effect of treatment measured by ODI is performed. The null hypothesis is that there is no difference in mean change of ODI from baseline to the end of each intervention period between the active burst stimulation periods and the placebo periods. The alternative hypothesis is that there is a difference between active burst stimulation and sham/placebo. The test will be performed at the two-sided 5% significance level. A difference in the effect of the treatment arms will be claimed if the null hypothesis is rejected. That is, the two-sided p-value is less than 5%. Superiority of active burst stimulation will be claimed if the two-sided p-value in the test comparing the change from baseline is less than 5%, and if the effect goes in favor of active stimulation.

5.4.2 Statistical interim analyses and stopping guidance

There were no interim analyses in this trial.

5.4.3 Timing of final analysis

The main analysis is planned when all study participants have concluded a minimum of 360 days of follow-up following implantation of the complete SCS system, all data up to one year has been entered, verified and validated, and the primary database has been locked.

5.4.4 Timing of outcome assessments

For all clinically planned measures, visits should occur within a time window of the scheduled visit. Visits outside these predefined time windows are regarded as protocol deviations. The target day and time windows are defined as:

Visit label	**Target day**	**Definition (Day window)**
Clinical assessment at the multidisciplinary outpatient clinic, initial evaluation of study eligibility, informed consent	-60	Prior to Day 0
Collection of patient reported outcome measures (PROMs) and activePAL registration*	-40	Prior to Day 0

Trial stimulation Registration of leg and back pain NRS.	-14	Prior to Day 0
Evaluation of trial stimulation and final evaluation of study eligibility. Registration of leg and back pain NRS.	Day 0 Eligible for study participation: implantation of complete SCS system.	Target day +/- 7 days
1st randomization	Day 1	Target day +/-2 days
Collection of PROMs, 2nd randomization	Day 90 from implantation	Target day +/- 15 days
activePAL registration*	Day 90-180	> 7 days prior to Day 180
Collection of PROMs, 3rd randomization	Day 180 from implantation	Target day +/- 15 days
activePAL registration*	Day 180-270	> 7 days prior to Day 270
Collection of PROMs, 4th randomization	Day 270 from implantation	Target day +/- 15 days
activePAL registration*	Day 270-360	> 7 days prior to Day 360
Collection of PROMs, final study visit	Day 360 from implantation	Target day +/- 15 days

*Three activePAL registrations are planned: 1) prior to the trial stimulation 2) once during sham/placebo, and 3) once during active burst stimulation

5.5 Blinding procedure

Quadruple blinding:
Participant
Care Provider
Investigator
Outcomes Assessor

The patients were blinded to the actual treatment allocation during the different study periods. The surgeons and all study personnel involved in handling the patients and collecting the study data (except those who perform the actual setting of the device) were blinded to the actual treatment allocation. All study personnel evaluation end points measures will be blinded to the actual treatment. All the tables and figures to be presented from the study will be settled before any data from the study is evaluated to avoid selective presentation of findings according to statistical results. The statistician performing the statistical procedures on the outcome of the study will be blinded. The data will only show treatment allocation as treatment A and treatment B. Then the tables and figures are filled in. To minimize the possibility of incidental unblinding the main outcome measure will be evaluated first, then the secondary endpoints, and lastly adverse effects. Only after all this has been performed and the procedures documented at the Unit for Applied Clinical Research (NTNU), the codes will be broken. The only remaining procedure will then be to substitute treatment A and B in the tables and figures with active and placebo. This ambitious procedure will secure maximum possible blinding of the study, integrity of the study and make the study results trustworthy.

6. Statistical principles

6.1 Confidence intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the null hypothesis will be discarded. Efficacy estimates for the two arms will be presented with two-sided 95% confidence intervals.

6.2 Adherence and protocol deviations

The number and proportion of patients that received the intervention they were randomized to will be presented

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:
Entering the trial when the eligibility criteria should have prevented trial entry
Outside the age criteria
Misdiagnosed
Insufficient leg pain NRS reduction following trial stimulation
Received other intervention than allocated to

The number (and percentage) of patients with major protocol deviations and detail of type of deviation will be provided. All randomized interventions will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

6.3 Analysis populations

We define the following populations in this trial:
All randomized patients: All patients that have been randomized regardless if they actually received treatment or not.
Full analysis set (FAS): All patients that are randomized, received treatment, and where ODI was measured at least once post baseline/following implantation of the complete SCS system. Patients are allocated to the treatment period they were randomized to.
Complete case set (CCS): The subset of patients in the FAS that has ODI measurements at all follow-up visits. Patients are allocated to the treatment period they were randomized to.

The FAS will be used for the primary analysis, while he CCS will be used for sensitivity analyses.

7. Trial population

7.1 Screening data, eligibility, and recruitment

The total number of screened patients and reasons for not entering the trial will be summarized and tabulated. A CONSORT flow diagram will be used to summarize the number of patients who were:
Assessed for eligibility
Eligible at initial evaluation
Eligible at initial evaluation and underwent trial stimulation
Eligible following trial stimulation
Eligible following trial stimulation but not randomized*
Received the randomized allocation
Did not receive the randomized allocation*
Lost to follow-up
Randomized and included in the primary analysis
Randomized and excluded from the primary analysis*

*Reasons will be provided

7.2 Withdrawal/Follow-up
The status of eligible and randomized patients at trial end will be tabulated by treatment group according to whether they
Completed intervention, but not assessments
Completed assessments, but not intervention
Withdrew consent
Did not complete follow-up
Unable to measure the primary endpoint due to:
Comorbidty that compromised treatment or testing
Death during follow-up

Time from randomization to treatment discontinuation and time from randomization to withdrawal/lost to follow-up will be presented graphically using a CONSORT flow diagram.

7.3 Baseline patient characteristics
The patient demographics and baseline characteristics include age, gender, body-mass index, educational level, comorbidity, American Society of Anesthesiologists physical status grade, smoking status, number of previous spine surgeries, baseline activity level, and baseline PROMs. The patient demographics and baseline characteristics will be summarized and presented using descriptive statistics (N, mean, standard deviation, median) for continuous variables, and number and percentages of patients for categorical variables. As this is a crossover trial, important clinical imbalances between treatment arms are unlikely.

8. Analysis

8.1 Analysis of the primary efficacy endpoint
8.1.2 Oswestry disability index (ODI)
The primary outcome is difference in mean change from baseline in disease specific functional outcome (ODI version 2.0) between active burst stimulation and placebo/sham.(1)

ODI has been translated into Norwegian and tested for psychometric properties.(2) The ODI questionnaire is used to quantify disability for degenerative conditions of the lumbar spine and covers intensity of pain, ability to lift, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. For each topic there are six statements describing potential scenarios, and patients select the one that most closely resembles their situation. The index is scored from 0 to 100. Zero means no disability and 100 reflects maximum disability.

8.1.2 Statistical methods
Mean +/- SD or summary statistics appropriate for the distribution will be reported for the primary outcome and each of the key secondary outcomes. The two interventions will be compared using a linear mixed model adjusting for random effects. The model will account for correlated data within the same subject. A 95% confidence interval will be reported for the difference between the interventions based on the linear mixed model. For the primary endpoint and other key endpoints listed in section 4, the type I error rate will be controlled at two-sided alpha = 0.05.

8.1.3 Missing data
Missing data will not be imputed for the primary analysis in this study. All statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our

goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

8.2 Analysis of the secondary endpoints

Regardless of the results of the primary outcome, summary statistics will be tabulated by treatment arm for EQ-5D, leg pain 0-10 NRS, back pain 0-10 NRS, and physical activity level (steps per day and time spent standing and walking). The two interventions will be compared using a linear mixed model adjusting for random effects. The Norwegian version of EQ-5D has shown good psychometric properties.(3) If the mean difference in ODI change between active stimulation and placebo exceeds the predefined minimal clinically important difference, a cost-effectiveness analysis will be performed (health care providers' cost per gained quality-adjusted life year)

8.2.1 Missing data

For the secondary outcomes, missing data will not be imputed in this study.

8.3 Subgroup analyses

No subgroup analyses are planned for this study.

9. Safety Analyses

9.1 Adverse Events

Complications, adverse events, and surgical revisions of the implanted SCS system are continuously registered and will presented. This includes but is not limited to thromboembolic events, wound healing problems, infections, postoperative hematoma, cerebrospinal fluid leak/unintentional durotomy, and nerve-damage.

9.2 Clinical Laboratory Parameters

Not applicable.

9.3 Vital Signs

Not applicable.

10. Statistical Software

All statistical analyses will be done using SPSS version 27 (IBM corp., Chicago, IL) and R version 3.6.3 (R Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

11. References

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