CLINICAL RESEARCH PLAN INVOLVING A MEDICAL DEVICE

"MEDULLARY STIMULATION"

TITLE: "Randomized, single-blind, multicenter, crossover, controlled clinical trial to compare the difference in visual analog scale in two modes of spinal cord stimulation in patients with postlaminectomy syndrome in test phase"

CODE: EST-MED-2018-01

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PROMOTOR: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)

NATIONAL COORDINATOR: Dr. Francisco José Sánchez Montero

A.1 GENERAL

TITLE

"Randomized, single-blind, multicenter, crossover, controlled clinical trial to compare the difference in visual analog scale in two modes of spinal cord stimulation in patients with postlaminectomy syndrome in test phase"

CODE

EST-MED-2018-01

PROMOTOR

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RESEARCH MEDICAL DEVICE

The neurostimulation system device Medtronic® consisting of electrodes Vectris SureScan MRI 1x8 Subcompact Model 977A 260/75/90 and a rechargeable neurostimulator compatible with magnetic resonance imaging.
The EVOLVE programming guide is enclosed with the device, which is a 1 KHz frequency programming protocol adapted to the Medtronic®: SureScanTM neurostimulation system.

Clasification

Randomized, open-label, crossover, multicenter phase IV clinical trial with medical device.

Ethics comitee

CEIM Hospital Universitario de Salamanca
CEIM Hospital San Pedro de Logroño.

Main objective

To compare the values of the visual analog scale (VAS) in patients with postlaminectomy syndrome with leg pain or leg and lumbar pain, applied at baseline and at the end of the test phase, using a single neurostimulator per patient, under conventional spinal cord stimulation (CMS) or under stimulation with the EVOLVE protocol (EME).

Design

Prospective clinical investigation in phase IV, randomized, comparative with control group, crossover and single-blind.

Disease or disorder under study

Postlaminectomy syndrome in patients undergoing spinal surgery.

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A.1 GENERAL

A.1.1 Introduction

It is estimated that one in five Europeans (19%) suffers from chronic pain. In Spain, recent data estimate that the prevalence is slightly lower than the European average (17%). 1 Chronic pain, in addition to considerably affecting the patient's work, social and family environment, represents a considerable economic burden for the healthcare system. 2 According to a European survey, half of chronic pain patients feel tired all the time and 40% feel helpless or unable to think or function normally. 3 Although the cost of chronic pain is difficult to calculate, as global data is not available, it is believed to cost more than 300 billion euros in Europe4 or around 1.53% of GDP. In Spain, it is estimated that the total cost (direct and indirect) of chronic pain is 16,000 million euros per year, which represents 2.5% of GDP. Thus, in Spain, neuropathic pain alone costs 5,064 euros per year/per patient. 5 These figures should, in any case, be viewed with caution, since there are no global studies in our country to support them either.

.- Lumbar pain

Chronic low back pain represents one of the most common causes of disability, being very prevalent and generating enormous direct and indirect socioeconomic costs, as well as a great demand for consultations in primary and specialized care [6]. It is also the main problem associated with a poor perceived quality of life in people with chronic pain.
[7]. Chronic low back pain has become one of the most expensive medical conditions to treat, with an adult incidence of 37% and a lifetime incidence of 60-85%, which generates very high costs [8,9]. The prevalence of low back pain in Spain is around 20%,
[10] and the general trend does not appear to be downward, with an increase in recent years [11].

.- Postlaminectomy syndrome or FBSS

A particularly relevant pain condition is post-laminectomy syndrome, which affects some patients after laminectomy back surgery. It occurs when the posterior laminectomy has failed to relieve the patient's back pain, resulting in associated disability. The portion of the vertebra that connects the main body of the bone to the spinous process is the lamina. Well, a laminectomy is the removal of the lamina or associated bone spurs, relieving the accumulated pressure on the spinal nerves in various back conditions. This pain, the most prominent symptom of the syndrome, persists in the back and/or legs despite surgery. However, this term is also referred to as failed back surgery syndrome or "failed back surgery syndrome" (FBSS), since in spine surgery there are anterior approaches that do not require laminectomy. This pain, which is referred to the lumbar area or the lower back or leg, appears after surgery without complications (compression, infection, etc.). The International Association for the Study of Pain defines FBSS as lumbar spinal pain of unknown origin persisting despite a surgical intervention or appearing after an intervention to treat spinal pain located in the same topographic area [12]. Although the terms postlaminectomy syndrome and FBSS are used interchangeably, they are not really synonymous. Even more recently, new terminology has been proposed, such as persistent postoperative syndrome (PPS).
[13] or lumbar postoperative syndrome, [14,15] not to imply that the pain is exclusively or necessarily due to surgical failure. The incidence of FBSS after back surgery is 10%-40%

[16]. In fact, the term FBSS encompasses several pathological conditions with common diagnoses such as foraminal stenosis, painful disc, pseudarthrosis, neuropathic pain, recurrent disc herniation, facet joint pain and sacroiliac joint pain [17]. The most important conditions are traditional postlaminectomy syndrome (as defined above) and lumbar canal stenosis.

Basically, two types of pain can be distinguished in postlaminectomy syndrome. One is lumbar, generally of somatic and mechanical characteristics, and the other is neuropathic, located in the lower extremities. Low back pain can also sometimes have neuropathic aspects, since the way in which most spinal surgery is currently performed causes important denervations of the paravertebral musculature of the operated area. Low back pain is therefore fundamentally musculoskeletal, with a pattern of irradiation that is generally not metameric, and may increase at night. It is mechanical, worsening with flexions, extensions and rotations of the spine. Neuropathic pain predominates in the lower extremities and frequently presents insidiously, with a metameric pattern of irradiation. Patients with neuropathic pain usually report allodynic sensations (non-nociceptive stimulus) in the extremity, and a decrease in temperature in the extremity, both subjectively and objectively, is frequently observed. In these neuropathic conditions there are paroxysms of pain and, on occasions, trophic and vasomotor changes may appear in the affected extremity [18].

The clinical history and the general characteristics of the pain will therefore define whether we are dealing with somatic pain due to excess nociception, neuropathic pain with a predominantly distal predominance, or if the picture is mixed. We can also evaluate the possible influence of the sympathetic nervous system in these pain syndromes according to the degree of vasomotor and thermoregulatory alterations in the lower extremities.

Post-laminectomy syndrome is not a diagnosis and the cause is unknown. One of the primary theories blames scar tissue developed in the epidural space of the spine after surgery as the cause of the pain, as it generates epidural fibrosis. Some of the other possible causes of post-laminectomy syndrome include: recurrence of disc herniation, disc degeneration, incomplete removal of the lamina, adhesive arachnoiditis, residual lateral foraminal restenosis, and problems beyond the strictly surgical (psychosocial and occupational) [19].

.- Treatment of postlaminectomy syndrome or FBSS

Although post-laminectomy syndrome can be long-lasting and can significantly interfere with an individual's lifestyle, proper treatment can provide great pain relief and improve the quality of life for these patients. Treatment options for postlaminectomy syndrome or FBSS include many alternatives ranging from pharmacological, surgical, different techniques and mixed. The most standardized treatment is epidural injection (block) of steroids, local anesthetics or other drugs (opioids, clonidine and orgoetine). [20] With these treatments, pain relief results can be achieved for up to 24 months. [21,22] Pharmacological treatments have been widely used but little studied. Opioids are usually associated with many adverse effects. Gabapentin produces an improvement over naproxen [23] or added to epidural steroid injections. [24] Spinal re-intervention has yielded very mixed results, ranging from 30% to 80% success [25-27] , but with a poor degree of evidence and rather short term. Root blocks allow us to correctly define whether or not the pain is dependent on one or more roots. Neuroablative techniques are also used. Epidural adhesiolysis has shown some short-term benefit over epidural injections [28-30] . Another option that is considered particularly in those patients in whom

medical treatment has failed and re-intervention is not advisable, is spinal cord stimulation, [31,32] on which the technique described in this protocol is based.

.- Medullary Stimulation

Melzack and Wall (1965) [33] proposed a completely new neurophysiological theory to try to explain how the central nervous system could act at the level of sensory afferents to produce different painful phenomena, the "gateway theory". According to this theory, the myelinated, large-caliber fibers inhibit, and the fine-caliber fibers, A-d and C, facilitate, respectively, the transmission of all nociceptive afferent information at the level of the spinal cord, specifically in the posterior horn. The myelin fibers would activate the T cells, but previously they would also activate the Rolando gelatinous substance, which in turn would exert a presynaptic inhibitory action on the T cells. On the other hand, the amyelinic fibers would facilitate the pain transmission cells (T cells), but previously inhibiting the gelatinous substance, thus losing its inhibitory function on transmission. Thus, this medullary control would normally act through myelin fibers inhibiting the passage of low threshold sensations, preventing them from being interpreted as painful. When the stimulus threshold is more intense, conducted by the myelin fibers, the impulses inhibit the gelatinous substance, so that the impulse has free passage to higher centers and these can still block the passage of the nociceptive sensation at the medullary level.

Spinal cord stimulation (also called spinal neurostimulation or spinal electrical stimulation) produces analgesia through electrical stimulation by means of electrodes placed in the epidural space of the spinal column at the dorsal level. In traditional stimulation, paresthesias are provoked. These paresthesias should cover at least the painful area. Spinal cord stimulation is effective in reducing neuropathic pain, improving function and improving quality of life in patients with FBSS. This technique shows its efficacy when other techniques fail [34].

Stimulation has also been compared to conventional medical treatment, showing improvement in low back and leg pain relief, quality of life, functional capacity and treatment satisfaction [35,36]. Stimulation is also cost-effective, [37,38] especially when long-term results (9 years) are assessed [38]. This stimulation technique is often underutilized despite the fact that it presents fewer complications and lower costs than re-intervention. [39]. Thus, complications are slightly more than twice as high with surgical re-intervention as with spinal cord stimulation [40].

.- Spinal cord stimulation technique

The components that make up the spinal cord stimulation equipment are:
- a neurostimulator (external or implantable)
- electrodes (which transmit the electrical charge)
- electrode extensions (allowing the electrode to be connected to the external neurostimulator)
- an external patient programmer to control the system.
- a charging system, if the neurostimulator is rechargeable.

The neurostimulator is the power source (battery) of the neurostimulation system. It contains electronic components that generate the electrical impulses. Once the electrodes are in place, a test stimulation is performed to confirm the correct position of the electrodes. During test stimulation, an external neurostimulator is used to determine whether an implantable neurostimulator is the appropriate choice for the patient.
The electrodes consist of thin wires with an insulating coating that are responsible for transmitting the electrical impulses to the area where pain signals are to be blocked.
In the test phase the electrodes require an extender to be connected to the external neurostimulator.
The patient programmer is a handheld device used to select and adjust the stimulation. It also has a detachable antenna in case it does not easily reach the neurostimulator implantation site.
In some cases an implanted charging system is used to charge the rechargeable neurostimulator battery (rechargeable neurostimulator).

Implantation of a spinal neurostimulation system is performed by placing the electrode (or electrodes) in the spinal epidural space, usually percutaneously. The procedure is performed in the operating room under local anesthesia or controlled sedation, so that the patient can cooperate and describe the paresthesia induced in the analgesic area. The placement and progression of the electrode(s) is performed under fluoroscopy. The implantation is performed in two phases: in the first phase the electrode(s) is connected to the external generator to test the result (test phase); in the second phase the definitive generator is implanted if the first phase has been successful.

In the first phase the epidural space is located and then the electrode(s) is inserted under fluoroscopic guidance, through the needle, until it is positioned at the dorsal level (T9-T10). Depending on the technique, number of electrodes, and experience, a surgical incision will be made prior to needle insertion. The optimal position of the electrode(s) will be reflected by the correct coverage of the pain area by paresthesias. Subsequently, the electrode is connected to the programmer, setting an amplitude, pulse duration and frequency determined objectively by obtaining an adequate level of paresthesias. Once the correct placement of the electrode(s) has been checked, it is fixed and tunneled, so that it faces outwards. The electrode(s) are then connected to the temporary percutaneous extension and, finally, loosely placed in the form of a loop, they are "buried" in the incision, so that they are protected. In phase 2, after a trial period (several days) if the improvement of pain is considered adequate by both the patient and the therapeutic team, the spinal cord stimulation system is permanently implanted. The generator is implanted under sedation and analgesia (the patient's collaboration is no longer necessary) in the chosen area in a subcutaneous pocket created at a depth of 1 cm from the skin surface. The connection of the electrode(s) to the generator is made by means of a tunneler.

.- Neurostimulation parameters

The parameters that need to be adjusted in spinal neurostimulation are three: frequency, amplitude and pulse width. Frequency determines the quality of paresthesia, the most commonly used being around 60 Hz; pulse width affects the area of paresthesia, and amplitude affects the intensity of the stimulus [41]. If at the end of the test phase (at the end of phase 1 discussed above) pain relief is reduced by 50% or more, the result of the procedure is considered positive [42].

JUSTIFICATION

A recent Cochrane Library review concludes that conventional spinal cord stimulation for FBSS pain relief requires more clinical studies and better designs to demonstrate its superiority over other therapeutic options [43]. Therefore, although spinal cord stimulation is accepted by the FDA (Food and Drug Administration) and the EMA (European Medical Agengy), new techniques are being introduced that offer better results in terms of pain relief [36,44]. Among these techniques is the high-dose modality, which avoids the annoying sensation of paresthesia that substitutes pain with the conventional technique. In order to provide greater rigor and scientific quality, the present study compares, using the same neurostimulator per patient, two different modes of spinal cord stimulation:

1. Conventional spinal cord stimulation (CS) (control or CS) with paresthesia and a standard frequency (60 Hz).
2. High-dose spinal cord stimulation (1000 Hz) or EVOLVE (EME) protocol (experimental arm or EME).

This comparison is carried out by means of a design with a high degree of scientific evidence, randomizing the global sample of patients to each of the two stimulation branches of the study (blinded for the patient) and crossing the branches after a washout period.

A.1.2 Identification of the clinical research plan

a) Title of clinical investigation

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"Randomized, single-blind, multicenter, crossover, controlled clinical trial to compare the difference in visual analog scale in two modes of spinal cord stimulation in patients with postlaminectomy syndrome in test phase"

b) Reference number identifying the specific clinical investigation
Protocolo reference: EST-MED-2018-01

c) Version: 2.0 date 04 june 2018

d) Summary of revision history in case of amendments
Not applicable.

e) Version/issue number and reference number, if any, with page number
Not applicable.

A.1.3 Promotor

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The sponsor should maintain an updated list of principal investigators, research centers and institutions. This list may be kept separate from the CIP. The final list should be provided with the final clinical investigation report.

A.1.5 Global overview of clinical research

Design
Prospective phase IV, randomized, crossover, single-blind, prospective clinical investigation.

Inclusion and exclusion criteria

The present study is aimed at a population of patients with postlaminectomy syndrome after back surgery. The inclusion and exclusion criteria are described below.

Inclusion criteria

1. Patients over 18 years of age.
2. Patients with FBSS syndrome with leg pain or leg and back pain.
3. Obtain a VAS score ≥ 7.
4. Having received pharmacological medical treatment for at least 6 months after back surgery.
5. The patient has signed the informed consent form.

Exclusion criteria

1. Patients under 18 years of age.
2. Patients requiring any diathermic energy source (microwaves, ultrasound or short wave).
3. Patients with a pacemaker.
4. Patients with a defibrillator.
5. Patients with a cochlear implant.
6. Patients with other active implanted devices.
7. Patients who are scheduled to undergo any of the following procedures during the duration of the study: magnetic resonance imaging, defibrillation or cardioversion, electrocautery, lithotripsy, radiofrequency or microwave ablation and any other high-frequency ultrasound procedure,
8. Women of childbearing age who are not using an adequate contraceptive method.
9. Pregnant or lactating women.
10. Participation in another trial.
11. Patients who have expressed their desire not to participate in the study and have not formed the informed consent form.
12. Patients with a previous failed spinal cord stimulation implant.

Number of participants

Twenty-four subjects will be selected who meet the inclusion criteria and do not meet any exclusion criteria, calculating a loss rate of 15%-20%36. 19-20 patients are expected to be included in the study.

Duration of clinical research

A total duration of 18 months plus an additional 6 months to submit the final report is foreseen, with the following schedule for the study:

Start of the study: planned for July 2018 To be determined based on deadlines.
Inclusion period: 16 months, until November 2019.
Follow-up period: planned until January 2020.
Analysis and report: expected in July 2020.

Valuation criteria

The primary endpoint is the variation in VAS between the end of EMC mode and EME mode.

STUDY OUTLINE

Evaluation	Visit 1 Basal	Visit 2	Visit 3 End of washing	Visit 4 EMC or EME	VIisit 5. End of washing	Visit 6 EMC or EME	Visita 7
DAY of the study	-3 *	-2	0	5	7	12	40±2
Selection Criteria Evaluation	X						
Explanation of study and signature of consent	X						
Clinical data collection	X						
Randomization		X					
VAS	X			X		X	X
Oswestry Questionnaire	X			X		X	x
Temporary electrode implant without stimulus		X					
Start of spinal cord stimulation according to randomization A or B (day 3)			X		X		
System tolerability		X	X	X	X	X	
Adverse effects		X	X	X	X	X	x
Subsequent follow-up							x

(*) window of -2 days with respect to Visit 3.

A.2 IDENTIFICATION AND DESCRIPTION OF THE PRODUCT UNDER INVESTIGATION

A Medtronic® neurostimulator that has implanted components that deliver electrical impulses to the area where pain signals are to be blocked, rechargeable and MRI compatible. The patient programmer is designed to program different rechargeable and non-rechargeable neurostimulators.

The neurostimulator is the power source (battery) of the neurostimulation system. It contains electronic components that generate the electrical impulses. During test stimulation, an external neurostimulator is used to determine if an implantable neurostimulator is the appropriate choice for the patient. The electrode is a set of thin wires with an insulating coating. An electrode has small metal poles near the tip. The poles transmit electrical impulses to the area where pain signals are to be blocked. Two are usually used. The extension is a set of thin wires with an insulating coating that connects the neurostimulator to an electrode. Not all neurostimulation systems include an extension. The patient programmer is a handheld device that the patient uses to select and

adjust the stimulation. In the present study, spinal cord stimulation using the EVOLVE programming flow and conventional stimulation at 60Hz will be used.

Storage conditions: The external neurostimulator is stored at room temperature. Extreme high or low temperatures and direct sunlight should be avoided. The device and system components are not water resistant. Moisture should not be allowed to enter the device or system components.

Indications for Use: Neurostimulation is indicated in failed back surgery and complex regional pain syndrome. Other more exceptional indications when other therapeutic options fail include refractory angina pectoris, coccygodynia, interstitial cystitis, perineal pain, peripheral vascular pain, radiculopathies and peripheral neuropathy.

Contraindications: Neurostimulation is contraindicated in shortwave diathermy, microwave diathermy and ultrasound diathermy. Diathermy energy can transfer through the implanted system and can damage tissues, causing serious injury or death.

Description of the indications for use: The instructions for use of the device are described in detail in Annex 2.

Programming of the implantable pulse generator

In the present study, paresthesia mapping will be used for both methods. For the high-dose experimental method (EME branch), the emitted frequency will be a 1 KHz, and the pulse amplitude will be increased until the patient perceives paresthesias in the appropriate coverage area. Depending on the participant's response to the paresthesia location, the anode and cathode settings will be changed to provide appropriate dermatome coverage. Once adequate anatomical coverage is confirmed, the pulse amplitude is decreased until the paresthesias disappear, and no new paresthesias manifest with spinal extension or flexion. For the conventional method (EMC branch), patients are allowed to optimize their stimulation finely over the coverage area. Each participant is given three program alternatives with small changes to adjust to the coverage areas during the study.

A.3 JUSTIFICATION OF THE CLINICAL RESEARCH DESIGN

Traditionally, pain relief by spinal cord stimulation is related to the appearance of paresthesias in the affected area. Several parameters are adjusted to maximize the area of overexposure, such as the frequency, [45-47] and pulse amplitude [48,49]. Although this technique has been successful in improving pain in many patients, paresthesias themselves can be bothersome. The occurrence of paresthesias has traditionally been considered a predictor of success in eliminating pain, [50] while the non-appearance of paresthesia would indicate failure. So far, few studies have reported pain relief below the threshold of paresthesia onset. Some clinical trials for pathologies other than the one considered in the present study have achieved relief below the threshold by reducing the amplitude of the stimulus [51,52]. Recently, however, it has been observed in a pilot study that, by increasing the frequency of spinal cord stimulation to 1 KHz, it is possible to significantly improve pain relief compared to conventional stimulation at a lower frequency based on the appearance of paresthesia [44].

A.4 RISKS AND BENEFITS OF THE PRODUCT IN CLINICAL RESEARCH

a) Expected clinical benefits

The benefits of spinal cord stimulation are well known and have been described in the introduction. The main benefit of spinal cord stimulation using the EVOLVE programming flow with a frequency of 1 KHz is to relieve leg pain (with or without low back pain) to a greater extent than the conventional system and without producing paresthesia.

b) Expected adverse effects of the product
Complications are independent of the stimulus used and are those inherent to the technique for implantation of the system according to standard clinical practice. These could be related to the electrode, the extension or the neurostimulator, which could move inside the body or erode the skin. Undesirable changes in stimulation could occur, possibly related to cellular changes around the poles, changes in pole position, loose electrical connections, or breakage of the electrode or extension. It is also possible that implanted materials could cause an allergic or immune response.

The neurostimulation system may unexpectedly stop working due to battery depletion or other causes. These situations, which may include electrical shorts or open circuits and conductor (wire) and insulation breakage, are unpredictable.

Other possible complications, more related to the technique, are infection, electrode migration, rejection and post-puncture headache.

All these possible complications are independent of the stimulus used and are specific to the technique for implantation of the system according to standard practice.

A.5 CLINICAL RESEARCH OBJECTIVES AND HYPOTHESES

This Clinical Research Plan has the following objectives:

a) primary and secondary objectives

Main objective:

- To compare the values of the visual analog scale (VAS) in patients with postlaminectomy syndrome with leg pain or leg and lumbar pain, applied at baseline and at the end of the test phase, with a single neurostimulator per patient, under conventional spinal cord stimulation (CMS) or under stimulation with the EVOLVE protocol (EME).

Secondary objectives:

1. To estimate the proportion of patients with a minimum 50% decrease in VAS score at 5 days relative to baseline in each type of spinal cord stimulation (EMC or EME).

2. To evaluate the disability associated with pain at the beginning of the study and its possible modifications during follow-up in each type of spinal cord stimulation.
3. To study the safety of the stimulation procedures under study in each type of spinal cord stimulation.

b) Hypothesis

The primary endpoint is the difference in VAS score applied after CME and after SCS compared to the VAS score applied at baseline assessment before spinal cord stimulation. It is assumed that SCS will achieve a 2.4 point reduction in VAS compared to CME, according to previous information [44].

c) Intended applications and performance of the product under investigation

The Medtronic® spinal neurostimulation system with EVOLVE flow programming is indicated for the pain treatment of failed back surgery syndrome and has all the elements for its application.

d) Risks and expected adverse effects of the product
See section A4

A.6 CLINICAL RESEARCH DESIGN

A.6.1 General

This is a prospective study, randomized to two modes of spinal cord stimulation control (CS) and experimental (EME), single-blind and crossover.

Patients will be included in the study by randomizing the spinal cord stimulation mode after signing the informed consent form and verifying that they meet all the inclusion criteria and none of the exclusion criteria. Randomization will be performed by telephone call to the central randomization center, which will assign the patient stimulation mode according to the randomized list.

The devices are delivered to the investigators duly manufactured and labeled and are deposited in the centers where they will comply with the appropriate maintenance and conservation conditions. The centers chosen to carry out the study have sufficient means and proven experience in the handling and maintenance of the devices.

A.6.2 Product under research and testing

In this study, the conventional spinal cord stimulation method (EMC limb) and the experimental 1 KHz spinal cord stimulation method with the EVOLVE programming guide (EME limb) will be used in the same patient after a washout period, randomizing the patient to start with one limb or the other. Randomization will be performed

telephonically by contact between the principal investigator and the central randomization center located at the CRO. It is planned to act in accordance with clinical practice in these patients, providing at all times what is necessary for the perfect treatment of the patients according to the knowledge and training of the professionals involved in the clinical research.

A.6.3 Participants

The criteria for the selection of the participant subjects are as follows.

.- Inclusion Criteria
Patients over 18 years of age.
2. Patients with FBSS syndrome with leg pain or leg and back pain.
3. Obtain a VAS score ≥ 7.
4. Having received pharmacological medical treatment for at least 6 months after back surgery.
5. The patient has signed the informed consent form.

Exclusion criteria

1 Patients under 18 years of age.
2 Patients requiring any source of diathermic energy (microwave, ultrasound or short wave).
3. Patients with a pacemaker.
4. Patients with a defibrillator.
5. Patients with a cochlear implant.
6. Patients with other active implanted devices.
7. Patients who are scheduled during the duration of the study for any of the following procedures: magnetic resonance imaging, defibrillation or cardioversion, electrocautery, lithotripsy, radiofrequency or microwave ablation, and any other high frequency ultrasound procedure,
8. Women of childbearing age who are not using an adequate contraceptive method.
9. Pregnant or lactating women.
10. Participation in another trial.
11. Patients who have expressed their desire not to participate in the study and have not formed the informed consent form.
12. Patients with a previous failed spinal cord stimulation implant.

Withdrawal criteria

Patients will be withdrawn from the study if after mapping of paresthesia the electrode is not placed in T9/T10.

Those patients who do not achieve paresthesia in the painful area in both modes will be withdrawn from the study.

The study will be withdrawn if the Safety and Monitoring Committee considers that the adverse effects are unacceptable.

In the event that the patient suffers an event that prevents continuation in the study (serious adverse effect or similar), he/she will be treated according to the appropriate clinical practice at that time and his/her study termination data will be recorded. The patient can withdraw voluntarily without changing the relationship with his physician or the care he expects from him.

Study and follow-up period

Regarding the moment of inclusion, it will be one day before the placement of the electrode(s) and three days before the beginning of the spinal cord stimulation, once it has been verified that they meet all the inclusion criteria and none of the exclusion criteria. The patients will be included in the study in a randomized manner, after they sign their voluntary participation in the study before any type of intervention is performed, for which they will be duly informed through the patient information sheet and the oral explanation provided by the researcher or authorized collaborator. Randomization will be carried out by telephone through contact between the principal investigator and the central randomization center of the CRO.

The expected duration of the clinical investigation is 16 months of recruitment in each center, plus 15 days of study and 1 month of patient follow-up, and will be maintained until the number of patients foreseen in the sample size described is reached.

The duration of each patient in the study will be 15 days from the day on which the study scales (VAS and quality of life) are performed at the baseline visit, plus 1 month of subsequent follow-up.

Twenty-four patients will be selected who meet the inclusion criteria and do not meet any exclusion criteria, calculating a loss rate of 15%-20%, it is expected that 19-20 patients will be included in the study.

The inclusion period has been estimated at 16 months for each center.

A.6.4 Procedures

The participants who take part in the clinical research follow the following procedures throughout the study. They are selected at the medical visit and once it has been verified that they meet all the inclusion criteria and none of the exclusion criteria and their possible participation in the study has been decided, their participation in the study is proposed to them by explaining the patient information sheet and signing the informed consent form. From that moment on, at visit 1 (which can be the same visit or a previous one, provided that no procedure related to the study is performed until the consent form is signed), the mode of spinal cord stimulation to be applied to the patient is randomized, with a single device for each patient, and the study procedures will be performed. Randomization will be performed by telephone contact to the central randomization center of the CRO.

The procedures used in this work to evaluate the efficacy of spinal cord stimulation are the visual analog scale (VAS) and the Oswestry (OC) questionnaire on disability associated with low back pain (Oswestry Disability Index). The VAS makes it possible to measure pain intensity with maximum reproducibility between observers. It consists of a horizontal line of 10 centimeters, at the ends of which are the extreme expressions of pain perception. On the left side is located the absence or lower intensity and on the right side the higher intensity. The patient is asked to mark on the line the point indicating the intensity (see appendix 3) [53]. The Owestry scale is the most recommended scale for measuring disability due to low back pain. [54] It consists of a self-administered questionnaire that measures limitations in daily activities. It consists of 10 questions with 6 possible answers each. The score for each answer ranges from 0 (less disability) to 5 (more disability). The result is expressed in % by dividing the total score by 50, with 0% being the least disability possible, and 100% the most disability. It is classified into 5 categories: minimal disability (0% to 20%), moderate disability (21% to 40%), severe disability (41% to 60%), paralyzed (61% to 80%) and category requiring more careful evaluation (81% to 100%, could be bedridden patients or those who exaggerate symptoms). (See Annex 4).

Study variables

The study is structured in 7 visits. The variables collected and structures of the visits are as follows:

.- Visit 1 (day -3 to -5)

The patient signs the informed consent for the study, once he/she has been informed of the nature of the study (the information may have been received at a previous visit). The selection criteria are reviewed (all the inclusion criteria must be met and none of the exclusion criteria must be met). Demographic data (age, sex), anthropometric data (weight, height), pathological history, history of vertebral and/or dorsolumbar pathology, history of spinal surgery, previous pharmacological medical treatment and nature of pain are collected. The VAS and the OC scale (disability associated with low back pain) are performed.

.- Visit 2 (day -2)

The electrode(s) is (are) placed. A single neurostimulator per patient (device). The patient is then randomized to one of the two modes of spinal cord stimulation EMC or EME, by telephone call, and an appointment is made for visit 3. Adverse effects and tolerability of the system (rejection, infection or migration) are assessed. A first 2-day washout period is initiated.

.- Visit 3 (day 0)

The first period of spinal cord stimulation begins with the branch to which the patient has been randomized: EMC or EME. If the patient has been assigned to the EMC control group, after mapping the search for the pain area, the neurostimulator is programmed to conventional stimulation with paresthesia at 60 Hz and a pulse width between 300-450 μs. If the patient has been randomized to the EMC experimental group, after mapping the search for the pain zone, stimulation is programmed at 90% of the subthreshold with a pulse width of 90 μs and frequency of 1000 Hz, placing the bipole in the T9-T10 space. The patient is asked if there have been any complications since electrode insertion (s).

.- Visit 4 (day 5)
VAS and OC scale are performed. The device is examined and questioned for possible adverse effects and tolerability of the system (rejection, infection or migration). The device is then deprogrammed and a second 2-day washout period is initiated.

.- Visit 5 (day 7)
Possible adverse effects and tolerability of the system (rejection, infection or migration) are questioned. The programming of spinal cord stimulation is started again, so that the patient is administered the MCE if he/she had received the MES, and vice versa.

.- Visit 6 (day 12)
The VAS and OC scale are performed. The device is re-examined and possible adverse effects and tolerability of the system are questioned. A final decision is made to implant or remove the device.

.- Visit 7 (4 weeks after final implantation/withdrawal of system)
The VAS and OC scale are performed. The device is re-examined and questioned for possible adverse effects and tolerability of the system.

A.6.5 Monitoring plan

The study will be monitored by personnel specifically contracted from a company external to the promoter, and an in-person visit will be made at the start, an intermediate visit, and a final visit at each participating center. At the beginning of the study, the first visit will be made, during which all aspects of the study will be explained to the research staff, the informed consent procedure will be explained, the protocol will be reviewed, the way in which patient data will be collected, the responsibilities of the researcher, the dispensing and maintenance of the samples and all related issues. Telephone follow-up will be provided to the centers throughout the duration of the study.

The monitor will have access to both paper and computerized medical records and will ensure that patient data are properly collected and stored in the investigator's file for the time required by current regulations.

The monitor will be informed of adverse events occurring during the clinical investigation through the investigator at each center and will report serious and related events to the authorities within the established time limits.

Evaluation	Visit 1 Basal	Visit 2	Visit 3 End of washing	Visit 4 EMC or EME	VIisit 5. End of washing	Visit 6 EMC or EME	Visita 7
DAY of the study	-3 *	-2	0	5	7	12	40±2
Selection Criteria Evaluation	X						
Explanation of study and signature of consent	X						
Clinical data collection	X						
Randomization		X					
VAS	X			X		X	X

Oswestry Questionnaire	X			X		X	x
Temporary electrode implant without stimulus		X					
Start of spinal cord stimulation according to randomization A or B (day 3)			X		X		
System tolerability		X	X	X	X	X	
Adverse effects		X	X	X	X	X	x
Subsequent follow-up							x

(*) window of -2 days with respect to Visit 3.

A.7 STATISTICAL CONSIDERATIONS

This is a multicenter, controlled, randomized (spinal cord stimulation method: EMC or EME), crossover and single-blind study.

First, a descriptive analysis of the study variables will be performed, calculating the absolute and percentage frequency (n and %) of each category in the qualitative variables; in the quantitative variables, we will first study whether they fit the Gaussian distribution by applying the Kolmogorv-Smirnov goodness-of-fit test to the "Normal" distribution, showing the means and standard deviations if yes, and the medians and 25th and 75th percentiles if no, and if no, the medians and 25th and 75th percentiles.

In order to respond to the main objective of the study, two variables will be calculated for each patient that reflect the difference between the initial VAS minus the final VAS, one for each type of stimulation (EMC or EME). We will calculate whether these differences conform to the Gaussian distribution. If they fit the "Normal" distribution, the means with their standard deviations will be calculated for each of them, with the Student's t-test for paired samples to study if this difference is statistically significant, these means will be adjusted for age and sex, establishing the possible statistical differences with a general linear model of repeated measures. In the case of not obtaining distributions that fit the "Normal", the medians and the 25th and 75th percentiles will be calculated, obtaining the possible statistical differences by applying the Wilcoxon test.

For the objective of estimating the proportion of patients with a minimum decrease of 50%, it will be calculated in each case which patients meet this condition, calculating the percentage of patients in each type of stimulation, and studying the possible statistically significant differences with the Mc Nemar test.

The disability associated with pain will be evaluated with the descriptive statistics already mentioned and for each moment of the study and in each type of stimulation.

Variables will be created with the differences between the initial and final quality of life scores, studying their differences with the same parameters and tests discussed for the differences in VAS.

The absolute and relative frequencies (%) of each of the adverse effects found in the follow-up will be calculated as a safety study, in the total of the study and for each type of stimulus. Possible differences will be studied with the Mc. Nemar test.

A statistical significance level of $p<0.05$ is considered, thus establishing a safety level of 95%.

All analyses will be performed with SPSS software version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.)

Sample size

The main objective of the study is to establish a mean difference in the decrease in VAS. Based on this, we estimate a difference between the two methods of spinal cord stimulation (EMC and EME) of 1.9 points, in agreement with previous data in the medical literature, [55] with standard deviation of 3.2 and 2.0, assuming a Spearman correlation between both values of 0.5 (minimum). Using the formula for paired mean difference, for a confidence level of 95% and a statistical power of 80%, 19 patients who meet the inclusion criteria and do not meet any exclusion criteria are required, calculating a loss rate of 20%, 24 patients are expected to be included in the study.

A.8 DATA MANAGEMENT

A clinical research data collection form (CRF) will be created, where each investigator will collect the data of each patient participating in the study.

In agreement with the scientific committee, minimum and maximum values will be established for each variable of the CRF, creating validation rules and messages to the user communicating the validation rule that is not being complied with, as well as input masks for the variables that require it, such as dates. It will be possible to proceed to fill the CRF in successive times, with the consequent saving at each moment.

A.9 AMENDMENTS

The Investigational Product, Protocol, CRF, informed consent or other subject information, or other clinical investigation documents may be amended during the clinical investigation if necessary. In this case a justification statement will be included with each amended section of a document. Proposed amendments to the Protocol will be agreed between the sponsor and the coordinating investigator. They should be notified to and approved by the CEIM and regulatory authorities if required and the version number and date of the amendments will be documented.

For non-substantive changes that do not affect the rights, safety, and welfare of human subjects and are not related to the objectives or endpoints of the clinical investigation, notification to CEIM and, where appropriate, to regulatory authorities will be sufficient.

A.10 DEVIATIONS FROM THE CLINICAL RESEARCH PLAN

Reports of deviations will be communicated to CEIM, if the deviation affects the rights, safety and welfare of the subjects or the scientific integrity of the clinical investigation. In such cases, written approval will be obtained from CEIM.

In emergency circumstances, deviations from the protocol to protect the rights, safety, and welfare of human subjects may proceed without prior approval of the sponsor and the CEIM. Such deviations should be documented and notified to the sponsor and CEIM as soon as possible.

A.11 PRODUCT ACCOUNTING

Access to investigational products will be controlled and used only in clinical research and in accordance with the protocol.

The sponsor will maintain records to document the physical location of investigational products from the time they are shipped to participating sites until they are returned or disposed of.

The principal investigator or an authorized designee should maintain records documenting the receipt, use, return, and disposal of investigational products. Such records shall include: date received, product identification, expiration and use date, subject identification, withdrawal date if applicable, and return date for products that were not used or expired.

A.12 COMPLIANCE STATEMENT

The clinical investigation will be carried out in accordance with the ethical principles set forth in the Declaration of Helsinki, will be conducted in compliance with this standard and any regional or national regulations as appropriate.

The clinical investigation will commence when the favorable opinion of the CEIM and the authorization of the AEMPS have been obtained as well as having fulfilled any additional requirements imposed.

It will have a civil liability insurance that guarantees the Promoter's Civil Liability derived from the clinical research, for the damages caused to the participating participants that fulfills the legal requirements established in the Spanish legislation. In addition, the Civil Liability of the investigator and his collaborators and of the Owner of each hospital where it is carried out is also covered.

A.13 INFORMED CONSENT PROCESS

Informed consent must be obtained from the participant in writing prior to any specific clinical research procedure, except when special circumstances apply. The principal

investigator or his/her assigned collaborator is responsible for the process of obtaining consent.

It should contain all aspects of the clinical investigation that are relevant to the subject's decision to participate. It should avoid any coercion or undue inappropriate influences or inducements on the participant to participate. Do not disregard or appear to disregard the legal rights of the subjects. Use the subject's own language in clear and understandable terms.

The subject will be provided sufficient time to read and understand the informed consent form and consider participation in the clinical investigation. It will include the dated handwritten signatures of the subject and the principal investigator or his/her authorized designee responsible for executing the informed consent process. The subject will be provided with a copy of the signed and dated form and any other written information.

Special circumstances for informed consent are as follows.

- Subjects who need legally authorized representatives. The legally authorized representative can give informed consent only if a subject is incapable of making the decision to participate and, the subject must also be informed about the clinical investigation to the extent of his or her capacity to understand.

- Subject unable to read or write: must be obtained using a supervised oral process, an independent witness must be present during the process. It should be read aloud and explained to the prospective subject or his or her legally authorized representative, and whenever possible, either should personally sign and date the form. The witness also personally signs and dates the form attesting that the information was accurately explained and that consent was freely given.

- Urgent treatments: Urgent treatments are not foreseen but if this is the case, if the patient's prior consent is not possible due to the patient's medical condition, the signature of his/her legally authorized representative will be requested. The participant or his/her legally authorized representative will be informed as soon as possible and will be asked to give consent as soon as his/her condition permits.

A.14 ADVERSE EVENTS, ADVERSE EFFECTS OF THE PRODUCT AND PRODUCT DEFICIENCIES

Definitions

Adverse Event (AE)
An adverse event (AE) is any unintended medical episode, unanticipated illness or injury, or any clinical sign, including an abnormal laboratory finding, in subjects, users, or any other person, whether or not related to the investigational product. Includes medical device or control; includes events related to the procedures used.

Serious Adverse Event (SAE)

Any adverse event that:

- Leads to death
- Serious deterioration in health status that results in:
    1. produced a life-threatening illness or injury; 2.
    2. Permanent damage to bodily structure or function
    3. Requires hospitalization or prolongation of hospitalization
    4. Unplanned medical/surgical intervention to avoid treatment or life-long injury to a bodily structure or function.
- Results in fetal damage, congenital anomaly or birth defect.

For reporting purposes, adverse events that are considered medically significant, even if they do not meet the above criteria, such as those that put the patient at risk or require intervention to prevent any of the above outcomes, will also be treated as serious.

Adverse Device Event (ADE)

An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or any malfunction of the investigational medical device. It includes any adverse event resulting from an error in the use of the investigational medical device.

Serious Adverse Device Event (ADE)

An adverse event of the product that has produced any consequence characteristic of a serious adverse event.

Unexpected serious adverse device event (USADE)

It is an adverse event of the product that due to its nature, incidence, intensity or consequence has not been identified in the updated version of the risk analysis report.

Product deficiencies

All deficiencies of a medical device related to: identity, quality, durability, reliability, safety/performance, malfunction/error of use, inadequate labeling.

Noticeable events

They are any AGEs; any deficiency of a medical device that could have led to an AGE if timely action had not been taken, no intervention had been made, or in less fortunate circumstances; or new findings and updates on reported events.

Expedited notification

The sponsor will notify the AEMPS of all serious adverse events whether they are related to the investigational medical device or not, whether they occur in Spain or in other states and whether they have occurred in the authorized clinical investigation or in other clinical investigations or in a different context of use, provided that such medical devices are not marketed in Spain.

For marketed products, including the medical device used as a control, the requirements of the European system of vigilance of medical devices will be taken into account in order to avoid possible duplications in the notification.

Expedited Notification Deadlines

The maximum notification period will be 15 calendar days from the moment the sponsor became aware of the serious adverse event. When the serious adverse event has caused the death of the subject, or endangered his life, the sponsor shall inform the AEMPS within a maximum of 7 calendar days from the moment the sponsor became aware of the case. Such information should be completed, as far as possible, within the following 8 days.

Recording and reporting of adverse events and incidents

All adverse events and incidents occurring from the inclusion of the patient in the study (i.e., from the signing of the consent form) until the end of the planned follow-up per patient should be recorded in the CRF by the investigator noting their characteristics. All adverse events should be recorded using medical terminology.

Procedures for reporting serious and unexpected adverse events and adverse incidents.

All serious adverse events and adverse incidents should be reported to the sponsor's safety committee. This will include, but is not limited to

- Death from any cause
- Life-threatening hemorrhage
- Intracranial hemorrhage
- Epidural hematoma
- Meningitis
- Cerebrovascular accident
- Deep thrombocytopenia (platelet count <50,000/mm3)

Any adverse and/or unexpected AAG and incident should be reported to the sponsor's designated CRO (TRIDE) within 24 working hours of knowledge of the event. All information related to SAEs will be reported by e-mail using the SAE and adverse event forms of the CRD of the investigation, which must be signed by the investigator himself or a collaborating member of his team.

To report an incident, it is necessary that it is associated with a medical device or with the information provided with the medical device and that the incident is such that it has resulted in death or serious deterioration in health, or that if it occurs again it could cause them.

The types of adverse incidents that should be reported are as follows:

1. Those that result in death
2. Those resulting in serious deterioration of the patient's, user's or other person's health status, such as:
   - Life-threatening illness or injury

- Permanent impairment of a bodily function or permanent damage to a bodily structure.
- A process that requires medical or surgical intervention to prevent permanent impairment of a bodily function or permanent damage to a bodily structure.

3. Potential incidents, which are those that could have resulted in death or serious deterioration of health, but which have not occurred due either to fortunate circumstances or to the intervention of healthcare personnel.

Incidents involving medical devices should be reported to the medical device vigilance point of the Autonomous Community. The communication should be made as soon as possible. It can be done by fax or by post. In the case of very serious incidents, it should be done as quickly as possible, by fax, until the means are available to send the communication "on line"; if fax is not available, it can be notified by telephone, sending the form by post afterwards. The form available in the CRF shall be used for this purpose.

A.15 VULNERABLE POPULATION

The clinical research will be carried out in participants whose diagnosis leads to an indication to receive the treatment under study within the general population and the inclusion of vulnerable population is not contemplated.

A.16 SUSPENSION OR EARLY DISCONTINUATION OF CLINICAL RESEARCH

The sponsor may suspend or terminate early either a clinical investigation at an individual investigational site or the entire clinical investigation for significant and documented reasons.

The national coordinator, a principal investigator, IRB/IEC or regulatory authority may suspend or terminate participation in the clinical investigation at the investigational sites for which it is responsible.

If suspicion of unacceptable risk to subjects arises during the clinical investigation, or when instructed to do so by the IRB/IEC or regulatory authority, the sponsor should suspend the clinical investigation while the risk is being determined. The sponsor should discontinue the clinical investigation if an unacceptable risk is confirmed.

The sponsor should consider discontinuing or suspending the participation of an investigational site or an individual investigator if monitoring or auditing identifies serious or repeated deviations by an investigator.

If suspension or early discontinuation occurs, the party so disposing should justify its decision in writing and promptly inform the other parties with whom it is in direct communication. The principal investigator and sponsor should keep each other informed of any communication received from either the CEIM or the regulatory authority.

If, for any reason, the sponsor suspends or discontinues research at an individual investigational site early, the sponsor should inform the responsible regulatory authority as appropriate and ensure that the principal investigator or sponsor notifies the CEIM. If the suspension or early discontinuation was in the interest of safety, the sponsor should inform all other principal investigators.

If suspension or early discontinuation occurs, the sponsor should remain responsible for providing the resources to fulfill the obligations of the protocol and existing agreements for follow-up of the subjects included in the clinical investigation and the principal

investigator or his authorized designee should promptly inform the subjects included at his investigational site, if appropriate. The method and timing of this communication will depend on the circumstances and perceived risks.
When the sponsor concludes an analysis of the reason for suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor should inform the principal investigators, the IRB/IECs, and, where appropriate, the regulatory authorities of the justification and provide them with the relevant data supporting this decision. The concurrence of the IRB/IEC and, where appropriate, the regulatory authorities should be obtained prior to resumption of the clinical investigation. If the subjects have been informed of the suspension, the principal investigator or his/her authorized designee should inform them of the reasons for resumption.

A.17 PUBLICATION POLICY

The sponsor expressly agrees to publish the results of the clinical investigation, whether positive or negative.

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ANNEX 1 ABBREVIATIONS AND DEFINITIONS

CEIM: Comité Ético de Investigación / Research Ethics Committee

CRF: Clinical data Research Form

OC: Oswestry questionaire

CRO: *Contract Research Organization*

EMC: Estimulación medular convencional / Conventional spinal cord stimulation

EME: Estimulación medular sistema EVOLVE / Spinal cord stimulation EVOLVE system

EVOLVE: Standardized guide to a programming flow of Medtronic® spinal neurostimulation systems: SureScan ™ MRI and AdaptativeStim ™.

FBSS: *Failed back surgery syndrome*

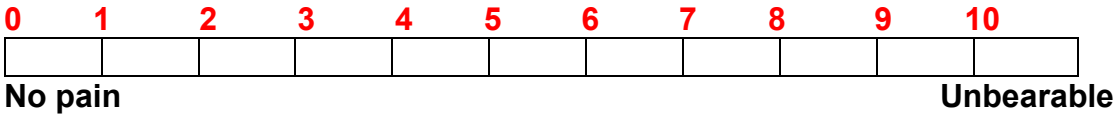
IRB/IECs: Institutional Review Board / Institutional Ethics Committee

VAS: Visual Analogue Scale

ANNEX II VISUAL ANALOG SCALE

VISUAL ANALOG PAIN INTENSITY SCALE

Indicate on this scale the intensity of your pain, where 0 is no pain at all and 10 is the most unbearable pain imaginable.



ANNEX III OSWESTRY QUESTIONNAIRE

OSWESTRY QUESTIONNAIRE ON DISABILITY ASSOCIATED WITH LOW BACK PAIN

Thank you for completing the questionnaire. It is designed to tell us how low back pain affects your ability to function in daily life.

Choose the option that applies to you at this time to answer each section below.

Selecciona la opción que mejor describa su problema en este momento.

Section 1. Pain intensity

- I can handle pain without taking painkillers [0 points].
- The pain is severe but I manage without taking painkillers [1 point].
- Painkillers relieve my pain completely [2 points].
- Painkillers give me some pain relief [3 points].
- Painkillers barely relieve my pain [4 points].
- Painkillers do not relieve my pain and I do not take them [5 points].

Section 2. Personal care

- I can manage on my own without it increasing my pain [0 points].
- I can manage on my own but it increases my pain [1 point].
- Self-care causes me pain and I have to do it slowly and carefully [2 points].
- I need some help but I manage to do most things on my own [3 points].
- I need help to do most things [4 points].
- I can't get dressed, have trouble washing myself and often stay in bed [5 points].

Section 3. Lifting weights

- I can lift heavy objects without increasing pain [0 points].
- I can lift heavy objects but it increases my pain [1 point].
- Pain prevents me from lifting heavy objects off the floor, but I can lift heavy objects if they are in a comfortable place (e.g., on a table) [2 points].
- Pain prevents me from lifting heavy objects, but I can lift light to medium objects if they are in a comfortable place [3 points]
- I can only lift very light objects [4 points].
- I am unable to lift or carry any objects [5 points].

Section 4. Walking

- Pain does not prevent me from walking any distance [0 points].
- Pain prevents me from walking more than one kilometer [1 point].
- Pain prevents me from walking more than 500 meters [2 points].
- Pain prevents me from walking more than 250 meters [3 points].
- I can only walk with a cane or crutches [4 points].
- I stay in bed most of the time and have to crawl to the bathroom [5 points].

Section 5. Sitting.

- I can sit in any type of chair for as long as I want [0 points].
- I can only sit in my favorite chair as long as I want [1 point].
- Pain prevents me from sitting for more than an hour [2 points].
- Pain prevents me from sitting for more than half an hour [3 points].
- Pain prevents me from sitting for more than 10 minutes [4 points].
- The pain prevents me from sitting [5 points].

Section 6. Standing

- I can stand as long as I want without increasing pain [0 points].
- I can stand as long as I want but it increases my pain [1 point].
- Pain prevents me from standing for more than one hour [2 points].
- Pain prevents me from standing for more than half an hour [3 points].
- Pain prevents me from standing for more than 10 minutes [4 points].
- The pain prevents me from standing [5 points].

Section 7. Sleeping

- Pain does not prevent me from sleeping well [0 points].
- I can only sleep if I take pills [1 point].
- Even taking pills I sleep less than 6 hours [2 points].
- Even taking pills I sleep less than 4 hours [3 points].
- Even taking pills I sleep less than 2 hours [4 points].
- The pain totally prevents me from sleeping [5 points].

Section 8. Sex life

- My sexual activity is normal and does not increase my pain [0 points].
- My sexual activity is normal but increases my pain [1 point].
- My sexual activity is almost normal but my pain is greatly increased [2 points].
- My sexual activity has been very limited because of the pain [3 points].
- My sexual activity is almost nil because of the pain [4 points].
- The pain prevents me from any kind of sexual activity [5 points].

Section 9. Social life

- My social life is normal and does not increase my pain [0 points].
- My social life is normal but increases my pain [1 point].
- The pain does not have a major effect on my social life, but it does impede my more energetic activities such as dancing [2 points]
- The pain has limited my social life and I do not go out as often [3 points].
- The pain has limited my social life to the home [4 points].
- I have no social life because of the pain [5 points].

Section 10. Travelling

- I can travel anywhere without increasing my pain [0 points].
- I can travel anywhere, but it increases my pain [1 point].
- Pain is severe, but I can endure trips of more than 2 hours [2 points].
- Pain limits me to trips of less than one hour [3 points].
- Pain limits me to short, necessary trips of less than half an hour [4 points].
- Pain prevents me from traveling except to go to the doctor or hospital [5 points].