CLINICAL INVESTIGATION PROTOCOL

Title:

"Epidural Pulsed Radiofrequency versus Epidural Steroids Injection for Treatment of Failed Back Syndrome: A Prospective, Randomized, Single-Blind and Multicenter Study"

Protocol Code:

EPIPUL

Sponsor:

Fundación Investigación HM Hospitales

Hospital Universitario HM Sanchinarro

Coordinating Investigator:

Dr. Agustín Mendiola de la Osa

Hospital Universitario HM Sanchinarro

Revisions:

Version	Date	Description
1.1	25th of March 2019	First revision and approval
1.2	18th of July 2019	Second revision and approval
1.3	26th of November 2019	Third revision and approval
1.4	11th of February 2020	Fourth revision and approval

SIGNATURE PAGE

Principal Investigator Signature

"I have read this clinical investigation plan and agree to participate in the clinical investigation by Fundación Investigación HM Hospitales. I agree to conduct this investigation according to the requirements of the clinical investigation plan and in accordance with the Declaration of Helsinki, ISO 14155-2011, EU and local regulations and conditions imposed by the reviewing Ethics Committee. I agree to supervise all Sub-Investigators at my site as well as the use of all of the devices at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study".

Name of Principal Investigator: _____

_____ _____ /_____ /_____

Signature *Date*

_____

Title

Sponsor Signature:

All information concerning the study device supplied by Fundación Investigación HM Hospitales in connection with this study, and not previously published, is considered confidential and proprietary information. This information includes the clinical investigation plan, subject informed consent and case report forms. This confidential information shall remain the sole property of Fundación Investigación HM Hospitales, shall not be disclosed to others without prior written consent from Fundación Investigación HM Hospitales and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Fundación Investigación HM Hospitales in connection with the development of the study device. This information may be disclosed as deemed necessary by Fundación Investigación HM Hospitales.

The below-named individuals are authorized to sign this clinical investigation plan and its amendments.

_____ _____ /_____ /_____

Signature *Date*

_____ _____

Printed Name *Title*

1. - SUMMARY

1. Study Title:	Epidural Pulsed Radiofrequency versus Epidural Steroids Injection for Treatment of Failed Back Syndrome: A Prospective, Randomized, Single-Blind and Multicenter Study
2. Sponsor:	Fundación Investigación HM Hospitales
3. Type of Clinical Investigation:	Clinical Investigation with CE-marked medical devices.
4. Coordinating Investigator:	Dr. Agustín Mendiola de la Osa, MD PhD.
5. Protocol Code:	EPIPUL
6. Geography	Spain
7. Clinical Sites:	• Hospital Universitario Puerta de Hierro (Madrid, Spain). • Hospital Universitario Rey Juan Carlos (Madrid, Spain). • Hospital Universitario de Sanchinarro (Madrid, Spain) • Hospital Fremap Majadahonda (Madrid, Spain) • Hospital Universitario La Fé (Valencia, Spain) • Hospital Clínico Universitario de Santiago (Santiago de Compostela, Spain)
8. Study Purpose:	The present pilot study suggests that the epidural application of PRF to the dorsal roots and proximal DRG can be safe and effective in the treatment of intractable pain after back surgery. Several explanatory hypotheses motivate further study of this apparent improvement over transforaminal PRF, which has produced inconsistent results in published reports to date.
9. Treatments	Experimental Group (62 patients): Epidural radiofrequency by catheter in the epidural space plus steroids administration. Control Group (62 patients): Epidural steroids injection.
10. Primary Endpoint:	Difference in pain reduction between the control group and the experimental group since the baseline visit and the 6 month visit evaluated by Visual Analogue Scale (VAS).
11. Secondary Endpoints:	• Change from Baseline in pain at 1, 2 and 4 months (Visual Analogue Scale, VAS). • Change from Baseline in disability at 1, 2 and 6 months (assessed by Oswestry Disability Index, ODI). • Change from Baseline in health survey at 1, 2, 4 and 6 (assessed by Short Form Health Survey, SF-12). • Change from Baseline in neuropathic pain at 1, 2 and 6 months (assessed by Douleur Neuropathique 4 Questions, DN4). • Change from Baseline in improvement of pain at 1, 2, 4 and 6 months (assessed by Patient Impression of Improvement, PGI-I). • Assessment of subject satisfaction with experimental procedure 2 and 6 months. • Incidence of unanticipated adverse device effects. • Change in opioid intake in 6 months. • Adverse events related to procedures (experimental group and control group).
12. Study Design:	Prospective, randomized, single-blind and multi-centre study. Controlled comparison between epidural steroids injection with catheter and epidural radiofrequency by catheter in the epidural space plus steroids administration. After the treatment, patients will be followed-up at 1, 2, 4 and 6 months.

13. Eligibility Criteria:	Inclusion Criteria: 1. Men and women over 18 years old. 2. Written informed consent according to ICH/GCP and Spanish legislation, obtained before any study procedure. 3. Pain VAS score at least 5 points. 4. Duration of pain at least 3 months after back surgery with conservative treatment. 5. Leg-dominant radicular pain deemed neuropathic based on clinical history and examination. 6. Responsive to selective radicular nerve block (bupivacaine 0.125%). 7. Patients who have had a previous epidural steroid injection. Exclusion Criteria: 1. Pregnancy or lactation. 2. Inability to give informed consent in the absence of a legal representative. 3. Subjects that are participating in a study with medicines or other clinical devices. 4 Those who show inability to follow the instructions or collaborate during the development of the study. 5. If in the opinion of the researcher there are findings in the physical examination, abnormalities in the results of the clinical analyses or other medical, social or psychosocial factors that could have a negative influence. 6. Patients with myelopathy, systemic diseases, infection (systemic or local), cancer, indication for immediate surgery, coagulation disorders, use of anticoagulants, diabetes mellitus or multiple sclerosis. 7. Life expectancy of less than one year. 8. A current diagnosis of a progressive neurological disease.
14. Study Population:	Patients with chronic lumbar radicular pain following failed back surgery.
15. Sample Size:	62 patients per group, a total of 124 patients.
16. Research Ethics Committee:	CEIm HM Hospitales
17. Calendar:	The total duration of the study from first enrolment to last subject last visit is estimated to be 28 months: • 4 months to prepare all documentation for contracts and Committee approval. • 12 months for enrolment. • 6 months follow up. • 6 months to close the investigation and provide final study report.

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3. - GENERAL INFORMATION

3.1 Clinical Investigation Identification

Protocol Code: EPIPUL

Title of the Clinical Investigation: Epidural Pulsed Radiofrequency versus Epidural Steroids Injection for Treatment of Failed Back Syndrome: A Prospective, Randomized, Single-Blind and Multicenter Study.

3.2 Type of Study

Clinical trial with a CE marked Medical Device used within its intended purpose and according to its authorized indications.

3.3 Description of the Device Study

3.3.1. RCE Introducer Cannulae (RCE-C916S-P).
3.3.2. RCE 40 cm Electrodes (RCE-E401519-P).
3.3.3. G4 RF Generator (RFG-4-120 V).
3.3.4. Disposable Ground Pads (DGP-PM-10).
3.3.5. Voltage Controlled Injection Electrode. Length 10 cm / Tip 5 mm / Echo RF (CR-10-P).

3.4 Data Related to the Sponsor

Fundación Investigación HM Hospitales,

Hospital Universitario HM Sanchinarro

Calle Oña 10

28050 Madrid (Spain)

E-mail:

3.5 Monitor Identification

Monitor to be assigned by the Sponsor.

3.6 Information on the Investigator Team

See Annex I.

3.7 Expected Duration of the Clinical Investigation

The overall duration of the study will be twenty-eight months, one year of recruitment and six months of follow-up, from the inclusion of the first patient until the last follow-up visit of the last patient.

3.8 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB), independent from the EPIPUL consortium, will be appointed to perform an independent supervision of the safety aspects of the study. The DSMB will have 3 members including at least one expert in clinical trial methodology and statistics, and one pain management expert independent from the study team. The DSMB will be established before the start of the study and will follow the procedures established in the "DSMB Charter for the EPIPUL study".

4. - JUSTIFICATION

Over the last twenty years, Pulsed Radiofrequency (PRF) has been applied to nerves as a less destructive alternative to thermal RF ablation (RFA) for pain reduction without disruption of somatic sensation and motor function [1]. PRF delivers RF in bursts that expose a target nerve to high-intensity electric fields (E-fields) but avoids gross thermal ablation by allowing electrically-generated heat to dissipate between bursts. Though the mechanism of PRF has not yet been fully established, theoretical and experimental findings suggest that the RF electric-field induces moderately disruptive [2, 3, 4, 5, 6, 7, 8] and neuromodulatory effects in primary sensory neurons and dorsal horn [2, 3, 7, 9, 10, 11, 12, 13, 14, 15, 16] that can reduce neuropathic hyperalgesia/allodynia [14, 15, 16, 17, 18, 19, 20, 21, 22]. Clinically, PRF is often applied using a "transforaminal" approach whereby a sharp RF cannula/electrode is positioned near a DRG and/or spinal nerve via the neural foramina. Transforaminal PRF of the DRG has been used for treatment of cervical radicular pain [23, 24, 25], lumbar radicular pain [24, 26, 27, 28, 29], postsurgical thoracic pain [26, 30], stump pain [31], postsurgical ilioinguinal neuralgia [32], and other pain disorders. PRF has also applied to the suprascapular nerve for shoulder pain [33, 34, 35], the saphenous [36] or sciatic nerves [37] for knee pain, the obturator and femoral nerves for hip pain [38], the genitofemoral or ilioinguinal or iliohypogastric nerve for groin pain or orchialgia [39], the lateral femoral cutaneous nerve for meralgia paresthetica [40], the intercostal nerve for postherpetic neuralgia [41], the Gasserian ganglion for trigeminal neuralgia [42], the greater and lesser occipital nerves for occipital neuralgia [43, 44], a stump neuroma for phantom limb pain [45], and other peripheral targets.

Failed Back Surgery Syndrome (FBSS) refers to a diverse array of chronic back or leg pain disorders that are either caused or untreated by a previous back surgery [46, 47, 48]. FBSS can involve multiple nociceptive and neuropathic pain etiologies for each patient, including internal disc disruption, facet and sacroiliac joint syndromes, structural instability, spondylitis, radiculitis, disc herniation, neural or spinal foramina stenosis, arachnoiditis, epidural and other postsurgical fibrosis, and other disorders. Whether due to FBSS inherent heterogeneity, multisegmental involvement or lack of specific diagnostic criteria, FBSS pain can be challenging to treat. Epidural steroids injection is currently the most common treatment for FBSS while transforaminal PRF

of the DRG and epidurolysis has produced mixed results [26, 27]. The present study explores the hypothesis that treatment of FBSS pain can be improved by epidural application of PRF to the DRG and dorsal nerve root, thereby reducing or blocking ectopic pain signals originating from sites of dorsal root irritation within the spine [49, 50, 51], in addition to ectopia from the DRG [49, 52, 53, 54, 55] and nociceptive signals from other painful anatomy. This study also explores the concept that epidural access can facilitate treatment of all affected dorsal roots and DRGs, some of which may be inaccessible transforaminal due to implanted hardware and bone anatomy.

Insausti et al. previously presented case reports about Epidural Radiofrequency with Catheter (ERC), wherein pulsed RF was delivered to lumbosacral nerve roots using an epidurolysis catheter inserted through the sacral hiatus without temperature control [56]. More recent case reports describe a similar technique using a catheter electrode that is specifically designed and indicated for radiofrequency treatment, and that includes a temperature sensor, an elongated 15-mm active tip, a generator connection, and an injection port (RCE-E401519-P, Cosman Medical, Inc., Burlington, MA, USA) [57,58]. Temperature monitoring was used to limit the risk of exposing spinal nervous tissue to neurolytic temperatures, and to maximize the electric-field dose (E-dose) under the 42 °C safety limit [3, 13, 59]. A longer active tip was used to increase the theoretical likelihood of placing the electrode active tip nearby the target nerve, and thus, of exposing that nerve to sufficiently strong E-fields.

The epidural orientation of the affected nerve roots may be particularly useful for PRF treatment of any pain syndrome involving direct irritation of DRG, including FBSS. Mechanical, chemical or ischemic nerve injury can cause ectopic firing that originates from both the site of injury and the DRG [51, 63]. While PRF is theorized to induce pain-relieving changes in the DRG and dorsal horn, structural and functional experiments also suggest that PRF may relieve pain at least in part using blockage of action potential propagation along smaller-diameter axons [4, 7]. Consistent with this, PRF is generally applied between the spinal cord and the site of a nerve injury when used to treat neuropathic pain caused by peripheral nerve damage. It can be reasonably hypothesized that treatment of pain involving nerve dysfunction within the spine would be improved by PRF application to the epidural nerves in epidural space before DRG is formed, so that pain signals generated in the central axon (dorsal root), soma (DRG), and peripheral axon (peripheral nerve) of afferent neurons are all blocked from entering the central nervous system.

Even if neuropathic pain is initiated only at a peripheral location, the application of PRF closer to the DRG has been associated with better outcomes [30], perhaps due to cessation or blockage of painful ectopic discharge emanating from the DRG in neuropathy [63]. Provided that the spinal canal is not itself restricted, epidural electrode placement can improve the positioning of the electrode active tip near the DRG, particularly at spinal levels that are inaccessible transforaminal due to implanted hardware, osteophytes overgrowth, or normal vertebral anatomy. Dorsal

roots and epidural nerves are organized somatotopically within the spinal canal [64], and each DRG is located at a regular position relative to the pedicle [65] which can be readily visualized radiographically relative to a radiopaque catheter electrode.

The PRF electric field strength decreases with distance from the electrode and across the width of a target nerve, so the relative position of a PRF electrode and target nerve likely affects efficacy [3]. Epidural placement may enhance nerve targeting and exposure to E-fields by tending to orient of the side of the electrode active tip across the nerve [3, 65], by allowing for use of a longer active tip (eg 15 mm epidurally vs. 5-10 mm transforaminal), and by avoiding physician hesitance to insert a sharp cannula deep into the neural foramina or near critical blood vessels [30]. The epidural approach also facilitates the treatment of pain disorders with multisegmental and bilateral involvement, by providing for targets of multiple spinal nerves through a single needle insertion. In contrast, the transforaminal approach requires a separate needle to be placed at each spinal level and side.

Differences in patient selection and methods from the previous study of transforaminal PRF [27] could also account for the apparent superiority of epidural over transforaminal PRF for the treatment of FBSS pain. In a previous study, PRF applied at each DRG for 120 seconds was unsuccessful in consistently reducing FBSS pain [27]. In the present study, PRF was applied at each level for 480 seconds. This longer treatment time likely increased the duration for which target nerves were exposed to the PRF electric field and could explain improved outcomes.

Temperature control is important for safe and effective application of PRF in the epidural space. Though no complications were reported during voltage-controlled epidural PRF [56], inadvertent exposure of nervous structures within the spinal canal to neurolytic temperatures could produce substantial complications. Temperature control also enables the delivery of the maximal pulsed RF electric field intensity and duration under the safety temperature limit of 42 °C [59], which was associated with greater pain reduction in a rat neuropathic pain model than was PRF delivery at 37 °C [13]. In the absence of temperature control, PRF efficacy may be limited by the need to preemptively moderate PRF parameters so that neurolytic temperatures are avoided under a wide variety of tissue conditions, electrode sizes, and patients [59]. These factors can vary greatly, as evidenced by our comparison of impedance and current measurements from small transforaminal electrodes and larger epidural electrodes.

5. - HYPOTHESIS AND ENDPOINTS

5.1 Hypothesis

This clinical investigation will intends to demonstrate reduction of chronic lumbar radicular pain following back surgery by epidural application of temperature-

controlled PRF to the dorsal radicular filaments proximal to the DRG and dorsal nerve root in the epidural space using a guidable, radio-opaque, catheter electrode (Boston Scientific RCE) having an elongated 15-mm active tip and a temperature sensor at its rounded distal point (Cosman RCE-E401519-P) versus epidural steroids injection.

5.2 Primary Endpoint

Difference in pain reduction between the control group and the experimental group since the baseline visit and the 6 month visit evaluated by Visual Analogue Scale (VAS).

5.3 Secondary Endpoints

5.3.1. Change from Baseline in pain at 1, 2 and 4 months (assessed by Visual Analogue Scale, VAS).

5.3.2. Change from Baseline in disability at 1, 2 and 6 months (assessed by Oswestry Disability Index, ODI).

5.3.3. Change from Baseline in health survey at 1, 2, 4 and 6 months (assessed by Short Form Health Survey, SF-12).

5.3.4. Change from Baseline in neuropathic pain at 1, 2 and 6 months (assessed by Douleur Neuropathique 4 Questions, DN4).

5.3.5. Assessment of improvement of pain with experimental procedure at 1, 2, 4 and 6 months (assessed by Patient Impression of Improvement, PGI-I).

5.3.6. Incidence of unanticipated adverse device effects.

5.3.7. Change in opioid intake in 6 months.

5.3.8. Adverse events related to procedures (experimental group and control group).

5.3.9. Assessment of subject satisfaction with experimental procedure at 2 and 6 months.

6. - ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

1. Men and women over 18 years old.
2. Written informed consent according to ICH/GCP and Spanish legislation, obtained before any study procedure.
3. Pain VAS score at least 5 points.
4. Duration of pain at least 3 months after back surgery with conservative treatment.
5. Leg-dominant radicular pain deemed neuropathic based on clinical history and examination.
6. Responsive to selective radicular nerve block (bupivacaine 0.125%).
7. Patients who have had a previous epidural steroid injection.

6.2 Exclusion Criteria

1. Pregnancy or lactation.
2. Inability to give informed consent in the absence of a legal representative.
3. Subjects that are participating in a study with medicines or other clinical devices.
4 Those who show inability to follow the instructions or collaborate during the development of the study.
5. If in the opinion of the researcher there are findings in the physical examination, abnormalities in the results of the clinical analyzes or other medical, social or psychosocial factors that could have a negative influence.
6. Patients with myelopathy, systemic diseases, infection (systemic or local), cancer, indication for immediate surgery, coagulation disorders, use of anticoagulants, diabetes mellitus or multiple sclerosis.
7. Life expectancy of less than one year.
8. A current diagnosis of a progressive neurological disease.

7. - STUDY DESIGN

7.1 Type of Clinical Investigation

Prospective, randomized, single-blind and multi-center study.

Controlled comparison between epidural and transforaminal electrode placement and epidural steroids injection.

7.2 Randomization Process

The clinical investigation will be single-blind. The assignment to the type of surgical treatment is carried out randomly and open for the investigators but not for

the patients. Randomization will be done with concealment of the randomization sequence and it takes place after informed consent has been signed.

7.3 Sample Size and justification

Pain reduction at least thirty millimeters between the baseline visit and the 6 months visit in patients assigned to the experimental group evaluated by the Visual Analogue Scale (VAS). Pain reduction of twenty millimeters less in the experimental group than in the control group since the baseline visit and the 6 months visit evaluated by the Visual Analogue Scale (VAS).

To achieve a power of 90.00% to detect differences in the contrast of the null hypothesis H_0: $\mu_1 = \mu_2$ through a bilateral T-Student Test for two independent samples, taking into account that the level of significance is 5%, and assuming that the mean of the difference in VAS of the 6-month radiofrequency plus steroid group is 40 mm, the average of the control group is 60 mm and the standard deviation of both groups is 30 mm, with an estimate of losses of the 20%, it will be necessary to include 62 patients per group, total of 124 patients.

7.4 Blinding

This study is single-blind.

7.5 Study Plan

7.5.1. Screening

At this clinic visit the subject will undergo the following evaluations:

- Sing Informed Consent.
- Demographics will be collected.
- A medical, pain and surgical history will be collected.
- Subjects will be asked to fill out VAS questionnaire.
- Medication use will be collected.
- Eligibility criteria will be evaluated.

All applicable information will be documented on a CRF.

7.5.2. Baseline* (within 30 days from Screening Visit)

At this clinic visit the subject will undergo the following evaluations:

- Randomization.
- Eligibility criteria will be re-evaluated.
- Any change of medication will be collected.

- Subjects will be asked to fill out standard questionnaires to assess (VAS, ODI, SF-12 and DN4).
- Subjects will be assessed for possible adverse events, if any.
- AP and lateral view lumbar imaging.
- Screening failures will be collected.

*Baseline and Treatment visits could be at the same time.

All applicable information will be documented on a CRF.

7.5.3. Treatment Visit (± 15 days)

At this clinic visit the subject will undergo the following evaluations:

- Treatment process.
- Study completion (if applicable).
- Adverse event monitoring.
- Deviation monitoring.
- Any change of medication will be collected.

7.5.4. 1 Month Visit (± 7 days)

At this clinic visit the subject will undergo the following evaluations:

- Any change of medication will be collected.
- Subjects will be asked to fill out standard questionnaires to assess (VAS, ODI, SF-12, DN4 and PGI-I).
- Subjects will be assessed for possible adverse events, if any.
- Adverse event monitoring.
- Deviation monitoring.

All applicable information will be documented on a CRF.

7.5.5. 2 Months Visit (± 14 days)

At this clinic visit the subject will undergo the following evaluations:

- Any change of medication will be collected.
- Subjects will be asked to fill out standard questionnaires to assess (VAS, ODI, SF-12, DN4 and PGI-I).
- Subjects will be assessed for possible adverse events, if any.
- Adverse event monitoring.
- Deviation monitoring.
- Subject questionnaire of treatment satisfaction.

All applicable information will be documented on a CRF.

7.5.6. 4 Months Visit (± 14 days)

At this clinic visit the subject will undergo the following evaluations:

- Any change of medication will be collected.
- Subjects will be asked to fill out standard questionnaires to assess (VAS, SF-12 and PGI-I).
- Subjects will be assessed for possible adverse events, if any.
- Adverse event monitoring.
- Deviation monitoring.

All applicable information will be documented on a CRF.

7.5.7. 6 Months Visit (± 20 days)

At this clinic visit the subject will undergo the following evaluations:

- Any change of medication will be collected.
- Subjects will be asked to fill out standard questionnaires to assess (VAS, ODI, SF-12, DN4 and PGI-I).
- Subjects will be assessed for possible adverse events, if any.
- Adverse event monitoring.
- Deviation monitoring.
- Subject questionnaire of treatment satisfaction.

All applicable information will be documented on a CRF.

7.5.8. Unscheduled Visit

At this clinic visit the subject will undergo the following evaluations:

- Any change of medication will be collected.
- Subjects will be asked to fill out standard questionnaires to assess (VAS, ODI, SF-12, DN4 and PGI-I).
- Subjects will be assessed for possible adverse events, if any.
- Study completion (if applicable).
- Adverse event monitoring.
- Deviation monitoring.
- Subject questionnaire of treatment satisfaction.

All applicable information will be documented on a CRF.

7.6 Evaluation Endpoints

- Primary endpoint

Visual Analogue Scale (VAS): The VAS measures the pain intensity reported by the subject. Subject scores the intensity of pain on a 10 mm line. The VAS in this study consists of a 10 mm line with one indicating "No Pain" and the other end indicating "Worst imaginable pain". Upon completion by the subject VAS scores will be measured and converted to a numeric value (0.0 mm to 10.0 mm) by site staff personnel. VAS is the most widely used outcome measure in assessing pain due to its documented reliability and validity, ease in administration, and minimal training requirements for the administrator.

Subjects will complete a mean VAS score for leg and back pain: at Baseline, months 1, 2, 4, 6 and if applicable at the Unscheduled visit. The change in leg and back pain VAS scores, the percentage change in leg and back pain VAS scores, and the responder rate for leg and back pain will be calculated and summarized for each visit.

- Secondary Endpoints.

- Oswestry Disability Index (ODI): The ODI measures functional disability as reported by the subject. Subjects will complete ODI during the study visits: at Baseline, months 1, 2, 6 and if applicable at the Unscheduled visit. The changes in functional disability will be summarized as continuous variables.

- Short Form Health Survey (SF-12): The SF-12 measure health status reported by subject at: Baseline, months 1, 2, 4, 6 and if applicable at the Unscheduled visit. The changes in health status will be summarized as continuous variables.

- Douleur Neuropathique 4 Questions (DN4): The DN4 measures the neuropathic pain reported by the subject. Subjects will complete DN4 during the study visits: at Baseline, months 1, 2, 6 and if applicable at the Unscheduled visit. The changes in neuropathic pain will be summarized as continuous variables.

- Patient Impression of Improvement questionnaire (PGI-I): The PGI-I measure subjective improvement in pain. Subjects will complete PGI-I form during the study visits at: month 1, 2, 4, 6 and if applicable at the Unscheduled visit.

- Medication Usage: morphine equivalent units of opioid medications; other non-opioid pain medications. Assessed at: Baseline, months 1, 2, 4, 6 and if applicable at the Unscheduled visit.

- 5-point scale where 1 is "very satisfied" to 5 that is "very dissatisfied"; their charging convenience and remote control use during the study visits: Months 2, 6 and if applicable at the Unscheduled visit. The responses will be summarized. Study personnel will be appropriately trained for administration of each test.

- Safety (device and procedures): Safety will be assessed by characterizing clinically meaningful change in adverse events at all study visits and in related to medical device or procedures.

7.7 Early Subject Withdrawal

Subjects may be withdrawn early from the study for a number of reasons, including but not limited to:

- Subject request.
- Investigator request.
- Subject lost to follow up.
- Subject death.
- Intolerable adverse events.

If a subject is discontinued from the study early, a Termination CRF will be completed describing the reason for discontinuation. The Investigator should make all attempts to conduct a visit within 10 days (±4 days) after withdrawal from the study. If a subject has withdrawn consent for the study, or is lost to follow-up, the completion of this visit is not imperative. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of that adverse event or determination that the subject's condition is stable.

In case of an Early Subject Withdrawal the subject will be assessed for adverse events, if any, and medication use. This will be documented on an Unscheduled Visit CRF.

In case the Early Subject Withdrawal happened at a study specific follow-up visit (see Table 1. Schedule of Events) no Unscheduled Visit CRF need to be completed.

7.8 Study Completion

All subjects enrolled in this study are expected to complete all scheduled visits through the 6 Months Follow-Up Visits. A Study Completion CRF should be completed at this visit. In situations where there is an ongoing device related adverse event, subjects will be followed until resolution of that adverse event or determination that the subject's condition is stable, at which point the Study Completion CRF should be completed.

7.9 Study Suspension and Termination

The study may be terminated when all of the requirements of the investigational plan have been fulfilled. Subjects will be considered to have completed all study requirements following completion of the 6 Months Follw-Up Visits. The clinical sites will be considered to have completed the study requirements at the end of the clinical site close out monitoring visit. The study will be considered terminated when

all close out visits have been completed and all Sponsor and Investigator reports have been issued.

Sponsor, the Investigators, or the EC may suspend or terminate the study early at any time. If the study is suspended or terminated prematurely, all currently enrolled subjects will be withdrawn from the study and a Study Completion/Termination CRF will be completed. If there is an ongoing event related to the device or therapy, the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable.

The Sponsor reserves the right to terminate the study, but intends only to exercise this right for valid scientific or business reasons, or reasons related to the protections of the study subjects. Investigators and ECs will be notified in writing in the event of study termination. Possible reasons for study termination include, but are not limited to the discovery of unexpected, significant, or unacceptable risk to subjects enrolled in the study.

The Sponsor reserves the right to stop the enrollment of subjects at a clinical site at any time after the clinical site initiation visit if no subjects have been enrolled, or if the clinical site has multiple deviations from the clinical investigational plan without justification, or fails to follow remedial actions. Possible reasons for suspending or terminating a clinical site may include, but are not limited to:

- Investigator non-compliance.
- Repeated failure to complete or submit CRFs in a timely manner.
- Failure to obtain written informed consent.
- Failure to report SAEs or USADEs to the Sponsor and/or EC within 24 hours of knowledge.
- Failure to control or account for investigational products used.

7.10 Definition of Population for Analyses

We define 3 different subject populations for analysis:

1. Intent-to-Treat (ITT)

- All subjects who receive any treatment of the groups (Experimental or Control)

2. Per Protocol (PP)

- All subjects who receive treatment of the study and complete the Primary Effectiveness Assessment (Primary Endpoint defined above).

3. ITT-Baseline (ITT-B)

• All subjects who complete baseline assessment. In order to capture AEs that occur prior to the 6 months follow-up visit.

8. – SAFETY ASPECTS

The definitions presented in this section allow for a clear understanding of adverse event data collection and reporting requirements.

Medical Device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article.

Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose (s) of:

- Diagnosis, prevention, monitoring, treatments or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- Investigation, replacement, modification, or support of the anatomy or of a physiological process,
- Supporting or sustaining life,
- Control of conception,
- Disinfection of medical devices and

Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means. The term 'medical device' is usually defined by national regulations.

8.1 Adverse Events

The following adverse events will be recorded in the eCRF of the study:

- All serious adverse events.
- All adverse events considered of interest for this study, regardless of their seriousness.

NOTE - As the primary efficacy measure in this study is pain, leg and back pain does not need to be reported as an adverse event unless it meets the definition of a serious adverse event. However, Investigators may, at their discretion, report any pain-related adverse events during the study.

8.1.1 Serious Adverse Event (SAE)

An adverse event (AE) includes any unforeseen illness or injury or adverse clinical sign (including abnormal laboratory results) related or not to the investigational product. This includes events related to the product or to the comparator, or to the procedures involved.

It will be considered a serious adverse event (SAE) when:

- Causes death.
- It leads to a significant deterioration in the patient's health that results in:
  - Illness or injury that threatens life.
  - A permanent deterioration of a body structure or function.
  - Hospitalization or prolongation of hospitalization.
  - Medical or surgical intervention to prevent a life-threatening illness, injury or permanent disability of a body structure or function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Adverse events of interest for this study will be considered:

- Duration of the procedures greater than 1 hour.
- Problems related to the surgical wound.
- Infection.

NOTES:

- Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
- A pregnancy is not considered to be a serious adverse event but will be captured in the CRF as a non-serious adverse event to allow follow-up on the outcome of the pregnancy
- Examples for serious deterioration are: cardiac arrest (CPR required), CVA, paralysis, sepsis, amputation, internal/external bleeding, cancer, fracture requiring intervention, myocardial infarction.

8.2 Adverse Device Effect (ADE)

An adverse event related to the use of a medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

This definition includes any event resulting from the use error or from intentional misuse of the medical device.

During this clinical investigation an event should be considered related to the device when it is the result of:

- The device components (e.g. lead, extension, Trial Simulator, Remote).
- The Therapy/simulation.

8.3 Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect that was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Those known adverse events related to the device, procedure or therapy is listed in the Risk Analysis section.

8.4 Anticipated serious adverse device effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Untoward medical occurrences that are not unanticipated, i.e. are unsurprising, are identified in the Physician Manual or CIP and ICF.

8.5 Device Deficiency

PRF is a CE marked (as well as TGA and FDA approved) device which meets vigilance reporting criteria. Device Deficiencies will be handled under the post-market surveillance / vigilance system from the Sponsor.

8.6 Serious adverse device effect

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.7 Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

- Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and no sequelae.

- Moderate: Interferes with the subject's usual activity or requires symptomatic treatment.
- Severe: Symptom(s) causing severe discomfort with significant impact of the subject's usual activity and requires treatment.

8.8 Reporting.

According to current regulations, professionals must report those incidents that are associated with a medical device or with the information provided with the product and that incident is such that is has caused death or a serious deterioration in health, or if it occurs again it can cause them.

An incident is understood to be any malfunction, failure ore deterioration of the characteristics or operation of a product, as well as any deficiency in the labelling or in the instructions for use that could or have led to death or serious deterioration of the condition health of a patient or a user. The types of adverse incidents that must be reported are the following:

1. Those that lead to death.

2. Those that give rise to a serious deterioration of the state of health of the patient, user or other person, such as:

- Illness or injury with threat to life.
- Permanent deterioration of a bodily function or permanent damage to a body structure.
- Process that requires medical or surgical intervention to avoid permanent deterioration of a bodily function or permanent damage to a body structure.

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

These incidents must be reported by the investigators. They must notify the sponsor of any serious incidents that may be related to the devices involved in the development of the investigation, through Annex III available at:

https://www.aemps.gob.es/vigilancia/productosSanitarios/vig-prof-nota.htm#II

And the sponsor must evaluate them and notify them to the surveillance points of medical devices of the CCAA, in accordance with the general guidelines established by the Medical Device Surveillance System for the notification of adverse incidents:

https://www.aemps.gob.es/surveillance/healthproducts/professional-monitoring.htm

The Sponsor contact information for these events is:

Dr. Agustín Mendiola de la Osa,

E-mail: epipulpdh@gmail.com

Table1. Schedule

Assessment								
Visit	Screening	Baseline	Treatment	1 month	2 months	4 months	6 months	Unscheduled
Window		Within 30 days from screening	± 15 days	± 7 days	± 14 days	± 14 days	± 20 days	
Pregnancy Test	X							
Sign Informed Consent	X							
Entry Criteria Evaluation	X	X						
Demographics	X							
Medical History	X	X						
Randomization		X						
Treatment Process			X					
Pain and Surgical History	X							
Medication Usage	X		X	X	X	X	X	X
VAS questionnaire		X		X	X	X	X	X
ODI questionnaire		X		X	X		X	X
SF-12 questionnaire		X		X	X	X	X	X
DN4 questionnaire		X		X	X		X	X
PGI-I questionnaire				X	X	X	X	X
Subject questionnaire of treatment satisfaction					X		X	X
AP and Lateral radiography imaging		X						
Deviation Monitoring			X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X
Screening Failures		X						
Study Completion			X				X	X

9. - TREATMENT DESCRIPTION

Both treatments (control group and experimental group) will always be performed in an ambulatory environment through sedation and anaesthesia.

The lower back and buttocks will be prepared for an aseptic technique. Lateral and AP views of the sacral foramina and hiatus will be taken and the entry point for the epidural needle will be marked on the surface of the skin, 1-2 cm caudal to the sacral hiatus. The skin and subcutaneous tissue underlying the entry site will be anesthetized using 1-2 ml of 1% lidocaine.

A 9-cm-long, 16-gauge (ga) epidural needle (Cosman RCE-C916S-P) is inserted through the skin and into the caudal canal, 1-2 cm beyond the sacral hiatus, ending at an angle of approximately 15º concerning the skin. Intravascular and subdural placement will be ruled out by injecting 1-1.5 ml of non-ionic radiographic contrast (180 mg of iohexol per ml) through the fluoroscopic needle in vivo.

9.1 Control Group. Epidural Steroids Injection.

A radiopaque, guidable radiofrequency electrode (Cosman RCE-E401519-P) will bend slightly at a 45º angle proximal to its metal tip and then be inserted through the needle. The electrode shall include an active 20/15 mm gauge tip, a 19/40 cm gauge shaft, a rounded distal point temperature sensor, an injection port and an integral generator connection. The electrode will be visualized by fluoroscopy as it is guided in the epidural space from the sacral canal to the lumbar vertebral canal.

The electrode will be connected to an output of the RF generator (Cosman RFG-4-120V/GF RF Generator). To provide a monopolar PRF operation, a ground pad (Cosman DGP-PM-10) will be placed on a shaved muscle part of the posterolateral thigh skin and connected to the reference socket of the RF generator with voltage 0 for 240 seconds (to ensure single-blind).

Intravascular and subdural placement will be ruled out by injecting 1-1.5 ml of non-ionic radiographic contrast (180 mg of iohexol per ml) through the integral injection port of the electrode under live fluoroscopy. Subsequently, betamethasone 12 mg will be administered.

After treatment, the needle and electrode will be removed. A sterile dressing will be applied over the needle insertion site. The patient will be monitored (visualized by fluoroscopy) while the sedation is removed, the motor dysfunction of the leg is verified and then the patient will be discharged.

9.2 Experimental Group. Epidural Pulsed Radiofrequency.

A radiopaque, guidable radiofrequency electrode (Cosman RCE-E401519-P) will bend slightly at a 45º angle proximal to its metal tip and then be inserted through the needle. The electrode shall include an active 20/15 mm gauge tip, a 19/40 cm gauge shaft, a rounded distal point temperature sensor, an injection port and an integral generator connection. The electrode will be visualized by fluoroscopy as it is guided in the epidural space from the sacral canal to the lumbar vertebral canal. The electrode will be connected to an output of the RF generator (Cosman RFG-4-120V/GF RF Generator). To provide a monopolar PRF operation, a ground pad (Cosman DGP-PM-10) will be placed on a shaved muscle part of the posterolateral thigh skin and connected to the reference socket of the RF generator.

The active tip of 15 mm of the electrode will be placed in the internal aspect of the pedicle in each of levels L4, L5 and / or S1, on the right or left side, according to the patient's pain distribution (Figure 1). Intravascular and subdural placement will be ruled out by injecting 1-1.5 ml of non-ionic radiographic contrast (180 mg of iohexol per ml) through the integral injection port of the electrode under live fluoroscopy. At each treated level, motor stimulation (50 Hz, 1 ms) of less than 0.4 volts will reproduce the patient's pain and motor stimulation (2 Hz, 1 ms) of less than 0.6 volts will result in a contraction muscle in the leg. The pulsed radiofrequency will be applied for 240 seconds (4 minutes), where the pulses of 45 volts and 20 milliseconds (ms) will be administered at 2 Hz (pulses per second) and the pulse width will be regulated to maintain the temperature at 42 ºC or less. (E-dose = Vary Width). The steady-state impedance and current will be measured for each PRF epidural treatment at L5 and S1 levels using the 20-gauge, 15 mm active tip.

After the experimental treatment, the needle and electrode will be removed without injecting or any other substance capable of producing pain relief. A sterile dressing will be applied over the needle insertion site. The patient will be monitored while the sedation is removed, the motor dysfunction of the leg is verified and then the patient will be discharged.

10. - PRACTICAL CONSIDERATIONS AND ETHICALS ASPECTS

10.1 General Considerations

The Clinical Investigation will be conducted under conditions of respect for the fundamental rights of the person and the ethical postulates that affect biomedical research with human beings, following the international recommendations included in the Declaration of Helsinki, and their subsequent revisions. Likewise, the national recommendations will be followed in accordance with the guidelines of the Spanish Agency of Medicines and Medical Devices.

During the conduct of this study, the researchers will strictly comply with the provisions of this protocol, fully completing the Data Collection Notebook.

10.2 Informed Consent

In accordance with the criteria of good clinical practice, the subjects will be duly informed of all the details concerning their participation in the study and will freely give their consent in writing.

10.3 About the Participating Staff

The researchers will follow the Good Clinical Practice guidelines. All information collected during the study must be recorded directly in the CRF. Any correction made in the CRF must be accompanied by the date and initials of the person who makes them.

15.2.1. Responsibilities

1. Investigator

The researcher must comply with following obligations:

- Commit to carry out the study in accordance with what is established in its protocol, ensuring that your participation in this study does not alter your clinical responsibilities or the normal functioning of the Service to which you belong.
- Inform those responsible for the management of the center to which they belong to their participation in the study.
- Inform research subjects and obtain their consent.
- Collect, record and notify the data correctly responding to its update and quality before the appropriate audits.
- You must answer any questions about the objectives, basic methodology and meaning of the results of the study before the scientific and professional community.

- Facilitate the inspections of the health authorities, which will keep the study documentation a minimum of 5 years after the presentation of the final report.
- It will be responsible for the information recorded in the CRD being accurate, truthful and obtained in the manner indicated in the protocol.
- The investigator is the only person who can and should know the origin of the data collected and associate them with the patient, being responsible for not showing in the CRD extra (unclaimed) information that can identify the patient (name, DNI / NIF, NASS, CIP, postal address, telephone ...).
- Especially, the researcher must ensure at all times the best possible care of the patient, always putting the well-being and safety of his patients.

2. Coordinating Investigator:

- The coordinating researcher must fulfill all the obligations as a researcher of the study and also must sign the protocol and any modification thereof together with the promoter, will be responsible together with the promoter in the preparation of the monitoring and final reports, will contribute to disseminate the results of the study in collaboration with the promoter.
- Send the protocol to the CEIm.

3. Sponsor:

- Will be responsible for ensuring compliance with the relevant legal regulations.
- Sign the protocol and any modification of it with the coordinating investigator.
- Present the study protocol and the follow-up and final reports, within the established deadlines and communicate, where appropriate, the interruption and the reasons for it.
- Provide a copy of the protocol and the documents that accredit the follow-up of the established procedures to those responsible for the entities providing health care services where the study will be carried out.

10.4 Security Devices and Confidentiality

The information obtained in the present study is confidential, with patients accepting, in writing, that researchers and Health Authorities have access to their medical records to verify the data or procedures of the study, without violating the

confidentiality of the data compliance with current legislation. In each participating centre, the clinical data will be identified by an alphanumeric code, which does not allow to identify the personal data of the patients, such as name, initials, address or other personal characteristic. Likewise, the confidentiality of the identity of the patients would be respected if the data obtained in this study were published.

The data of the subjects included in the study will be treated in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27 2016 and according to the Spanish Law, The Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights regarding the protection of individuals with regard to treatment of personal data and the free circulation of these data, and in the other applicable legislation in force regarding the protection of personal data.

11. - ECONOMICAL ASPECTS

11.1 Insurance Policy

According with current clinical trial legislation, this clinical trial does not require an insurance policy since the devices under study are used under the authorized conditions of use and the study does not imply an increase in the risk to the patient.

12. - PUBLICATIONS RIGHTS

Principal Investigator shall have the right to publish the results of the Study in any abstract, paper, presentation or manuscripts (not limited enumeration).

Principal Investigator shall give BOSTON SCIENTIFIC a reasonable period of 30 (thirty days) to review and comment upon an intended publication of Principal Investigator regarding the results of the Study prior to publication, to determine if any Intellectual Property Rights and/or Confidential Information should be removed. BOSTON SCIENTIFIC shall respond promptly in writing to Principal Investigator with any comments or objections, setting forth such information in reasonably sufficient detail.

Principal Investigator shall consider BOSTONS'S SCIENTIFIC comments and/or objections in good faith and shall cause any and all appropriate changes to be made prior to further distribution and publication.

13. - STATISTIC ANALYSIS

A descriptive analysis of the categorical variables was performed using absolute and determined frequencies; and in the numerical variables, through the mean and

standard or median deviation and 25th and 75th percentiles, according to compliance with the assumption of normality.

The analysis of the main variable, pain difference between baseline measurement and 6 months after treatment in the radiofrequency group plus steroids vs steroids, will be carried out using a contrast of means with the t-Student or U Mann-Whitney test in case of not being able to fulfill the corresponding assumptions.

The size of the effect is estimated with Cohen's letter, interpreting a Cohen's letter <0.01 as "very small", between 0.01 to 0.2 as a "small" effect, around 0.5 an "average" effect ", from 0.8 to infinity, a" large "effect, according to the categorization of Cohen and Sawilowsky (Cohen, Jacob (1988). Statistical analysis of power for behavioral sciences. Routledge; Sawilowsky, S (2009). "New effect size rules of thumb". Journal of Modern Applied Statistical Methods. 8 (2): 467–474.).

If the imbalance is observed between the two groups, linear regression will be executed to adjust for variables that are observed unbalanced between them.

The level of significance has been set at 0.05. The statistical package used is Stata / IC v.15.1. (StataCorp. 2017. Stata Statistical Software: version 15. College Station, TX: StataCorp LLC).

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15. - ANEXES

15.1 Annex I. Information on the Investigator Team

Name	Centre	Title
Agustín Mendiola	HM Hospitales	Coordinating/ Principal Investigator
Manuel Agustín Herrero	H. U. HM Sanchinarro	Site Principal Investigator
Sandra Helena Martínez	H. U. Puerta de Hierro	Site Principal Investigator
Moisés Vásquez	H. U. Rey Juan Carlos	Site Principal Investigator
Rogelio Rosado	H. Fremap	Site Principal Investigator
María Ángeles Canós	H. U. La Fé de Valencia	Site Principal Investigator
Pablo López	H. C. U. Santiago	Site Principal Investigator

15.2 Annex II. Study Forms

NOTE: All forms will have the following header and footer so that they are perfectly identified

1.- Header:

"Epidural Pulse Radiofrequency for Treatment of Failed Back Syndrome: Prospective, Randomized, Single-Blind Study"

Patient ID Number:	**Name:**
Date Of Visit (*DD/MM/YYYY*)**:**	**Sign:**

2.- Footer:

Confidentiality: The data of the subjects included in the study will be treated in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27 2016 and according to the Spanish Law, The Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights regarding the protection of individuals with regard to treatment of personal data and the free circulation of these data, and in the other applicable legislation in force regarding the protection of personal data.

15.2.1. Visual Analogue Scale (VAS)

VIAUSAL ANALOGUE SCALE (VAS) OF PAIN

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

Pain assessment
Instructions: Place a vertical bar (|) in the place of the line that describes the average pain that have you felt in the last 7 days.

PAIN BACK

No Pain _____ The worst pain imaginable

Patient marked average (cm): [ ]

15.2.2. Oswestry Disability Index (ODI)

Oswestry Disability Index (ODI)

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

Instructions: This questionnaire is designed to provide information on how back problems affect your ability to perform daily activities. Complete each section. In each one, check only the box that best suits your situation today.

Section 1: Pain Intensity

☐ I have no pain at the moment. [0 points]

☐ The pain is very mild at the moment. [1 point]

☐ The pain is moderate at the moment. [2 points]

☐ The pain is fairly severe at the moment. [3 points]

☐ The pain is very severe at the moment. [4 points]

☐ The pain is the worst imaginable at the moment. [5 points]

Section 2: Personal Care

☐ I can look after myself normally without causing extra pain. [0 points]

☐ I can look after myself normally but it is very painful. [1 point]

☐ It is painful to look after myself and I am slow and careful. [2 points]

☐ I need some help but manage most of my personal care. [3 points]

☐ I need help every day in most aspects of self care. [4 points]

☐ I do not get dressed, wash with difficulty and stay in bed. [5 points]

Section 3: Lifting

☐ I can lift heavy weights without extra pain. [0 points]

☐ I can lift heavy weights but it gives extra pain. [1 point]

☐ Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned, e.g. on a table. [2 points]

☐ Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned. [3 points]

☐ I can lift only very light weights. [4 points]

☐ I cannot lift or carry anything at all. [5 points]

Section 4: Walking

☐ Pain does not prevent me walking any distance. [0 points]

☐ Pain prevents me walking more than one mile. [1 point]

☐ Pain prevents me walking more than a quarter of a mile. [2 points]

☐ Pain prevents me walking more than 100 yards. [3 points]

☐ I can only walk using a stick or crutches. [4 points]

☐ I am in bed most of the time and have to crawl to the toilet. [5 points]

Section 5: Sitting

☐ I can sit in any chair as long as I like. [0 points]

☐ I can sit in my favourite chair as long as I like. [1 point]

☐ Pain prevents me from sitting for more than 1 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]

☐ Pain prevents me from sitting at all. [5 points]

Section 6: Standing

☐ I can stand as long as I want without extra pain. [0 points]

☐ I can stand as long as I want but it gives me extra pain. [1 point]

☐ Pain prevents me from standing for more than 1 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]

☐ Pain prevents me from standing at all. [5 points]

Section 7: Sleeping

☐ My sleep is never disturbed by pain. [0 points]

☐ My sleep is occasionally disturbed by pain. [1 point]

☐ Because of pain I have less than 6 hours sleep. [2 points]

☐ Because of pain I have less than 4 hours sleep. [3 points]

☐ Because of pain I have less than 2 hours sleep. [4 points]

☐ Pain prevents me from sleeping at all. [5 points]

Section 8: Sex Life (if applicable)

☐ My sex life is normal and causes no extra pain. [0 points]

☐ My sex life is normal but causes some extra pain. [1 point]

☐ My sex life is nearly normal but is very painful. [2 points]

☐ My sex life is severely restricted by pain. [3 points]

☐ My sex life is nearly absent because of pain. [4 points]

☐ Pain prevents any sex life at all. [5 points]

Section 9: Social Life

☐ My social life is normal and causes me no extra pain. [0 points]

☐ My social life is normal but increases the degree of pain. [1 point]

☐ Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g. sport, etc. [2 points]

☐ Pain has restricted my social life and I do not go out as often. [3 points]

☐ Pain has restricted social life to my home. [4 points]

☐ I have no social life because of pain. [5 points]

Section 10: Traveling

☐ I can travel anywhere without pain. [0 points]

☐ I can travel anywhere but it gives extra pain. [1 point]

☐ Pain is bad but I manage journeys over two hours. [2 points]

☐ Pain restricts me to journeys of less than one hour. [3 points]

☐ Pain restricts me to short necessary journeys under 30 minutes. [4 points]

☐ Pain prevents me from travelling except to receive treatment. [5 points]

Douleur Neuropathique 4 questions (DN4)

Douleur Neuropathique 4 Questions (DN4)

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

Instructions: Answer the four questions below with Yes or No for each item:

Question 1: dose your pain present one or more of the following characteristics?

1. Pain feels like burning YES / NO
2. Sensation of painful cold YES / NO
3. Pain feels like electric shocks YES / NO

Question 2: in the same area, is your pain associated to one or more symptoms?

4. Tingling YES / NO
5. Pins and needles YES / NO
6. Numbness YES / NO
7. Itching YES / NO

(Now your doctor will perform a physical examination)

Question 3: in is the pain located in an area where the exam unveils?

8. Hypoesthesia to touch? YES / NO
9. Hypoesthesia to pinprick? YES / NO

Question 4: is the pain provoked or increased by

10. Brushing? YES / NO

PATIENT SCORE: ☐

15.2.3. Short Form Health Survey (SF-12)

SHORT FORM HEALTH SURVEY (SF-12)

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general would you say your health is:

☐ Excellent

☐ Very Good

☐ Good

☐ Fair

☐ The Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2. Moderate activities, such as moving a table, pushing a vacuum cleaner, cowling, or playing golf:

☐ Yes, limited a lot

☐ Yes, limited a little

☐ No, not limited at all

3. Climbing several flights of stairs:

☐ Yes, limited a lot

☐ Yes, limited a little

☐ No, not limited at all

During the past week, have you had any of the following problems with your work or other regular daily activities as a result of physical health?

4. Accomplished less than you would like:

☐ Yes

☐ No

5. Were limited in the kind of work or other activities

☐ Yes

☐ No

During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you like:

☐ Yes

☐ No

7. Didn't do work or other activities as carefully as usual:

☐ Yes

☐ No

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all

☐ A little bit

☐ Moderately

☐ Quite a bit

☐ Extremely

These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week

9. Have you felt calm and peaceful?

☐ All of the time

☐ Most of the time

☐ A good bit of the time

☐ Some of the time

☐ A little of the time

☐ None of the time

10. Did you have a lot of energy?

☐ All of the time

☐ Most of the time

☐ A good bit of the time

☐ Some of the time

☐ A little of the time

☐ None of the time

11. Have you felt downhearted and blue?

☐ All of the time

☐ Most of the time

☐ A good bit of the time

☐ Some of the time

☐ A little of the time

☐ None of the time

12. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time

☐ Most of the time

☐ A good bit of the time

☐ Some of the time

☐ A little of the time

☐ None of the time

15.2.4. Short Form Health Survey (SF-12)

Patient General Impression of Improvement (PGI-I)

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

Since the beginning of the study, my general state of health

☐ Very much improved

☐ Much improved

☐ Minimally improved

☐ No change

☐ Minimally worse

☐ Very much worse

15.2.5. Subject Satisfaction

SUBJECT SATISFACTION

Sponsor: Fundación Investigación HM Hospitales
Principal Investigator: Dr. Agustín Mendiola de la Osa
Protocol Code: EPIPUL
Form Version: *1.0 of 26th of July 2019*

How satisfied are you with the treatment?

☐ Very satisfied

☐ Satisfied

☐ Not sure

☐ Dissatisfied

☐ Very dissatisfied