NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain

Low back pain of unknown cause (non-specific) can be long term (chronic) and difficult to treat (refractory). In this procedure, a cut is made on the lower back or upper buttock and a small battery-powered device (neurostimulator) is placed under the skin. Two wires are placed near the nerves that control the muscles either side of the spine (lumbar multifidus muscles) and connected to the neurostimulator. After the procedure, the patient uses a remote control to stimulate the nerves using low-voltage electricity. This is usually done twice a day for about 30 minutes. The aim is to stimulate the lumbar muscles and reduce pain.

Contents

Abbreviations

Word or phrase	Abbreviation
Chronic low back pain	CLBP
Chronic mechanical low back pain	CMLBP
Clinical Global Impression	CGI
Confidence interval	CI
Cumulative-proportion-of-responders analysis	CPRA
European quality of life score on 5 dimensions	EQ-5D
Interventional procedure	IP
Interventional procedures advisory committee	IPAC
Intention to treat	ITT
Low back pain	LBP
Minimal clinically important difference	MCID
National Institute for Health and Care Excellence	NICE
Non-specific chronic low back pain	NSCLBP
Numerical rating scale	NRS
Oswestry Disability Index	ODI
Percent-of-pain-relief	PPR
Quality of life	QoL
Randomised controlled trial	RCT
Standard deviation	SD
Subject Global Impression of Change	SGIC
Treatment Satisfaction Questionnaire	TSQ
Visual analogue scale	VAS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional

procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2021.

Procedure name

- Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain

Professional societies

- UK Spine Societies Board (UKSSB)
- British Association of Spinal Surgeons (BASS)
- Faculty of Pain Medicine, Royal College of Anaesthetists
- British Pain Society
- Neuromodulation Society of UK and Ireland.

Description of the procedure

Indications and current treatment

Non-specific chronic low back pain (NSCLBP) can present in various ways, including as neuropathic pain (associated with damage to the nervous system) or nociceptive pain (associated with physical damage to joints, muscles and ligaments). It can be exacerbated by movements. In some people the pain can resolve spontaneously. NSCLBP is a common condition with several recognisable contributing or causative factors. These include functional instability of the spine caused by dysfunction of the lumbar multifidus (large muscles that support the lower back) and arthrogenic muscle inhibition.

Treatments for low back pain are described in NICE's guideline on low back pain and sciatica in over 16s: assessment and management. Conservative pain management includes pharmacological treatments (such as oral non-steroidal anti-inflammatory drugs, and weak opioids with or without paracetamol) and non-interventional treatments (such as self-management advice and education,

exercise, manual therapies, and combined physical and psychological therapy). Patients with severe chronic low back pain that is refractory to conservative treatments may be offered interventional procedures (such as radiofrequency denervation and epidural injections) or surgery (such as spinal fusion procedures).

What the procedure involves

The procedure is done under general anaesthesia, or local anaesthesia with sedation. A pulse generator (neurostimulator) is implanted in a subcutaneous pocket created in the lower back or upper buttock. Under fluoroscopic guidance through a midline approach, 2 stimulating leads are inserted. The distal ends of each lead have 4 stimulating electrodes. They are positioned next to the spinal column, near the medial branch of the L2 motor nerve supply (dorsal ramus nerve) to the multifidus muscles, and fixed using flexible tines. The leads are tunnelled internally, then the proximal ends are connected to the pulse generator and the position is checked radiographically.

Approximately 14 days after the implantation procedure, the patient can start to use the device to manage their pain. While lying prone, they use a handheld wireless remote control to deliver stimulation to the nerve supply of the lumbar multifidus muscles, which causes them to contract. This is usually done twice a day for about 30 minutes each time. The pulse generator can be programmed to deliver stimulation between any pair of electrodes on each lead if needed.

The aim of neurostimulation is to help the body regain multifidus neuromuscular control by 'activating' the lumbar muscles and stabilising the spinal column, reducing chronic pain.

Efficacy summary

Improvement in back pain

A randomised, blinded sham-controlled trial of 204 patients with CMLBP and impaired multifidus control who had an implanted neuromuscular restoration stimulator reported that the proportion of 'responders' in the ITT analysis (that is, more than 30% relief on the low back pain VAS without an increase in analgesics) at 120-day follow up were not significantly different in the therapeutic stimulation group than in the low-level sham-stimulation control group (57% compared with 47%; difference of 10%; 95% CI, -3.3% to 24.1%; p=0.138; Gilligan 2021). The control group crossed over to active stimulation after the 120-day visit. After 2-year follow up (in the overall cohort), the proportion of patients experiencing ≥30% improvement in VAS was 82.6% (128/155; 95% CI 76.6% to 88.6%), the proportion of patients experiencing ≥50% improvement in

VAS was 71.6% (111/155;95% CI 64.5% to 78.7%), and the proportion of patients experiencing ≥70% improvement in VAS was 61.9% (95% CI 54.3% to 69.6%). The proportion of patients experiencing LBP resolution (VAS≤2.5 cm) was 66.5% (103/155) after 2 years (95% CI 59.0% to 73.9%; Gilligan 2021).

In the RCT at 120-day follow up, the average LBP VAS improved from 7.3±0.7 cm at baseline to 4.0±2.7 cm in the therapeutic group and 4.8±2.9 cm in the sham control group. The mean group difference was significantly in favour of the therapeutic stimulation treatment group (-3.3 compared with -2.4; difference of -0.9 cm; 95% CI -1.6 to -0.1 cm; p=0.032). The cumulative-proportion-of-responders analysis showed that therapeutic stimulation was superior to sham control (p=0.0499). The difference in proportion of LBP resolution (VAS<2.5 cm) was not statistically significant between the 2 groups (34% compared with 28%; difference of 6%; 95% CI -6.5 to 19.0%; p=0.335). At 1-year follow up in the overall cohort (n=176), mean average LBP had improved by -4.3±2.6 cm (95% CI -4.7 to -3.9; p<0.0001) or -58.9±35.0% (95% CI -64.1 to -53.6%; p<0.0001), and 74% (130/176) of patients had a 30% or greater improvement; 64% of patients had a 50% or greater improvement; and 52% reported LBP resolution (VAS≤2.5 cm). A reduction in mean LBP VAS from 7.3±0.7 at baseline to 2.4±0.2 at 2-year follow up for completed cases (difference of -4.8±0.2, 95% CI -5.24 to -4.5, or percentage difference of -66.7±2.6, 95% CI -71.7 to -61.6; p<0.0001) was reported (Gilligan 2021).

A prospective case series (initial open-label study) of 53 patients with CMLBP, implanted with a neurostimulator for contraction of the lumbar multifidus, reported satisfactory improvement in LBP. Back pain (7-day average, evaluated on a 10-point NRS, with 0 indicating no pain and 10 worst pain) reduced from 6.8±0.8 at baseline to -2.5±0.3 (p<0.0001) at 90-day follow up. The responder rate (defined as patients with at least a 2-point reduction in the mean 7-day average NRS pain score from baseline to 90 days post-stimulation without a clinically meaningful increase in LBP medications) was 58% (30/52). The percentage of patients with an improvement of at least the MCID of 2 points in LBP in the single day NRS (without a clinically meaningful increase in LBP medications at 90 days) was 63% (33/52), 61% (31/51) and 57% (27/47) at 90 days, 6 months and 1 year, respectively (Deckers 2018). After 4-year follow up, 73% of patients experienced a clinically meaningful improvement of at least the MCID on NRS (defined as a change in at least 2 points). There was a reduction in mean NRS from 6.8±0.8 at baseline to 3.2±0.4 at 4 years (difference of 3.6, p<0.001; Mitchell 2021).

A prospective case series (open-label study) of 42 patients with CMLBP, implanted with a neurostimulator for contraction of the lumbar multifidus, reported that the mean NRS improved from 7.0±0.2 at baseline to 3.5±0.3 (p<0.001) after 2-year follow up for complete cases. Sixty eight per cent (25/37) of patients experienced ≥30% improvement in NRS and 57% (21/37) experienced at least a

≥50% improvement in NRS after 2 years. Sixty five per cent (24/37) reported mild to negligible pain (NRS≤3) after 2 years (Thomson 2021).

A case series of 26 patients with continuing CLBP despite physical therapy and medical treatment and no prior surgery, implanted with pulse generators and leads, reported that average LBP (measured on a VAS 100 mm scale) improved significantly at 3 and 5 months follow up (therapy withdrawal phase; decreased from 67.3±11.1 mm at baseline to 40.8±23.8 mm at 3 months, change of 26.4±22.3 mm [p<0.0001] and 39.7±33.4 at 5 months, change of 27.6±27.3 [p=0.0005]). A minimally important change of either ≥15 mm or ≥30% in VAS was reported in 74% (14/19) of patients and 67% (12/18) of patients at 3- and 5-month follow up (Deckers 2015).

Oswestry Disability Index (ODI)

In the RCT of 204 patients comparing therapeutic stimulation (n=102) with low-level sham stimulation (n=102), disability measured using the 100-point ODI showed that ODI scores were statistically significantly better in the therapeutic stimulation treatment group at 120-day follow up compared with baseline. The ODI scores improved from 39.1±10.3 at baseline to 22.3±14.5 in the therapeutic group and 25.7±15.0 in the sham control group (mean difference -17.5±15.1 and -12.2±14.6; difference of -5.4 points between groups; 95% CI -9.5 to -1.2 points; p=0.011). At 1-year follow up, in the overall combined cohort (n=176), ODI scores improved by -19.9±1.2 points from baseline (95% CI -22.3 to -17.6; p<0.0001) or -50.5±38.7% (95% CI -56.3 to 44.8; p<0.0001). At 2-year follow up, a reduction in mean ODI from 39.1±10.3 at baseline to 17.6±1.2 for completed cases was reported (difference of -21.4, 95% CI -24.0 to -18.7 or percentage difference of -54.3%±3.2 (-95% CI -60.6% to -48.0%; p<0.0001); 61.3% (95/155) of patients experienced a ≥20 point improvement in ODI (95% CI 53.6% to 69.0%; Gilligan 2021).

In the prospective case series (initial open-label study) of 53 patients, disability measured using the 100-point ODI (with scores of 21 to 40% indicating moderate disability and scores of 41 to 60% indicating severe disability) showed that the percentage of patients with MCID improvement of more than 10 points in ODI was 52% (27/52), 57% (29/51) and 60% (28/47) at 90 days, 6 months and 1 year, respectively (Deckers 2018). After 4-year follow up, 76% of patients experienced a clinically meaningful improvement of at least the MCIC on ODI (defined as a change in at least 10 points). There was a reduction in mean ODI in completed cases from 44.9±10.1 at baseline to 23.0±0.4 at 4 years (difference of 21.9, p<0.001; Mitchell 2021).

A prospective case series (open-label study) of 42 patients with CMLBP, implanted with a neurostimulator for contraction of the lumbar multifidus, reported a reduction in mean ODI for complete cases from 46.2±2.2 at baseline to

29.2±3.1 (difference of 17.0, p<0.001) after 2 years; 51.4% of patients (19/37) experienced a ≥15 point improvement in ODI and 43.2% (16/37) of patients experienced a ≥20 point improvement in ODI after 2 years (Thomson 2021).

The case series of 26 patients reported that disability scores (measured using the 100-point ODI scale) significantly improved at 3- and 5-month follow up (therapy withdrawal phase; decreased from 38.5±14.6 at baseline to 27.6±15.6 at 3 months, change of 10.9±9.6 [p=0.0001] and 29.6±29.3 at 5 months, change of 12.1±14.4 [p=0.0017]). A minimally important change of either ≥10 points or ≥30% on the ODI score was reported in 63% (12/19) of patients and 53% (10/19) of patients at 3- and 5-month follow up. Forty five per cent (5/11) of patients on disability leave returned to work by 3 months (Deckers 2015).

Quality of life (QoL; EQ-5D)

In the RCT of 204 patients comparing therapeutic stimulation (n=102) with low-level sham stimulation (n=102), QoL measured using the EQ-5D score on 5 dimensions (EQ-5D-5L) questionnaire showed that the EQ-5D-5L index scores were statistically significantly better in the therapeutic stimulation treatment group at 120-day follow up compared with baseline. The scores improved from 0.585±0.174 at baseline to 0.758±0.160 in the therapeutic stimulation group and 0.713±0.160 in the sham control group (mean difference 0.186 compared with 0.115; difference of 0.071 between groups; 95% CI 0.018 to 0.123; p=0.009). At 1-year follow up, in the overall combined cohort (n=176), the improvement in EQ-5D was 0.198±0.0.16 (95% CI 0.167 to 0.229; p<0.0001). At 2-year follow up, an increase in EQ-5D from 0.585±0.174 at baseline to 0.798±0.013 in complete cases was reported (difference of 0.218±0.017, 95% CI 0.184 to 0.253; p<0.0001; Gilligan 2021).

In the prospective case series (initial open-label study) of 53 patients, QoL measured using the EQ-5D questionnaire showed that the percentage of patients with MCID improvement of at least 0.03 points in EQ-5D was 88% (46/52), 82% (42/51) and 81% (38/47) at 90 days, 6 months and 1 year, respectively (Deckers 2018). After 4-year follow up, the mean EQ-5D increased from 0.434±0.185 at baseline to 0.721±0.035 (difference of 0.287, p<0.001; Mitchell 2021).

A prospective case series (open-label study) of 42 patients with CMLBP, implanted with a neurostimulator for contraction of the lumbar multifidus, reported an increase in EQ-5D from 0.425±0.035 at baseline to 0.680±0.030 at 2 years for complete cases (difference of 0.254, p<0.0001; Thomson 2021).

The case series of 26 patients reported that QoL (measured using EQ-5D questionnaire) significantly improved at 3- and 5-month follow up (at therapy withdrawal phase; EQ-5D score increased from 0.43±0.34 at baseline to 0.70±0.21 at 3 months, improvement of 0.27±0.24 points [p=0.0002] and

0.20±0.43 at 5 months [p=0.06]). At 3 months, 84% (16/19) of patients reported an increase in EQ-5D scores and none reported a decrease (Deckers 2015).

Patient satisfaction

In the prospective case series (initial open-label study) of 53 patients, 89%, 84% and 81% of patients reported being either 'satisfied' or 'very satisfied' with their treatment at 90 days, 6 months and 1 year, respectively (Deckers 2018). At 4 years 97% (32/33) of participants reported being 'very satisfied' with the treatment (Mitchell 2021).

In the RCT of 204 patients comparing therapeutic stimulation (n=102) with low-level sham stimulation (n=102), the difference in proportion of patients 'definitely satisfied' (measured using a treatment satisfaction questionnaire) was statistically significantly better in the therapeutic stimulation treatment group at 120-day follow up (61.0 compared with 40.0; difference of 21%; 95% CI 7.9 to 34.9%; p=0.002). At 1-year follow up in the combined cohort (n=176), 78% of patients answered 'definitely satisfied' on the treatment satisfaction questionnaire (Gilligan 2021). In the open-label follow up of the RCT of 204 patients, 80% (124/155) of patients answered 'definitely satisfied' on the treatment satisfaction questionnaire (95% CI 73.7% to 86.3%; Gilligan 2021).

Safety summary

Overall adverse events (related to the procedure, device and/or simulation)

In the RCT of 204 patients, 4% (8/204) of device or procedure-related serious adverse events were reported within 120-days follow up. Most happened within 30 days and were procedure related (Gilligan 2021).

A total of 76 adverse events were reported in 66% (35/53) of patients in the case series (initial open-label study) of 53 patients which used a lateral surgical approach in most cases. None of these were classified as serious events. Fourteen of these events in 21% (11/53) of patients were procedure related, 39 events in 47% (25/53) of patients were device related, 7 events in 9% (5/53) of patients were device or procedure related, and 16 events in 29% (15/53) of patients were simulation related (Deckers 2018).

A prospective case series (open-label study) of 42 patients with CMLBP, implanted with a neurostimulator for contraction of the lumbar multifidus, reported 20 adverse advents related to the procedure, the device, or stimulation across 28.6% (12/42) of patients, 15 of which were resolved with reprogramming. The biggest proportion of events were stimulation related (Thomson 2021).

A total of 97 adverse events were reported in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use. Of these, 60 were related to the device, the procedure or both (27 device related,13 procedure related and 20 both device and procedure related) and happened in 74% (20/27) of patients (Deckers 2015).

Procedure-related adverse events

14 procedure-related adverse events (wound pain, inflammation, haematoma or postoperative discomfort) were reported in 21% (11/53) of patients in the case series (initial open-label study) of 53 patients. Seven events in 9% (5/53) of patients were device or procedure related (seroma or inflammation because of lead incision, and postoperative nervous system irritation). These events happened at rates of 1% to 5% (Deckers 2018).

13 procedure-related adverse events (pain [3 events], abnormal healing [1 event], nausea or vomiting related to anaesthesia [1 event], nervous system injury [2 events], musculoskeletal stiffness [2 events], infection [2 events], seroma [1 event], and risk associated with surgery [1 event]) were reported in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use (Deckers 2015).

In the RCT of 204 patients, 3% (6/204) of patients developed a pocket infection (which resolved after device explantation and antibiotic treatment), 1 patient had an intraoperative upper airway obstruction that resolved, and 1 patient developed an ongoing non-radicular patch of numbness on the surface of the thigh (further details were not reported; Gilligan 2021).

In the case series (open-label study) of 42 patients, 7.1% (3/42) experienced implant site pocket pain, 2.4% (1/42) experienced implant site blisters, 2.4% (1/42) experienced implant site pocket infection and 2.4% (1/42) experienced wound pain (Thomson 2021).

Device-related adverse events

39 adverse events in 47% (25/53) of patients were device related (loss of stimulation [23 events], pocket or lead discomfort [13 events] and undesired sensations [3 events]) in the case series (initial open-label study) of 53 patients (Deckers 2018).

Lead fractures and inadequate stimulation

Lead conductor fractures because of tight bending in 44 leads (implanted using lateral approach) leading to loss of stimulation and high impedance on 1 of the conductors on the stimulation channels was observed in 53% (28/53) of patients

in the case series (initial open-label study) of 53 patients. Thirteen had surgical revision to implant new leads, 7 were reprogrammed to resume bilateral stimulation by a different electrode configuration, 3 had continued therapy with unilateral stimulation, 3 had the system turned off, and 2 had the system explanted. A modified implant procedure using a midline approach reduced the risk of lead bending and conductor fractures (Deckers 2018).

Inadequate stimulation (because of lead migration in 8, high impedance in 2, pulse generator malfunction in 2, and reason not specified in 1) was reported in 48% (13/27) of patients in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use (Deckers 2015).

Lead conductor fractures were reported in 2 patients in the case series (open-label study) of 42 patients; these fractures were resolved in both patients (Thomson 2021).

Over stimulation

Over stimulation of tissue was reported in 11% (3/27) of patients (5 events) in the case series of 26 patients (Decker 2015).

In the case series (open-label study) of 42 patients, 10 events of overstimulation of tissue were reported in 16.7% (7/42) of patients, 7 of which were resolved (Thomson 2021).

Undesired sensations

Undesired sensations in the target or non-target area were reported in 7% (2/27) of patients in the case series of 26 patients (Deckers 2015).

21 events of device or simulation-related undesired sensations in the target area, including muscle fatigue, were reported in 29% (15/53) of patients in the case series (initial open-label study) of 53 patients (Decker 2018).

Lead migration

One lead migration leading to loss of sensation was reported in a patient in the case series (initial open-label study) of 53 patients (Deckers 2018, Mitchell 2021).

Twenty one lead migrations leading to inadequate stimulation or surgical revision happened in 48% (13/27) of patients in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use. Five events happened between implantation and 3-month follow up. Five patients had more than 2 migrations, 2 had more than 3 migrations, and 1 had 4 migrations (Deckers 2015).

Other device-related events

Pain (5 events), and tissue injury and fever in 1 patient each, were reported in the case series of 26 patients (Deckers 2015).

In the case series (open-label study) of 42 patients, 1 patient experienced leg pain (unresolved) and 1 patient experienced a synovial cyst (which was later resolved; Thomson 2021).

Surgical revisions

In the open-label follow up of an RCT, 22.1% (45/204) of patients had a total of 47 surgical interventions; 15.7% (32/204) of systems were removed (with 1/204 systems being reimplanted), 2% (4/204) of implant pulse generators were repositioned and 5% (10/204) of patients had leads replaced. Reasons for device removal were lack of effectiveness (9), infection (6), and as a safety precaution before an MRI scan (4; Gilligan 2021).

In the case series (open-label study) of 42 patients, 4.7% (2/42) of patients had surgical revisions to replace leads after lead fracture (Thomson 2021).

Twenty surgical revisions were done in 63% (17/27) of patients in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use. These were for repositioning 12 lead migrations in 10 patients, high impedance in 2 patients, implanted pulse generator migration in 2 patients, discomfort because of lead anchor in 2 patients, pulse generator failure in 1 patient and device explantation in 1 patient (Decker 2015).

Thirteen patients with lead fractures had surgical revisions to implant new leads in the case series (initial open-label study) of 53 patients (Deckers 2018).

Device explantation

Device explantation was reported in 15.7% (32/204) of patients in the open-label follow up of the RCT. These were because of lack of efficacy in 5% (9/204) of patients, infection in 2.9% (6/204) of patients, as a safety precaution before an MRI scan in 2% (4/204) of patients, resolution of LBP in 1 patient and relocation to a remote area without device follow-up infrastructure in 1 patient. One patient who had the device explanted after infection was reimplanted after infection resolution (Gilligan 2021).

Device explantation was reported in 16/53 (30.2%) of patients. Device explantation was because of lack of clinical benefit in 20.8% (11/53) of patients, device migration in 1.9% (1/53) of patients and after clinical benefit in 7.5% (4/53) of patients (Mitchell 2021, Deckers 2018).

Device explantation was reported in 9.5% (4/42) of patients in the case series (open-label study) of 42 patients because of lack of efficacy (Thomson 2021).

Device explantation (because of infection and lead migration) was needed in 1 patient in the case series of 26 patients that used an earlier version of the device and surgical technique no longer in use (Deckers 2015).

Adverse events unrelated to the procedure

Thirteen serious adverse events were reported in the open-label follow up of the RCT but were reviewed by the clinical events committee and adjudicated as unrelated to the device or procedure (Gilligan 2021).

Sixty nine adverse events unrelated to the procedure were reported in 53% (28/53) of patients in the case series (initial open-label study) of 53 patients. Three of these were serious events and included surgical removal of a uterine fibroid, non-cardiac chest pain and a cerebrovascular accident (Deckers 2018).

Thirty seven adverse events unrelated to the device or procedure were reported in the case series of 26 patients (Deckers 2015).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse event: bleeding. They considered the following theoretical adverse event: nerve damage (damage to spinal nerve root).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. The following databases were searched, covering the period from their start to 26-11-2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with refractory non-specific chronic low back pain.
Intervention/test	Neurostimulation of lumbar muscles.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 327 patients from 1 RCT (described in 2 publications), 1 case series (described in 2 publications) and another 2 small case series.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on neurostimulation of lumbar muscles for refractory non-specific chronic low back pain

Study 1 Gilligan C (2021)

Study details

Study type	Randomised sham-controlled trial (ReActiv8-B Study NCT02577354)
Country	International study: United States, Australia and Europe (26 centres)
Recruitment period	2016 to 2018
Study population and number	n=204 patients with refractory CMLBP and impaired multifidus control implanted with a neurostimulator. Treatment group (therapeutic stimulation, n=102) versus control group (low-level sham stimulation, n=102). The control group crossed over to active stimulation after the 120 day visit. Duration of back pain: mean 14±11 years. Percent of days with LBP in past year: 97±8%.
Age and sex	Treatment group: mean age 46±10 years; 55% (56/102) female Sham control group: mean age 48±9 years; 53% (54/102) female
Patient selection criteria	Inclusion criteria: patients between 22 to 75 years, with continuing and refractory CMLBP (despite more than 90 days of medical management and no specified physical therapy); reported a 7-day recall of average LBP of ≥6.0 and ≤9.0 cm (on the 10 cm VAS); had an ODI of ≥21 and ≤60 points (on a scale from 0 to 100); and had a positive prone instability test suggesting impaired motor control of the multifidus muscle and lumbar segmental instability. Exclusion criteria: prior lumbar spine surgery below T8, any previous rhizotomy or rhizolysis procedure on the dorsal root ganglion or medial branch at or below T8; anaesthetic block or epidural steroids at or below T8, spinal fusion at any level; CLBP amenable to surgery; leg pain worse than back pain, or radiculopathy below the knee; neurological deficit with back pain; sacroiliac joint pain; scoliosis or correction surgery, comorbid pain conditions; opioid use of more than 120 mg; any pain-related

	disability, compensation or litigation issues; psychological or psychiatric disorder.
Technique	Neurostimulator device (ReActiv8 System, Mainstay Medical Limited) was implanted to simulate the medial branch of the dorsal ramus nerve to elicit episodic contraction of the lumbar multifidus. Devices were activated and therapeutic stimulation in treatment group was programmed at a frequency of 20 Hz, a pulse width of 214 microseconds and participant-specific pulse amplitudes and configurations to elicit contractions for 10 seconds twice per minute during the stimulation session. For the sham-control group stimulation parameters were programmed to low amplitude and frequency values (unipolar stimulation from the proximal electrode with 3 stimulation pulses of 0.1mA and 31microseconds delivered every 2 minutes during the stimulation session). Stimulation was delivered (using a wireless activator) for two 30-minute sessions per day while in prone or side lying position. All patients had same visit schedule and interaction during programming and had undergone physical therapy with on average 31 sessions. 75% patients had current lead and 25% patients had old lead (no longer in use).
Follow up	120 days (for blinded phase of study); 1 and 2 years (after unblinding for combined cohort).
Conflict of interest/source of funding	Mainstay Medical sponsored and contributed to the study, and investigators were paid directly or indirectly (received consultancy fees and research grants from Mainstay Medical, as well as from other medical companies). One author reports receiving stock options from Mainstay Medical.

Analysis

Follow-up issues: 3 patients (2 treatment and 1 sham) were lost to follow up at 120 days. After crossover, 7 patients were lost to follow up, and 21 missed follow-up visits. Longitudinal follow-up data was available for 93% (190/204) participants at 6 months, 86% (176/204) at 1 year, and 79% (156/204) at 2 years. 5% (10/204) participants missed follow-up visits and 19% (38/204) were withdrawn from the study before completion because of permanent system explant (in 31 patients) or otherwise lost to follow up (7 patients).

Study design issues: randomised double-blinded sham-controlled international multicentre trial at 26 sites done as per the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), National Institutes of Health (NIH) research standards and US Food and Drug Administration (FDA) guidance; adequately powered, randomisation was done post-implantation, assignment to groups was done from the database maintained by an independent organisation; physicians received prior implantation training. All those who were involved in the study were blinded using several measures except statisticians who analysed the results. After primary outcome

assessment at 120 days (blinded phase), patients were unblinded and 101 receiving sham were offered therapeutic stimulation. Results were reported as per CONSORT guidelines. Independent oversight by different committees was done to periodically review trial results.

Primary efficacy outcome was difference in proportions of responders in the treatment and sham-control group at 120 days (with an improvement in 7-day average LBP VAS of ≥30% and no increase in analgesics from baseline) and analysis was done in the ITT cohort. Secondary outcomes included ODI, QoL measured with the EQ-5D questionnaire, percent-of-pain-relief (PPR), Subject-Global-Impression-of-Change (SGIC), LBP resolution (VAS≤2.5 cm), Treatment Satisfaction Questionnaire (TSQ), Clinical-Global-Impression-of-Change (CGI), and analgesics use. Serious device- or procedure-related adverse events were recorded.

Population outcomes: demographic and baseline characteristics were similar between the 2 groups. Of all participants, prior to study, 12% had undergone medial branch rhizotomy, 49% had spinal injections and 37% had opioid analgesics for LBP.

Other issues: Imputation for missing data was stratified according to reason for missingness. Baseline observation carried forward (BOCF), was used for participants withdrawn for reported lack of efficacy at any time, or for permanent explant after infection. For those withdrawn for other reasons or random missed visits, the mixed-effects model repeated measures (MMRM) approach was used to provide implicit imputations of missing data for continuous outcomes.

Key efficacy findings

Number of patients analysed: 204

Outcome measures at 120 days (blinded phase)

-	Baseline (n=204) mean±SD	Therapeutic stimulation % (n=100)	Sham control stimulation % (n=101)	Difference between groups (95% CI)	P value
Proportion of patients with an improvement in LBP VAS of ≥30% and no increase in analgesics Responders ITT, % (n)	-	57.1%	46.6%	10.4 (-3.3, 24.1)	0.138

Cumulative proportion of responders (analysis of primary outcome data)	-	N=102	N=102	NA	0.0499
Average LBP VAS (cm)*	7.3±0.7	4.0±2.7	4.8±2.9		
Change in average LBP VAS from baseline cm)	-	-3.3±2.7	-2.4±2.9	-0.9 (-1.6, -0.1)	0.032
Change in VAS from baseline (%)	-	-44.6±36.8	-33.3±40.8	-11.2 (0.4, 22.0)	0.042
Mean ODI, points^^	39.1±10.3	22.3±14.5	25.7±15.0		
Change in ODI from baseline	-	-17.5±15.1	-12.2±14.6	-5.4 (-9.5, -1.2)	0.011
Change in ODI from baseline (%)	-	-43.0±34.3	-31.2±38.2	-11.8 (-21.9, -1.7)	0.022
Mean EQ-5D index**	0.585±0.174	0.758±0.160	0.713±0.160		
Change in EQ-5D from baseline	-	0.186±0.199	0.115±0.178	0.071 (0.018, 0.123)	0.009
Mean percent pain relief (%)	-	51.7±32.3	35.0±35.8	16.8 (7.3, 26.3	<0.001
Proportion of patients for whom SGIC was ‘better’ or ‘much better’	-	54% (54/100)	33.7% (34/101)	20.3% (6.9, 33.8)	0.004
Proportions of patients for whom CGI was ‘much better’	-	57 (57/100)	22 (22/100)	35 (22.3, 47.7)	<0.001
Proportion of LBP resolution (VAS≤2.5 cm)	-	34 (34/100)	27.7 (28/101)	6.3 (-6.5, 19)	0.335
Patient satisfaction (TSQ was ‘definitely satisfied’)	-	61 (61/100)	39.6 (40/101)	21.4 (7.9, 34.9)	0.002

*Scores on the VAS for average recall LBP over past 7 days, range from 0 to 10, with higher scores indicating severe pain.

^^Scores on the ODI range from 0 to 100, with higher scores indicating severe disability.

**Scores on the EQ-5D-5L index range from -0.5 to 1, with higher scores indicating better quality of life.

Prespecified secondary analysis of the primary outcome data

Low back pain–VAS trajectory between groups

-	**Average LBP VAS (cm)**	
	Treatment group	**Sham group**
Blinded phase		
Baseline	7.3±0.7 (n=102)	7.2±0.7 (n=102)
14 days	5.3* (n=101)	5.4* (n=101)
45 days	4.6* (n=99)	4.7* (n=101)
75 days	4.3* (n=99)	4.6* (n=100)
120 days	4.0±2.7 (n=100)	4.8±2.9 (n=101)
Unblinded phase		
-	**Treatment group**	**Crossover group**
180 days	3.6* (n=96)	3.8* (n=93)
240 days	3.2* (n=91)	3.6* (n=93)
360 days	3.1* (n=87)	2.9* (n=89)

*Values estimated from graph.

The mean group difference in VAS improvement at 120 days was 0.9 cm in favour of the treatment group (-3.3 versus -2.4, -0.9 cm, 95% CI -1.6 to -0.1 cm; p=0.032).

Prespecified cumulative-proportion-of-responders analysis (CPRA) of ITT primary outcome data

Improvement in LBP VAS at 120 days with no increase in analgesics (%)	**Cumulative proportion of participants (%)***	
	Therapeutic stimulation (n=102)	**Sham stimulation (n=102)**
≥-40	98	96
≥-30	97	95
≥-20	97	94
≥-10	94	89

≥0	89	78
≥10	81	63
≥20	70	52
≥30	57	47
≥40	51	40
≥50	43	34
≥60	35	31
≥70	28	24
≥80	24	19
≥90	16	11

*All values estimated from graph (CPRA used a comparison of ranks of the percentage of 'responders' across the range of possible response thresholds and compared treatment groups at any responder level).

CPRA primary outcome data showed that across all possible response thresholds, treatment was superior to sham-control (p=0.0499).

Increased use of analgesics

Eighteen participants (9 in each group) reported increased use of analgesics. In 6 cases, in the treatment group, the increase in use of analgesics were related to other medical problems (an ankle fracture, a tooth extraction, upper respiratory tract infection, anal abscess, knee injury, and a renal stone) but not LBP.

Clinical patient-reported outcomes (unblinded phase – complete cases)

-		Mean (SE) or % (n/N)^ (95% CI)		
	Mean±SD at baseline (n=204)	**6 months (n=190)**	**1 year (n= 176)**	**2 years (n=156)**
VAS				
Mean LBP VAS (cm)	**7.3±0.7**	**3.7 (0.2)**	**3.0 (0.2)**	**2.4 (0.2)**
Change in mean VAS (cm)	-	-3.6 (0.2) (-3.9, -3.3)	-4.3 (0.2) (-4.7, -3.9)	-4.8 (0.2) (-4.6, -3.8)
Change in mean VAS (%)	-	-48.6 (2.7) (-53.9, -43.3)	-58.9 (2.6) (-64.1, -53.6)	-66.7 (2.6) (-71.7, -61.6)
≥30% improvement in mean VAS (%)	-	66.1 (125/189) (59.4, 72.9)	73.9 (130/176) (67.4, 80.4)	82.6 (128/155) (76.6, 88.6)
≥50% improvement in mean VAS (%)	-	52.9 (100/189) (45.8, 60.0)	63.6 (112/176) (56.5, 70.7)	71.6 (111/155) (64.5, 78.7)

≥70% improvement in VAS (%)	-	33.9 (64/189) (27.1, 40.6)	46.6 (82/176) (39.2, 54.0)	61.9 (96/155) (54.3, 69.6)
LBP resolution (VAS ≤2.5 cm)	-	39.2 (74/189) (32.2, 46.1)	51.7 (91/176) (44.3, 59.1)	66.5 (103/155) (59.0, 73.9)
ODI				
Mean ODI	**39.1±10.3**	21.9 (1.1)	19.0 (1.4)	17.6 (1.2)
Change in ODI (SE)	-	-17.0 (1.1) (-19.2, -14.8)	-19.9 (1.2) (-22.3, -17.6)	-21.4 (1.3) (-24.0, -18.7)
Change in ODI (%)	-	-43.0 (2.8) (-48.5, -37.4)	-50.5 (2.9) (-56.3, -44.8)	-54.3 (3.2) (-60.6, -48.0)
≥20 Pt. improvement in ODI (%)	-	48.1 (91/189) (41.0, 55.3)	57.4 (101/176) (50.1, 64.7)	61.3 (95/155) (53.6, 69.0)
Composite of VAS and ODI				
≥50% improvement in mean VAS and/or ≥20 Pt. ODI	-	63.5 (120/189) (56.6, 70.4)	73.3 (129/176) (66.8, 79.8)	77.3 (119/154) (70.7, 83.9)
≥50% improvement in VAS and ≥20 Pt. ODI	-	37.8 (71/188) (30.8, 44.7)	47.7 (84/176) (40.3, 55.1)	56.5 (87/154) (48.7, 64.3)
EQ-5D-5L index	**0.585±0.174**	0.765 (0.010)	0.780 (0.012)	0.798 (0.013)
Change in EQ-5D-5L index	-	0.180 (0.014) (0.153, 0.207)	0.195 (0.016) (0.167, 0.229)	0.213 (0.017) (0.184, 0.253)
PPR (%)	-	55.0 (2.5) (50.1, 59.9)	65.7 (2.4) (60.9, 70.5)	72.1 (2.4) (67.3, 77.0)
SGIC 'Better' or 'Much better'	-	57.4 (109/190) (50.3, 64.4)	71.6 (126/176) (64.9, 78.3)	78.6 (121/154) (72.1, 85.1)
TSQ 'Definitely satisfied'	-	64.7 (123/190) (57.9, 71.5)	78.2 (136/174) (72.0, 84.3)	80.0 (124/155) (73.7, 86.3)
CGI 'Much better'	-	56.8 (108/190) (49.8, 63.9)	73.3 (129/176) (66.8, 79.8)	77.6 (118/152) (71.7, 84.3)

^=Mean (SE) for continuous outcomes and % (n/N) for binary outcomes.

Clinical patient-reported outcomes – imputed cases

		Mean (SE) or % (n/N)^ (95% CI)		
-	**Mean±SD at baseline (n=204)**	**6 months (n=204)**	**1 year (n=204)**	**2 years (n=204)**
VAS				
Mean LBP VAS (cm)	**7.3±0.7**	**3.9 (0.2)**	**3.4 (0.2)**	**3.1 (0.2)**
Change in mean VAS (cm)	-	-3.4 (0.2) (-3.8, -3.1)	-3.9 (0.2) (-4.3, -3.6)	-4.2 (0.2) (-4.6, -3.8)
Change in mean VAS (%)	-	-47.1 (2.6) (-52.3, -41.9)	54.3 (2.7) (-59.5, -49.0)	-58.1 (2.7) (-63.4, -52.8)
≥30% improvement in mean VAS (%)	-	63.2 (3.5) (56.5, 70.0)	66.9 (3.4) (60.3, 73.6)	71.6 (3.3) (65.1, 78.1)
≥50% improvement in mean VAS (%)	-	51.0 (3.6) (44.0, 58.0)	58.0 (3.5) (51.1, 65.0)	62.1 (3.5) (55.1, 69.0)
≥70% improvement in VAS (%)	-	33.2 (3.4) (26.5, 39.9)	43.0 (3.6) (36.1, 50.0)	54.3 (3.7) (47.1, 61.5)
LBP resolution (VAS ≤ 2.5 cm)	-	38.3 (3.5) (31.4, 45.1)	47.7 (3.5) (40.7, 54.6)	57.6 (3.6) (50.5, 64.7)
ODI				
Mean ODI	**39.1±10.3**	22.7 (1.0)	20.7 (1.0)	20.2 (1.0)
Change in ODI (SE)	-	-16.4 (1.0) (-18.4, -14.4)	-18.4 (1.0) (-20.4, -16.4)	-18.9 (1.0) (-21.0, -16.8)
Change in ODI (%)	-	-41.5 (2.7) (-46.8, -36.1)	-46.4 (2.8) (-51.8, -41.0)	-47.5 (2.8) (-53.0, -42.0)
≥20 Pt. improvement in ODI (%)	-	46.7 (3.5) (39.8, 53.7)	53.4 (3.5) (46.5, 60.3)	54.8 (3.6) (47.7, 61.9)
Composite of VAS and ODI				
≥50% improvement in mean VAS and/or ≥20 Pt. ODI	-	60.4 (3.5) (53.6, 67.2)	67.4 (3.4) (60.8, 74.0)	67.4 (3.5) (60.4, 74.3)
≥50% improvement in VAS and ≥20 Pt. ODI	-	36.8 (3.4) (30.0, 43.5)	44.0 (3.6) (37.0, 51.1)	49.9 (3.6) (42.8, 57.1)

EQ-5D-5L index	**0.585±0.174**	0.758 (0.011)	0.762 (0.011)	0.768 (0.011)
Change in EQ-5D-5L index	-	0.173 (0.011) (0.151, 0.194)	0.177 (0.011) (0.156, 0.199)	0.183 (0.011) (0.161, 0.205)
PPR (%)	-	53.3 (2.5) (48.4, 58.2)	60.7 (2.5) (55.8, 65.6)	62.3 (2.5) (57.3, 67.3)
SGIC 'Better' or 'Much better'	-	55.1 (3.5) (48.2, 62.0)	65.9 (3.4) (59.3, 72.5)	68.6 (3.4) (61.9, 75.2)
TSQ 'Definitely satisfied'	-	62.8 (3.4) (56.0, 69.5)	71.8 (3.2) (65.5, 78.1)	68.3 (3.4) (61.6, 75.1)
CGI 'Much better'	-	55.0 (3.6) (48.0, 62.0)	67.5 (3.4) (60.8, 74.1)	66.6 (3.6) (59.6, 73.7)

^=Mean (SE) for continuous outcomes and % (n/N) for binary outcomes.

Continuous outcomes remained statistically significant ($p<0.0001$) and clinically meaningful at all follow ups when using imputed data.

Medication use

Of the 57/156 participants who used opioids at baseline and had a 2-year follow up, 60% had either voluntarily stopped or decreased use and only 1 patient had increased intake.

Key safety findings

Adverse events

	Events, n	**% (n=patients)**
Device and procedure related serious adverse events (all happened before 120 days)	**8**	**3.9 (8/204)**
Infection (resolved after system explant, and antibiotics)	6	2.9 (6/204)
Intra-procedural upper-airway obstruction (resolved)	1	0.5 (1/204)
Non-radicular patch of numbness on thigh (ongoing)	1	0.5 (1/204)
Lead migrations	0	0
Surgical interventions	**30**	**13.2 (27/204)**
System removal	**19**	**9.3 (19/204)**
Lack of effectiveness	9	4.4 (9/204)
Infection	6	2.9 (6/204)
To facilitate MRI	4	2.0 (4/204)
Revision	**10**	**4.9 (10/204)**
Lead replacements	6	2.9 (6/204)
Pulse generator repositioned	4	2.0 (4/204)
Re-implanted system post-infection	1	0.5 (1/204)
Unrelated adverse events	**7**	**3 (7/204)**

Device and procedure related serious adverse events

	0–6 months		6–12 months		12–24 months	
-	Number of events	% of patients (n=204)	Number of events	% of patients (n=204)	Number of events	% of patients (n=204)
All device and procedure related SAEs	**8**	**3.9 (8/204)**	**0**	**0**	**0**	**0**
Infection (resolved)	6	2.9 (6/204)	0	0	0	0
Intra-procedural upper airway obstruction (resolved)	1	0.5 (1/204)	0	0	0	0
Non-radicular patch of numbness on thigh (ongoing)	1	0.5 (1/204)	0	0	0	0

Surgical reinterventions

	0–6 months		6–12 months		12–24 months	
-	Number of events	% of patients (n=204)	Number of events	% of patients (n=204)	Number of events	% of patients (n=204)
All surgical interventions*	**14**	**6.4 (13/204)**	**16**	**6.8 (14/204)**	**18**	**8.8 (18/204)**
System removal						
All system removal	**8**	**4.4 (9/204)**	**11**	**5.4 (11/204)**	**13**	**6.4 (13/204)**
Reported lack of efficacy	1	0.5 (1/204)	8	3.4 (7/204)	9	3.9 (8/204)
Infection	6	2.9 (6/204)	0	0	0	0
Facilitate MRI	1	0.5 (1/204)	3	1.5 (3/204)	2	1.0 (2/204)
Participant relocation	0	0	0	0	0	0.5 (1/204)
LBP pain relief	0	0	0	0	0	0.5 (1/204)

Re-implant post-infection	1	0.5 (1/204)	0	0	0	0
Revision						
All revision	**5**	**2.5 (5/204)**	**5**	**2.5 (5/204)**	**5**	**2.5 (5/204)**
Lead replacement	3	1.5 (3/204)	3	1.5 (3/204)		2.0 (2/204)
Pulse generator repositioning	2	1.0 (2/204)	2	1.0 (2/204)	1	0.5 (1/204)

Note: Patients may have had more than 1 intervention so the total number of surgical interventions is not equal to the sum of each category. Overall, 22.1% (45/204) of patients underwent a total of 47 surgical interventions.

Study 2 Deckers K (2018), Mitchell B (2021)

Study details

Study type	Prospective case series (ReActiv8-A Study NCT01985230- initial open label study)
Country	Australia, United Kingdom and Belgium
Recruitment period	2014 to 2015
Study population and number	n=53 patients with CMLBP who have failed conventional therapy and are not candidates for surgery or spinal cord stimulation (SCS). Duration of back pain: mean 14.3 years.
Age and sex	Mean age 44 years; 57% (30/53) female
Patient selection criteria	Inclusion criteria: adult patients (aged 18 to 65 years) with predominant chronic low back pain for more than 90 days, with no history of prior surgery or currently indicated for spinal surgery, not eligible for spinal cord stimulation, and with no satisfactory pain relief despite medical management (including at least physical therapy and medication) for 1 year, ODI score 25 to 60%, NRS 6.0 to 9.0 at baseline, medications at stable dose 30 days prior to enrolment. Exclusion criteria: BMI more than 35, indication for back surgery, leg pain worse than back pain or radiculopathy below the knee, back pain exclusions, diagnosis or correction of scoliosis, neurological deficit, sacroiliac joint pain, oral morphine use, rhizotomy procedure of medial branch below T8 in the prior year, anaesthetic block of medial branch or epidural, steroids for back pain in 30 days, previous back surgery below T8, previous thoracic or lumbar sympathectomy, depression, psycho-social problems.
Technique	Implantation with a neurostimulator device (ReActiv8, Mainstay Medical Limited-old lead design) to simulate the medial branch of the dorsal ramus of the L2 nerve root to elicit episodic contraction of the lumbar multifidus. In the first 47 patients, leads were placed using the 'lateral' surgical approach and in the last 6 subjects, the approach was modified, and the leads (including any replacements) were placed using the 'midline' surgical approach. This was to reduce mechanical stresses on the leads which were found to be responsible for lead conductor fractures and loss of stimulation. The electrodes were placed at the same anatomical target in both the midline and the lateral approaches. Devices were activated 2 weeks after implantation and programmed via radio frequency telemetry. Patients used a wireless activator to deliver 2 daily 30-minute stimulation sessions with the program cycling through 10 seconds of stimulated contractions followed by 20 seconds of relaxation.

Follow up	1 year; 4 years
Conflict of interest/source of funding	Study was sponsored by Mainstay Medical. Authors have also received consultancy fees and research grants from Mainstay Medical, and other medical companies.

Analysis

Follow-up issues: few patients were lost to follow up (1 at 90 days, 2 at 6 months, and 6 at 1 year). Sixteen of 53 patients withdrew from the study before completion because of device removal (11 without clinical benefit, 4 with clinical benefit, and 1 because of device migration). One further patient was lost to follow up and 2 patients missed their 4-year visit.

Study design issues: small international multicentre study at 10 sites; primary performance outcome was improvement in low back pain evaluated on an NRS. Patients recorded daily average and the mean NRS was calculated for the prior 7 days. Primary efficacy endpoint was responder analysis. Secondary outcome measures included ODI and QoL measured with the EQ-5D questionnaire and treatment satisfaction on a 5-point Likert scale. Minimally clinically important change (MCIC) threshold was defined as a change in 2 points on NRS, 10 points on ODI and 0.1 for EQ-5D.

Key efficacy findings

Number of patients analysed: 53

Outcome measures

Performance measure	**Baseline (n=53) mean ± SE; %**	**90 days (n=52) mean ± SE; %**	**6 months (n=51) mean ± SE; %**	**1 year (n=47) mean ± SE; %**	**2 years (n=39)**	**3 years (n=37 for NRS, n=34 for ODI and EQ-5D)**	**4 years (n=33 for NRS, n=31 for ODI and EQ-5D)**
Back pain (7 day average NRS)^							
7 day average NRS^	6.8±0.8	4.3±2.1	4.6	4.4^^^	4.1^^^	3.5^^^	3.2±0.4^^^
Improvement from baseline–		-2.5±0.3 (p<0.0001)	-	-			

absolute change							
Improvement from baseline–% change		36% (p<0.0001)					
Responder rate**		58 (30/52)	NR	NR			
Back pain (single day NRS)*							
Single day NRS	6.8±0.8	4.3±2.2	4.6±2.5	4.4±2.7			
Improvement from baseline–absolute change		-2.5±0.3 (p<0.0001)	-2.2±0.4 (p<0.0001)	-2.4±0.4 (p<0.0001)			
Improvement from baseline–% change		-35%	-32%	-33%			
MCID >2 point improvement (% of subjects)		63% (33/52)	61% (31/51)	57% (27/47)			
Disability on ODI^^							
ODI	44.9±10.1	31.3±17.6	32.8±20.3	30.7±19.2	28^^^	26^^^	23.0±3.2^^^
Improvement from baseline–absolute change		-13.4±2.2 (p<0.0001)	-11.6±2.4 (p<0.0001)	-14.3±2.3 (p<0.0001)			
MCID >10 point improvement (% of subjects)***		52% (27/52)	57% (29/51)	60% (28/47)			
QoL on EQ-5D							
	0.434±0.185	0.648±0.195	0.622±0.235	0.654±0.217	0.68^^^	0.71^^^	0.721±0.035^^^

Improvement from baseline–absolute change		0.213±0.025 (p<0.0001)	0.184±0.032 (p<0.0001)	0.219±0.028 (p<0.0001)			
MCID >0.03 point improvement (% of subjects)***		88% (46/52)	82% (42/51)	81% (38/47)			

^10-point NRS with 0 indicating 'no pain' and 10 'worst imaginable pain'.

^^100-point ODI with scores of 21–40% indicating moderate disability and scores of 41–60% indicating severe disability.

^^^Results estimated from graph – less precision available.

*Patients reported single day low back pain NRS for back pain assessment after 90 days.

**Patients with an improvement of at least the MCID of more than 2-point in low back pain NRS without a clinically meaningful increase in LBP medications at 90 days.

***The MCID for ODI is a change of 10 points and the MCID for EQ-5D is a change of at least 0.03 points.

Prespecified analysis of completed case cohorts:

Mean improvement in low back pain from NRS baseline (6.8±0.8 for original cohort, 6.7±1.2 for 4-year completed cohort)					
Follow-up period	**1-year completed case cohort (n=47)**	**2-year completed case cohort (n=39)**	**3-year completed case cohort (n=37)**	**4-year completed case cohort (n=33)**	**Standard deviation**
1 year	2.4	2.6	2.7	2.6	0.14
2 years	-	2.7	2.8	2.8	0.08
3 years	-	-	3.3	3.2	0.10
4 years	-	-	-	3.5	-
Mean improvement in back pain-related disability from ODI baseline (44.9±10.1 for original cohort, 43.8±9.9 for 4-year NRS completed cohort)					
Follow-up period	**1-year completed case cohort (n=47)**	**2-year completed case cohort (n=39)**	**3-year completed case cohort (n=35)**	**4-year completed case cohort (n=32)**	**Standard deviation**
1 year	14.3	16.4	17.4	17.1	1.39
2 years	-	17.0	17.9	18.9	0.95
3 years	-	-	19.7	20.3	0.37
4 years	-	-	-	22.2	-

Mean improvement in QoL from EQ-5D baseline (0.434±0.185 for original cohort, 0.444±0.186 for 4-year NRS completed cohort)					
Follow-up period	**1-year completed case cohort (n=47)**	**2-year completed case cohort (n=39)**	**3-year completed case cohort (n=35)**	**4-year completed case cohort (n=32)**	**Standard deviation**
1 year	0.219	0.247	0.245	0.235	0.01
2 years	-	0.244	0.256	0.263	0.00
3 years	-	-	0.288	0.286	0.00
4 years	-	-	-	0.285	-

Composite success (patients with an improvement of the MCID in 1 or more of the outcome measures NRS, ODI or EQ-5D)

At 90 days, 6 months and 1 year, 94%, 87% and 87% of the patients met at least 1 MCID criteria and 40% or more had improvements in all 3 outcomes.

73% of patients experienced a clinically meaningful improvement of at least the MCIC on NRS, and 76% experienced a clinically meaningful improvement of at least the MCIC on ODI. 62.5% of patients experienced a clinically meaningful benefit of at least the MCIC in both NRS and ODI. Mean improvements from baseline were statistically significant ($p<0.001$) and clinically meaningful for all follow ups.

Patient satisfaction

89%, 84% and 81% of the patients were 'satisfied' or 'very satisfied' with their treatment at 90 days, 6 months and 1 year, respectively. In the completed case cohort treatment, satisfaction at 4 years was reported as 'Very Satisfied' in 97% (32/33) of patients.

Device use

From activation to 90 days follow up: 86±2% (52±9.5 min/day) of the maximum 60 minutes per day was used. Between 6 months to 1 year, 67% of available stimulation was delivered.

Key safety findings

Adverse events

	% (n=events)	**% (n=patients)**
Total adverse events	n=145	
Related to procedure, device and/or stimulation (none were serious)^	**52% (76/145)**	**66 (35/53)**
Procedure related (wound pain, inflammation, haematoma, postoperative discomfort)	18 (14/76)	21 (11/53)

Device related (loss of stimulation [23 in 17 patients], pocket/lead discomfort [13 in 12 patients], 3 undesired sensations)	51 (39/76)	47 (25/53)
Device/procedure related (seroma/inflammation because of lead incision, postoperative nervous system irritation)	9 (7/76)	9 (5/53)
Device/stimulation related (undesired sensations in target area, muscle fatigue)	21 (16/76)	29 (15/53)
Lead migration (leading to loss of sensation)	1	1
Unrelated to procedure (3 were serious: surgical removal of uterine fibroid, non-cardiac chest pain, cerebrovascular accident)	48 (69/145)	53 (28/53)
Overall device explantation (within 1 year) (1 because of lead migration before 90 days follow up, 4 because of lack of efficacy within 1 year)	9.4 (5/53)	-
Device explantation at 4 years	-	
Device explantation (without clinical benefit)	-	20.8% (11/53)
Device explantation (with clinical benefit)	-	7.5% (4/53)
Device explantation because of lead migration	-	1.9% (1/53)

^Loss of stimulation, pocket discomfort and undesired sensations in the target area were the most frequent AEs and accounted for 57% of the related AEs. The remaining 33 related AEs happened at rates of 1 to 5%.

Device problems (leading to loss of stimulation)

-	**% (n)**
Total device problems*	70 events
Lead conductor fractures because of tight bending (in those implanted using lateral approach) leading to loss of stimulation, high impedance [>5000 X] post-implantation (on one of the conductors on the stimulation channels)^	53% (28/53) 44 leads
Surgical revision to implant new leads	13
Reprogrammed to resume bilateral stimulation via a different electrode configuration	7
Continued therapy with unilateral stimulation	3
System turned off	3
System explanted	2

^Modified implant procedure using a midline approach reduced the risk of lead bending and conductor fracture.
*8 at implant, resolved prior to completion of surgery.

Study 3 Thomson S (2021)

Study details

Study type	Prospective case series (PMCF open label study)
Country	United Kingdom
Recruitment period	Not reported
Study population and number	n=42 patients with CMLBP that has not responded to physiotherapy or medication, and with no indications for surgery. Mean duration of CMLBP: 13.7±10.2 years.
Age	Mean age 47.2±11.0 years, 40% female
Patient selection criteria	Inclusion criteria: adult patients with a history of mechanical CLBP lasting more than 90 days that was refractory to physiotherapy or medication. Exclusion criteria: clear indications for surgery, additional clinical conditions with potential impact on therapeutic delivery or assessment of pain relief.
Technique	Patients were implanted with a restorative neurostimulation device (ReActiv8 System) through the midline surgical approach. Devices were activated around 14 days after implantation, and patients used a wireless activator to deliver 2 daily 30-minute stimulation sessions while resting in either a prone or lateral position.
Follow up	2 years
Conflict of interest/source of funding	Study was sponsored by Mainstay Medical. Authors have also received consultancy fees and research grants from Mainstay Medical and other medical companies.

Analysis

Follow-up issues: 3 patients withdrew from the study before 1 year, and 1 before 2 years because of inadequate pain relief and subsequent device explantation. One further patient was lost to follow up before 2 years.

Study design issues: small multicentre case series study. Primary performance outcome was improvement in pain using the mean NRS calculated for the prior 7 days. Primary efficacy end point was responder analysis. Secondary outcome measures included ODI and QoL measured with the EQ-5D questionnaire.

Study population issues: mean BMI 29.7±6.0, 33% previous rhizotomy (14/42), 19% current smokers (8/42).

Other issues: Impact of missing data at 1 and 2 years was estimated using a simple last observation carried forward imputation.

Key efficacy findings

- Number of patients analysed: 42

Clinical patient-reported outcomes – complete cases

	Baseline (n=42)	45 days (n=42)	90 days (n=42)	180 days (n=42)	1 year (n=39)	2 years (n=37)
Mean NRS	7.0±0.2	5.6±0.3	5.5±0.4	5.2±0.4	4.7±0.4	3.5±0.3 (p<0.0001)
≥30% improvement in NRS (%)	-	-	33*	45*	49*	67.6 (25/37)
≥50% improvement in NRS (%)	-	-	21*	24*	39*	56.8 (21/37)
Mean ODI	46.2±2.2	-	37*	36*	32*	29.2±3.1 (p<0.0001)
≥15 Pt. improvement in ODI (%)	-	-	24*	33*	41*	51.4 (19/37)
≥20 Pt. improvement in ODI (%)	-	-	14*	26*	31*	43.2 (16/37)
Mean EQ-5D	0.426±0.035	-	0.58*	0.57*	0.62*	0.680±0.030 (p<0.0001)

*Values estimated from graph – less precision available.

Clinical patient-reported outcomes – imputed cases at 1 and 2 years (n=42)

	Baseline	1 year	2 years
Mean NRS	7.0±0.2	4.9±0.4	4.0±0.4
Mean ODI	46.2±2.2	33*	32*
Mean EQ-5D	0.426±0.035	0.60*	0.61*

*Values estimated from graph –less precision available.

The proportion of patients experiencing at least 50% improvement in NRS pain scores at 2 years was 57% (21/37), and 65% (24/37) reported mild to negligible pain (NRS≤3).

At 2 years, 51.4% of patients (19/37) experienced a clinically meaningful (≥15-point improvement) in ODI disability score with 43% of patients (16/37) experiencing ≥20-point improvement in ODI.

Key safety findings

No serious adverse events were reported.

Event	Number of events	% of patients (n=42)	Number of events resolved
Total adverse events	20	28.6% (12/42)	15/20 (75%)
Overstimulation of tissue	10	16.7% (7/42)	7/10 (70%)
Implant site pocket pain	3	(3/42)	2/3 (66.6%)
Lead conductor fracture	2	(2/42)	2/2 (100%)
Implant site blisters	1	(1/42)	1/1 (100%)
Implant site pocket infection	1	(1/42)	1/1 (100%)
Pain in leg	1	(1/42)	0/1 (0%)
Synovial cyst	1	(1/42)	1/1 (100%)
Wound pain	1	(1/42)	1/1 (100%)

Study 4 Deckers K 2015

Study details

Study type	Case series (feasibility study)
Country	Belgium and the UK (4 sites)
Recruitment period	2011 to 2012
Study population and number	n=26 patients with CLBP despite physical therapy and medication and no prior surgery. Duration of CLBP: 6.2 years (range 1.2 to 29.6)
Age	Mean age 43.9 years; 62% female (16/26)
Patient selection criteria	Inclusion criteria: patients between 18 to 60 years, with CLBP for more than 90 days, ODI above 25, refractory to physical therapy and medications; compromised neural drive to the lumbar multifidus on a prone weighted upper extremity lift test (WUELT) determined by a change in thickness of less than 20% of the lumbar multifidus during contraction on the right or left side at L4 or L5. Exclusion criteria: patients with BMI above 35, with an indication for surgery or prior back surgery, previous interventions including medial branch rhizotomy, with implanted devices and not suitable for neuromodulation therapies, inability, or unwillingness to comply with study protocol.
Technique	Patients were implanted with commercially available implantable neurostimulation pulse generators and leads, positioned adjacent to the medial branch of the dorsal ramus of the spinal nerve as it crosses the L3 transverse process. A lateral surgical approach was used. Once position of the leads is confirmed, they are attached to muscular fascia using suture sleeve partially inserted into the muscle. Episodic electrical stimulation resulted in contraction of the lumbar multifidus muscle. Patients self-administered stimulation using an external controller, twice daily for 20 minutes.
Follow up	3 and 5 months
Conflict of interest/source of funding	Authors have served as speakers, consultants or advisory board members for the company (Mainstay Medical), and 3 were employed by them.

Analysis

Follow-up issues: follow up was short term, and several patients lost to follow up because they withdrew from the study before 3 months (1 before implantation, 1 after implant abandoned, 5 because of lead migration,1 after infection and 1 because of unrelated medical intervention).

Study design issues: a multicentre small feasibility study with 1 month therapy withdrawal phase (between 4 and 5 months); the sample size was further reduced as several patients withdrew from study and efficacy was assessed in only 19 patients. Primary outcomes were low back pain (assessed on VAS 100 mm scale), disability (assessed using 100-point ODI scale) and QoL (assessed using EQ-5D) scores at 3 and 5 months and were compared to baseline. Patients continued pre-implantation medications and exercise for LBP during the study. There was heterogeneity in stimulation therapy, medications used and exercise therapy.

Study population issues: 42% of patients experienced bilateral LBP and 57.7% experienced unilateral LBP.

Key efficacy findings

- Number of patients analysed: 28
- Mean duration of procedure: 105 ± 39 minutes

Clinical outcomes (n=19)

	Baseline (mean±SD)	**3 months (post activation) (mean±SD)**	**Change from baseline (mean±SD)**	**Response rate, % (n)***	**5 months (post activation off)** (mean±SD)**	**Change from baseline (mean±SD)**	**Response rate, % (n)***
Average low back pain (VAS, mm)	67.3±11.1	40.8±23.8	26.4±22.3 (p<0.0001)	73.7 (14/19)	39.7±33.4 (n=18)	27.6±27.3 (p=0.0005)	66.7 (12/18)
Disability (ODI)	38.5±14.6	27.6±15.6	10.9±9.6 (p=0.0001)	63.2 (12/19)^	29.6±29.3 (n=19)	12.1±14.4 (=0.0017)	52.6 (10/19)
QoL (EQ-5D)^^	0.43±0.34	0.70±0.21	0.27±0.24 (p=0.0002)			0.20±0.43 (p=0.06)	-

*Response criteria (minimally important clinical change) were either ≥30% or ≥15 mm for LBP VAS and ≥30% or ≥10 points for ODI.
**Stimulation was suspended between 4 and 5 months.
^45% (5/11) of patients on disability leave for their LBP at baseline had resumed work by 3 months.
^^At 3 months, 84.2% (16/19) reported an increase in EQ-5D and none reported a decrease. 52.6% (10/19) reported improvement in QoL at 5 months.

Medication use (n=19)
Twelve patients were on medication for LBP at implantation and 7 were not. At 3 months, of the 12 on medications, 8 stopped use or decreased in number and dose and 4 had no change in their medication.

Key safety findings

Adverse events (n=27 who had implantation)

Adverse events	**% (n)**	**Number of events**
Total adverse events	-	97
Related to device and/or procedure	**74 (20/27)**	**60**
Procedure related	-	13
Device related	-	27
Both device and procedure related	-	20
Unrelated to device or procedure	-	**37**
Adverse events		
Lead migration (leading to inadequate stimulation or surgical revision)*	48.1 (13/27)^	21
Inadequate stimulation (lead migration in 8, high impedance in 2, pulse generator malfunction in 2, reason not specified in 1)	48.1 (13/27)	13
Pain	14.8 (4/27)	8
Over stimulation	11.1 (3/27)	5
Undesired sensations (target/non-target area)	7.4 (2/27)	2
Tissue injury	3.7 (1/27)	1
Fever	3.7 (1)	1
Abnormal healing	3.7 (1/27)	1
Nausea or vomiting (related to anaesthesia)	3.7 (1/27)	1
Nervous system irritation/injury	3.7 (1/27)	2
Musculoskeletal fitness	7.4 (2/27)	2
Infection (needed device removal)	3.7 (1/27)	1
Seroma	3.7 (1/27)	1
Risk with any surgical procedure	3.7 (1/27)	1
Surgical revisions and device explant	**-**	**20**
Lead migration (11 repositioned, 1 explanted)	37.0 (10/27)	12
High impedance	7.4 (2/27)	2
IPG migration	7.4 (2/27)	2

IPG failure	3.7 (1/27)	1
Discomfort because of lead anchor	7.4 (2/27)	2
Explant (because of infection and lead migration)	3.7 (1/27)	1

*5 events happened between implantation and 3 months. Five patients had more than 2 migrations, 2 had more than 3 migrations, and 1 had 4 migrations.

Validity and generalisability of the studies

- There is only limited published literature (1 RCT and 3 small case series) on neurostimulation of lumbar muscles with short-term follow up.
- The RCT compared therapeutic stimulation with low-level stimulation sham control.
- There are no studies comparing this treatment with current standard of care.
- The feasibility study (Deckers 2015) used standard spinal cord stimulator leads from other manufacturers. The frequent lead migrations observed in this study led to the development of the ReActiv8 lead with exclusive distal fixation tines.
- ReActiv8-A Study (Deckers 2017) was performed using the ReActiv8 lead and a 'lateral' surgical approach for the first 47 subjects. To mitigate the risk of lead conductor fractures associated with the lateral approach, the lead trajectory was modified to the 'midline approach'.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Electrical stimulation to improve muscle strength in chronic respiratory conditions, chronic heart failure and chronic kidney disease. Interventional procedures guidance 677 (2020). Available from https://www.nice.org.uk/guidance/IPG677

- Peripheral nerve-field stimulation for chronic low back pain. Interventional procedures guidance 451 (2013). Available from https://www.nice.org.uk/guidance/IPG451
- Deep brain stimulation for refractory chronic pain syndromes (excluding headache) Interventional procedures guidance 382 (2013). Available from https://www.nice.org.uk/guidance/IPG382

Technology appraisals

- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from https://www.nice.org.uk/guidance/TA159

NICE guidelines

- Low back pain and sciatica in over 16s: assessment and management. NICE guideline 59 (2016). Available from https://www.nice.org.uk/guidance/NG59

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three professional expert questionnaires for neurostimulation of lumbar muscles for refractory non-specific chronic low back pain was submitted and can be found on the NICE website.

Patient commentators' opinions

Twenty-two commentaries from patients who have had this procedure were discussed by the committee. The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing studies

- **NCT02577354:** ReActiv8 Implantable Neurostimulation System for Chronic Low Back Pain **(ReActiv8-B).** international multicentre prospective randomised blinded controlled trial with one-way crossover (appropriate stimulation eliciting multifidus contractions versus sub-threshold stimulation, 30 minutes twice a day sessions); n=204; patients in control arm crossed over to treatment arm after primary outcome assessment; primary outcomes: comparison of responder rates for low back pain VAS between treatment and control groups, device or procedure related adverse events. Study location: USA, Australia, Belgium, The Netherlands, UK. **Study completion date December 2023.**
- NCT03255200: ReActiv8 Post Market Surveillance Registry for the **ReActiv8** Implantable Neurostimulation System for Chronic Low Back Pain (**ReActiv8-C)**. observational cohort study, n=50, primary outcomes: rates of low back pain, adverse events; location: Germany. **Study completion date December 2023, status: recruiting.**
- NCT01985230: Investigation of the **ReActiv8** Implantable Stimulation System for Chronic Low Back Pain (post marketing clinical follow up [PMCF] - **ReActiv8-A continuation study**). Interventional single group assignment, n=96, primary outcome: low back pain assessed on NRS, adverse events at 90 days; study location: Australia, Belgium, UK (8 sites). **Study completion date December 2024; status: active.**

References

1. Gilligan C, Volschenk W, Russo M et al. (2021) An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: a randomized sham-controlled clinical trial. PAIN, Publish ahead of print. DOI: 10.1097/j.pain.0000000000002258

   Gilligan C, Volschenk W, Russo M et al. Long-Term Outcomes of Restorative Neurostimulation in Patients with Refractory 2 Chronic Low Back Pain Secondary to Multifidus Dysfunction: 2-Year Results of the 3 ReActiv8-B Pivotal Trial. Accepted for publication in Neuromodulation: Technology at the Neural Interface.

2. Deckers K, De Smedt K, Mitchell B et al. (2018) New therapy for refractory chronic mechanical low back pain—Restorative neurostimulation to activate the lumbar multifidus: one year results of a prospective multicentre clinical trial, Neuromodulation 21, 48–55.

   Mitchell B, Deckers K, De Smedt K et al. (2021) Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation Technology at the Neural Interface. E-pub ahead of print. DOI:10.1111/ner.13477

3. Thomson S, Chawla R, Love-Jones S et al. (2021) Restorative Neurostimulation for Chronic Mechanical Low Back Pain: Results from a Prospective Multi-centre Longitudinal Cohort Pain Therapy. 2021 Dec; 10(2): 1451–65.

4. Deckers K, De Smedt K, van Buyten JP et al. (2015) Chronic low back pain: restoration of dynamic stability. Neuromodulation; 18(6): 478–86.

Literature search strategy

Databases	Date searched	Version/files	Number retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	07/07/2021	Issue 7 of 12, July 2021	R: 2 P: 0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	07/07/2021	Issue 7 of 12, July 2021	11
International HTA database (INAHTA)	07/07/2021	-	0
MEDLINE (Ovid)	07/07/2021	1946 to July 06, 2021	21
MEDLINE In-Process (Ovid)	07/07/2021	1946 to July 06, 2021	7
MEDLINE Epubs ahead of print (Ovid)	07/07/2021	July 06, 2021	14
EMBASE (Ovid)	07/07/2021	1974 to 2021 July 06	76

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1 Chronic Pain/ (15325)
2 ((chronic or prolong* or persist* or mechanical or severe or nociceptive or refractory or disabling) adj4 pain*).tw. (94399)
3 (CLBP or CMLBP or NSLBP).tw. (1408)
4 Low Back Pain/ (22279)
5 (back adj4 (pain* or ache* or aching)).tw. (43081)
6 (low* adj4 (back pain* or back ache* or backache*)).tw. (25260)
7 lumbago.tw. (1254)
8 Intervertebral Disk Displacement/ (18840)
9 ((slipped or hernia* or prolaps*) adj4 (disc* or disk*)).tw. (12375)
10 ((discogenic* or diskogenic*) adj4 pain*).tw. (853)
11 Sciatica/ (5019)
12 sciatica*.tw. (3939)
13 Intervertebral Disc Degeneration/ (5448)
14 (intervertebr* adj4 (disc* or disk*) adj4 degenerat*).tw. (2905)
15 (radicular adj4 pain*).tw. (2683)
16 Radiculopathy/ (5206)
17 (lumbar adj4 radiculopath*).tw. (763)
18 (nerve root* adj4 (pain* or avulsion or compress* or disorder* or pinch* or inflam* or imping* or irritat* or entrap* or trap*)).tw. (2504)

19 Muscle Strength/ (20518)
20 (Arthrogenic adj4 muscle* adj4 inhibition*).tw. (34)
21 or/1-20 (181565)
22 Lumbosacral region/ (12639)
23 Paraspinal Muscles/ (1013)
24 (lumbar or lumbo-sacral or "lumbo sacral").tw. (94741)
25 (mulitfid* or paraspinal* or sacrospinal* or paraverteb* or sacroverteb*).tw. (7813)
26 or/22-25 (106201)
27 Electric Stimulation/ (113884)
28 Electric Stimulation Therapy/ (20642)
29 (electr* adj4 stimulat*).tw. (71535)
30 (neurostimulat* or neuromodulat*).tw. (16052)
31 ((implant* adj4 pulse adj4 generat*) or IPG).tw. (1390)
32 ((dorsal ramus or nerve*) adj4 stimulat*).tw. (35869)
33 (Multifid* adj4 contract*).tw. (35)
34 or/27-33 (189911)
35 21 and 26 (26961)
36 35 and 34 (462)
37 reactiv8.tw. (1)
38 36 or 37 (462)
39 Animals/ not Humans/ (4726676)
40 38 not 39 (381)
41 limit 40 to ed=20201126-20210731

Appendix

There were no additional papers identified.