Stimulation therapy settings were within the range of conventional parameters for both groups. The only difference between treatment groups was enabling the feedback mechanism in the closed-loop group.

Outcomes

The primary outcome, tested at 3 months (the primary analysis) and at 12 months (an additional prespecified analysis) after the permanent implant, was a composite outcome: the proportion of patients who responded to spinal cord stimulation therapy for overall back and leg pain (≥50% reduction in VAS score) without an increase in baseline pain medications. Secondary outcomes assessed the percentage change from baseline in leg pain VAS and back pain VAS, prevalence of high responders (≥80% reduction) for overall back and leg pain, and prevalence of responders (≥50% reduction) for back pain VAS, all at 3 months and 12 months. Additional secondary outcomes were collected as per IMMPACT recommendations,[22] including functional disability measured by the ODI;[23] emotional functioning measured by the Profile of Mood States (POMS);[24] sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI);[25] quality of life measured by the Short Form Health Survey (SF-12, version 2)[26] and the European Quality of Life Five-Dimensional Five-Level questionnaire (EQ-5D-5L);[27] Patient Global Impression of Change; patient satisfaction; opioid usage;[28] and objective device data characterising use, spinal cord activation, and neurophysiological properties (eg, conduction velocity). A pain map, stimulation characteristics, and posture change assessment were also collected as additional secondary outcomes; however, the results are not reported here because these are not validated measures.

The ECAP amplitude (measured by the device in μV) is representative of the number of spinal cord fibres activated by stimulation. The device measures an ECAP amplitude (ie, spinal cord activation level) for each stimulus and stores these as histogram data when the patient is outside the clinic. ECAP histograms show the number of stimuli that occur at each ECAP amplitude and are an objective measure of the amount of spinal cord activation over time. The histograms also elucidate how patients adjust to or manage stimulation in the real world (compared with the level set in the clinic under the clinician's guidance). The histogram data reported are for patients' preferred (or most used) programme during the week before the scheduled visits. The mode ECAP amplitude is a measure of the most frequent spinal cord activation level for a given period. Patients' spinal cord activation outside the clinic was compared with their therapeutic window and the comfort level programmed in the clinic. The therapeutic window was defined by the ECAP amplitude measured at patient perception threshold, when the patient reported initially feeling stimulation, to the ECAP amplitude at the maximum level the patient could withstand, also known as the discomfort threshold. Therefore, the therapeutic window in the Evoke study defined the range of therapeutic spinal cord activation in all postures. Other published reports have defined the therapeutic window by the stimulation current amplitude at these levels,[29] but this would only be applicable in one posture.[3,17] The comfort level is the ECAP amplitude perceived as comfortable by the patient.

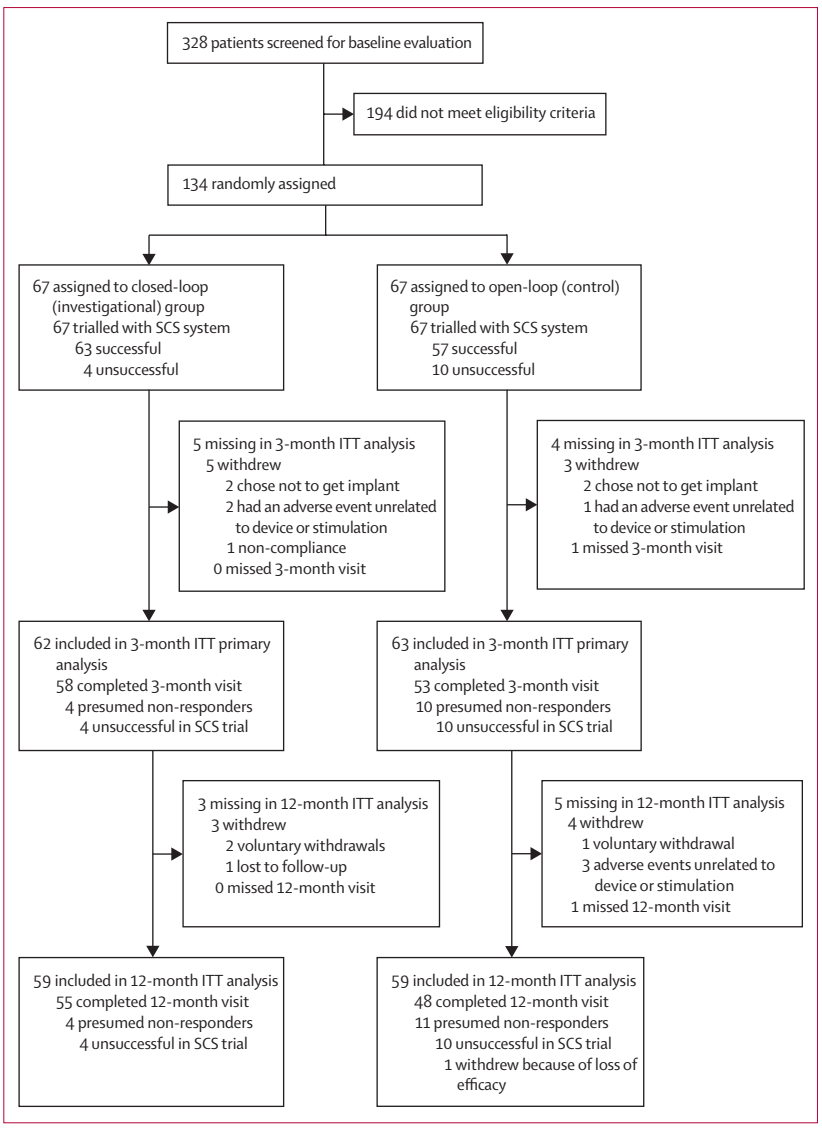


Figure 2: **Trial profile**
SCS=spinal cord stimulation. ITT=intention-to-treat.

All adverse events were reported by the investigators throughout the course of the study and reviewed and adjudicated by a masked, independent, clinical events committee.

Statistical analysis

A minimum of 60 patients per group (120 in total) were required to have at least 80% power to determine non-inferiority of the primary outcome at a one-sided significance level (α) of 0·05 and a non-inferiority margin

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	Closed-loop group (n=67)	Open-loop group (n=67)
Age (years)	54·6 (9·7)	55·9 (11·6)
Sex		
Women	33 (49%)	32 (48%)
Men	34 (51%)	35 (52%)
Body-mass index (kg/m²)	31·3 (5·7)	32·4 (6·8)
Duration of pain (years)	13·6 (9·6)	11·2 (9·9)
Cause of pain, not mutually exclusive		
Arachnoiditis	0	2 (3%)
Complex regional pain syndrome I	0	1 (2%)
Degenerative disc disease	33 (49%)	42 (63%)
Failed back surgery syndrome	38 (57%)	41 (61%)
Internal disc disruption or tear or discogenic pain	7 (10%)	10 (15%)
Lumbar facet-mediated pain	8 (12%)	8 (12%)
Mild-moderate spinal stenosis	26 (39%)	27 (40%)
Radiculopathy	61 (91%)	59 (88%)
Sacroiliac joint-mediated pain	9 (13%)	5 (8%)
Spondylolisthesis	6 (9%)	5 (8%)
Spondylosis with myelopathy	2 (3%)	3 (5%)
Spondylosis without myelopathy	26 (39%)	24 (36%)
Other chronic pain	6 (9%)	3 (5%)
Baseline pain medication usage	63 (94%)	59 (88%)
Opioids	41 (61%)	40 (60%)
Non-opioids*	51 (76%)	52 (78%)
Previous non-invasive therapies†	65 (97%)	64 (96%)
Previous interventional procedure‡	63 (94%)	62 (93%)
Previous back surgery§	39 (58%)	41 (61%)

Data are mean (SD) or n (%). *Non-opioid pain medication classes include anticonvulsant, antidepressant, local anaesthetic, muscle relaxant, non-steroidal anti-inflammatory drugs, and other pain medications. †Non-invasive therapies include acupuncture, aquatherapy, assistive device, biofeedback, chiropractic care, exercise therapy, massage therapy, psychotherapy, physical therapy, and transcutaneous electro-nerve stimulator. ‡Interventional procedures include ankle surgery, benign cyst removal, block or injection (other), epidural steroid injection, facet joint injection, intradiscal bilateral lumbar biacuplasty, intradiscal procedure (eg, intradiscal electrothermal therapy), lumbar rhizotomy, lumbar surgical ablation, lumbar sympathetic block, medial branch block, radio frequency denervation, sacroiliac joint injection, and trigger point injection. §Back surgeries include artificial disc replacement, discectomy or microdiscectomy, foraminotomy, kyphoplasty or vertebroplasty, laminectomy, nucleoplasty (eg, disc decompression, and laser surgery), spinal fusion, back surgery (not otherwise specified), and back surgery (other).

Table 1: **Baseline demographics and characteristics for all randomly assigned patients**

(δ) of 10%. To account for potential patient loss to follow-up of up to 10%, 134 patients were randomly assigned. Each site was not permitted to enrol more than 26 patients (approximately 20% of the total study population).

The primary analysis was done at 3 months and an additional prespecified analysis was done at 12 months after the permanent implant. The primary analysis set was the intention-to-treat population, which included all randomly assigned patients who either had known outcome status or were presumed non-responders (ie, patients with <50% pain reduction in overall back and leg pain at the trial, patients who withdrew because of poor or no efficacy, or patients who withdrew because of a device-related or stimulation-related adverse event). All other missing data were classified as missing at random.

The primary composite outcome was analysed through the normal approximation to the binomial distribution, with an unpooled estimate of the SE and with no correction for continuity. Non-inferiority of the closed-loop system compared with the open-loop spinal cord stimulation was assessed against a δ of 10% at an α of 0·05. If non-inferiority was met, then superiority was tested at a two-sided α of 0·05.

For the secondary VAS outcomes, the normal approximation to the binomial was used for binary outcomes and a two-sample *t*-test was used for continuous outcomes. A hierarchical testing approach was followed to control for type 1 error. If non-inferiority was met, then superiority was tested.

The additional patient-reported outcomes were compared between treatment groups by use of Fisher's exact tests for categorical measures and two-sample *t*-tests for continuous measures with two-sided α of 0·05. Non-parametric Kruskal-Wallis tests were used for the device data measurements because of the observed distributions of the data.

All statistical analyses were done with SAS, version 9.4, and SAS Enterprise Guide, version 7.1. This study is registered with ClinicalTrials.gov, NCT02924129, and is ongoing.

Role of the funding source

The funder of the study, in collaboration with physicians and researchers in the field, participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 27, 2017, and Jan 16, 2018, 328 patients were screened. Between Feb 21, 2017, and Feb 20, 2018, 134 patients were enrolled and randomly assigned (67 to each treatment group). Follow-up was complete through to 12 months (figure 2). The intention-to-treat population with evaluable data comprised 62 patients in the closed-loop group and 63 in the open-loop group at 3 months (the timing of the primary analysis), and 59 patients in the closed-loop group and 59 in the open-loop group at 12 months. Masking was maintained during the full study duration, with no patients or investigators being made aware of the treatment assignments in either group.

There were no between-group differences in the diagnoses, previous treatments, or other baseline demographics or characteristics (table 1). All patients in both groups had a diagnosis of chronic intractable back and leg pain. The most common causes of pain in both groups were radiculopathy (in 61 [91%] patients in the closed-loop

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	3 months				12 months			
	Closed-loop group	Open-loop group	Difference (95% CI)	p value	Closed-loop group	Open-loop group	Difference (95% CI)	p value
VAS percentage change from baseline*†‡								
Overall pain	73·8% (28·0)	59·4% (35·8)	14·4% (3·0 to 25·8)	0·013	72·3% (29·0)	56·2% (38·5)	16·0% (3·6 to 28·5)	0·012
Back pain (hierarchical secondary outcome)	72·1% (29·4)	57·5% (36·4)	14·6% (2·9 to 26·3)	0·015§	69·4% (30·6)	54·0% (39·5)	15·4% (2·5 to 28·3)	0·020§
Leg pain (hierarchical secondary outcome)	76·8% (28·3)	67·8% (35·5)	9·0 (–2·4 to 20·4)	0·0006¶	72·9% (31·0)	62·1% (37·5)	10·7% (–1·8 to 23·3)	0·0007¶
VAS responder rates*‖								
Overall pain ≥50% reduction (primary outcome)	51/62 (82%)	38/63 (60%)	21·9% (6·6 to 37·3)	0·0052§	49/59 (83%)	36/59 (61%)	22·0% (6·3 to 37·7)	0·0060§
Back pain ≥50% reduction (hierarchical secondary outcome)	50/62 (81%)	36/63 (57%)	23·5% (7·8 to 39·2)	0·0033§	47/59 (80%)	34/59 (58%)	22·0% (5·8 to 38·3)	0·0079§
Leg pain ≥50% reduction	50/62 (81%)	43/63 (68%)	12·4% (–2·7 to 27·5)	0·0020¶	49/59 (83%)	36/59 (61%)	22·0% (6·3 to 37·7)	0·0060§
VAS high responder rates*‖								
Overall back and leg pain ≥80% reduction (hierarchical secondary outcome)	36/62 (58%)	27/63 (43%)	15·2% (–2·1 to 32·5)	0·0023¶	33/59 (56%)	22/59 (37%)	18·6% (1·0 to 36·3)	0·039§

Data are mean (SD) or n/N (%). VAS=Visual Analog Scale. *Patients who had an increase from baseline in study indication pain medications within 4 weeks of the outcome visit were considered failures or had a change from baseline value of zero imputed. †Presumed non-responders had their last value carried forward. ‡Positive change indicates improvement. §Superiority of closed-loop group compared with open-loop group. ¶Non-inferiority (δ=10%) of the closed-loop group compared to the open-loop group. ‖Presumed non-responders were imputed as failures.

Table 2: **Summary of pain outcomes**

group *vs* 59 [88%] in the open-loop group), failed back surgery syndrome (in 38 [57%] patients in the closed-loop group *vs* 41 [61%] in the open-loop group), and degenerative disc disease (33 [49%] in the closed-loop group *vs* 42 [63%] in the open-loop group). 39 (58%) patients in the closed-loop group and 41 (61%) in the open-loop group had previous back surgery. Mean baseline overall scores were 81·9 mm (SD 10·6) for back and leg pain, 81·4 mm (10·2) for back pain, and 82·2 mm (10·8) for leg pain in patients in the closed-loop group; and 82·3 mm (8·8) for back and leg pain, 80·4 mm (11·2) for back pain, and 80·0 mm (9·9) for leg pain for patients in the open-loop group.

The primary outcome, the proportion of responders with 50% or greater reduction in overall back and leg pain with no increase in pain medications, was met by a greater proportion of patients in the closed-loop group than in the open-loop group at 3 months (51 [82·3%] of 62 patients in the closed-loop group *vs* 38 [60·3%] of 63 in the open-loop group; difference 21·9%, 95% CI 6·6–37·3) and at 12 months (49 [83·1%] of 59 in the closed-loop group *vs* 36 [61·0%] of 59 in the open-loop group; difference 22·0%, 6·3–37·7). Non-inferiority was met at 3 months (p<0·0001) and 12 months (p<0·0001), as was superiority (3 months, p=0·0052; 12 months, p=0·0060; table 2; appendix p 8).

All VAS-related secondary outcomes were non-inferior in the closed-loop group compared with those in the open-loop group, with the majority achieving superiority at 3 and 12 months (table 2; appendix p 7). In both groups, stimulation relieved overall back and leg pain as well as in each region, with some patients classified as responders (with ≥50% reductions) or high responders (with ≥80% reductions). Patients in the closed-loop group, however, consistently reported greater pain relief than did those in the open-loop group. The 7-day pain diary and in-clinic VAS scores were highly correlated for both treatment groups, with the Pearson correlation coefficient (ρ) ranging from 0·89 to 0·94.

A significant and clinically important improvement from baseline was observed at 3 and 12 months in both treatment groups in all other patient-reported outcomes, including ODI, POMS, PSQI, EQ-5D-5L, and SF-12. In general, the improvement was greater in the closed-loop group than in the open-loop group, with significant differences seen in POMS total mood distrubance score and SF-12 mental health composite scale score at 3 and 12 months (appendix p 9).

At 12 months, opioid use was reduced or eliminated in 17 (55%) of 31 patients in the closed-loop group and in 12 (40%) of 30 in the open-loop group who were taking opioids at baseline. The reductions in average daily morphine mg equivalents (MMEs) did not differ significantly between the two groups (from 80·1 MMEs [SD 105·3] at baseline to 45·0 MMEs [45·9] at 12 months in the closed-loop group [27·3% reduction]; and from 66·4 MMEs [86·2] at baseline to 44·5 MMEs [39·8] at 12 months in the open-loop group [23·4% reduction]; p=0·72). One (3%) patient in the closed-loop group and two (7%) in the open-loop group increased their MME at 12 months.

The median conduction velocity of the stimulated nerve fibres, the speed at which an action potential propagates along the neural pathway, was within the range of Aβ fibres at 3 months (57·3 m/s [IQR 53·3–66·9] in the closed-loop group *vs* 58·9 m/s [54·5–65·1] in the open-loop group; p=0·43) and at 12 months (60·2 m/s [53·2–67·7] in the closed-loop group *vs* 58·9 m/s [54·1–67·6] in the open-loop group; p=1·00).[30]

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	3 months			12 months		
	Closed-loop group	Open-loop group	p value	Closed-loop group	Open-loop group	p value
In-clinic						
Therapeutic window width* (μV)	97·0 (59·0–185·0)	84·0 (35·0–195·0)	0·15	110·0 (68·0–170·0)	61·5 (34·0–160·0)	0·024
Patient perception threshold (μV)	5·5 (2·0–15·0)	6·0 (1·5–11·5)	0·72	5·0 (1·0–16·0)	6·0 (2·0–12·0)	0·96
Comfort level (μV)	31·5 (13·0–69·0)	32·0 (9·5–60·5)	0·30	27·0 (17·0–70·0)	16·0 (7·0–49·0)	0·028
Maximum level (μV)	99·5 (67·0–212·0)	96·0 (31·0–182·0)	0·061	112·0 (72·0–189·0)	62·0 (36·0–173·0)	0·025
Outside-clinic						
Percentage time in therapeutic window	91·1% (57·5–99·1)	59·5% (32·5–72·5)	<0·0001	95·2% (63·2–99·8)	47·9% (31·0–70·5)	<0·0001
Percentage time below therapeutic window	4·7% (0·6–39·4)	39·7% (22·1–65·8)	<0·0001	1·7% (0·0–36·8)	48·3% (17·1–66·2)	<0·0001
Percentage time above therapeutic window	0·0% (0·0–0·2)	0·7% (0·2–3·4)	<0·0001	0·0% (0·0–0·3)	0·3% (0·0–3·8)	0·0008
Mode ECAP amplitude (μV)	33·0 (12·5–52·0)	4·3 (1·5–12·5)	<0·0001	27·0 (15·0–72·5)	4·5 (2·5–19·5)	<0·0001
Mode ECAP amplitude/comfort level†	0·8 (0·5–1·1)	0·1 (0·1–0·5)	<0·0001	0·9 (0·6–1·3)	0·4 (0·2–0·7)	<0·0001

Data are median (IQR). ECAP=evoked compound action potential. *Perception threshold to maximum. †The ratio of the mode ECAP amplitude to the comfort level is a measure of how close the most frequent spinal cord activation level experienced outside the clinic is to the comfort level determined inside the clinic, where a value of 1 is indicative of spinal cord activation centred at the comfort level.

Table 3: **Spinal cord activation measurements**

	Closed-loop group (n=67)		Open-loop group (n=67)		Total (n=134)	
	Events	Patients	Events	Patients	Events	Patients
Total adverse events*	150	45 (67%)	104	45 (67%)	254	90 (67%)
Serious						
No	134	42 (63%)	93	43 (64%)	227	85 (63%)
Study related†	22	12 (18%)	9	9 (13%)	31	21 (16%)
Yes‡	16	10 (15%)	11	8 (12%)	27	18 (13%)
Study related†	1	1 (2%)	2	2 (3%)	3	3 (2%)
Unanticipated adverse device effect§	0	0	0	0	0	0

Data are n or n (%). *Adverse events were defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in patients, whether or not they were related to the investigational medical device. †Adverse events adjudicated as definitely or possibly related to the device, procedure, or stimulation therapy were considered study related. ‡Serious adverse events were defined as events that led to death; led to a serious deterioration in the health of the patient and resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, prolonged hospital admission, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or led to fetal distress, fetal death, or congenital anomaly or birth defect. §Unanticipated adverse device effects were defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Table 4: **Summary of adverse events for all randomly assigned patients**

ECAP amplitudes at 3 months were similar for both groups for variables obtained in the clinic: therapeutic window width and comfort level. At 12 months, the width of the therapeutic window increased in the closed-loop group and decreased in the open-loop group as a result of changes in the maximum tolerable activation level. Additionally, whereas the ECAP amplitude for the comfort spinal cord activation target level was maintained for patients in the closed-loop group at 12 months compared with that at 3 months, it decreased by half for patients in the open-loop group.

Outside the clinic, the most-frequent (mode) spinal cord activation levels, indicating as-used amplitudes, were more than six times greater for patients in the closed-loop group than for those in the open-loop group. The ratio of the mode to the comfort level was closer to 1 in the closed-loop group than in the open-loop group, indicating that, in general, the most frequent spinal cord activation level outside the clinic for patients in the closed-loop group was closer to their comfort level determined in the clinic than it was for patients in the open-loop group. The proportion of time that patients' spinal cord activation levels were within their therapeutic window was higher for patients in the closed-loop group than for those in the open-loop group, with less time spent below and above the therapeutic window (table 3; appendix p 10).

The type, nature, and severity of adverse events were similar between treatment groups (table 4; appendix pp 11–12). 34 study-related adverse events occurred in 24 patients (23 adverse events in the closed-loop group, in 13 [19%] patients [95% CI 10·8–30·9], and 11 adverse events in the open-loop group in 11 [16%] patients [8·5–27·5]). The most frequently reported study-related adverse events in both treatment groups were lead migration (nine [7%] patients), implantable pulse generator pocket pain (five [4%]), and muscle spasm or cramp (three [2%]). Eight adverse events related to stimulation therapy occurred in seven (5%) patients (four in the closed-loop group and three in the open-loop group), including muscle spasm or cramp (three [2%] patients), unwanted stimulation location (two [2%]), lower extremity dysaesthesia (one [1%]), low back pain (one [1%]), and nausea or vomiting, or both (one [1%]). Three serious adverse events in three (2%) patients (one in the closed-loop group and two in the open-loop group) were study related, but not stimulation related, including wound infection (one [1%] patient), epidural abscess (one [1%]), and lead breakage or fracture (one [1%]).

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Discussion

In our study, the primary composite outcome, which assessed substantial (≥50%) improvement in overall back and leg pain[31] without an increase in pain medications, successfully showed the superiority of ECAP-controlled, closed-loop spinal cord stimulation compared with fixed-output, open-loop stimulation. We also observed greater improvements with closed-loop than with open-loop spinal cord stimulation in all predefined secondary outcomes assessing pain outcomes. More than half of patients in the closed-loop group were high responders, with 80% or greater reductions in overall back and leg pain. Furthermore, high responders showed more clinically meaningful changes in other patient-reported outcomes than other patients, highlighting the value of achieving this high threshold. Indeed, this study provided evidence of significant improvement from baseline, including clinically important changes, in other validated patient-reported outcome measures covering functional disability, emotional functioning, sleep quality, health-related quality of life, and patient-reported global impression of change in both treatment groups. In general, the improvement was greater in the closed-loop group than in the open-loop group, although the difference was not significant for all measures (appendix p 9).

Unique to the field of neuromodulation, this study collected in-vivo, real-time, continuous neurophysiological data directly from the spinal cord in response to treatment during daily use. To the best of our knowledge, this study is the first to compare the controlled level of spinal cord activation (and the associated pain relief afforded with a novel closed-loop technology) with uncontrolled stimulation, as is the case with all available spinal cord stimulation devices. These objective measurements, collected in a double-blind randomised controlled trial, provide a level of evidence that is unmatched in this field. The responder rates observed in this study are among the highest shown for any randomised controlled trial of spinal cord stimulation to date.[12,30–33] The use of objective measures to individually optimise and improve patient therapy might have contributed to the high response rates.

Improvements in patient-reported outcomes were seen in parallel with voluntary opioid reduction or elimination in 55% of patients in the closed-loop group and in 40% in the open-loop group, 12 months after the implant. Average daily opioid dosage decreased to approximately 45 MMEs in both treatment groups, in alignment with existing practice guidelines.[34,35] Although this trial was not specifically designed to assess opioid use, the findings from this study suggest that opioid use might be reduced with this form of spinal cord stimulation therapy.

The differences in outcomes between closed-loop and open-loop spinal cord stimulation cannot be attributed to programming parameters, device usage, patient baseline characteristics, or underlying neurophysiology (ie, ability to recruit and activate the same nerve fibre types), as these were shown to be equivalent in both treatment groups. The conduction velocities measured corroborate the theory that the stimulation targets for pain relief are fibres that conduct in the Aβ range of conduction velocity.[36] However, differences in spinal cord activation between groups were observed outside the clinic in a real-world setting. On average, spinal cord activation was maintained within the therapeutic window, closer to the comfort level, for a greater percentage of the time with closed-loop than with open-loop spinal cord stimulation (table 3; appendix p 10). Therefore, greater rates of improvement in subjective outcomes coincided with higher, more consistent spinal cord activation within patients' therapeutic range of activation in the closed-loop group.

Additionally, from the 3-month to 12-month follow-up, the upper boundary of the therapeutic window shifted for both groups, increasing for closed-loop and decreasing for open-loop spinal cord stimulation (table 3; appendix p 10). Although additional investigation is warranted, expansion of the usable activation range and maintenance of the comfort level for closed-loop spinal cord stimulation might be the reason for continued long-term efficacy. Conversely, continual contraction in the usable activation range and decrease in comfort level to avoid overstimulation for open-loop spinal cord stimulation could compromise pain relief over time and lead to premature explants because of decreased efficacy.[13,14] As has been previously reported,[3] patients with fixed-output systems typically reduce stimulation amplitude to improve tolerability and reduce episodes of overstimulation. However, this approach also reduces the magnitude of analgesia that can be achieved by decreasing the level of stimulation to below the patient's therapeutic window. The reduction in the therapeutic window is likely to be due to overstimulation, increasing the sensitivity of the patient to the stimulation sensation,[37] which would, with a concomitant reduction in the level of spinal cord activation (as patients turn stimulation down), lead to loss of therapeutic effect over time. The relative contributions of neurophysiological and psychophysical components to the sensitisation remain to be identified.

A particularly interesting finding was that the efficacy rates recorded in the control group (fixed-output, open-loop spinal cord stimulation) were higher than those reported for all available conventional spinal cord stimulation systems.[9–12,32] In this study, the same device was used in both treatment groups to measure spinal cord activation and neurophysiology because no other device on the market had this capability. With other systems, programming is done through subjective report of paraesthesias or pain relief by the patient. In this study, both the closed-loop and open-loop groups were programmed with in-vivo, real-time ECAP measurements from the spinal cord in addition to patient feedback. ECAP measurement provides insight into activation of the spinal cord that drives inhibition of pain processing pathways and thus this information can be used to determine the optimal stimulation therapy settings. Even in the absence of

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closed-loop stimulation, objective measurement of ECAPs during the programming phase might, in and of itself, have improved outcomes with open-loop stimulation to a level not typically seen with conventional spinal cord stimulation systems.

The randomised, double-blind study design was developed to be generalisable, preserve objectivity, and minimise bias. Patient selection criteria were based on key clinical features of chronic back and leg pain consistent with the standard practice for spinal cord stimulation. The randomisation in this study produced well matched treatment groups with regard to baseline characteristics and neurophysiological properties, supporting the validity of the comparisons between groups. Additionally, none of the patients or investigators were unmasked to the treatment assignment, reducing the potential of data being systematically distorted by knowledge of the treatment received. The rate of adherence to the trial-regimen schedule and the rate of follow-up were both high. The trial was powered adequately to detect differences in the primary outcome between groups. Additionally, to preserve the experiment-wise error rate of 0·05, a closed hierarchical testing procedure was used for the predefined secondary outcomes.

All spinal cord stimulation studies done in the USA use sponsor field clinical engineers to program the device, which might be considered a limitation and source of bias compared with other countries that use clinic staff. In this study, the investigators, who were masked to the treatment assignment, documented their oversight confirming comprehensive programming and optimisation for all study participants.[21] As per protocol, and as shown by the results, patients in both treatment groups received equal care, with the same degree of programming for both groups. The use of the same device in both treatment groups might be considered another limitation, because the control therapy was not commercially available. However, this approach made it possible to have a double-blind study and to investigate a new objective measure of the effectiveness of spinal cord stimulation by use of ECAP amplitude to measure spinal cord activation.

In conclusion, the results of this double-blind randomised controlled trial provide evidence for the safety and significantly superior clinical efficacy of a novel, closed-loop system compared with a fixed-output, open-loop spinal cord stimulation for pain relief in patients with chronic intractable back and leg pain. This study shows that a patient-specific therapeutic window defined objectively by spinal cord activation levels can be identified and targeted to improve spinal cord stimulation programming. Closed-loop spinal cord stimulation provided greater levels of spinal cord activation, within the therapeutic window, which suggests a mechanistic explanation for the superior results. Although preliminary, we believe this is the first step in the field of neuromodulation, moving towards a mechanism-based, personalised therapy founded on an objective outcome measure.[38]

Contributors
All authors made substantial contributions to the study design, data acquisition, data analysis, and data interpretation, actively participated in drafting and critically revising the manuscript, provided final approval of the submitted version, and agree to be held accountable for the accuracy and integrity of the finished publication.

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Declaration of interests
NM reports serving as a consultant for Boston Scientific, Sollis Therapeutics, and Relievant Medsystems; receiving research support for Mallinckrodt, Mesoblast, Halyard, and Neuros Medical; and serving as an independent medical monitor for DRG stimulation "Accurate study" sponsored by Abbott (formerly Spinal Modulation) and the closed-loop spinal cord stimulation "Evoke study" sponsored by Saluda Medical, the HF-10 for PDN "Senza-PDN study" sponsored by Nevro Corporation, the Mild Procedure for LSS "Motion study" sponsored by Vertos Medical, and the Ultra High Pulse Width SCS "Hi-Fi study" sponsored by Nuvectra. RML reports having stock options in Bioness, Nalu, Nevro, Vertos Medical, and Saluda Medical, and being a consultant for Abbott, Nalu, Nuvectra, and Saluda Medical. TRD reports serving as a consultant for Abbott, Axonics, CornerLoc, Ethos, Flowonix Medical, Nalu, Saluda Medical, SpineThera, Vertiflex, and Vertos Medical; being a scientific advisory board member for Abbott, Flowonix Medical, Nalu, and Vertiflex; being a research investigator for Abbott, Mainstay, Saluda Medical, Vertiflex; having stock options in Axonics, Bioness, CornerLoc, Nalu, Saluda Medical, SpineThera, Vertiflex, and Vertos; and owning a patent for DRG Surgical Leads. LK reports receiving research grants from Biotronik, Gimer Medical, Neuros Medical, and Nevro; and serving as a consultant for Abbott, Nalu, Nevro, and Stimgenics. SL reports receiving a research grant from Avanos, Biotronik, Nevro, Saluda Medical, Semnur Pharmaceuticals, Sollis Pharmaceutical, SPR Therapeutics, and Vertiflex; being a consultant for Abbott, Avanos, BioTras, Nalu Medical, Nevro, Saluda Medical, SI Bone, Vertiflex, and Vertos; owning stock in Nevro; and being on a scientific advisory board for BioTras. KA reports having an active research grant (for this study) with Saluda Medical; being on scientific advisory boards for Biotronik, Nalu Medical, Nevro, and Saluda Medical; being a consultant for Biotronik, CereVu Medical, ENSO, Nalu Medical, Nevro, and Saluda Medical; and having minor stock options with CereVu Medical, ENSO, and Nalu Medical. CWH reports serving as a consultant for Saluda Medical. SMR reports serving as a consultant for Cerebral Therapeutics and Saluda Medical; and being a researcher for Biotronik, Flowonix Medical, Medtronic, and Saluda Medical. SMF reports serving as a consultant for Abbott, Medtronic, Nevro, Saluda Medical, SPR Therapeutics, and Vertiflex; being a researcher for Abbott, Biotronik, Medtronic, Nuvectra, and Saluda Medical; having stock options in SpineThera, SPR Therapeutics, Stimgenics, Thermaquil; and having equity interest in Saluda Medical. JEP reports serving as a consultant for Abbott, Flowonix Medical, Genetech, Saluda Medical, SPR Therapeutics, Stimgenics, Stoke, TerSera Therapeutics, Thermaquil, Vertiflex, and Vertos; serving as an investigator for Abbott, AIS HealthCare, Biotronik, Flowonix Medical, Saluda Medical, Thermaquil, and Vertiflex; and owning stock in Celeri Health, SPR Therapeutics, Stimgenics, Thermaquil, and Vertos. CAG reports being a consultant for Abbott, Boston Scientific, Medtronic, Nevro, and SPR Therapeutics. FAQ reports being a researcher/investigator for Saluda Medical. PSS reports serving as a consultant and CEC member for Saluda Medical. JS reports having served as a consultant for St. Jude and Boston Scientific. JC reports being a consultant for Abbott, Biotronik, CornerLoc, Nevro, Saluda Medical, SPR Therapeutics, Stimgenics, and Vertiflex. MIY reports being a consultant for Nevro and a clinical researcher/investigator for Boston Scientific and Nevro. TS reports being a consultant for Nevro. DB, RG, GG, EH, DKa, AK, DKi, AL, DM, MO, JP, PS, and NS reports being an employee of Saluda Medical. LP reports being a medical monitor for Saluda Medical, a principal investigator for Abbott, a consultant for Medtronic, and a

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research consultant for Nalu Medical. SJC, AHB, and CKK declare no competing interests.

Data sharing

Saluda Medical is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis datasets), as well as other information (eg, protocols and clinical study reports), provided the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, contact Saluda Medical online.

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References

1 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150:** 971–79.

2 Bradley K. The technology: the anatomy of a spinal cord and nerve root stimulator: the lead and the power source. *Pain Med* 2006; **7** (suppl 1): S27–34.

3 Ross E, Abejón D. Improving patient experience with spinal cord stimulation: implications of position-related changes in neurostimulation. *Neuromodulation* 2014; **17** (suppl 1): 36–41.

4 Holsheimer J. Principles of neurostimulation. In: Electrical stimulation and the relief of pain: pain research and clinical management series, vol 15. Amsterdam: Elsevier, 2003: 17–36.

5 Struijk JJ. The extracellular potential of a myelinated nerve fiber in an unbounded medium and in nerve cuff models. *Biophys J* 1997; **72:** 2457–69.

6 Brown EA, Ross JD, Blum RA, Yoonkey Nam, Wheeler BC, Deweerth SP. Stimulus-artifact elimination in a multi-electrode system. *IEEE Trans Biomed Circuits Syst* 2008; **2:** 10–21.

7 Zhang TC, Janik JJ, Grill WM. Modeling effects of spinal cord stimulation on wide-dynamic range dorsal horn neurons: influence of stimulation frequency and GABAergic inhibition. *J Neurophysiol* 2014; **112:** 552–67.

8 James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1789–858.

9 Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007; **132:** 179–88.

10 North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005; **56:** 98–107.

11 Taylor RS, Desai MJ, Rigoard P, Taylor RJ. Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. *Pain Pract* 2014; **14:** 489–505.

12 Kapural L, Yu C, Doust MW, et al. Novel 10-khz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology* 2015; **123:** 851–60.

13 Van Buyten J-P, Wille F, Smet I, et al. Therapy-related explants after spinal cord stimulation: results of an international retrospective chart review study. *Neuromodulation* 2017; **20:** 642–49.

14 Pope JE, Deer TR, Falowski S, et al. Multicenter retrospective study of neurostimulation with exit of therapy by explant. *Neuromodulation* 2017; **20:** 543–52.

15 Haugen F. Basic Dynamics and Control. Norway: Skien, 2010.

16 Schultz DM, Webster L, Kosek P, Dar U, Tan Y, Sun M. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician* 2012; **15:** 1–12.

17 Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain* 2012; **153:** 593–601.

18 Parker JL, Karantonis DM, Single PS, et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation* 2013; **16:** 295–303.

19 Russo M, Cousins MJ, Brooker C, et al. Effective relief of pain and associated symptoms with closed-loop spinal cord stimulation system: preliminary results of the Avalon study. *Neuromodulation* 2018; **21:** 38–47.

20 Levy R, Deer TR, Poree L, et al. Multicenter, randomized, double-blind study protocol using human spinal cord recording comparing safety, efficacy, and neurophysiological responses between patients being treated with evoked compound action potential-controlled closed-loop spinal cord stimulation or open-loop spinal cord stimulation (the Evoke Study). *Neuromodulation* 2019; **22:** 317–26.

21 US Food and Drug Administration. Guidance for industry: investigator responsibilities — protecting the rights. safety, and welfare of study subjects. October, 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects (accessed Oct 21, 2019).

22 Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; **113:** 9–19.

23 Savre I, Fairbank J. Oswestry Disability Index information booklet, 1st edn. Lyon: Mapi Research Trust, 2011.

24 McNair D, Heuchert J. Profile of mood states—technical update. North Tonawanda, NY: Multi-Health Systems, 2003.

25 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28:** 193–213.

26 Maruish ME, ed. User's manual for the SF-12v2 Health Survey, 3rd edn. Lincoln, RI: QualityMetric Incorporated, 2012.

27 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–36.

28 National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version. https://www.cdc.gov/drugoverdose/resources/data.html (accessed Oct 22, 2019).

29 Law JD. Spinal stimulation: statistical superiority of monophasic stimulation of narrowly separated, longitudinal bipoles having rostral cathodes. *Appl Neurophysiol* 1983; **46:** 129–37.

30 de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* 2014; **155:** 2426–31.

31 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; **9:** 105–21.

32 Deer T, Slavin KV, Amirdelfan K, et al. Success using neuromodulation with BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. *Neuromodulation* 2018; **21:** 56–66.

33 Rigoard P, Basu S, Desai M, et al. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. *Pain* 2019; **160:** 1410–20.

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