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A prospective long-term follow-up of dorsal root ganglion stimulation for the management of chronic intractable pain

Sam Eldabe, MD[1], Sue Copley, MSc[1] Ashish Gulve, MD[1], Ganesan Baranidharan, MD[2], Beatrice Bretherton, PhD[2], Anu Kansal, MD[1], Grace Madzinga, BSc[1], Morag Brookes, MSc[1], Simon Thomson, MBBS[3], Rui V Duarte, PhD[4]

[1]Department of Pain Medicine, The James Cook University Hospital, Middlesbrough, UK

[2]Leeds Neuromodulation Centre, Leeds Teaching Hospitals, Leeds, UK

[3]Department of Anaesthesia, Basildon and Thurrock University Hospitals, Basildon, UK

[4]Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK

Address for correspondence: Prof Sam Eldabe, Department of Pain and Anaesthesia, The Murray Building, The James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW, UK.Email: seldabe@nhs.net, Telephone: +44 (0)1642850850

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Abstract

Initial clinical studies have shown that stimulation of the dorsal root ganglion (DRG) can significantly reduce chronic intractable pain. However, clinical data on long-term results and complications of these systems is limited. The aim of this prospective study is to report on a single centre long-term follow-up of DRG stimulation for intractable chronic pain. Participants were implanted with DRG stimulation devices between 2013 and 2015 with an observation period of 24 months. Patients were contacted again in 2020 for a final follow-up (i.e., between 5 to 7 years post-implantation). Forty-two participants were recruited, of whom 32 received the fully implantable pulse generator (IPG). At final follow-up, 50% (16/32) of participants were still using DRG stimulation. Two participants still had the original IPG and 14 had received a replacement IPG. Pain scores were significantly reduced at 24 months, mean difference (MD) 1.7 (95% confidence interval [CI]: 0.2 to 3.3, P=0.03) and at last follow-up, MD 2.1 (95% CI: 0.3 to 4, P=0.03). Significant improvements were observed for health-related quality of life. The findings were generally robust to imputation methods of missing data. IPGs of 8 patients were explanted due to dissatisfaction with pain relief. In conclusion, DRG stimulation can provide effective pain relief and improved quality of life in patients suffering with neuropathic pain, although this study had a revision rate of 42% within the first 24 months, and 56% of IPGs that were replaced due to battery depletion, had a shorter than expected battery life.

Keywords: Chronic pain, Neurostimulation, Complex regional pain syndrome, Causalgia, Dorsal, root ganglion stimulation, Back pain, Leg pain, Neuropathic pain

Introduction

Chronic neuropathic pain is a disabling and severe pain condition.[19] Conventional treatments such as analgesics, nerve blocks and physical therapy provide limited relief with some resulting in unacceptable side effects.[1; 21]

Spinal Cord Stimulation (SCS) and Dorsal Root Ganglion Stimulation (DRGS) have reported effectiveness in the treatment of neuropathic pain.[14] Although conventional SCS often provides significant pain relief from whole limb pain, focal pains limited to discreet areas such as hands, feet and groin often prove difficult to target.[19] The higher levels of stimulation currents needed to provide sufficient coverage to the focal pain areas often result in stimulation of larger areas that were otherwise pain-free. Even with precise SCS lead placement, the natural variation in the distance between the stimulating electrode and the neural target due to changes in posture or coughing,[18] results in clinically significant changes in levels of stimulation, requiring the patient to adjust the stimulation amplitude in order to minimise overstimulation or under stimulation which may in turn result in reduced levels of analgesia.[18]

DRGS is a targeted form of neurostimulation that has been shown in one randomised controlled trial (RCT) to be superior to SCS in the treatment of complex regional pain syndrome (CRPS),[4] and effective for the treatment of neuropathic pain to the trunk and/or limbs when conventional medical management has been ineffective.[3] Furthermore, DRGS

has been shown to provide a more consistent stimulation with greater precision than SCS, and minimal postural effects.[2; 4; 15] DRG stimulation targets the primary sensory neurons that innervate the painful distal anatomical regions, enabling small areas of pain to be precisely targeted and avoiding diffusing the energy through the spinal cord, unlike SCS.[22]

However, the use of DRGS is not without its issues; although some studies report few device-related complications,[13; 22] others reported a higher rate of adverse events (AEs) compared to SCS.[4] Furthermore, methodologies of reporting of AEs differ between studies, with varying methods of presenting incidence rates.[4; 16] Reports of follow-up periods are typically limited to 12 months, which may also not reflect the true occurrence of AEs across the lifetime of the device. This time-limited follow-up may also account for the optimal pain relief outcomes and improvements to quality of life reported in several studies [4; 8; 16; 22] as any longer-term variations in outcomes have not been presented. This prospective study reports on the long-term outcomes and complications of DRGS up to between 5- and 7-years follow-up.

Materials and Methods

Design and Patients

This study was a prospective, single centre, single arm trial designed to assess the clinical effects of the commercially available Axium® Neurostimulator System, initially and subsequently Proclaim DRG® in the management of chronic intractable pain, based at The James Cook University Hospital (JCUH), UK. Subjects that were routinely scheduled to receive DRGS were asked to participate in the study. These were adult patients (≥18 years of age) referred to the Pain Clinic with chronic, intractable pain for at least 6 months with an average baseline pain rating of 60 mm on the visual analogue scale (VAS) in the primary region of pain who had failed conservative treatments for chronic pain including but not

limited to pharmacological therapy, physical therapy and interventional pain procedures. Patients also had to be able and willing to comply with the follow-up schedule and protocol, able to provide written informed consent and in the opinion of the investigator, the patient was psychologically appropriate for the implantation for an active implantable medical device. Exclusion criteria consisted of female subject of childbearing potential was pregnant/nursing, planning to become pregnant or unwilling to use approved birth control; escalating or changing pain condition within the past month as evidenced by investigator examination; subject has had corticosteroid therapy at an intended site of stimulation within the past 30 days; has had radiofrequency treatment of an intended target DRG within the past 3 months; currently with an active implantable device including implantable cardioverter-defibrillator, pacemaker, SCS or intrathecal drug pump; unable to operate the device; current active infection; had, in the opinion of the investigator, a medical comorbidity that contraindicated placement of an active medical device; participated in another clinical trial within 30 days; had a coagulation disorder or used anticoagulants that, in the opinion of the investigator, precluded participation; had been diagnosed with cancer in the past 2 years. Potential participants were screened based upon the eligibility criteria, consented with a Research Ethics Committee (REC) approved Patient Informed Consent Form, and enrolled into the trial (REC no. 12/NE/0283, Newcastle 2 REC).

Screening trial and Implantation

Following informed consent and baseline assessment, participants began phase one of a two-phase treatment process.

Phase 1 was the screening trial phase and consisted of percutaneously implanting neurostimulator leads into the epidural space over the DRG and attaching them to an external neurostimulator (Figure 1). This system was then trialled during the procedure and if

clinically necessary the screening trial phase would continue for up to 30 days. If the subject experienced clinically sufficient pain relief overall in their primary area of pain being treated during the trial phase, they progressed to Phase 2, the implantation phase. In this phase, eligible subjects willing to continue with the implant underwent surgery to insert the fully implantable pulse generator (IPG). If the epidural leads were removed during the trial period, new leads were implanted at this time. The implanted leads were connected to the IPG which was then placed under the skin.

[Insert Figure 1 here]

Post-implant programming to adjust stimulation settings occurred either immediately after the surgery or the day following implantation. Each subject received a hand-held Patient Programmer that could be used to adjust stimulation amplitude as needed throughout the study duration.

Participants were allowed to continue using medication for the treatment of their pain condition. The prescription of medication for pain was dictated by the study Principal Investigators and/or sub-investigator as per standard of care.

Data Collection and Follow-Up

Participants were implanted with DRGS between February 2013 and February 2015. The 24-month follow-up period ended in December 2016. Patients who still had a DRG implant were followed-up again in August 2020.

Baseline demographics were recorded at the time of recruitment to the study, and participants were asked to complete outcome measures at 1, 3, 6, 12, 24 months (±2 weeks) and last follow-up. The primary outcome measure was pain intensity using a VAS.[20] Secondary outcome measures comprised health-related quality of life (HRQoL [EQ-5D-3L][6]) and

patient satisfaction (Patients' Global Impression of Change [PGIC][10]). Patients rated their global impression of change using the PGIC at final assessment only. Participants were asked to rate their overall condition along a seven point scale, from 'Very much worse – 7' to 'Very much improved – 1'.

Prior to completing the outcome assessments, the subjects were able to have his/her stimulator reprogrammed if needed; this took place at the same appointment. If desired, the investigators were able to call the subjects for evaluation at 8-weeks, 9-months and 18 months post-implant. During the course of the trial, subjects had the option to return to the study site at any time to have their neurostimulator re-programmed to achieve maximal benefit or to report or resolve any adverse effects. For the purposes of this manuscript this last follow-up, occurring between 5- and 7-years from baseline, will be termed the 7-year follow-up for brevity; this contact was conducted via telephone contact under a service evaluation approval (number 8275).

Statistical analysis

Descriptive statistics are used to summarise the demographic characteristics. Data are reported as mean and standard deviation (SD). Paired-sample t-tests were used to compare differences in outcome measures between baseline and follow-ups at 24 months and 7 years. We report the mean difference and 95% confidence intervals (CIs). Primary analysis was conducted with complete data sets. Secondary analyses were undertaken to compare VAS and HRQoL scores at 24 months and 7 years follow-up using first observation carried forward (FOCF) and last observation carried forward (LOCF) methods of imputation. Statistical significance was judged at the 5% level. Statistical tests were performed using SPSS (IBM SPSS Statistics, Version 26.0. Armonk, NY: IBM Corp).

Results

Patient demographic characteristics are presented in Table 1. Of the 42 participants recruited to the study, 2 were withdrawn from the study prior to the implant (new pain in the surgical site due to a fall [n=1], withdrawn pre-trial due to unrelated medical condition [n=1]), and 7 participants had a 'failed trial' due to insufficient pain relief (Figure 2). Thirty-two participants went on to receive an IPG for the treatment of a clinical diagnosis of chronic post-surgery pain (n=13) (post-thoracotomy, post-appendectomy, post herniotomy and orchidectomy groin pains), CRPS Type I of the lower limb (n=8), CRPS Type II (n=3), postherpetic neuralgia chest wall (n=2), phantom limb pain (n=2), peripheral neuropathy (n=3) and failed back surgery syndrome (n=1). The stimulation parameters following implantation of the device are presented in Supplementary material 1 of this manuscript (available at http://links.lww.com/PAIN/B437).

Of the 32 participants who went on to receive the IPG, 5 had the device explanted due to lack of perceived benefit (n=4) or requiring high amplitude and changed to rechargeable SCS with stimulation not delivered to the DRG (n=1), and 4 withdrew from the study (lost to follow-up [n=1], dissatisfied with the device [n=1], amputation of affected limb [n=1], death unrelated to study [n=1]). The patient who withdrew from the study due to planned amputation of the limb by reason of worsening CRPS, had effective paraesthesia but insufficient pain relief. They proceeded to above knee amputation with the DRGS left in situ; pain improved slightly but stimulation provided by the DRGS did not then target the thigh which had then become problematic with CRPS and painful cramps. Subsequently, the patient underwent a successful trial of SCS so received full SCS implantation, at which point the DRGS was removed.

[Insert Table 1 here]

At 24 months, 24 participants were still enrolled in the study, of whom 22 provided complete data on pain intensity and HRQoL (incomplete data [n=1], missing data [n=1]). At the time of the last follow-up, 16 participants still had a DRG stimulator, 14 of whom reported on pain intensity and HRQoL (unable to contact [n=2]).

[Insert Figure 2 here]

Significant differences between baseline and 24 months were observed for pain intensity (mean difference: 1.7, 95% CI: 0.2 to 3.3, P=0.03) (Table 2). At last follow-up the mean difference for pain intensity was 2.1 (95% CI: 0.3 to 4.0, P=0.03).

[Insert Table 2 here]

The mean difference for EQ-5D-3L score between baseline and 24 months was -0.13 (95% CI: 0.31 to 0.04, P=0.13) and at last follow-up was -0.25 (95% CI: -0.46 to -0.04, P=0.02).

The findings for pain intensity and EQ-5D-3L scores were generally robust to imputation analysis for the handling of missing outcome data. Reductions in VAS were observed at 24 months and last follow-up when compared to baseline irrespective of data set. However, increases in pain intensity are observed between 24 months and last follow-up using FOCF or LOCF methods. Increases in EQ-5D-3L scores are observed between baseline and follow-ups irrespective of data set.

The increase in both pain relief and quality of life was reflected in participants' responses to the PGIC questionnaire. Average PGIC was 2.14 (median PGIC=2, range 1-4).

Adverse events

During the 24 months follow-up, of the 32 participants who received the full implant of DRGS, 22 participants (69%) had 33 device or procedure related complications (see Table 3). Fourteen participants (44%) underwent 17 revisions of the device, and 4 participants (12.5%) had the device explanted (dissatisfied [n=3], change to SCS with rechargeable IPG [n=1]).

[Insert Table 3 here]

At the time of the last follow-up, 16 participants retained a DRGS system of whom two still had the original IPG in situ. Seven devices were explanted between 24 months and the last follow-up (Table 4; Figure 3). A further participant had died who still had the IPG in situ.

[Insert Table 4 here]

[Insert Figure 3 here]

From the start of the study to the final follow-up in August 2020, seven participants had 10 revisions for replacement batteries that had expired prior to 4 years. Due to this short duration of battery life, for the purpose of this article, these are considered to be adverse

events. Two participants had 2 and 3 revisions between the start of the study up to the follow-up date, due to premature expiry of battery, with the IPGs lasting for 17 & 14, and 19, 8 & 37 months respectively before end of service. The first of these replacements for both patients were within 24-months, with subsequent replacements after the initial 24-month duration. Excluding the participants who had explants due to dissatisfaction or other clinical indication, the average duration of the implantation period was 35 months. In total, 18 IPGs were replaced due to battery depletion in 15 participants, with an average battery life of 30 months. Of these, 10 were for premature battery depletion of less than 4 years duration (56%) (Table 5).

Participants had between 1 and 3 leads implanted (1 lead [n=11], 2 leads [n=18], 3 leads [n=3]). The duration of battery life appeared to be moderately negatively related to the number of leads implanted, with a correlation of r=-0.536 (Pearson's correlation coefficient) between months of battery duration and number of implanted leads.

[Insert Table 5 here]

Discussion

DRGS provided statistically significant pain relief at 24 months and 7-years follow-up in a population of heterogeneous neuropathic pain patients. In the 75% of participants who retained the system during the 24 months, pain intensity reduced by an average of 25.6% from baseline, with an associated improvement in HRQoL. The 16/32 (50%) participants who retained the system at 7-year follow-up, reported an average reduction in pain of 29%. These

levels of analgesia remain clinically and statistically significant although considerably lower than reports of reductions in pain at 12 months ranging from 52% to 81.4%.[4; 7; 13; 16]

However, investigation of the impact of missing data on pain and HRQoL using either FOCF or LOCF (i.e., including patients who were withdrawn from the study due to dissatisfaction and lack of pain relief), suggests the outcomes are considerably worse than those reported in other studies with shorter follow-ups. Although the impact on pain and HRQoL remains statistically significant with FOCF, the mean differences in pain score from baseline to 24 months of 0.9 (95%CI 0.1 to 1.8) and 7-year follow-up of 0.7 (95%CI 01 to 1.4) are at best modest and considerably lower than previously reported in studies with shorter follow-ups.

For 19 of 41 participants eligible for trial, DRGS was ineffective; 8 participants perceived no benefit during the trial, a further 3 were explanted due to inadequate pain relief and one due to high current consumption during the first 24 months. Between the 24 months and 7-year follow-up, a further 7 participants had explants due to inadequate pain relief and lead migration, thus highlighting the importance of the long-term follow-up. Omitting the participant who was withdrawn from the study prior to any intervention, 46% of all participants either experienced no pain relief or required an explant due to dissatisfaction with the pain relief experienced. This is comparable with other studies which report a large number of participants either experiencing a failed trial or requiring explants, with reduced participant numbers as the follow-up period increases.[16; 19]

High failure rates were noted by Horan et al,[12] who found that from a cohort of 43 participants, 23%(n=10) felt no benefit from DRGS at trial and a further 42% of those receiving the IPG (n=14) required explant due device related issues, or lack of perceived benefit. At final follow-up, only 19 participants retained the device (57% of those implanted, or 44% of all participants) with only 14 participants retaining a fully functioning system

(42% who received IPG, or 33% of participants). Morgalla et al[19] recommend DRGS as an effective treatment for chronic neuropathic pain, but also found that 18% perceive no benefit at trial, and do not report reasons why only 51% of implanted participants were followed up for 3 years, leaving 49% unaccounted for. Similarly, Liem et al[16] report that 60% of subjects achieved at least 50% improvement of overall pain at 12 months but reported outcomes for only 49% of participants retained at final assessment.

In this study, AEs were reported at a rate of 69% which appears higher than other reports.[4; 16] However, computation of percentages of AEs differ between studies; we recorded AEs as a percentage of those participants who received the IPG rather than the number recruited, which otherwise would have been a comparable rate of 55%. Our criteria for AEs was broad, whereas other studies only report AEs relating to the device,[4] or exclude lead revisions.[13] Calculation methods vary between studies, with affected participants recorded as a percentage of total trial numbers (including those who had no intervention), thus reducing the reported percentages of participants with AEs;[4] or AEs reported only as a total number, or categories of AEs calculated as a percentage of total AEs, not the actual number or proportion of affected participants,[16] making direct comparisons unworkable.

Complications due to defective leads were common, with 10 out of 17 revisions performed in the first 24 months due to fracture or migration (Figure 4) on 9 participants (59% of revisions), plus a further participant who requested explant due to lead migration (31%[10/32] of participants who received an IPG). Six further revisions were performed for loss of stimulation (some with associated high impedance which indicates lead fracture) although leads were not further examined during revision. The predominance of lead-related AEs is comparable to the findings of an observational multicentre cohort study, which reported that 13 of 33 patients (39%) who were implanted with FDA-approved DRGS systems, required revisions for lead defects.[12] Although it has been suggested that the high

rate of lead-related revisions is related to an earlier “Ball Tip” lead design that has since been replaced by a “Slim Tip”,[11; 17] both types of lead were used during this study (Figure 5).

[Insert Figure 4 here]

[Insert Figure 5 here]

Horan et al[12] observed that although DRGS resulted in almost 50% reduction in pain score at 12 months for those patients still implanted, the treatment was compromised by the problems relating to maintaining and revising the system. Fourteen out of 33 participants (42.4%) had explants within the follow-up period. This is similar to our levels of explants, with 4 explants being performed within 24-months, and a further 9 from 24-months to end of follow-up including two explants following withdrawal from the study due to dissatisfaction (equivalent to an explant rate of 40.6%). We compared our findings to those of Leeds Teaching Hospitals where of 93 patients who had full implants of IPG devices between 2012 and 2019, 48 patients had revisions (52%), 7 patients had 2 revisions and 3 patients had 3 revisions. Ten devices were replaced due to premature battery failure (11%). Rechargeable DRG devices may have the potential to minimise the need for early replacement of IPGs due to battery depletion. However, currently only non-rechargeable devices are commercially available for DRG stimulation. Twenty-nine patients had explants of the IPG due to insufficient pain relief (n=26), infection (n=2) or need of an MRI (n=1) (data from personal correspondence with G.Baranidharan & B.Bretherton). These findings, stand in sharp contrast to the findings of Deer et al[5] that DRGS AE rates were similar or lower than those reported with SCS. This may be explained by the different methodologies of both studies. Deer et al’s findings were based on data supplied by the manufacturer compiled primarily from customer complaints and included data from 500 DRGS implants over a two-year period, whereas we

followed a small cohort for seven years. Our data, similar to those of Horan's, shows clearly that AEs leading to device explant accumulate over time.

The FDA, noting the higher incidence of procedure related AEs for DRGS compared to SCS reported in the ACCURATE study[4] mandated a physician training program prior to patient implantation.[9] Although it is argued in some studies the rate of AEs may relate to implanter learning curve,[12; 17] physicians at both JCUH and Leeds had been implanting DRGS for at least 12 months before the start of the study, leading us to conclude that the high rate of AEs is more likely to relate to hardware issues than physician performance.

Strengths and limitations

This study has several strengths; it is a prospective study with 24 months observation, with a further follow-up of remaining participants to 7-years post initial implant. To the authors' knowledge, no other study of DRGS has reported on participant outcomes to this duration. The study was based in clinical practice, using a heterogeneous population with limited eligibility criteria, thus providing 'real world' data. Implanting clinicians (AG, GB and SE) were experienced in SCS and DRG implantation techniques and acted as mentors on the manufacturer's DRG implant training program, limiting the possibility that rates of AEs and lower reductions of reported pain relief were a result of practitioner technique.

There are also limitations to this study. Firstly, the data reported above is from a single centre, although we were able to present personal communication regarding retrospective data on DRGS from a second centre. However, this data, and the JCUH complications data from 24 months to final follow-up was obtained retrospectively, therefore subject to limitations of clinician recording and researcher data collection. Differing follow-up times limit any direct comparison. The participant cohort who received implantation was reduced from 32 to 16 at final follow-up, of whom only 14 provided data. The long-term follow-up

data does not reflect the whole implanted cohort, only those sufficiently satisfied with the device to continue with the treatment, as more than half the cohort was either withdrawn from the study, had an explant or was lost to follow-up.

Conclusion

As in previous studies, we found that DRGS provides significant levels of pain relief in a majority of patients who have a successful trial. However, this response does not persist in the longer term for over a quarter of patients, and there is a need to investigate the responses of those who request explantation due to dissatisfaction. Future studies should assess all key measures at the point where a participant is withdrawn. Until then, they will remain unrepresented in the literature, with only those with successful outcomes being evaluated. Key data may consequently be lost, resulting in misleadingly high reports of satisfaction. With 7 participants having 10 replacements due to premature battery failure, 17 revisions performed within the first 24 months, and 19 further revisions following this, the rate of AEs may be considered excessive to the point of limiting the utility of the device.

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References

[1] Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Pm&r 2011;3(4):345-352. e321.

[2] Chang Chien GC, Mekhail N. Alternate Intraspinal Targets for Spinal Cord Stimulation: A Systematic Review. Neuromodulation : journal of the International Neuromodulation Society 2017;20(7):629-641.

[3] Deer, Hunter CW, Mehta P, Sayed D, Grider JS, Lamer TJ, Pope JE, Falowski S, Provenzano DA, Esposito MF, Slavin KV, Baranidharan G, Russo M, Jassal NS, Mogilner AY, Kapural L, Verrills P, Amirdelfan K, McRoberts WP, Harned ME. A Systematic Literature Review of Dorsal Root Ganglion Neurostimulation for the Treatment of Pain. Pain Medicine 2020;21(8):1581-1589.

[4] Deer, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Obray J, Scowcroft J, Golovac S, Kapural L, Paicius R, Kim C, Pope J, Yearwood T, Samuel S, McRoberts WP, Cassim H. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain (03043959) 2017;158(4):669-681.

[5] Deer T, Pope J, Hunter C, Falowski S, Kapural L, Kramer J, Levy R. Safety Analysis of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Pain. Neuromodulation 2020;23(2):239-244.

[6] Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: results from a UK general population survey, 1995.

[7] Eldabe S, Burger K, Moser H, Klase D, Schu S, Wahlstedt A, Vanderick B, Francois E, Kramer J, Subbaroyan J. Dorsal Root Ganglion (DRG) Stimulation in the Treatment of Phantom Limb Pain (PLP). Neuromodulation 2015;18(7):610-617.

[8] Eldabe S, Espinet A, Wahlstedt A, Kang P, Liem L, Patel NK, Vesper J, Kimber A, Cusack W, Kramer J. Retrospective Case Series on the Treatment of Painful Diabetic Peripheral Neuropathy With Dorsal Root Ganglion Stimulation. Neuromodulation: Technology at the Neural Interface 2018;21(8):787-792.

[9] FDA. Summary of Safety and Effetiveness Data (SSED): Dorsal root ganglion stimulator for pain relief. 2016.

[10] Guy W. ECDEU assessment manual for psychopharmacology: US Department of Health, Education, and Welfare, Public Health Service …, 1976.

[11] Horan M, Blichfeldt-Eckhardt MR. Response to Letter to the Editor Regarding "Complications and Effects of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Neuropathic Pain: A Nationwide Cohort Study in Denmark". Neuromodulation: Technology at the Neural Interface 2020;23(7):1047-1047.

[12] Horan M, Jacobsen AH, Scherer C, Rosenlund C, Gulisano HA, Søe M, Sørensen JCH, Meier K, Blichfeldt-Eckhardt MR. Complications and effects of dorsal root ganglion stimulation in the treatment of chronic neuropathic pain: a nationwide cohort study in Denmark. Neuromodulation: Technology at the Neural Interface 2020.

[13] Huygen, Liem L, Cusack W, Kramer J. Stimulation of the L2–L3 Dorsal Root Ganglia Induces Effective Pain Relief in the Low Back. Pain Practice 2018;18(2):205-213.

[14] Koetsier E, van Kuijk SMJ, Melli G, Dukanac J, Barbero M, van Zundert J, Joosten EA, Maino P. Dorsal Root Ganglion Stimulation for the Management of Intractable Painful Polyneuropathy: A Prospective Pilot Study. Neuromodulation : journal of the International Neuromodulation Society 2020.

[15] Kramer J, Liem L, Russo M, Smet I, Van Buyten J-P, Huygen F. Lack of Body Positional Effects on Paresthesias When Stimulating the Dorsal Root Ganglion (DRG) in the Treatment of Chronic Pain. Neuromodulation: Technology at the Neural Interface 2015;18(1):50-57.

[16] Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion in the Treatment of Chronic Neuropathic Pain. Neuromodulation 2014;18(1):41-48.

[17] Lubenow T, Nijhuis H. Response to "Complications and Effects of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Neuropathic Pain: A Nationwide Cohort Study in Denmark". Neuromodulation: Technology at the Neural Interface 2020;23(7):1046-1046.

[18] Mekhail, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, Hunter CW, Rosen SM, Costandi SJ, Falowski SM, Burgher AH, Pope JE, Gilmore CA, Qureshi FA, Staats PS, Scowcroft J, Carlson J, Kim CK, Yang MI, Stauss T. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. Lancet Neurology 2020;19(2):123-134.

[19] Morgalla, Fortunato M, Lepski G, Chander BS. Dorsal Root Ganglion Stimulation (DRGS) for the Treatment of Chronic Neuropathic Pain: A Single-Center Study with Long-Term Prospective Results in 62 Cases. Pain Physician 2018;21(4).

[20] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17(1):45-56.

[21] Schu S, Gulve A, ElDabe S, Baranidharan G, Wolf K, Demmel W, Rasche D, Sharma M, Klase D, Jahnichen G, Wahlstedt A, Nijhuis H, Liem L. Spinal Cord Stimulation of the Dorsal Root Ganglion for Groin Pain-A Retrospective Review. Pain Practice 2015;15(4):293-299.

[22] Van Buyten J-P, Smet I, Liem L, Russo M, Huygen F. Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series. Pain Practice 2015;15(3):208-216.

Figure Legends

Figure 1. Percutaneous insertion of DRGS trial lead through epidural needle

Figure 2. Study flow diagram

Figure 3. Kaplan-Meier plot of time to DRGS explant

Figure 4. Radiograph of the lumbar spine showing a correctly positioned lead in the left L4/5 foramen positioned to replace a migrated DRGS lead in the epidural space

Figure 5. Radiograph showing two intact DRG leads in position with 4 contacts each (red arrows) and broken fragment of a ball tip lead trapped in ligament flavum (black arrow)

Table 1. Patient demographic characteristics

Variable	Patients for trial	Implanted patients
Number of patients	42	32
Age, years (SD)	52.02 (11.55)	53.03 (10.36)
Sex M(%), F(%)	22(52%), 20(48%)	M 15 (46.9%), F 17(53.1%)
Age (M), (F)	M 55.3; F 48.5	M 58.7; F 48.1
Area of pain		
• Arm/hand	0	0
• Thorax/abdomen	19	17
• Leg/Foot	21	15
• Back and limb pain	2	0
Diagnosis		
• CPSP	16	13
• CRPS Type I	8	8
• CRPS Type II	4	3
• PHN	2	2
• Phantom limb pain	3	2
• Peripheral neuropathy	6	3
• FBSS	3	1

CPSP=chronic post-surgery pain; CRPS=complex regional pain syndrome; PHN=postherpetic neuralgia; FBSS=failed back surgery syndrome; F=female; M=male; SD=standard deviation

Table 2. Outcome scores at baseline and follow-up

	Baseline	24 months		7 years	
	N Mean (SD)	N Mean (SD)	Mean difference (95% CI)	N Mean (SD)	Mean difference (95% CI)
Complete cases (i.e., those with no missing data)					
Pain intensity (VAS)	22 7.1 (1.8)	22 5.3 (2.9)	1.7 (0.2 to 3.3)*	14 5.1 (2.9)	2.1 (0.3 to 4.0)*
HRQoL (EQ-5D-3L)	23 0.23 (0.38)	23 0.36 (0.40)	-0.13 (-0.31 to 0.04)	14 0.49 (0.18)	-0.25 (-0.46 to -0.04)*
First observation carried forward					
Pain intensity (VAS)	41 7.1 (1.67)	41 6.2 (2.5)	0.9 (0.1 to 1.8)*	41 6.4 (0.7)	0.7 (0.1 to 1.4)*
HRQoL (EQ-5D-3L)	42 0.21 (0.34)	42 0.28 (0.36)	-0.07 (-0.17 to 0.02)	42 0.29 (0.32)	-0.08 (-0.16 to -0.01)*
Last observation carried forward					
Pain intensity (VAS)	41 7.1 (1.67)	41 6.1 (2.6)	1.0 (0.1 to 1.9)*	41 6.2 (2.7)	0.9 (0.0 to 1.9)
HRQoL (EQ-5D-3L)	42 0.21 (0.34)	42 0.32 (0.37)	-0.11 (-0.22 to 0.0)*	42 0.34 (0.30)	-0.14 (-0.25 to -0.02)*

CI=confidence interval; HRQoL=health-related quality of life; PGIC=patient global impression of change; SD=standard deviation; VAS=visual analogue scale

* $p<0.05$

Table 3. Adverse events during the 24 months follow-up

Patients needing revisions of the device (n=14) **Revisions carried out (n=17)**	**Reasons for revisions of the device***	
	Additional leads added	1
	Battery depleted	2
	Loss of stimulation	6
	Lead migration	6
	Software malfunction	1
	Infection	1
	Fractured lead	4
	IPG moved	1
Device explants (n=4)	**Reasons for explants**	
	Dissatisfied with device/pain relief (including lead migration n=1)**	2
	Patient requiring high amplitude, change to rechargeable SCS	1
	Pain over IPG site, lack of perceived benefit	1
Complications (n=33)	Infections	2
	Pain at IPG site	6
	Lead fracture	5
	Lead migration	5
	Dural puncture	2
	IPG moved	1

	Early battery depletion – replacement IPG	2
	Patient switching device off	1
	Lack of paraesthesia/pain relief	8
	IPG malfunction	1

IPG=implantable pulse generator; SCS=spinal cord stimulation

* Some patients reported more than one reason for revision of the device

** One participant had a lead migration but did not have revision, decided on explant due to dissatisfaction

Table 4. Reasons for device revision or explant between 24 months and last follow-up

Patients needing revisions of the device between 24 months and last follow-up (n= 16, includes revision on participant who died prior to follow-up n=1, attempted revision leading to explant n=1)	**Reasons for revisions of the device**	
	Depleted battery – replacement IPG	15
	Depleted battery <4 year duration	7 participants, 8 replacements
	Lack of adequate paraesthesia	1
	Lead fracture/lead revision	2
Revisions carried out (n= 19, participants with multiple revisions n=3, some revisions for multiple reasons)	Lead migration	4
Device explants (n=7)	**Reasons for explants**	
	Change to SCS for improved analgesia	3
	Lack of pain relief	2
	Unsuccessful revision of DRGS – changed to SCS	1
	Lead migration – changed to SCS	1

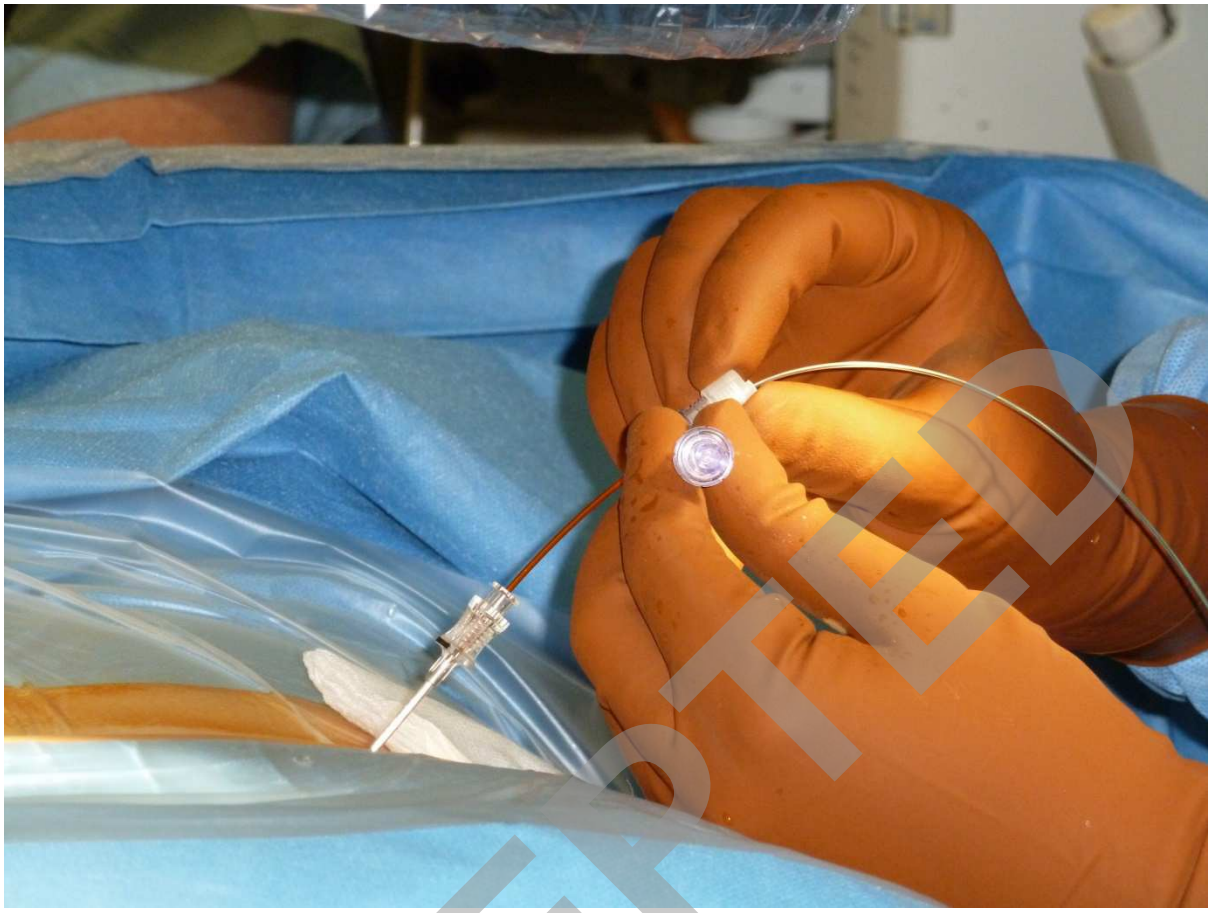
DRGS=dorsal root ganglion stimulation; IPG=implantable pulse generator; SCS=spinal cord stimulation

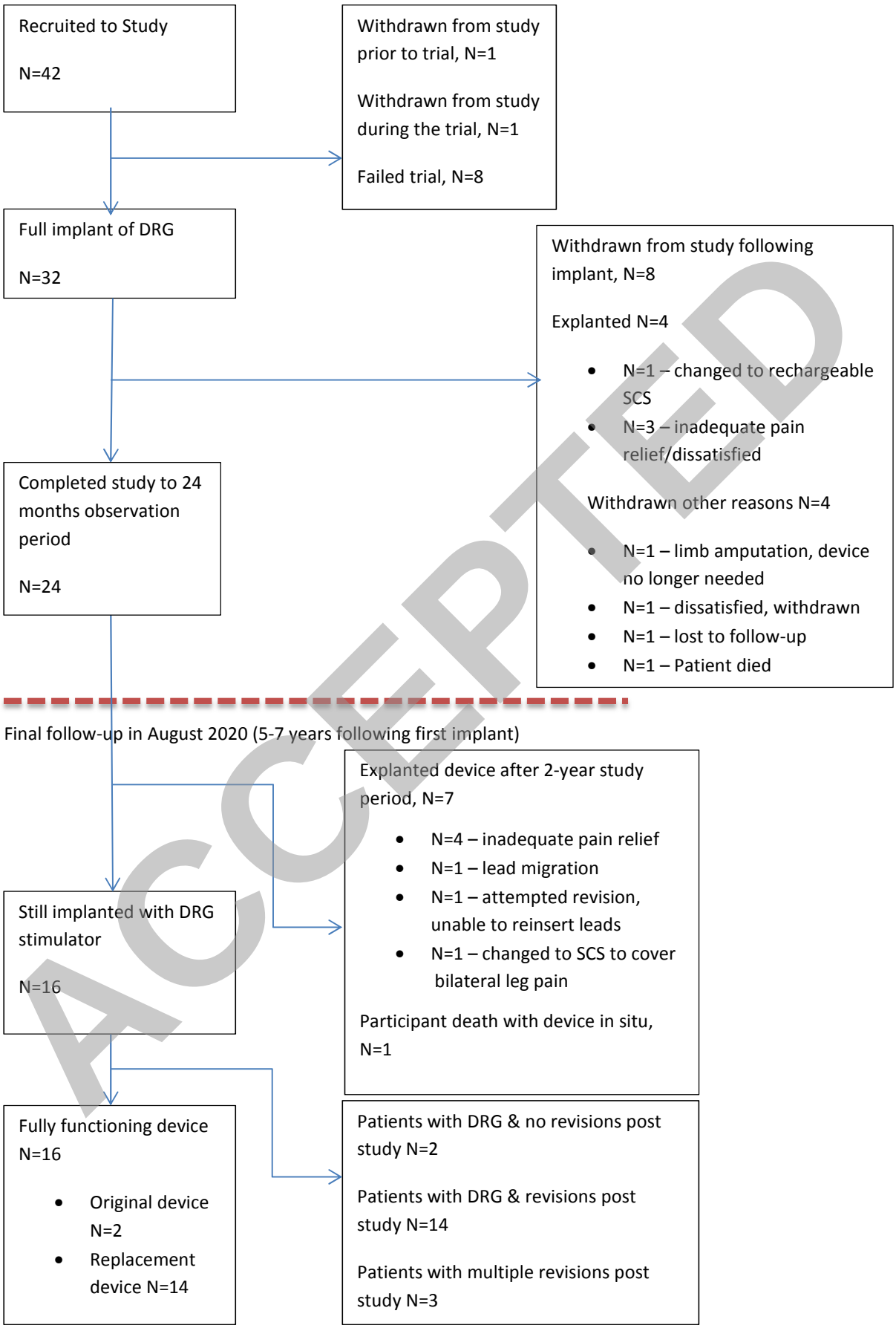
Table 5. Duration of implants

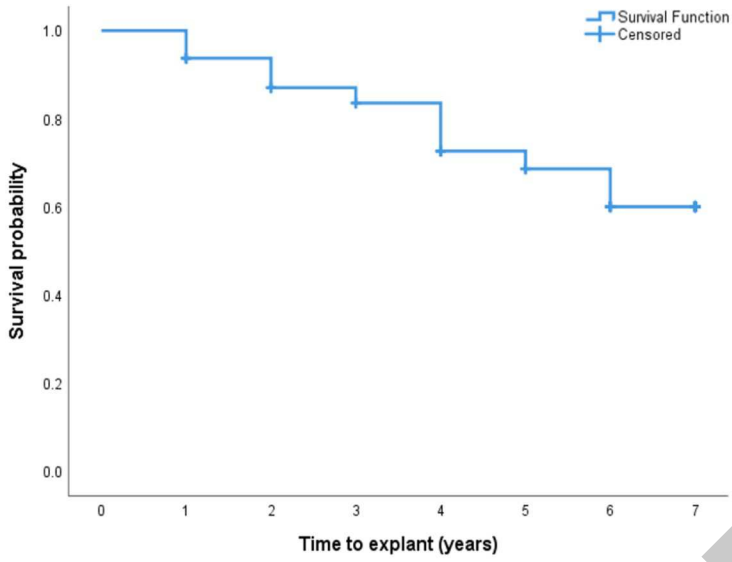
Duration of implants	Months
Average duration of implantation prior to explant during whole period	38
Maximum duration of IPG up to last follow-up	78
Minimum duration of implant	1*
Standard deviation of duration of implants	19.7
Average duration of IPG if satisfied with DRGS	39.4
Average duration of IPG if explanted due to dissatisfaction/lack of pain relief	35.4
Minimum duration of battery life	8
Average duration of battery life if changed due to depletion	30

DRGS=dorsal root ganglion stimulation; IPG=implantable pulse generator

*Device was removed due to infection (n= 1), patient treated and new DRGS implanted







Number at risk	32	32	28	25	23	18	16	9
Explants	0	2	2	1	3	1	2	0
Cumulative explants	0	2	4	5	8	9	11	11