OPEN

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000001977

Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness (TRIAL-STIM)? a randomised controlled trial

Sam Eldabe, MD[1] Rui V Duarte, PhD[2] Ashish Gulve, MD[1] Simon Thomson, MBBS[3] Ganesan Baranidharan, MD[4] Rachel Houten, MSc[2] Susan Jowett, PhD[5] Harbinder Sandhu, PhD[6] Raymond Chadwick, DClinPsych[7] Morag Brookes, MSc[1] Anu Kansal, MD[1] Jenny Earle, BA[8] Jill Bell, BEd[8] Jennifer Robinson, RGN[1] Sarah Walker, PhD[9] Shelley Rhodes, PhD[9] Rod S Taylor, PhD[9,10]

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

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

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

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

[5]Health Economics Unit, University of Birmingham, Birmingham, UK

[6]Warwick Medical School, University of Warwick, Warwick, UK

[7]School of Health and Social Care, Teesside University, Middlesbrough, UK

[8]Patient and Public Involvement Representatives, Middlesbrough, UK

[9]Exeter Clinical Trials Unit, College of Medicine and Health, University of Exeter, Exeter, UK

[10]Institute of Health and Well Being, University of Glasgow, Glasgow, UK

Address for correspondence: Sam Eldabe, Department of Pain and Anaesthesia, The James Cook University Hospital, Cheriton House, Marton Road, Middlesbrough TS4 3BW, UK. Email address: seldabe@mac.com, Telephone: +44 (0)1642282417

Conflict of interest statement: SE has received consultancy fees from Medtronic Ltd, Mainstay Medical, Boston Scientific Corp, and Abbott. He has received department research funding from the National Institute of Health Research, Medtronic Ltd and Nevro Corp. RVD has received consultancy fees from Medtronic Ltd and Boston Scientific Corp. AG has received honoraria for consulting as well as advisory board meetings for Nevro Corp, Boston Scientific Corp and Abbott. ST has received consultancy fees from Boston Scientific Corp and Mainstay Medical. He has received department research funding from the National Institute of Health Research, Boston Scientific Corp and Mainstay Medical. GB has a consulting agreement and is on the advisory board for Nevro Corp, Nalu Medical Inc, Abbott and Boston Scientific Corp. RST has received consultancy fees from Medtronic Ltd, Saluda Medical and Nevro Corp. The other authors declare no competing interests.

Abstract

Spinal cord stimulation (SCS) is an established treatment of chronic neuropathic pain. Although a temporary SCS screening trial is widely used to determine whether a patient should receive permanent SCS implant, its evidence base is limited. We aimed to establish the clinical utility, diagnostic accuracy, and cost-effectiveness of an SCS screening trial. A multicentre single-blind, parallel two-group randomised controlled superiority trial was undertaken at three centres in United Kingdom. Patients were randomised 1:1 to either SCS

screening trial strategy (TG) or no trial screening strategy (NTG). Treatment was open label, but outcome assessors were masked. The primary outcome measure was numerical rating scale (NRS) pain at six-months follow-up. Between June 2017 and September 2018, 105 participants were enrolled and randomised (TG=54, NTG=51). Mean NRS pain decreased from 7.47 at baseline (before SCS implantation) to 4.28 at 6-months in TG and from 7.54 to 4.49 in NTG (mean group difference: 0.2, 95% CI: -1.2 to 0.9, p=0.89). We found no difference between TG and NTG in the proportion of pain responders or other secondary outcomes. SCS screening trial had a sensitivity of 100% (95% CI: 78 to 100) and specificity of 8% (95% CI: 1 to 25). The mean incremental cost-effectiveness ratio of TG versus NTG was £78,895 per additional quality-adjusted life-year (QALY) gained. In conclusion, although the SCS screening trial may have some diagnostic utility, there was no evidence that an SCS screening trial strategy provides superior patient outcomes or is cost-effective compared to a no trial screening approach.

Keywords: randomised controlled trial; screening trial; spinal cord stimulation; neuropathic pain; cost-effectiveness

INTRODUCTION

Neuropathic pain is a complex and heterogeneous disorder that affects up to 8% of the adult population [3] with substantial impact on health-related quality-of-life (HRQoL).[42; 43] Despite the availability of numerous pharmacological options, up to 50% of patients with neuropathic pain fail to obtain pain relief from pain relieving medication.[17]

Spinal cord stimulation (SCS) is an effective treatment for severe neuropathic pain.[32] In Europe, North America and many other countries, clinical guidelines, and healthcare payers

typically require patients to undergo a successful SCS screening trial to be able to receive an SCS implant.[4; 5; 11; 32] The approach to SCS screening trials varies between countries and clinical centres from a test stimulation of a few minutes immediately prior to permanent SCS implantation [44] to a test period as long as 28 days.[4] The primary aim of a screening trial is to allow the patient to test the efficacy of the SCS. An expert clinical panel has defined a successful trial as the patient reporting ≥50% pain relief with stable or reduced pain medications and with stable levels of daily activity.[11]

A screening trial appears to be a low burden ("try before you buy") intervention as it allows patients to experience the sensation generated by SCS and its interaction with body movements, determine the appropriate lead location, and to formulate a broad evaluation of the pain relief; and provides physicians with an estimate of electrical current consumption required from the device that guides their choice of a relatively expensive SCS implantable pulse generator (IPG) and choice between paddle lead or percutaneous leads. However, SCS screening trials are not without their drawbacks: they require a duplication of a clinical procedure; they expose patients to a higher risk of infection (due to bacterial colonisation of the lead skin exit site); indeed 28-day trials have been associated with higher infection rates when compared with shorter trial durations.[34; 36] Screening trials using permanent anchored lead have resulted in an increasing number of wound infections (6.52%) and poor wound healing (4.35%) when compared to percutaneous temporary lead trials (1.35% and 0% respectively).[38] Furthermore, SCS trials can be associated with moderate surgical pain up to six days following the procedure calling into question a patient's ability to judge the impact of SCS on their original pain.[6] Percutaneous insertion of SCS leads have on occasion resulted in epidural and intracranial bleeding and even death.[1; 39]

In summary, whilst SCS screening trials are used worldwide as part of routine clinical practice to assess whether an SCS device should be made available to patients, there is limited evidence for their use and they may have limited clinical value, increased patient risk, and higher healthcare costs. We present the first randomised controlled trial (RCT) designed to determine the clinical utility and cost effectiveness of a SCS screening trial. We hypothesised that a no SCS screening trial strategy will be superior to an SCS screening trial and more cost-effective for patients with chronic neuropathic pain.

METHODS

Study design and participants

TRIAL-STIM was a multicentre, single-blind, parallel two group randomised trial with an economic evaluation (ISRCTN, ISRCTN60778781). Our full study protocol has been published elsewhere.[15]

Patients were recruited from the outpatient clinics of three participating sites in United Kingdom (UK): South Tees Hospitals NHS Foundation Trust (The James Cook University Hospital), Basildon and Thurrock University Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust. Inclusion criteria were adults (≥18 years) who are clinically considered to be candidates for SCS in accord with current NHS guidance (NICE TA159);[32] pain of neuropathic nature of an intensity of at least 5 as assessed on a numerical rating scale (NRS); persistent pain for more than six-months despite appropriate conventional medical and surgical management including transcutaneous electric nerve stimulation (TENS), acupuncture, oral analgesic agents, cognitive behavioural therapy as well as nerve blockade where appropriate; satisfactory multidisciplinary assessment by a team with expertise in delivering SCS therapy; and capacity to provide informed consent.

Exclusion criteria were: the presence of an on-going pain condition considered by the investigator to overshadow the neuropathic pain condition to be treated with SCS; current or previous treatment with an implanted pain relief device; current participation or planned participation in other studies that may confound the results of this study; ongoing anticoagulation therapy, which cannot be safely discontinued; poor cognitive ability or lack of capacity; unable to undergo study assessments or complete questionnaires independently; and patient was pregnant or planning to become pregnant during the course of the study.

Patients who were scheduled to have an SCS trial were approached and given a Patient Information Sheet to take home to read. Informed consent was obtained from suitable patients following a reasonable period of time by one of the Principal Investigators or delegated individuals at each site following International Conference on Harmonisation/ Good Clinical Practice (ICH/GCP) guidelines.[33]

The study was approved by the UK Health Research Authority North East Research Ethics Committee (17/NE/0056). The trial was conducted and reported in accordance with CONSORT guidelines.[37]

Randomisation and masking

Participants were allocated in a 1:1 ratio to one of two groups: either a strategy of a screening trial followed by SCS implantation based on the screening trial result (TG) or a no trial screening SCS implantation only strategy (NTG). Patients were randomly assigned to groups by means of a password-protected web-based system developed and maintained by Exeter Clinical Trials Unit (ExeCTU). Allocation was stratified by centre and minimised on patient age (≥65 or < 65 years), gender, and presence of FBSS. Once the patient completed the screening interview and baseline data collection interview, the researcher accessed the

randomisation website using a unique username and password. Treatment allocation was concealed from the patients, investigator, and site staff.

It is not possible to blind patients, clinicians, or all of the research team to group allocation. However, to minimise assessment bias we sought to blind researchers undertaking outcome assessment and data analysts to group allocation by masking them from group allocation. Each site team consisted of blinded and unblinded assessors. These did not cross roles or exchange information. Database entries were also clearly divided into blinded and unblinded sections with no potential for cross data entry since blinded assessor login only allowed access to a limited set of data. Data analysts were masked to group allocation until the analyses were presented to the Trial Steering Committee (TSC).

Procedures

Screening Trial and Implantation strategy (TG)

Patients randomised to this arm received a screening trial consisting of passage of either an external or internalised tunnelled SCS lead or leads attached to an external stimulator as per centre's routine practice. Taking into consideration the RCTs [25; 26] included in the clinical evidence section of NICE TA159 [32] as well as international guidelines,[11] a successful screening trial was defined as ≥50% pain relief and satisfactory on table paraesthesia coverage (i.e. ≥80%) of the pain area, reduction in pain medications or improved quality of life and function, and successful location of leads at anatomical target for paraesthesia free therapies. Patients with an unsuccessful screening trial were not implanted but all patients were to be followed-up to six-months. Successful trial patients had the implantable pulse generator (IPG) implanted on a separate occasion.

Implantation only strategy (NTG)

In the implantation only strategy group, all patients with satisfactory on table paraesthesia coverage (i.e. ≥80%) of the pain area and no dislike of sensations,[16] and satisfactory anatomical lead location for paraesthesia free devices received a permanent implant in one surgery.

Outcomes

The primary outcome measure was the pain numerical rating scale (NRS) at 6-months follow-up.[14] Secondary outcome measures included mean pain intensity measured on the NRS over four days, the proportion of patients achieving at least 50% and 30% pain relief at six-months as measured on the NRS,[14] health-related quality-of-life (EQ-5D-5L),[21] function (Oswestry Disability Index),[18] patient satisfaction (Patients' Global Impression of Change),[20] and complication rates.

Diagnostic performance of the SCS trial stimulation was reported as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios.

The economic analysis (appendix pp 6-16) was conducted from an NHS perspective with additional analyses presented from a societal perspective to include productivity losses. For each patient enrolled in the trial, clinical data and resource events at specific measurement points including the day of the intervention, three and six-months follow-up were registered in the case report form (CRF).[28] These included appointments with healthcare professionals, procedures performed, investigations, inpatient hospitalisations, treatment given, management of adverse events and work absenteeism related with the chronic pain condition.

All unit costs were for the price year 2017-2018. Intervention costs were taken from standard national costs. Secondary care data were valued using the National Reference Costs from the Department of Health.[12] Primary and community based health services were valued using National Reference Costs from the Personal Social Services Research Unit.[8] Productivity costs were valued from the patient's perspective using the human capital approach. The appendix shows full details of all unit costs.

Statistical analysis

The study was powered to detect a statistically significant and clinically meaningful between-group difference using our primary outcome based on an intention-to-treat analysis. Assuming that the SCS screening trial has little or no clinical utility we hypothesised superiority of the no-screening strategy over the screening strategy. For a pain NRS (scores 0–10), IMMPACT proposes a minimal clinically important difference (MCID) of 2 points.[14] Based on a typical pain NRS standard deviation of 2.5 seen in previous SCS RCTs, at 90% power, 5% alpha and a worst-case attrition rate of 30%, we required a total of 50 patients recruited per group.

A sample size of 50 patients in the TG arm determined our precision to estimate the specificity and sensitivity of the SCS screening test. Given the lack of previously published sensitivity and specificity values for the SCS screening test, Table 1 presents the margins of error of estimation (width of the 95% confidence interval (CI)) based on 50 patients in the implantation strategy arm across a range of possible values of diagnostic performance.

[Insert Table 1 here]

Comparison of effectiveness

Analyses were conducted and reported in accord with CONSORT recommendations.[37] Primary analysis was conducted on an intention-to-treat basis (i.e. according to randomised group allocation) and compared primary and secondary outcomes at six-month follow-up between randomised groups with complete data sets. Continuous outcomes were compared using linear regression methods adjusting for baseline outcome scores and stratification/minimisation variables. Binary outcomes were compared using logistic regression analysis with adjustment for stratification/minimisation variables and site. A number of secondary analyses were undertaken: (1) comparison of primary and secondary outcomes at 3-months in patients with complete data; (2) comparison of primary and secondary outcomes at 3 and 6-months follow up using different methods of imputation that included multiple imputation, last observation carried forward (LOCF), worst case scenario (LOCF and then reduce outcomes by the minimum important difference i.e. NRS add 2.0, EQ-5D subtract 0.1, ODI add 5.0; PGIC if missing assume dissatisfied) and best case scenario (LOCF and the increase outcomes by minimum important difference i.e. NRS subtract 2.0, EQ-5D add 0.1, ODI subtract 5.0, PGIC if missing assume satisfied); (3) exploratory subgroup analyses using interaction terms for stratification and minimisation variables and type of stimulation (conventional, high frequency, burst) for primary outcome.

Diagnostic performance

Analyses were conducted and reported in accord with Standards for Reporting of Diagnostic Accuracy Studies (STARD) recommendations.[2] Cross-tabulation was used to report the SCS screening trial results (fail versus success) versus SCS pain relief (≥50% versus <50%) at 3 and 6-months follow-up. Positive and negative predictive value and likelihood ratios are

also reported. Given the loss of follow up of negative trial screens, post-hoc best and worst case sensitivity analyses were undertaken – base case: assume missing screen negatives are true negatives (i.e. have <50% pain relief at follow-up), or worst case: assume missing screen negatives are false negatives (i.e. have ≥50% pain relief at follow up).

Economic analysis

Analyses were conducted and reported in accord with Consolidated Health Economic Evaluation Reporting Standards (CHEERS) recommendations.[23] Differences in costs and utilities between the groups were compared using linear regression methods adjusting for baseline EQ-5D-5L index scores and stratification/minimisation variables. The base-case economic analysis compared TG versus NTG from an NHS perspective, with additional analysis presented to include productivity losses. A cost-utility analysis was conducted and the incremental cost-effectiveness ratio (ICER) reported. This was done by calculating the ratio of the difference in mean costs and mean change in quality adjusted life years (QALY) in terms of health-related quality of life gained. Uncertainty around the cost and effectiveness estimates was represented by cost-effectiveness acceptability curves.

All analyses were prespecified in a detailed statistical analysis plan and a health economic analysis plan that were reviewed by the independent TSC. All analyses were undertaken using STATA v16.0.

RESULTS

Of 137 patients assessed between June 2017 and September 2018, 105 (63%) were eligible to participate. The primary reason for exclusion was declining to participate (Figure 1). Of the 105 participants, 54 were randomly allocated to the trial screening strategy group (TG).

Seven TG patients withdrew prior to trial screen; of the remaining 47, 5 (11%) had an unsuccessful trial screen and 42 (89%) had a successful trial screen and were implanted with an SCS system. The mean screening trial duration was 9.3 days (SD=4; median=7; range 5 to 22). Thirty-three (70%) of the screening trials were definitive trials (i.e. permanent anchored lead) and 14 (30%) were external lead trials (i.e. percutaneous temporary lead). Of the 51 NTG patients, 49 received an SCS implant.

[Insert Figure 1 here]

Study participants had an average age of 50.4 years and relatively equal representation by sex, with a mean NRS pain of 7.5 and primarily an FBSS diagnosis (53%) (see Table 2). The baseline characteristics and outcome scores of the TG and NTG groups were relatively well balanced, the only exception being the duration of pain that was somewhat longer in the NTG group.

Primary outcome data were available for 85 (81%) patients at 3 months (37 TG and 48 NTG) and 89 (85%) patients (41 TG and 48 NTG) at 6 months. There was no evidence of difference in the age, gender distribution, duration of pain or baseline outcome score of patients who were lost to follow up at either 3 or 6-months compared to those with data.

[Insert Table 2 here]

There was no difference in the primary outcome of clinic assessed NRS score between TG and NTG at 6-months follow up (mean difference: 0.2, 95% CI: -1.2 to 0.9, P=0.74) (see Table 3). There was evidence of substantial reduction in mean NRS pain from baseline to 6-

months for both TG (7.5 to 4.3) and NTG (7.5 to 4.5). No between group difference at 6-months was seen for the secondary outcomes of 4-day diary NRS, EQ-5D-5L, ODI, PGIC and 30% and 50% pain reduction. Improvements were seen in 4-day diary NRS, EQ-5D-5L, and ODI from baseline to 6-months in both groups. A similar pattern of primary and secondary outcome results was seen at 3-months with exception of 30% pain relief that was higher for TG (74%) than NTG (48%) (appendix, supplementary table 1, available athttp://links.lww.com/PAIN/B94).

The finding of no difference between TG and NTG at 6-months was robust to various imputation analyses for the handling of missing outcome (appendix, supplementary table 2, available athttp://links.lww.com/PAIN/B94). Exploratory interaction analyses showed no significant subgroup effects for NRS pain at 6-months follow-up by site (P=0.25), gender (P=0.17), age (P=0.96), FBSS or not (P=0.85), and type of stimulation (P=0.70) (appendix, supplementary table 3, available athttp://links.lww.com/PAIN/B94). Our analysis of concomitant analgesia found no difference between groups that could account for our findings (appendix, supplementary table 4, available athttp://links.lww.com/PAIN/B94).

[Insert Table 3 here]

Diagnostic performance results of the trial screen at 3 and 6-months follow up are reported in Table 4. All patients that reported ≥50% pain relief at 6-months follow-up had a positive trial screen (i.e. ≥50% pain relief) and therefore a sensitivity of 100%. Of the 26 participants who reported <50% pain relief at 6-months, two had negative screening trials i.e. specificity of 8%.

Of the 5 participants who had a negative screening trial (i.e. <50% pain relief) (see Figure 1), data was only available at 6-months for two participants who both reported <50% pain relief. If it was assumed that all 3 patients with a negative test who dropped out had ≥50% pain relief at 6-months, this would give a sensitivity of 83% and specificity of 8% (see appendix, supplementary table 5, available athttp://links.lww.com/PAIN/B94). Alternatively, if it was assumed that they had <50% pain relief at 6-months, this would give a sensitivity of 100% and specificity of 17% (see appendix, supplementary table 6, available athttp://links.lww.com/PAIN/B94). A similar pattern of results was seen at 3-months follow up.

[Insert Table 4 here]

A screening trial strategy was estimated to cost £19,073.38 per participant in TG, with an implant only strategy estimated to cost £17,487.90 per participant in NTG (mean difference £1,341.22 (95% CI -34.26 to 2,832.85). Results including productivity losses were also non-significant (appendix, supplementary table 16, available athttp://links.lww.com/PAIN/B94). Cost-effectiveness analysis suggests that from an NHS perspective, the TG strategy generates more QALYs but at an increased cost, thus producing an ICER of £78,895 per additional QALY gained when adjusted for baseline EQ-5D-5L index score and pre-specified stratification variables. The probability of a screening trial strategy being cost-effective at £20,000 or £30,000 per additional QALY gained (i.e. the threshold commonly adopted in decisions made by NICE), is 9.2% and 13.8% respectively.

Adverse events at 3 and 6-months follow-up are descriptively reported by TG and NTG (appendix, supplementary table 7 and 8, available athttp://links.lww.com/PAIN/B94). One

patient in TG experienced a serious adverse event related to an infected haematoma. Eight participants experienced a total of 10 adverse events in both TG and NTG. However, the NTG experienced less device related AE (n=2) compared to the TG (n=5). In total three participants all randomised to the TG group experienced implant related wound infections (all received a definitive trial), of which two required SCS explant, and one was treated with antibiotics. The patients in TG that experienced anchor site pain, new neurological change and lead migration requiring reoperation all received an external trial. Moderate to severe pain around the implant was reported by two subjects, one in TG and one in NTG.

DISCUSSION

Our results indicate that whilst an SCS screening trial may have some diagnostic utility, it provides no patient outcome benefits compared to a no screening trial and direct to permanent SCS implantation strategy. Our economic evaluation also shows that an SCS trial is not a cost-effective use of healthcare resources.

Prior to this study, there was a limited evidence base for the use of SCS screening trials. The success of screening trials (i.e. ≥50% pain relief) in recent RCTs have ranged from 88%[26] to 93%.[24] However, the proportion of patients reporting ≥50% pain relief at three or six-months follow-up ranges only from 48% to 76%.[10; 24; 26] Diagnostic blocks prior to radiofrequency denervation can be considered akin to screening trials prior to SCS implantation and its usefulness has also been questioned. One RCT evaluating diagnostic nerve blocks before proceeding to radiofrequency denervation found that these increased costs and decreased the overall success rate.[7] Another RCT found that the use of prognostic genicular nerve block did not improve the rate of treatment success.[29]

A retrospective study reporting on outcomes following different screening trial strategies observed that a percutaneous temporary lead trial was associated with fewer false positives and wound related complications as compared to a permanent anchored lead trial.[38] A retrospective review of 80 patients that received SCS following an on-table trial reported that at 12-monts follow-up 40% of the patients no longer required analgesic medication and for 37% of patients the pain was manageable with first line analgesics.[19] A post-hoc analysis of the PROMISE RCT observed that the only significant contributing factor to infection was trial duration supporting the hypothesis of a cause-effect relationship between trial duration and the risk of infection.[34]

In a study specifically addressing the role of screening trials, Weinand et al retrospectively reviewed 54 patients with chronic low back and/or lower extremity pain, who underwent acute on table trial or a prolonged home trial of an average of 5.0 days.[44] Similar to our findings, the study reported that acute (on table) and prolonged SCS screening trials have equivalent predictive value for long-term pain control using SCS.

In contrast to our reported positive predictive value (PPV) of 38% (95% CI: 36 to 41), Weinand et al reported PPV of 82% and 86% for acute and prolonged screening trials respectively. The difference is attributable to the higher proportions of long term responders (≥50% pain relief) in the Weinand study (i.e. 31/38 for acute screening and 31/36 for prolonged screening) in comparison to our relatively low proportion of responders of 19/48 and 15/41 for NTG and TG respectively. This difference in responder rates may reflect the heterogeneous neuropathic pain population recruited in our study as well as the retrospective design and single centre setting of the Weinand study.

Screening trials have been suggested to exclude good candidates for SCS. Oakley reported a small case series of 12 patients implanted with SCS despite failing a screening trial.[35] Despite an average pain relief of 21% at the end of screening trials, these went on to report an average pain reduction of 44% at six months post SCS implant. We note that the study by Oakley et al has several limitations including study design, small sample size and assessment of pain intensity which was based on difference between SCS device off versus SCS device on instead of differences between timepoints. In the current study, we were unable to explore the number of false negative trial responders due to clinical reasons as well as funding restrictions.[32]

In relation to the economic evaluation, Duarte and Thomson carried out a cost impact analysis from a UK NHS perspective, considering trial to implant rates reported in the literature.[13] They concluded that considerable savings could be obtained by adopting an implantation only strategy without a screening trial. They estimated the point at which equivalent costs would be observed between a trial screening and implantation only strategies. At a base price of £17,422 per rechargeable SCS device this would occur at the point where 20 out of 100 patients fail a screening trial. Our findings support those of Duarte and Thomson. Indeed we found the total cost to be greater in TG (i.e. screening trial) at £19,073 compared to NTG (no screening trial) at £17,488. The ICER adjusted for stratification variables was £78,895 per additional QALY gained. The probability of a screening trial being cost-effective at a threshold of £30,000 per QALY is only 13.8%. Therefore, the limited patient benefit obtained by the use of screening trials results in a significantly higher cost to the health service. Such costs may only be mitigated in settings where trial failure rates are considerably higher than those observed in this study which reflects European guidance, procedure and SCS trial success rates. An implant rate of 91.6%

had previously been reported for one of the sites in this study,[41] and the implant rate of 88% observed in the PROCESS RCT included two of the three participating sites in the current RCT.[26] In contrast US trial success rates reportedly range from as low as 41.4%,[22] up to 64.7%.[31] The difference between US and European trial success rates may relate to the more ready access to psychological evaluation in Europe or to a difference in the medical indications of the population being tested or the difference in healthcare setting and payer (e.g. reimbursement not dependent on outcome), physician and patient expectations. However, trial success rates reported in recent RCTs conducted in the US [10; 24; 30] are more similar to those observed in Europe, which suggests that our results may be generalisable to current US practice.

Strengths and limitations

To our knowledge this is the first randomised controlled study to examine the clinical utility and diagnostic value of SCS screening trials. Our study was independently funded and conducted with oversight from a registered clinical trials unit. To date only two other RCTs assessing the impact of SCS have reported industry independent funding, and both recruited considerably fewer patients from a smaller number of centres.[9; 25] The recruitment from three UK centres makes our findings generalisable to UK and possibly European practice. In addition the use of pragmatic inclusion criteria that closely mirror the UK NICE guidance as well as the use of devices from all major SCS manufacturers ensures that our findings portray the real world impact of SCS.

We sought to eliminate participant expectation bias through use of a carefully balanced message to participants around the benefits/risks of screening trials. In addition we blinded observers and analysts to group allocation.

All devices were programmed by pain clinic nurses within the routine clinical setting and at routine clinical review timepoints selected to limit participant burden. Only two individual programming appointments occurred outside the study visits.

Finally, this is the first RCT to examine the role of SCS as a generic intervention rather than a device specific outcome. SCS devices were programmed to paresthesia, 10Khz and burst modes of stimulation. While the study was not powered to detect statistically significant differences between the three programming modalities, we were unable to observe clinically relevant differences.

Our study has some limitations. Due to the nature of the study interventions, we were unable to blind participants or physicians. As this was a pragmatic trial reflecting UK clinical practice, we did not test for neuropathic pain since NICE guidance does not dictate the use of a test other than clinical diagnosis. Inclusion of a population based on IASP criteria or any specific diagnostic neuropathic pain test may not represent the population treated with SCS in UK clinical practice thus limiting our ability to influence UK practice and commissioning. Our findings specifically on the diagnostic utility of the screening trial are compromised by the small number of subjects failing a screening trial as well as the loss to follow up of 3/5 patients with a failed screening trial. Finally, our findings on the diagnostic utility and cost-effectiveness of screening trials may not be applicable to other healthcare settings (such as United States) where trial success rates are typically much lower than seen in this study and other European settings.[22; 31]

Practice implications

Our findings have substantial potential implications for the future practice. Over the last 50 years, screening trials have been used to determine the suitability of patients for permanent SCS implantation. Indeed, many healthcare systems (e.g. UK, Belgium) mandate that patients with chronic pain cannot be provided with a SCS system without first demonstration of positive screening trial. However, our results challenge this dogma. Although more evidence needs to be collected on the utility of SCS screening trials in different healthcare settings and clinical patient populations, our findings indicate that SCS screening trials should certainly no longer be mandatory. Instead, future patient selection for SCS should be based on careful multidisciplinary clinical assessment of their suitability that includes a psychological evaluation by an experienced psychologist, rather than the application of a simple screening trial. Since completion of the TRIAL-STIM study, a European consensus and educational tool on the appropriate referral and selection of patients with chronic pain for SCS has been published.[40] The tool supports reliance on multidisciplinary selection rather than trial periods as the dominant criterion to predict successful long-term SCS outcome.

The COVID-19 pandemic raises additional concerns into risks associated with potentially avoidable surgical procedures as is the case of a two stage surgery due to a screening trial of SCS. High-rates of mortality (20.5%) and intensive care unit admission (44.1%) have been reported in patients that had elective surgeries during the incubation period of COVID-19.[27] Screening trials are likely to be undesirable from the perspective of both care giver and patient in this new era post-COVID-19.

In conclusion, the results of this RCT indicate that whilst there may be some diagnostic utility of a screening trial strategy for SCS implantation, compared to a no screen strategy

there is no patient outcome benefit. Furthermore, we found that a screening trial strategy incurs more costs in a UK NHS setting and is unlikely to represent value for money.

Authorship statement

SE, RVD, AG, ST, SJ, HS, RC, MB, JB, JE and RST were responsible for the original proposal, securing funding for the trial and drafting the original protocol. SE as chief investigator had overall responsibility for the management of the study. AG, ST and GB had responsibility for the Middlesbrough, Basildon and Leeds sites, respectively. MB coordinated the data collection. SW and RST wrote the statistical analysis plan and did the statistical analysis. RVD and SJ wrote the health economic analysis plan and RH did the health economic analysis. SE, RVD and RST wrote the initial draft of the manuscript. All authors contributed to, and approved the final version of the manuscript.

Acknowledgments

This research was funded by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme (project number: PB-PG-0815-20028). The funder of the study had no role in study design, data collection, data analysis, interpretation of data, or writing of the paper. The views expressed in this publication are those of the authors and do not necessarily reflect those of the RfPB programme, NIHR, NHS or the Department of Health and Social Care. We thank the Exeter Clinical Trials Unit who provided support for the trial and the independent members of our Trial Steering Committee (Professor Richard North and Professor Alan Batterham) for their valuable advice and support during the project. Most importantly, we thank all the participants for their time and commitment to this study.

REFERENCES

[1] Amirdelfan K, Vallejo R, Benyamin R, Yu C, Yang T, Bundschu R, Yearwood TL, Sitzman BT, Gliner B, Subbaroyan J, Rotte A, Caraway D. High-Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Combined Neck and Arm Pain: Results From a Prospective Multicenter Study. Neurosurgery 2019.

[2] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ (Clinical research ed) 2015;351:h5527.

[3] Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136(3):380-387.

[4] Camberlin C, San Miguel L, Smit Y, Post P, Gerkens S, De Laet C. Neuromodulation for the management of chronic pain: implanted spinal cord stimulators and intrathecal analgesic delivery pumps. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE), 2012.

[5] Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Electrical Nerve Stimulators (160.7), 2020.

[6] Chincholkar M, Eldabe S, Strachan R, Brookes M, Garner F, Chadwick R, Gulve A, Ness J. Prospective analysis of the trial period for spinal cord stimulation treatment for chronic pain. Neuromodulation : journal of the International Neuromodulation Society 2011;14(6):523-528; discussion 528-529.

[7] Cohen SP, Williams KA, Kurihara C, Nguyen C, Shields C, Kim P, Griffith SR, Larkin TM, Crooks M, Williams N, Morlando B, Strassels SA. Multicenter, randomized, comparative cost-effectiveness study comparing 0, 1, and 2 diagnostic medial branch

(facet joint nerve) block treatment paradigms before lumbar facet radiofrequency denervation. Anesthesiology 2010;113(2):395-405.

[8] Curtis L, Burns A. Unit Costs of Health and Social Care 2018, 2018.

[9] De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, Sanchis-Lopez N. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain medicine (Malden, Mass) 2017;18(12):2401-2421.

[10] Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, Tavel E, Staats P, Falowski S, Pope J, Justiz R, Fabi AY, Taghva A, Paicius R, Houden T, Wilson D. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation : journal of the International Neuromodulation Society 2018;21(1):56-66.

[11] Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, Levy RM, Abejon D, Buchser E, Burton A, Buvanendran A, Candido K, Caraway D, Cousins M, DeJongste M, Diwan S, Eldabe S, Gatzinsky K, Foreman RD, Hayek S, Kim P, Kinfe T, Kloth D, Kumar K, Rizvi S, Lad SP, Liem L, Linderoth B, Mackey S, McDowell G, McRoberts P, Poree L, Prager J, Raso L, Rauck R, Russo M, Simpson B, Slavin K, Staats P, Stanton-Hicks M, Verrills P, Wellington J, Williams K, North R. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation : journal of the International Neuromodulation Society 2014;17(6):515-550; discussion 550.

[12] Department of Health. National Schedule of Reference Costs 2017/18, 2018.

[13] Duarte RV, Thomson S. Trial Versus No Trial of Spinal Cord Stimulation for Chronic Neuropathic Pain: Cost Analysis in United Kingdom National Health Service. Neuromodulation : journal of the International Neuromodulation Society 2019;22(2):208-214.

[14] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

[15] Eldabe S, Gulve A, Thomson S, Baranidharan G, Duarte R, Jowett S, Sandhu H, Chadwick R, Brookes M, Tariq A, Earle J, Bell J, Kansal A, Rhodes S, Taylor RS. Does a Screening Trial for Spinal Cord Stimulation in Patients with Chronic Pain of Neuropathic Origin have Clinical Utility and Cost-Effectiveness? (TRIAL-STIM Study): study protocol for a randomised controlled trial. Trials 2018;19(1):633.

[16] Eldabe S, Raphael J, Thomson S, Manca A, de Belder M, Aggarwal R, Banks M, Brookes M, Merotra S, Adeniba R, Davies E, Taylor RS. The effectiveness and cost-effectiveness of spinal cord stimulation for refractory angina (RASCAL study): study protocol for a pilot randomized controlled trial. Trials 2013;14:57.

[17] Enke O, New HA, New CH, Mathieson S, McLachlan AJ, Latimer J, Maher CG, Lin CC. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2018;190(26):E786-e793.

[18] Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980;66(8):271-273.

[19] Gopal H, Fitzgerald J, McCrory C. Spinal cord stimulation for FBSS and CRPS: A review of 80 cases with on-table trial of stimulation. J Back Musculoskelet Rehabil 2016;29(1):7-13.

[20] Guy W. Clinical global impressions, ECDEU Assessment Manual for Psychopharmacology. Rockville: National Institute of Mental Health, 1976.

[21] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-1736.

[22] Huang KT, Martin J, Marky A, Chagoya G, Hatef J, Hazzard MA, Thomas SM, Lokhnygina Y, Lad SP. A national survey of spinal cord stimulation trial-to-permanent conversion rates. Neuromodulation : journal of the International Neuromodulation Society 2015;18(2):133-139; discussion 139-140.

[23] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ (Clinical research ed) 2013;346:f1049.

[24] Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. 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(4):851-860.

[25] Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. The New England journal of medicine 2000;343(9):618-624.

[26] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. 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(1-2):179-188.

[27] Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, Zhan LY, Jia Y, Zhang L, Liu D, Xia ZY, Xia Z. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020:100331.

[28] Manca A, Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, Taylor RJ, Goeree R, Sculpher MJ. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). Eur J Pain 2008;12(8):1047-1058.

[29] McCormick ZL, Reddy R, Korn M, Dayanim D, Syed RH, Bhave M, Zhukalin M, Choxi S, Ebrahimi A, Kendall MC, McCarthy RJ, Khan D, Nagpal G, Bouffard K, Walega DR. A Prospective Randomized Trial of Prognostic Genicular Nerve Blocks to Determine the Predictive Value for the Outcome of Cooled Radiofrequency Ablation for Chronic Knee Pain Due to Osteoarthritis. Pain medicine (Malden, Mass) 2018;19(8):1628-1638.

[30] Mekhail N, 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, Poree L. 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. The Lancet Neurology 2020;19(2):123-134.

[31] Murphy KR, Han JL, Hussaini SM, Yang S, Parente B, Xie J, Lad SP. The Volume-Outcome Effect: Impact on Trial-to-Permanent Conversion Rates in Spinal Cord Stimulation. Neuromodulation : journal of the International Neuromodulation Society 2017;20(3):256-262.

[32] NICE. Technology appraisal guidance [TA159]: Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. London: National Institute for Health and Care Excellence, 2008.

[33] NIHR. A Pocket Guide to Good Clinical Practice, Including the Declaration of Helsinki. Vol. Version 2.1. . Leeds: NIHR Clinical Research Network, 2011.

[34] North R, Desai MJ, Vangeneugden J, Raftopoulos C, Van Havenbergh T, Deruytter M, Remacle JM, Shipley J, Tan Y, Johnson MJ, Van den Abeele C, Rigoard P, On Behalf Of The Promise Study G. Postoperative Infections Associated With Prolonged Spinal Cord Stimulation Trial Duration (PROMISE RCT). Neuromodulation : journal of the International Neuromodulation Society 2020.

[35] Oakley JC, Krames ES, Stamatos J, Foster AM. Successful long-term outcomes of spinal cord stimulation despite limited pain relief during temporary trialing. Neuromodulation : journal of the International Neuromodulation Society 2008;11(1):66-73.

[36] Rigoard P, Basu S, Desai M, Taylor R, Annemans L, Tan Y, Johnson MJ, Van den Abeele C, North R. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. Pain 2019;160(6):1410-1420.

[37] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed) 2010;340:c332.

[38] Simopoulos T, Sharma S, Aner M, Gill JS. A Temporary vs. Permanent Anchored Percutaneous Lead Trial of Spinal Cord Stimulation: A Comparison of Patient Outcomes and Adverse Events. Neuromodulation : journal of the International Neuromodulation Society 2018;21(5):508-512.

[39] Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, Kessels AG, van Kleef M. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes care 2014;37(11):3016-3024.

[40] Thomson S, Huygen F, Prangnell S, De Andrés J, Baranidharan G, Belaïd H, Berry N, Billet N, Cooil J, De Carolis G, Demartini L, Eldabe S, Gatzinsky K, Kallewaard J, Meier K, Paroli M, Stark A, Winkelmüller M, Stoevelaar H. Appropriate referral and selection of patients with chronic pain for Spinal Cord Stimulation: European consensus recommendations and e-health tool. European Journal of Pain 2020;In press.

[41] Thomson SJ, Kruglov D, Duarte RV. A Spinal Cord Stimulation Service Review From a Single Centre Using a Single Manufacturer Over a 7.5 Year Follow-Up Period. Neuromodulation : journal of the International Neuromodulation Society 2017;20(6):589-599.

[42] Torrance N, Lawson KD, Afolabi E, Bennett MI, Serpell MG, Dunn KM, Smith BH. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? Pain 2014;155(10):1996-2004.

[43] Torrance N, Smith BH, Lee AJ, Aucott L, Cardy A, Bennett MI. Analysing the SF-36 in population-based research. A comparison of methods of statistical approaches using chronic pain as an example. Journal of evaluation in clinical practice 2009;15(2):328-334.

[44] Weinand ME, Madhusudan H, Davis B, Melgar M. Acute vs. Prolonged Screening for Spinal Cord Stimulation in Chronic Pain. Neuromodulation : journal of the International Neuromodulation Society 2003;6(1):15-19.

FIGURE LEGENDS

Figure 1. Trial profile

Table 1. Margins of error of estimation

Diagnostic performance	Sensitivity*	Specificity*
100%	8.9%	30.9%
80%	15.7%	35.5%
60%	16.7%	33.8%
40%	15.2%	37.9%

*Assuming 40/50 patients have ≥50% pain-relief @six-months

Table 2. Baseline characteristics and outcome scores

	TG **(n = 54)**	**NTG** **(n = 51)**	**Both groups** **(n = 105)**
Age, mean (SD)	49.4 (12.6)	51.5 (10.9)	50.4 (12.0)
Gender, male n (%)	22 (41)	22 (43)	44 (42)
Cause of pain, n (%) *(Primary diagnosis)*			
CRPS type I	8 (15)	1 (2)	9 (9)
CRPS Type II	1 (2)	2 (4)	3 (3)
Radiculopathy	8 (15)	12 (23)	20 (19)
Arachnoiditis	1 (2)	0 (0)	1 (1)
Chronic Post Surgery Pain	6 (11)	2 (4)	8 (8)
Neuropathic low back pain	5 (9)	4 (8)	9 (9)
FBSS	28 (52)	28 (55)	56 (53)
Other	9 (17)	13 (25)	22 (21)
Duration of pain (months), mean (SD)	108 (98)	128 (100)	117 (99)
Previous surgery relevant to the pain, n (%) *(Pain Aetiology classification)*	24 (44)	25 (49)	49 (47)
Surgery	15 (28)	17 (33)	32 (31)
Medical condition	3 (6)	3 (6)	6 (6)
Road Traffic Accident	15 (28)	9 (18)	24 (23)
Other – trauma, accident (work related/ falls etc)	3 (6)	5 (10)	8 (8)

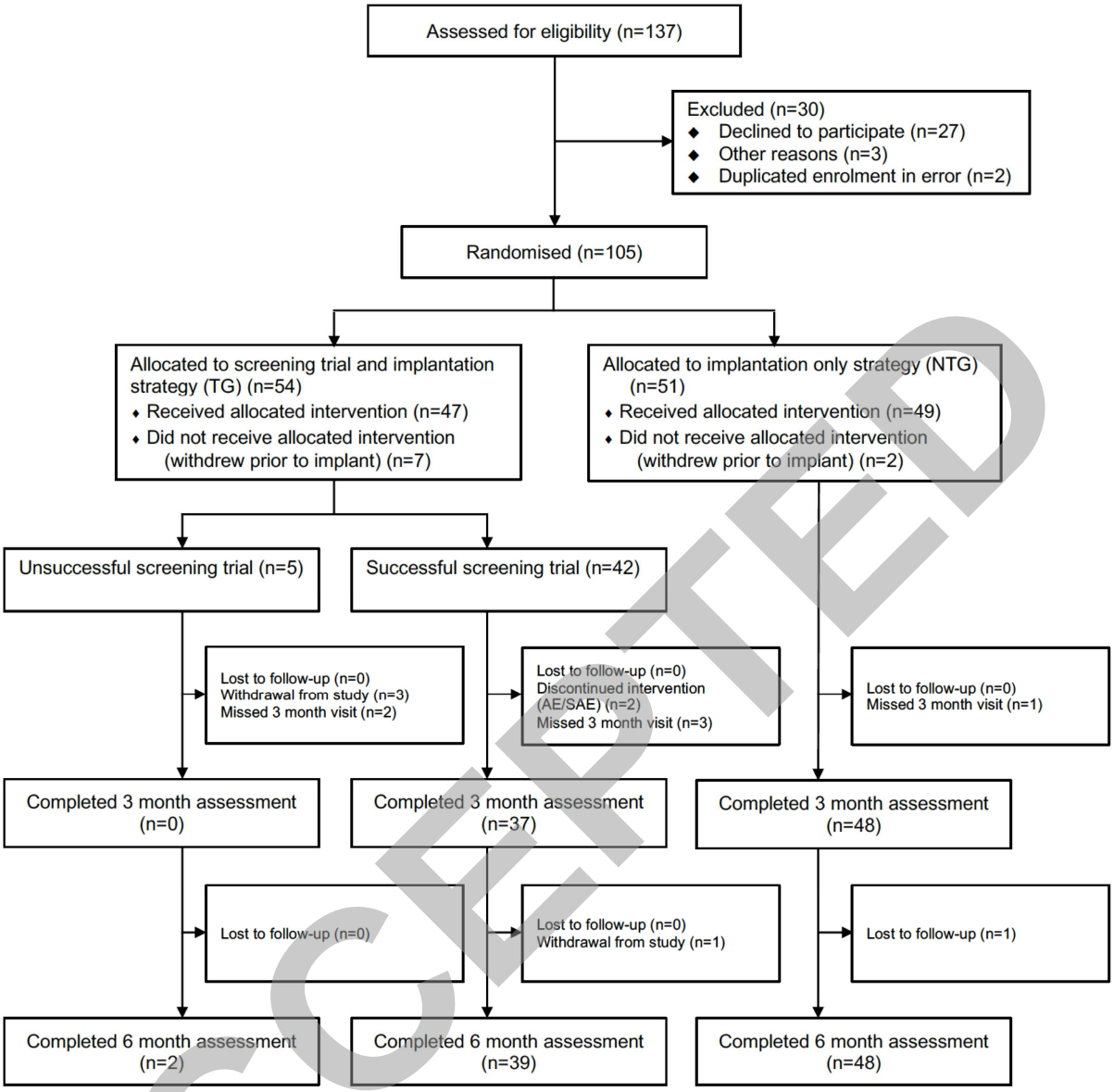
Other			
Pain medication intake, n (%)			
Analgesics	53 (98)	50 (98)	103 (98)
Anti-depressants	47 (87)	45 (88)	92 (88)
(Tricyclics/Tetracyclics/SSRIs)	40 (74)	38 (74)	78 (74)
Anticonvulsants	17 (31)	23 (45)	40 (38)
Muscle relaxants	44 (81)	39 (76)	83 (79)
NSAIDS	48 (89)	45 (88)	93 (89)
Opioids (transdermal/oral etc)	6 (11)	8 (16))	14 (13)
Sedatives	6 (11)	8 (16)	14 (13)
Steroids	12 (22)	8 (16)	20 (19)
Transdermal anaesthetics	6 (11)	3 (12)	9 (9)
Others			
Pain NRS, mean (SD)	7.5 (1.1)	7.5 (1.1)	7.5 (1.1)
ODI, mean (SD)	56.1 (13.6)	57.6 (14.9)	56.9 (14.2)
EQ-5D index, mean (SD)	0.32 (0.22)	0.30 (0.24)	0.31 (0.23)

Table 3. Clinical effectiveness – primary complete case analysis of primary and secondary outcomes at 6-months follow up

	TG (n=41)		NTG (n=48)		Between group difference	
	Baseline Mean (SD) or n/N	Follow up Mean (SD) or n/N	Baseline Mean (SD) or n/N	Follow up Mean (SD) or n/N	Mean difference or Odds ratio (95% CI)	P-value
Primary outcome						
Pain NRS: clinic	7.5 (1.1)	4.3 (2.4)	7.5 (1.1)	4.5 (2.5)	0.2 (-1.2 to 0.9)	0.74
Secondary outcomes						
Pain NRS: 4 day	7.3 (1.1)	4.1 (2.4)	7.4 (0.9)	4.8 (2.6)	0.3 (-0.8 to 1.4)	0.60
Pain relief ≥50%	-	15/41 (37%)	-	19/48 (40%)	1.2 (0.4 to 1.7)	0.73
Pain relief ≥30%	-	23/41 (56%)	-	28/48 (58%)	1.3 (0.5 to 3.2)	0.55
EQ-5D-5L	0.32 (0.22)	0.57 (0.24)	0.30 (0.24)	0.53 (0.27)	-0.06 (-0.16 to 0.04)	0.23
PGIC	-	38/39 (97%)	-	41/47 (87%)	0.2 (0.0 to 2.6)	0.20
ODI	56.1 (13.6)	36.2 (18.4)	57.6 (14.9)	41.4 (23.4)	1.7 (-5.8 to 9.2)	0.65

Table 4. Diagnostic performance of test screen – observed data

3-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	17	20	37
Trial screen negative	0	0	0
Totals	17	20	37
Sensitivity (%)	100 (95% CI: 80 to 100)		
Specificity (%)	0 (95% CI: 0 to 17)		
Positive Likelihood Ratio	1.00 (95% CI: 1.00 to 1.00)		
Negative Likelihood Ratio	Not calculable		
Positive Predictive Value (%)	46 (95% CI: 46 to 46)		
Negative Predictive Value (%)	Not calculable		
6-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	15	24	39
Trial screen negative	0	2	2
Totals	15	26	41
Sensitivity (%)	100 (95% CI: 78 to 100)		
Specificity (%)	8 (95% CI: 1 to 25)		
Positive Likelihood Ratio	1.08 (95% CI: 0.97 to 1.21)		
Negative Likelihood Ratio	0.00		
Positive Predictive Value (%)	38 (95% CI: 36 to 41)		
Negative Predictive Value (%)	100		


Assessed for eligibility (n=137)
Excluded (n=30)
Declined to participate (n=27)
Other reasons (n=3)
Duplicated enrolment in error (n=2)
Randomised (n=105)
Allocated to screening trial and implantation strategy (TG) (n=54)
Received allocated intervention (n=47)
Did not receive allocated intervention (withdrew prior to implant) (n=7)
Allocated to implantation only strategy (NTG) (n=51)
Received allocated intervention (n=49)
Did not receive allocated intervention (withdrew prior to implant) (n=2)
Unsuccessful screening trial (n=5)
Successful screening trial (n=42)
Lost to follow-up (n=0)
Withdrawal from study (n=3)
Missed 3 month visit (n=2)
Lost to follow-up (n=0)
Discontinued intervention (AE/SAE) (n=2)
Missed 3 month visit (n=3)
Lost to follow-up (n=0)
Missed 3 month visit (n=1)
Completed 3 month assessment (n=0)
Completed 3 month assessment (n=37)
Completed 3 month assessment (n=48)
Lost to follow-up (n=0)
Lost to follow-up (n=0)
Withdrawal from study (n=1)
Lost to follow-up (n=1)
Completed 6 month assessment (n=2)
Completed 6 month assessment (n=39)
Completed 6 month assessment (n=48)