Full Title: A randomised double-blinded sham controlled cross-over trial of tined lead sacral nerve stimulation testing for chronic constipation

Running head: Sacral nerve stimulation for constipation

Authors

Yan Yiannakou[1]; Kevin Etherson[2]; Helen Close[3]; Adetayo Kasim[4]; Mark Mercer-Jones[5]; Stefan Plusa[6]; Rebecca Maier[7]; Susan Green[8]; Jeremy Cundall[8]; Charles Knowles[9]; James Mason[10].

1 Consultant Neurogastroenterologist, County Durham and Darlington NHS Foundation Trust, Durham, UK

2 Consultant Colorectal Surgeon, North Tees & Hartlepool NHS Foundation Trust, Stockton, UK

3 Health Research Methodologist, Institute of Health and Society, Newcastle University, UK

4 Senior Statistician, Durham University, Durham, UK

5 Consultant Colorectal Surgeon, Gateshead Health Foundation Trust, Gateshead, UK

6 Consultant Colorectal Surgeon, Newcastle University Teaching Hospitals, Newcastle, UK

7 Deputy Lead for Clinical Trials & Engagement, Newcastle Clinical Trials Unit, Newcastle University, UK

8 Consultant General and Colorectal Surgeon, County Durham and Darlington NHS Foundation Trust, Durham, UK

9 Professor of Surgery and Hon Consultant Colorectal Surgeon, Queen Mary University of London, London, UK

10 Professor of Health Economics, Warwick Medical School, Warwick University, Warwick, UK

Corresponding author[1]: yan.yiannakou@nhs.net

Abstract

Objectives

Sacral nerve stimulation (SNS) may provide long-term symptom relief to patients suffering chronic constipation. Patients are currently selected for SNS using a 2-week peripheral nerve evaluation (PNE) comprising stimulation via temporary leads. However, only 40% of test responders receive long-term benefit from treatment meaning that healthcare costs per successfully treated patient are too high. The primary objective was to assess tined-lead testing to predict benefit from SNS for chronic constipation.

Methods

A randomised double-blind sham-controlled cross-over design evaluated enhanced PNE (ePNE) using tined quadripolar electrode leads over 6 weeks. The design differentiated between patients with discriminate and indiscriminate responses to testing. *A score improvement of 25% or more was considered to be a positive response within a stimulation period.* The primary outcome was the proportion of patients demonstrating a reduction ≥ 0.5 in constipation symptom score (PAC-SYM) at 6 months.

Results

A total of 45 patients were randomised, of whom 29 (64.4%) were test-phase responders. Of these, 27 were implanted providing permanent SNS. During ePNE, 7 (18%) were discriminate responders, 22 (56%) were indiscriminate responders and 10 (26%) were non-responders. Six patients were withdrawn during the test phase due to infection or non-compliance. At 6 months, there was no significant difference in primary outcome between discriminate and indiscriminate responders (60% vs 57%, p=0.76). The study was terminated prematurely due to a persistent *infection rate of 10 (22%) during ePNE of which 9 (20%) were severe.*

Conclusions

ePNE is a poor predictor of treatment response at 6 months. This suggests a strong and persistent placebo response during both SNS PNE and treatment. An extended 6 week PNE poses a high risk of infection.

Keywords: tined lead testing; sacral nerve stimulation; chronic constipation

Introduction

Chronic constipation (CC) is present in 12-17% of the population [1] and, when mild, is readily managed in community settings. However, a cohort of refractory patients have severely impaired quality of life [2] leading to significant socio-economic costs [3,4]. Some of these patients fail to respond to conservative therapies and require resectional surgical procedures which are associated with high complication rates and uncertain efficacy [5,6].

Sacral nerve stimulation (SNS), usually involving a temporary test followed by permanent implantation of a tined lead connected to a pulse generator, has been proposed as a less invasive treatment for patients with CC. In the UK SNS is approved for both faecal incontinence and urological dysfunction [7,8] but has insufficient evidence to support routine use for CC where the majority of studies have been retrospective. Early cohort studies in CC showed high response rates (87-90%) [9-11], but more recent studies have been less positive (33-61% response rates) [12,13]. One very recent high quality prospective study has suggested a very low response rate (19%) [14], though all patients were implanted as temporary testing was felt to be non-discriminatory and had been shown in a previous study to be compounded by a placebo effect [15].

Patients undergoing SNS have traditionally been selected with a 2-3 week temporary test (percutaneous nerve evaluation, PNE) involving the insertion of a temporary lead which has a single non-tined electrode. There has been a move to use a (permanent) tined lead as part of a two-stage, single lead procedure for urological disorders; the testing lead remains in place as the definitive treatment lead giving hypothetically better discrimination by allowing a longer duration of testing, more electrodes, and remaining consistent in position [16,17]. Unfortunately this may still not differentiate a true therapeutic response from a placebo effect.

The basis for a further trial was that a) an enhanced testing period could identify and exclude placebo responses and b) even if a relatively small proportion of patients were accurately and reliably identified as responsive during testing, this would promote effective and cost-effective selection of patients for long-term treatment. We planned a six-week testing phase with sub-sensory ACTIVE/SHAM stimulation periods with long-term follow-up to 6 months. The overall aim of the study was to determine whether blinded sub-sensory tined lead testing could correctly predict 6-month treatment response after SNS implantation. We hypothesised that a discriminant response during ePNE would lead to a higher proportion of patients defined as long-term responders (i.e. those demonstrating a reduction of 0.5 or more in a patient assessment of constipation symptoms score [PAC-SYM]) when compared to those demonstrating an indiscriminate response.

Methods

Trial design

The TiLTS trial used a randomised double-blind sham-controlled 2-period cross-over design to assess response to temporary stimulation. The cross-over design alternated each patient between ACTIVE and SHAM sub-sensory stimulation periods of 2 weeks with a central 2 week washout (6 weeks in total). Patients were randomised [using a permuted block to ensure equal allocations] in a 1:1 ratio [stratified by sites] to either group A [ACTIVE (1) - SHAM (0)] or group B [SHAM (0) - ACTIVE (1)] order of sacral nerve stimulation during the testing ePNE phase of the trial, and were told that either or both periods may be active.

Responders to each stimulation period were assessed using a simple visual analogue scale: TiLTS-VAS score. This scale was a 0-100 visual analogue scale of patients' self-assessment of the effectiveness of the testing period in improving their symptoms. This score was assessed at the end (day 14) of each 2 week period including the washout. A score improvement of 25% or more was considered to be a positive response within a stimulation period. This low threshold was chosen to ensure adequate numbers of patients were implanted.

Based on their response to the two stimulation periods (ACTIVE and SHAM) patients were classified as discriminate responder (response to active only), indiscriminate responder (response to SHAM +/- ACTIVE) or non-responder (see figure 1).

At the end of testing, patients classified as non-responders underwent removal of tined lead while those classified as discriminate or indiscriminate responders proceeded to implantation of the Interstim 2 [Medtronic US, model 3058] implantable pulse generator (IPG) with permanent supra-sensory sacral nerve stimulation. Patients with an IPG underwent follow-up assessments at 3 months while all patients (with or without IPG) underwent follow-up assessments at 6 months (Figure 2: patient flowchart).

Patients

Adult patients presenting for treatment of refractory idiopathic CC (using the ROME III criteria for functional constipation [18]) were recruited and consented. These patients represented treatment refractory cases who had failed medical treatments including multiple laxatives, prucalopride and minimally invasive treatments such as trans-anal irrigation and biofeedback therapy. Patients with concurrent diseases that could affect treatment including progressive neurological disease, or unstable doses of anti-cholinergic, iron supplements, antidepressants, or opioid medication, were excluded. Patients underwent defecating proctography as part of standard care to exclude obstructing ano-rectal conditions. *All patients had transit studies and*

defecating proctograms. Patients with obstructed defecation were excluded. Baseline data were recorded including demographics, relevant medical history and quality-of-life (QOL). Patients were recruited from three sites in the North-East of England. Two other sites which planned to recruit failed to do so due to local withdrawal of funding of the procedure.

Interventions

The surgical technique for the trial was standardised at protocol inception during an investigators meeting. Surgeons at each site were experienced at SNS placement (>100 procedures) and agreed common practice on the correct positioning of the tined lead and IPG using standard and established aseptic techniques. Identification of significant infection rates during the trial led to a thorough review and consultation about aseptic procedures. This review included independent microbiological review of the literature and culture results; a detailed root cause analysis of infected cases looking at factors such as surgical technique and preparation, and interviews with staff and experts. Changes were made across all centres, however infections continued to be reported following these changes (described below).

Patients were admitted as a day case and all procedures were performed under general anaesthesia with prophylactic intravenous antibiotics administered. This was originally Gentamycin 80mg IV within 60 minutes of skin incision. Following early participant infections and further expert microbiology advice this was changed to either [depending on MRSA status and allergies] Flucloxacillin 1G IV and Gentamycin 120mg IV, or Teicoplanin 400mg IV and Gentamycin 120mg IV within 60 minutes of skin incision. The patient was positioned by the surgeon in the prone position. A 5mm transverse incision was made over the sacrum at the level of the 3rd foramina to aid tined lead insertion and tunnelling of an adequate length of tined lead for later IPG connection. All implantable materials were soaked in Gentamycin solution. Under image intensified fluoroscopic guidance the testing trochar was inserted into the S3 foramina, and the side with the strongest low voltage anal motor response (bellows response) selected. The tined lead was inserted into the 3rd sacral foramina unilaterally and position confirmed by fluoroscopic visualisation and pulse stimulation of all 4 electrodes resulting in the correlating bellows response. The tined lead was tunnelled ipsilaterally to the buttock where a subcutaneous pocket (for future IPG) was formed for connection to an extension lead. This lead was exited on the contralateral side to minimise infection risk by ensuring an adequate tunnel length to the potential IPG pocket. The wounds were closed with absorbable sutures to the fat and subcuticular layers, and a 3M™ Tegaderm™ dressing applied to the wounds and wire to minimise infection risks. The external component of the exit lead was anchored to the skin with another dressing to prevent traction on the exit site.

Participants classed as test responders proceeded to IPG implantation and connection of in-situ tined lead as follows; prophylactic intravenous antibiotics were administered as before. The lateral (potential IPG site) buttock incision was re-opened and a suitable cavity dissected to contain the IPG. This was the ipsilateral side of the internally tunnelled tined lead. The extension lead was disconnected and discarded after removal via the exit site, with careful attention not to contaminate the IPG pocket. The tined lead was connected to the IPG (Interstim 2, Medtronic model 3058) in the usual manner, and both soaked in Gentamycin solution. The wound was closed with absorbable sutures to the fat and subcuticular layers and a dressing applied. Local anaesthetic was injected around the wound edges to aid with post-operative analgesia.

Blinding procedures

All investigators, the research fellow and participants were blinded to group allocation. Only the trials unit and a delegated un-blinded member of the research team at each centre were privy to the groupings. The blinding required the delegated team member to modify the test box at the appropriate time intervals during testing, and prohibited the investigators and research fellow from being involved in this process. Suitable training was provided to the delegated team member on stimulator box adjustment before commencing the trial. The un-blinded delegated team member performing test box adjustments was excluded from any other data collection as part of the trial. The blinded team members collected the assessment forms from the patient at the adjustment intervals, which were then used to complete CRFs and interpret response according to the TiLTS-cc VAS. Blinded researchers were aware of response, but blinded as to whether this was a discriminate or indiscriminate response.

Patients were blinded successfully through use of subsensory stimulation. Their threshold of stimulation perception was evaluated at each adjustment interval and a 5 minute period of nerve habituation was performed at this level. The habituated sensory threshold was then re-evaluated and the active subsensory stimulation was set to 75% of this threshold to guarantee a true subsensory test. The stimulator was then sealed with a unique sequential alphanumeric security seal to ensure the device could not be tampered with (by the participant or blinded team members through battery removal or device adjustment); seal voiding excluded patient data from the final analysis.

External test stimulators (Medtronic models 3625 and 3531)

During trial setup it was observed by the research team that the original analogue Medtronic testing SNS stimulator commonly referred to as “the brown box” by clinicians (model 3625), was unacceptably variable in its output waveform. An internal quality review[19] found wide variability in device (new and re-used)

stimulation parameters using a cross calibrated oscilloscope (Tektronix model 2230) and counter-timer (Black Star Apollo 100). Consequently all model 3625 devices were accurately calibrated prior to each use. An identical study[20] [4] of the stimulation parameters of the "Verify" (model 3531) found this new digital device to be 4 orders of magnitude less variable, and as such was selected as the sole study testing device once obtained. All patients in the study used this "Verify" model.

Outcome measures

The primary endpoint was the proportion of patients demonstrating a reduction of 0.5 or more in a patient assessment of constipation symptoms score (PAC-SYM) at 6 months. *The 12-item PAC-SYM questionnaire is divided into three symptom subscales: rectal (three items); abdominal (four items) and stool (five items). Items are scored on 5-point Likert scales, with scores from 0 to 4 (0 'symptom absent' - 4 'very severe'). A mean total score from 0-4 is generated by dividing the total score by the number of questions completed; the lower the total score, the lower the symptom burden [21].* Secondary endpoints included number of discriminant and non-discriminant responders, scores from daily diary exercises, quality of life (measured using PAC-QOL, EQ-VAS, TilTS-VAS and Euro-QOL-5D), and constipation symptoms scores (Cleveland clinic questionnaire and Wexner Score).

Adverse events

Patients were monitored for procedure-related adverse events and complications. Adverse events were recorded from the beginning of day 1 of trial intervention, until completion of phase 3. These were reviewed on a regular basis by an independent data monitoring committee. Adverse events were summarised and tabulated.

Sample Size

From audit data, we estimated that 40% of patients would have a discriminate response to testing, and 70% of those would continue to benefit at 6 months. For the 60% of patients with an indiscriminate response, we estimated 20% would respond at 6 months. Assuming 90% power, alpha = 5%, and an allocation ratio of 1:1.5, the trial sample size required for responders was 50. Allowing for loss to follow-up of 20% the required sample size was 60 responders. Assuming 20% of patients failed to respond, the sample size (of responders and non-responders) required was 75.

Statistical analyses

All analyses of the continuous efficacy endpoints were based on mixed effects models. Study groups were tested at the 2-sided 5% significance level. All analyses of binary endpoints were based on logistic regression for primary endpoint and

generalised estimating equations for secondary binary endpoints. Analysis was performed in SAS® 9.4 and R v3.2.3.

Trial registration

The trial was registered with the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) with a registration number ISRCTN44563324 (http://www.isrctn.com/ISRCTN44563324).

Ethical approval

The study was approved by the NRES Committee North East-York, REC reference number 12/NE/0228 on 24/08/2012. A Trial Steering Committee provided study oversight and an independent Data Monitoring Committee met to review data regularly throughout the study.

Results

The trial was terminated prematurely due to a persistent and unacceptably high serious infection rate (see below). A total of 45 patients were randomised from the target of 75. Data on all randomised patients are shown in table 1. Of the total, 43 (96%) were female with a median age of 40yrs (range: 18yrs to 68yrs) and a median duration of constipation symptoms of 18yrs (range: 3yrs - 45yrs). At baseline, patients had a high constipation symptom burden (PAC-SYM mean score 2.19 ±0.86; PAC-QoL mean score 2.70 ±0.82), *the majority had slow transit (n=30; 67%)* and high comorbidity; a total of 37 (82%) patients had at least one co-morbidity with a median of 2 (range: 1-9) patients per co-morbidity. The most common reported co-morbidities were anxiety and depression.

Response to interventions

10 patients (26%) were non-responders (table 2) and were not implanted in accordance with the protocol. A total of 6 patients were withdrawn during ePNE (1 due to non-compliance, and 5 due to lead site infection. Twenty-nine patients (29/45: 64.4%) were responders to the testing phase. Of these, 7 (18% total) were discriminate responders and 22 (56% total) were indiscriminate responders. Of the 29 responders, 27 were implanted with a permanent IPG (2 were not implanted; 1 patient declined and 1 had a lead site infection precluding implantation) (Fig 2: patient flow chart).

Clinical outcomes

A total of 33 patients were followed up to 6 months (see figure 2). A total of 15 (57.7%) patients with IPG responded to SNS treatment at 6 months based on the primary endpoint. Five patients (71.4%) without IPG also showed a reduction of more than 0.5 in PAC SYM score. The Quality of life score (PAC-QOL) improved at 12 weeks but deteriorated at 6 months follow-up (figure 3), while other scores (Cleveland and Wexner) showed improvements at 6 months (figure 4). Table 3 suggests small improvements in constipation symptoms among patients with IPG.

Prediction of 6 month clinical outcome.

At 6 months there was no significant difference between discriminate and indiscriminate responders (60% vs 57%, p=0.76) in meeting the primary endpoint (≥0.5 point reduction in PAC SYM score, Table 4).

The TiLTS VAS score at 2 and 6 weeks during ePNE was evaluated as a prognostic measure for response at 6 months (PAC-SYM) but failed to identify patients more likely to benefit from SNS treatment (active - sham: 3% 95%CI: -45% to 51%). TiLTS VAS did not discriminate well between responders and non-responders at 6 months: Sensitivity = 75.0% (95% CI: 56.0% to 94.0%), Specificity = 15.4% (95% CI: 0.0% to 35.0%), Positive Predictive Value = 57.7% (95% CI: 38.7 to 76.7%), Negative Predictive Value = 28.6% (95% CI: 0.0%-62.0%), (Table 5). The failure to discriminate between the active and sham phases is illustrated in Figure 5.

A key design feature was the sub-sensory, blinded stimulation. Figure 6 shows no significant differences during the testing phase by timing or sequence confirming that blinding was successful.

Adverse events

During testing and follow-up phases, there were a total of 103 adverse events experienced by 40 (89%) patients, of which 56 events were considered related to the trial (Table 6). Of the related events, 11 were severe. There were a total of 10 infections, of which 9 were severe and led to urgent removal of the tined lead during testing phase (n=6, 13% of 45) or IPG (n=3, 11% of 27). The one superficial infection responded to treatment during the testing phase. Of the 3 infections affecting those with IPGs, all were late (>4 months following implantation) with one identified at the 6-month follow-up. Changes in surgical practice failed to reduce the infection rate.

Two patients became pregnant during the study contrary to protocol and participant information sheet advice; both resulted in live births of which one has a diagnosis of atrial septal defect, ventricular septal defect and pulmonary stenosis.

Discussion

The initial enthusiasm for SNS in constipation produced by early studies has been tempered by later reports suggesting very low response rates. Most recently two prospective randomised studies have been completed [14, 22] showing poor response rates and no difference between sham and active intervention for primary outcomes. These findings have mirrored both our own clinical experience in over 50 patients followed over 3-4 years (unpublished audit data*) and also findings from recent systematic reviews of SNS for both constipation and faecal incontinence [23,24].* If there were effective alternative treatments for these patients there would be little benefit from further study. But patients considered for SNS are, by definition, refractory to all other conservative measures and have symptoms which produce a major impact on well-being. Thus, even if a minority of patients benefit, the treatment would be a valuable therapeutic option if long term responders could be accurately identified by temporary testing. The predictive value of temporary testing seems reasonable in faecal incontinence [25], but possibly less effective in patients with constipation. We sought to design a testing process which could be used in routine clinical practice and which would differentiate placebo and therapeutic response.

The profiles of patients on SHAM and ACTIVE stimulation periods were similar, suggesting that blinding was successful. The results confirmed what is already known: that subjective assessment of response (in this case through a visual analogue scale) is a poor predictor of long term outcome. In this study we used a low threshold (25% improvement) to determine patients who would receive an implanted device. This was to make sure enough patients were implanted and allow for that fact that temporary testing might give false negatives as well as false positives. A post-hoc analysis was conducted looking at those patients who had scored 50% or more on the VAS – a more typical threshold for decision to implant – but this analysis (not shown) did not alter our conclusions *(Table 7&8).*

The analysis of discriminate and indiscriminate responses was disappointing. In fact 21/26 (81%) of implanted patients had indiscriminate responses (i.e. had responded to the SHAM stimulation) and importantly discriminate responses were no better at identifying improved long term response. Possible causes for this are that sub-sensory stimulation is inadequate as a test of response, or that the long term responses are themselves prolonged placebo responses.

The trial was terminated early due to a high and persistent infection rate, precluding conclusions about overall efficacy and completion of planned analyses of secondary outcomes and health economic analysis.

Fifteen (56%) implanted patients were responders at six months according to a 0.5 point drop in PAC-SYM. This may be challenged as most studies using PAC-SYM have used a -1.0 point change to denote response. A recent study has shown that

the minimum clinically important difference for PAC-SYM is -0.65 [21]. Thus, the proportion of responders we report is very much an upper limit both in terms of threshold of response and the fact that this was assessed at 6 months, beyond which we would expect some drop-off in effect as shown in the study by Patton et al [14]. These factors undermine further the responder rate, which is relatively modest, and suggest that a valuable treatment response is unlikely. The mean values for changes to outcome variables (PAC-SYM, PAC-QOL, EQ5D, EQVAS and Cleveland Clinic Score) were modest and imprecise. The mean PAC-QOL was most improved at 3 months and then deteriorated at 6 months, possibly suggesting a drop-off of effect, chance effect, or a placebo response.

The infection rate (22%) was higher than expected and most infections were severe. This led to a thorough review of aseptic procedures (including external consultation), expert review of antibiotic prophylaxis and a root cause analysis of the first 8 infections. The stringency of surgical aseptic procedures and antibiotic prophylaxis were increased and appropriate amendments made to the study protocol. Despite these, further infections occurred and the Chief Investigator and Trial Steering Committee decided to terminate the study. *The infection rate in patients having SNS for faecal incontinence in the sites undertaking the TiLTS trial is <3%. This was audited during the time of the study as part of the root cause analysis and confirmed to be low. The method of percutaneous testing for faecal incontinence used the standard 2-week test period, with explanting of the temporary lead and re-implantation of a tined lead for permanent stimulation. It follows that the cause of the high infection rate seen in the TiLTS study was related to the prolonged use of percutaneous lead testing.*

Initial studies of single lead 2-stage tined lead testing have focussed on efficacy [16,17] with little mention of adverse events, but a larger and more recent study has emphasized a higher rate of infection, reported to be 12% [26]. Our experience leaves cause for concerns about the safety of tined lead testing, which is now becoming more popular in clinical urological practice. There is a possibility that a single lead procedure will always pose a higher risk as the lead is externalised for a period of time and so can become sub-clinically contaminated, leading to infection at a later time. Dudding and Vaisy [27] sought to understand this risk by culturing the tip of temporary stimulation leads which had been in place for a mean of 21 days and found that 7/13 (54%) were colonised by bacteria.

Our study has a number of limitations. The early cessation of the trial, with 45 patients recruited, was 30 patients short of the target and has meant that definitive conclusions on long term efficacy are tentative. The predictive failure of discriminate testing could be related to the cut-off used to denote a test responder.

Despite these reservations the data are in keeping with the most recent prospective studies, suggesting that SNS is not likely to be effective in the management of

constipation and that high placebo response rates occur in temporary testing, irrespective of attempts to reduce this. Importantly we have found a very high infection rate using 6-week tined lead temporary stimulation despite considerable attempts to reduce this risk. We believe that the extended use of tined lead testing requires further safety assessment before widespread use.

Acknowledgements

The study team wish to acknowledge the collaborators in this study: Professor Graeme Duthie, Mr Varma Jag; the hospital research teams that supported them; County Durham and Darlington NHS Foundation Trust, Barts Health NHS Trust, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Gateshead Health NHS Foundation Trusts for infrastructural support. In addition, we wish to thank staff at Durham Clinical Trials Unit, Jennifer Wilkinson and Catherine Frost; independent members of the Study Steering Committee, Mike Bramble (Chair), Adam Farmer, Virginia Aken; the Data Monitoring Committee, Tim Butler (Chair), Karen Nugent, Colin Rees.

Conflicts of Interest and Source of Funding:

Prof Charles Knowles has served as a speaker, and a regular consultant for the Medtronic Global Expert Panel for GI/GU.

Medtronic Ltd (UK), manufacturers of SNS leads and neuromodulators supplied the tined leads for the study, but were not involved with study design, data collection or analysis.

This manuscript presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-1010-23212). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *The American journal of gastroenterology*. 2011 Sep 1;106(9):1582-91.
2. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Alimentary pharmacology & therapeutics* 2010;31(9):938-49 doi: 10.1111/j.1365-2036.2010.04273.x[published Online First: Epub Date]|.
3. Flik CE, Laan W, Smout AJ, Weusten BL, de Wit NJ. Comparison of medical costs generated by IBS patients in primary and secondary care in the Netherlands. *BMC gastroenterology*. 2015 Nov 26;15(1):1.
4. Yiannakou Y, Eugenicos M, Sanders DS, Emmanuel A, Whorwell P, Butt F, *et al*. Diagnosis and management of moderate-to-severe irritable bowel syndrome with constipation (IBS-C) in the UK: the IBIS-C study. *Gut.* 2015 Jun 1;64(Suppl 1):A323-.
5. Riss S, Herbst F, Birsan T, Stift A. Postoperative course and long term follow up after colectomy for slow transit constipation–is surgery an appropriate approach?. *Colorectal Disease*. 2009 Mar 1;11(3):302-7.
6. Dudekula A, Huftless S, Bielefeldt K. Colectomy for constipation: time trends and impact based on the US Nationwide Inpatient Sample, 1998–2011. *Alimentary pharmacology & therapeutics*. 2015 Dec 1;42(11-12):1281-93.
7. NICE. (2004). Sacral nerve stimulation for urge-incontinence and urgency-frequency IPG64. *National Institute of Clinical Excellence*, all.
8. NICE. (2010). Sacral nerve stimulation for faecal incontinence: guidance IPG99. *National Institute of Clinical Excellence*, All.
9. Kamm MA, Dudding TC, Melenhorst J, Jarrett M, Wang Z, Buntzen S *et al.* Sacral nerve stimulation for intractable constipation. *Gut* 2010;59(3):333-40
10. Sharma A, Liu B, Waudby P, Duthie G. Sacral neuromodulation for the management of severe constipation: development of a constipation treatment protocol. *Int J Colorectal Dis* 2011;26(12):1583-7.
11. Govaert B, Maeda Y, Alberga J, Buntzen S, Laurberg L, Baeten CG. Medium-term outcome of sacral nerve modulation for constipation. *Dis Colon Rectum* 2012;55(1):26-31.
12. Ortiz H, de Miguel M, Rinaldi M, Oteiza F, Altomare D. Functional outcome of sacral nerve stimulation in patients with severe constipation. *Dis Colon Rectum* 2012;55(8):876-80.
13. Graf W, Sonesson AC, Lindberg B, Akerud P, Karlbom U. Results after sacral nerve stimulation for chronic constipation. *Neurogastroenterol Motil* 2015;27(5):734-9.
14. Patton V, Stewart P, Lubowski DZ, Cook IJ, Dinning PG. Sacral Nerve Stimulation Fails to Offer Long-term Benefit in Patients With Slow-Transit Constipation. *Diseases of the Colon & Rectum.* 2016 Sep 1;59(9):878-85.
15. Dinning PG, Hunt L, Patton V, Zhang T, Szczesniak M, Gebski V, *et al*. Treatment efficacy of sacral nerve stimulation in slow transit constipation: a two-phase, double-blind randomized controlled crossover study. *The American journal of gastroenterology*. 2015 May 1;110(5):733-40.

16. Hetzer FH, Hahnloser D, Knoblauch Y, Löhlein F, Demartines N. New screening technique for sacral nerve stimulation under local anaesthesia. *Techniques in coloproctology*. 2005 Apr 1;9(1):25-8.
17. Spinelli M, Weil E, Ostardo E, Del Popolo G, Ruiz-Cerdá JL, Kiss G, *et al*. New tined lead electrode in sacral neuromodulation: experience from a multicentre European study. *World journal of urology*. 2005 Jul 1;23(3):225-9.
18. Drossman DA, Corazziari E, Delvaux M. Rome III: *The Functional Gastrointestinal Disorders*. 3rd edition.: McLean:Degnon Associates., 2006.
19. Etherson K, Davidson A, Yiannakou Y, Mason J. Surgeons-Don't Forget to Calibrate! Findings from a Sacral Nerve Test Stimulator. *Gut* 2013;62(Suppl 2):A27.3-A28 doi: 10.1136/gutjnl-2013-305143.64[published Online First: Epub Date]|.
20. Etherson KJ, Davidson A, Close H, Yiannakou Y, Mason JM. PTU-171 Calibration test findings of the new verify sns test stimulator. *Gut* 2015;64(Suppl 1):A138.2-A39 doi: 10.1136/gutjnl-2015-309861.286[published Online First: Epub Date]|.
21. Yiannakou Y, Tack J, Piessevaux H, Dubois D, Quigley EM, Ke MY, *et al*. The PAC-SYM questionnaire for chronic constipation: defining the minimal important difference. *Alimentary pharmacology & therapeutics.* 2017 Dec 1;46(11-12):1103-11.
22. Zerbib F, Siproudhis L, Lehur PA, Germain C, Mion F, Leroi A, *et al*. Randomized clinical trial of sacral nerve stimulation for refractory constipation. *Br J Surg.* 2016 Oct 25. doi: 10.1002/bjs.10326. [Epub ahead of print]
23. *Pilkington SA, Emmett C, Knowles CH, Mason J, Yiannakou Y; NIHR CapaCiTY working group; Pelvic floor Society. Surgery for constipation: systematic review and practice recommendations: Results V: Sacral Nerve Stimulation. Colorectal Dis. 2017 Sep;19 Suppl 3:92-100. doi: 10.1111/codi.13780. Review. PubMed PMID: 28960926.*
24. *Thaha MA, Abukar AA, Thin NN, Ramsanahie A, Knowles CH. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database Syst Rev 2015 Aug 24;8:CD004464.*
25. Altomare DF, Giuratrabocchetta S, Knowles CH, Muñoz Duyos A, Robert-Yap J, Matzel KE. Long-term outcomes of sacral nerve stimulation for faecal incontinence. *British Journal of Surgery.* 2015 Mar 1;102(4):407-15.
26. Guralnick ML, Benouni S, O'Connor RC, Edmiston C. Characteristics of infections in patients undergoing staged implantation for sacral nerve stimulation. *Urology.* 2007 Jun 30;69(6):1073-6.
27. Dudding T, Vaizey C. Bacterial colonization of stimulation electrode wires in patients undergoing temporary sacral nerve stimulation. *Colorectal Disease*. 2010 Feb 1;12(2):141-3.

Table 1: Trial Population Baseline Characteristics

1 PAC-SYM: Patient Assessment of Constipation-Symptoms

Characteristics	Number (%)	Mean ± SD	Median(Min-Max)
Total number	45 (100%)	-	-
Female	43 (96%)	-	-
Age	45 (100%)	40.9±13.5	40.0(18.0 - 68.0)
PAC SYM[1]	45 (100%)	2.19±0.86	
PAC QoL[2]	45 (100%)	2.70±0.82	
EQ-VAS[3]	45 (100%)	50.93±18.40	
EQ-5D[4]	40 (89%)	0.48±0.37	
Duration of constipation symptoms	45 (100%)	17.64±11.14	18.0(3.0 – 45.0)
Currently treated for constipation	42 (93%)	-	-
Other comorbid conditions	37 (82%)	2.81±1.96	2.0 (1.0 – 9.0)
Current Mental ill-health	13 (29%)	-	-
Previous Appendicitis	7 (16%)	-	-
Endometriosis	4 (9%)	-	-

2 PAC QoL: Patient Assessment of Constipation Quality of Life questionnaire

3 EQ-VAS: Quality of Life Visual Analogue Scale

4 EQ-5D: Quality of Life Questionnaire

Table 2: Response to active/sham testing (n=39[1])

Active	Sham	Response	N[1]
+	-	Discriminate	7
+	+	Indiscriminate	18
-	+	Indiscriminate	4
-	-	No response	10

[1]6 withdrawals prior to end of 6 week testing period

Table 3: Secondary outcomes comparing difference from baseline at 2, 4, 6, 12 and 24 weeks FOR IPG PATIENTS ONLY (n=27)

	Weeks (mean score (95% CI)				
Outcome	2	4	6	12	24
PAC SYM[1]	-0.57(-0.86,-0.27)	-0.45(-0.75, -0.15)	-0.85(-1.15, -0.54)	-1.03(-1.39, -0.07)	-0.69(-1.00, -0.37)
PAC QOL[2]					
ALL				-0.84(-1.19, -0.48)	-0.50(-0.82, -0.17)
Physical				-1.56(-2.13, -0.98)	-0.62(-1.14, -0.10)
Psychosocial				-1.10(-1.64, -0.56)	-0.68(-1.18, -0.19)
Worries				-1.22(-1.70, -0.75)	-0.66(-1.10, -0.22)
Satisfaction				-0.98(0.61, 1.35)	0.27(-0.09, 0.62)
EQ5D[4]				0.21(0.03, 0.38)	0.10(-0.05, 0.25)
EQVAS[3]				15.5(3.13, 27.87)	3.77(-8.34, 15.88)
Cleveland					-0.54(-0.76, -0.32)

1 PAC-SYM: Patient Assessment of Constipation-Symptoms

2 PAC QoL: Patient Assessment of Constipation Quality of Life questionnaire

3 EQ-VAS: Quality of Life Visual Analogue Scale

4 EQ-5D: Quality of Life Questionnaire

Table 4: Response to SNS at 6 months (PAC SYM >=0.5) according to discriminate/indiscriminate response at 6 weeks (n=26)

TiLTS-cc_VAS Classification	Reduction in PAC SYM >= 0.5		**Total**
	Responder (%)	Non-Responder (%)	
Discriminate Responder	3(60.0)	2(40.0)	**5**
Indiscriminate Responder	12(57.1)	9(42.9)	**21**
RD = 0.03(-0.45, 0.51), P-value = 0.7586			

Table 5: Response at 6 months comparing TiLTS-cc-VAS with PAC SYM for IPG patients

TiLTS-cc_VAS Classification	Reduction in PAC SYM >= 0.5		**Total**
	Responder (%)	Non-Responder (%)	
Responder	15(57.7)	11(43.3)	**26**
Non Responder	5(71.4)	2(28.6)	**7**
Sensitivity(%) = 75.0(56.0, 94.0), Specificity(%) = 15.4(0.0, 35.0) PPV(%) = 57.7(38.7, 76.7), NPV = 28.6 (0.0, 62.0)			

Table 6: Adverse events according to severity

Category	**Number of events**	**Number of patients (%)**
Adverse events (All)	103	40 (89%)
Related to study intervention	56	40 (89%)
Severe and related	11	11 (24%)
Infections (related)	10	10 (22%)
Severe infections leading to tined lead removal during testing phase	6	6 (13%)
Severe infections leading to IPG removal during follow-up	3	3 (7%)

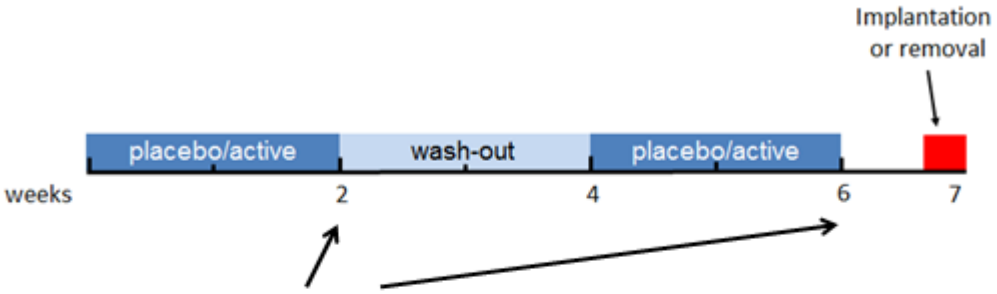
Table 7: Response to SNS at 6 months (PAC SYM >=0.5) according to discriminate/indiscriminate response at 6 weeks (n=19)

TiLTS-cc_VAS Classification (>50%)	Reduction in PAC SYM >= 0.5		**Total**
	Responder (%)	Non-Responder (%)	
Discriminate Responder	2(50.0)	2(50.0)	**4**
Indiscriminate Responder	10(66.7)	5(33.3)	**15**
RD = -0.17(-0.71, 0.37), P-value = 0.6027			

Table 8: Response at 6 months comparing TiLTS-cc-VAS with PAC SYM for IPG patients

TiLTS-cc_VAS Classification (>50%)	Reduction in PAC SYM >= 0.5		**Total**
	Responder (%)	Non-Responder (%)	
Responder	12(63.2)	7(36.8)	**19**
Non Responder	8(57.1)	6(42.9)	**14**
Sensitivity(%) = 60.0(36.1, 80.9), Specificity(%) = 46.2(19.2, 74.9) PPV(%) = 63.2(38.4, 83.7), NPV = 42.9 (17.7, 71.1)			

Figure 1 Algorithm of temporary testing and classification of temporary test responses.



Assessment at 2 and 6 weeks with TILTS-VAS.
Responder to each stimulation period = improvement 25% or more

Overall response classified as below:

Active stim	Sham stim	
-	-	Non-response
+	-	Discriminate response
+	+	Indiscriminate response
-	+	

Figure 2: Patient flowchart

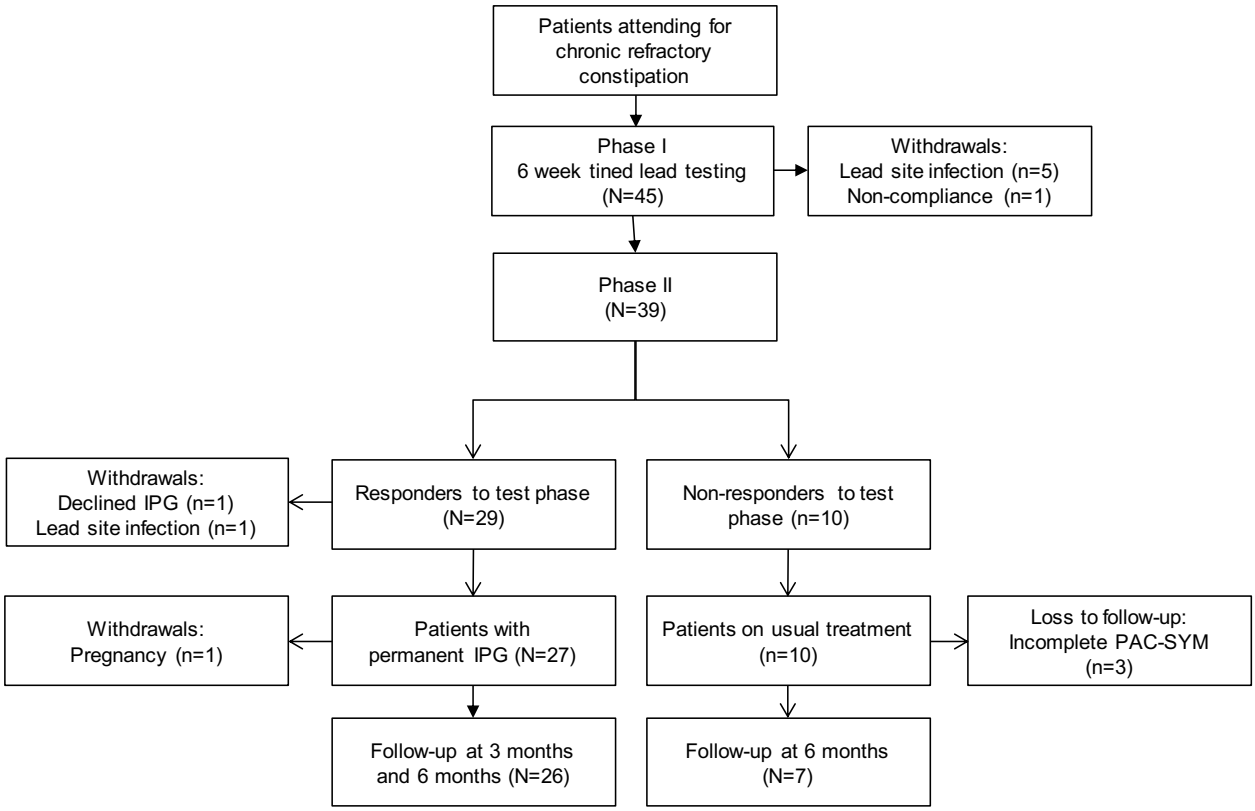


Figure 3: PAC QoL scores (means) from baseline to 6 months for IPG patients

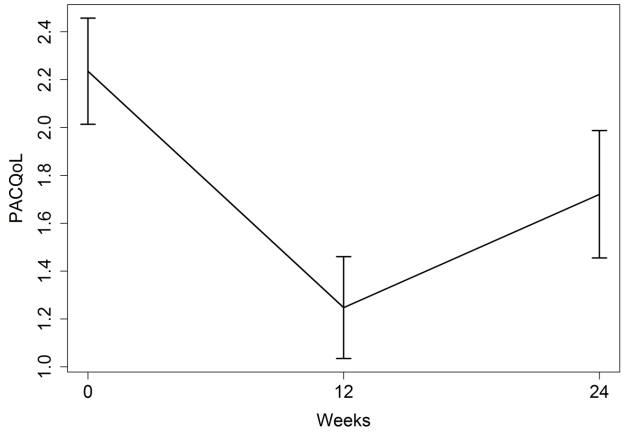


Figure 4: Cleveland and Wexner scores from baseline to 6 months for IPG patients

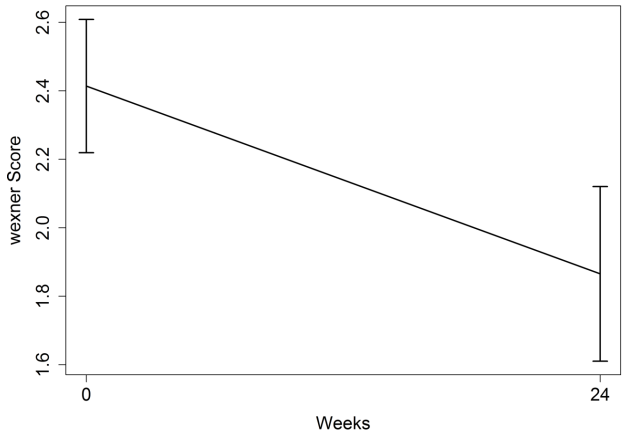


Figure 5: Longitudinal profiles of TiLTS VAS during testing phase

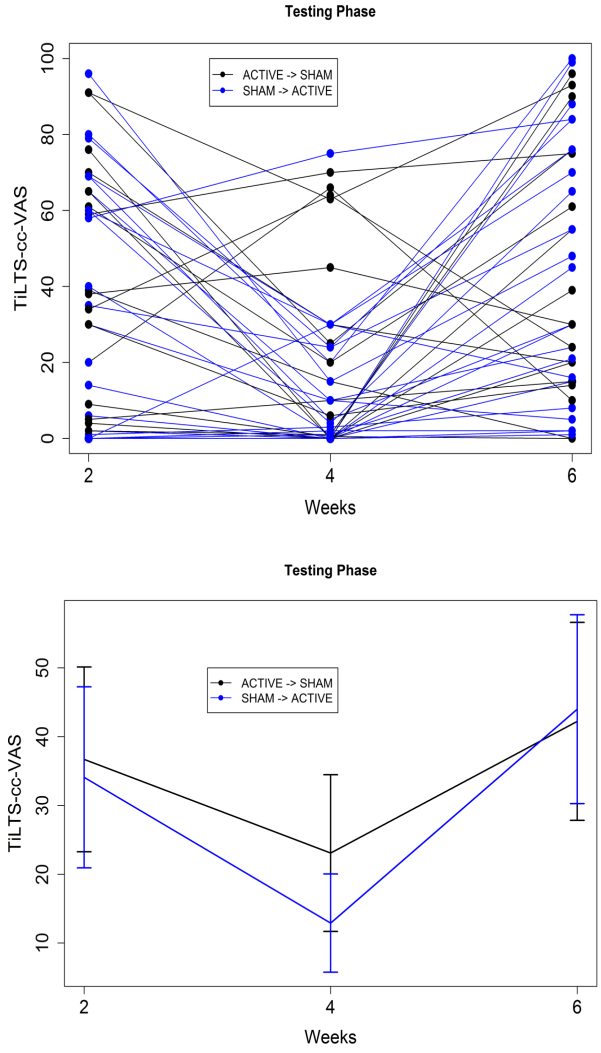
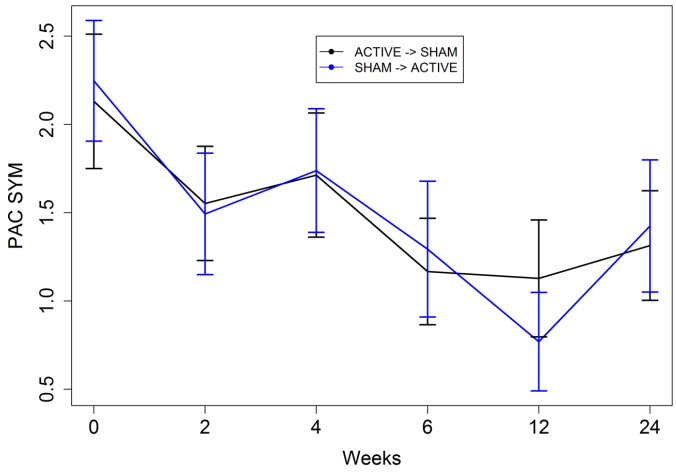


Figure 6: PAC SYM average profiles by randomisation order for IPG patients



NB: active +/- sham stimulation occurs only during week 0-6