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National Institute for Health Research

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Emma J Horrocks,[1]* Stephen A Bremner,[2] Natasha Stevens,[2] Christine Norton,[3] Deborah Gilbert,[1] P Ronan O'Connell,[4] Sandra Eldridge[2] and Charles H Knowles[1]

[1]National Centre for Bowel Research and Surgical Innovation, Blizard Institute, Queen Mary University of London, London, UK
[2]Pragmatic Clinical Trials Unit, Blizard Institute, Queen Mary University of London, London, UK
[3]Florence Nightingale Faculty of Nursing and Midwifery, King's College London, London, UK
[4]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

*Corresponding author

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Abstract

Double-blind randomised controlled trial of percutaneous tibial nerve stimulation versus sham electrical stimulation in the treatment of faecal incontinence: CONtrol of Faecal Incontinence using Distal NeuromodulaTion (the CONFIDeNT trial)

Emma J Horrocks,[1]* Stephen A Bremner,[2] Natasha Stevens,[2] Christine Norton,[3] Deborah Gilbert,[1] P Ronan O'Connell,[4] Sandra Eldridge[2] and Charles H Knowles[1]

[1]National Centre for Bowel Research and Surgical Innovation, Blizard Institute, Queen Mary University of London, London, UK
[2]Pragmatic Clinical Trials Unit, Blizard Institute, Queen Mary University of London, London, UK
[3]Florence Nightingale Faculty of Nursing and Midwifery, King's College London, London, UK
[4]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

*Corresponding author e.j.horrocks@qmul.ac.uk

Background: Faecal incontinence (FI) is a common condition which is often under-reported. It is distressing for those suffering from it, impacting heavily on their quality of life. When conservative strategies fail, treatment options are limited. Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive outpatient treatment, shown in preliminary case series to have significant effectiveness; however, no randomised controlled trial has been conducted.

Objectives: To assess the effectiveness of PTNS compared with sham electrical stimulation in the treatment of patients with FI in whom initial conservative strategies have failed.

Design: Multicentre, parallel-arm, double-blind randomised (1 : 1) controlled trial.

Setting: Eighteen UK centres providing specialist nurse-led (or equivalent) treatment for pelvic floor disorders.

Participants: Participants aged > 18 years with FI who have failed conservative treatments and whose symptoms are sufficiently severe to merit further intervention.

Interventions: PTNS was delivered via the Urgent® PC device (Uroplasty Limited, Manchester, UK), a hand-held pulse generator unit, with single-use leads and fine-needle electrodes. The needle was inserted near the tibial nerve on the right leg adhering to the manufacturer's protocol (and specialist training). Treatment was for 30 minutes weekly for a duration of 12 treatments. Validated sham stimulation involved insertion of the Urgent PC needle subcutaneously at the same site with electrical stimulation delivered to the distal foot using transcutaneous electrical nerve stimulation.

Main outcome measures: Outcome measures were assessed at baseline and 2 weeks following treatment. Clinical outcomes were derived from bowel diaries and validated, investigator-administered questionnaires. The primary outcome classified patients as responders or non-responders, with a responder defined as someone having achieved ≥ 50% reduction in weekly faecal incontinence episodes (FIEs).

Results: In total, 227 patients were randomised from 373 screened: 115 received PTNS and 112 received sham stimulation. There were 12 trial withdrawals: seven from the PTNS arm and five from the sham arm. Missing data were multiply imputed. For the primary outcome, the proportion of patients achieving a $\geq 50\%$ reduction in weekly FIEs was similar in both arms: 39 in the PTNS arm (38%) compared with 32 in the sham arm (31%) [odds ratio 1.28, 95% confidence interval (CI) 0.72 to 2.28; $p = 0.396$]. For the secondary outcomes, significantly greater decreases in weekly FIEs were observed in the PTNS arm than in the sham arm (beta –2.3, 95% CI –4.2 to –0.3; $p = 0.02$), comprising a reduction in urge FIEs ($p = 0.02$) rather than passive FIEs ($p = 0.23$). No significant differences were found in the St Mark's Continence Score or any quality-of-life measures. No serious adverse events related to treatment were reported.

Conclusions: PTNS did not show significant clinical benefit over sham electrical stimulation in the treatment of FI based on number of patients who received at least a 50% reduction in weekly FIE. It would be difficult to recommend this therapy for the patient population studied. Further research will concentrate on particular subgroups of patients, for example those with pure urge FI.

Trial registration: Current Controlled Trials ISRCTN88559475.

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List of abbreviations

CI	confidence interval
CONFIDeNT	CONtrol of Faecal Incontinence using Distal NeuromodulaTion
CONSORT	Consolidated Standard of Reporting Trials
CRF	case report form
DSMC	Data and Safety Monitoring Committee
EQ-5D	European Quality of Life-5 Dimensions
FI	faecal incontinence
FIE	faecal incontinence episode
FIQoL	Faecal Incontinence Quality of Life Index
GIQoL	Gastrointestinal Quality of Life Index
GP	general practitioner
ICC	intracluster correlation coefficient
OAB	overactive bladder
PTNS	percutaneous tibial nerve stimulation
SAE	serious adverse event
SF-36	Short Form Questionnaire-36 items
SMCS	St Mark's Continence Score
SNS	sacral nerve stimulation
TENS	transcutaneous electrical nerve stimulation
TMG	Trial Management Group
TNS	tibial nerve stimulation
TSC	Trial Steering Committee
TTNS	transcutaneous tibial nerve stimulation
VAS	visual analogue scale

Plain English summary

Faecal incontinence occurs when a person passes faeces (stools) without the usual control. It is a distressing and common condition, although it is under-reported because of embarrassment. There are few treatment options available. Percutaneous tibial nerve stimulation (PTNS) is a relatively new treatment, which involves electrically stimulating a nerve at the ankle using a very small needle (similar to acupuncture). Few studies have been performed to quantify how successful it is, but early results of PTNS suggest that it is as good as other more expensive and invasive treatments.

The aim of this research was to determine how effective PTNS is in the treatment of patients with faecal incontinence by comparing it with sham treatment (fake stimulation). This was carried out by comparing the number of people who experienced successful treatment in the PTNS group with the sham group. Treatment was considered 'successful' if faecal incontinence episodes were reduced by half or more.

In total, 227 patients in 18 UK specialist centres took part. They were randomly allocated, 115 to PTNS and 112 to sham stimulation. Each patient filled in bowel diaries and questionnaires before and 2 weeks after treatment to compare the arms.

The results showed that the proportion of patients in whom treatment was successful was similar in both groups (38% in the PTNS group compared with 31% in the sham treatment group). This means that PTNS is not significantly better than sham stimulation. This results will be important in guiding whether or not PTNS should be made available to patients in the NHS and beyond.

Scientific summary

Background

Faecal incontinence (FI) poses a significant UK public health problem, with an estimated prevalence of 11–15% among adults. It is known to be an under-reported problem that significantly impacts on quality of life. It often causes social and psychological disability, leading to stigmatisation and social exclusion.

Management of FI is challenging owing to a widespread lack of expertise, high prevalence and multiple aetiologies. Neuromodulation is a relatively new treatment modality for FI. It is based on recruitment of residual anorectal neuromuscular function pertinent to continence by electrical stimulation of the peripheral nerve supply, without the need for surgery to the anus itself.

Tibial nerve stimulation is a minimally invasive neuromodulatory modality. The tibial nerve contains afferent and efferent fibres originating from the fourth and fifth lumbar nerves and first, second and third sacral nerves. Thus, stimulation of the tibial nerve is thought to lead to improved continence in a similar way to sacral nerve stimulation but without the need for a permanent surgically implanted device. Tibial nerve stimulation is an outpatient treatment which can be delivered by any trained health-care professional. Two main delivery methods are described: percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS). The main perceived advantage of PTNS over TTNS is the proximity of the needle to the tibial nerve, enabling higher treatment amplitude to be delivered while avoiding the painful skin sensations associated with transcutaneous treatment.

Observational studies of PTNS have shown improvements in most outcome measures (bowel diary, Cleveland Clinic Incontinence Score and quality-of-life measures) after treatment, compared with baseline. A small three-arm RCT of PTNS versus TTNS versus sham showed effects of both treatments over sham, with PTNS appearing superior.

Percutaneous tibial nerve stimulation may offer a repeatable, low-cost (estimated at £5916 for the first 10 years based on 6-monthly top-up sessions) minimally invasive outpatient technique. It may, therefore, offer a genuinely new option in the pathway to treat FI.

Objectives

The aim of this study was to assess the clinical effect of PTNS compared with sham electrical stimulation in the treatment of patients with significant FI. Clinical outcomes, derived from bowel diaries and validated, investigator-administered questionnaires, were assessed at baseline and 2 weeks following a 12-week course of treatment. Outcomes were as follows.

Primary outcome

Responder versus non-responder, defined as a patient achieving ≥ 50% reduction in faecal incontinence episodes (FIEs) per week.

Secondary outcomes

- Percentage change in FIEs per week (i.e. patients achieving ≥ 25%, ≥ 75% or 100% reduction in weekly FIEs).
- Change in FIEs per week as a continuous measure.
- Change in symptom severity score: St Mark's Continence Score (SMCS).
- Change in disease-specific quality-of-life scores:
  - Gastrointestinal Quality of Life Index
  - Faecal Incontinence Quality of Life Index.
- Change in generic health-related quality-of-life measures: Short Form Questionnaire-36 items.
- Change in patients' health status and overall health using European Quality of Life-5 Dimensions questionnaire.
- Change in a patient-centred outcomes visual analogue scale questionnaire.
- Likert scale of patients' global impression of success (scale of 0–10).
- Qualitative data:
  - patient-perceived impression of change in use of incontinence pads and constipating medications
  - patient-perceived impression of change in urinary symptoms
  - patient impression of the treatment in general
  - patient-perceived allocation (PTNS or sham).

Other outcomes recorded at each visit

- Stimulation parameters.
- Adverse events and concomitant medications.

Methods

This study was a UK-based multicentre, pragmatic, parallel-arm, double-blind, randomised controlled trial. There was equal allocation between the arms, with stratification by sex and centre.

Centres with specialist expertise in FI and adequate staffing (at least two staff members), which demonstrated expertise with PTNS, were invited to participate in the study. All adult patients with FI symptoms sufficiently severe to warrant intervention in whom appropriate conservative therapies had failed were invited to participate. Inclusion and exclusion criteria were as follows.

Inclusion criteria

- Faecal incontinence sufficiently severe to warrant intervention (as recommended by the principal investigator at each site).
- Failure of appropriate conservative therapies.
- Age ≥ 18 years.

Exclusion criteria

- Inability to provide informed consent for the research study.
- Inability to fill in the detailed bowel diaries required for outcome assessments (this excluded participants who do not speak/read English).
- Neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (including any participant with painful peripheral neuropathy).

- Anatomical limitations that would prevent successful placement of needle electrode.
- Other medical conditions precluding stimulation, for example bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis.
- Congenital anorectal anomalies or absence of native rectum due to surgery.
- A cloacal defect.
- Present evidence of external full-thickness rectal prolapse.
- Previous rectal surgery (rectopexy/resection) done < 12 months previously (24 months for cancer).
- Stoma in situ.
- Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea.
- Pregnancy or intention to become pregnant.
- Previous experience of sacral nerve stimulation or PTNS.

Each patient was scheduled to attend for 14 study visits, the first for eligibility checking, visits 2–13 for collection of baseline data followed by delivery of treatment (PTNS or sham) and the final study visit for the collection of outcome data. Participants who recorded zero incontinent episodes on initial bowel diary were not excluded from the study.

Percutaneous tibial nerve stimulation was delivered via the Urgent® PC device (Uroplasty Limited, Manchester, UK), a hand-held pulse generator unit, with single-use leads and fine needle electrodes. The needle was inserted near the tibial nerve on the right leg, adhering to the manufacturer's protocol (and specialist training). Treatment was for 30 minutes weekly for 12 treatments. Validated sham stimulation involved insertion of the urgent PC needle subcutaneously at the same site with electrical stimulation delivered to the distal foot using transcutaneous electrical nerve stimulation. Participants were blinded to treatment allocation, and all equipment was hidden from their view. Standard instructions were read to all participants prior to every treatment, with patient contact limited to questions regarding adverse events, concomitant medications, loperamide and incontinence pad usage in order to standardise treatment. To maintain treatment quality, each researcher underwent individual training on how to deliver PTNS and sham treatment, and technique was assessed at 6-monthly intervals.

Randomisation, with allocation concealment, was undertaken using a bespoke web-based computer program held at Nottingham Clinical Trials Unit. Following input of participant details, immediate on-screen randomisation occurred. Allocation was on a 1 : 1 basis, with initial stratification by sex and then, because the numbers of males was expected to be very small and we wanted to achieve an overall balance of males in each group, stratification of females only by centre.

Sample size calculation was based on an estimated PTNS treatment response of 55% and a sham response of 35%. Overall, 212 participants were required for the analysis with 80% power at the 5% significance level. Statistical analysis, on an intention-to-treat basis, was carried out using Stata version 12.1 (StataCorp LP, College Station, TX, USA), interfacing with Realcom Impute (2007, Centre for Multilevel Modelling, University of Bristol, Bristol, UK), which was used to multiply impute missing outcome and baseline covariate data. Per-protocol analysis, sensitivity analyses and subgroup analyses were subsequently performed.

Results

Eighteen UK centres recruited participants for the trial between 23 January 2012 and 31 October 2013. In total, 373 participants were screened and, of these, 227 (61%) were randomised. Of these, 115 participants were randomised to receive PTNS and 112 randomised to receive sham electrical stimulation. The number of participants per site ranged from 1 to 45 (median 10 patients). There were 12 participant withdrawals, seven from the trial and five from treatment.

Baseline

Ninety per cent of the participants recruited were female and the mean age was 57 years, with a range of 20–85 years. Mean symptom duration was 8 years, with a range of 5 months to 50 years. Demographics and clinical symptom profiles of the two arms were evenly matched.

Baseline bowel diaries demonstrated a median of 6.0 FIEs per week among PTNS patients, comprising a median of 3.0 urge FIEs and a median of 2.0 passive episodes. Patients in the sham arm experienced a median of 6.9 FIEs per week, with a slightly higher rate of passive FI (median 3.0 episodes) than urge episodes (median 2.5 episodes).

Baseline SMCSs were similar between the arms, with a mean of 14.4 (standard deviation 3.7) in the PTNS arm and 15.4 (standard deviation 4.1) in the sham arm. All 211 participants who completed the SMCS had significant FI, on the basis of their score being > 5.

Primary outcome

The percentage of patients achieving a ≥ 50% reduction in weekly FIEs was similar in both arms, at 38% in the PTNS arm and 31% in the sham arm [odds ratio 1.283, 95% confidence interval (CI) 0.722 to 2.281; $p = 0.396$].

Secondary outcomes

No significant difference was observed between the PTNS and sham arms in the number of participants achieving ≥ 25%, ≥ 75% and 100% reduction in weekly FIEs. There was, however, a significantly greater decrease in total weekly FIEs in the PTNS arm than in the sham arm (difference in means –2.3, 95% CI –4.2 to –0.3; $p = 0.02$). This included a reduction in the number of urge FIEs weekly (–1.5, 95% CI –2.7 to –0.2; $p = 0.02$) but not in the number of passive FIEs (–0.64, 95% CI –1.67 to 0.40; $p = 0.23$).

No significant difference in SMCSs was observed between the two arms following treatment (difference in means –0.047, 95% CI –1.033 to 0.939; $p = 0.93$). No significant differences were seen in the disease-specific (Faecal Incontinence Quality of Life Index and Gastrointestinal Quality of Life Index) or generic (Short Form Questionnaire-36 items) quality-of-life measures between the PTNS and sham arms following treatment.

The improvement in the patient-centred outcomes score was significantly greater in the PTNS arm than in the sham arm (difference in means –0.545, 95% CI –1.081 to –0.008; $p = 0.047$). No significant difference existed in patients' global impression of success between the PTNS and the sham arms (difference in means 0.808, 95% CI –0.055 to 1.672; $p = 0.068$).

There were virtually no differences between the two arms either at baseline or post treatment in respect of either the European Quality of Life-5 Dimensions index or the visual analogue scale, with scores on both scales remaining unchanged over time.

Other outcomes

In the PTNS arm, 57 out of 107 (54%) participants thought that they had received PTNS and 48 out of 107 (46%) participants thought that they had received sham treatment. In the sham arm of the trial, 32 out of 103 (31%) participants thought that they had received PTNS and 71 out of 103 (69%) participants thought that they had received sham treatment. These results are indicative of effective blinding.

Among participants who used loperamide, the majority in both the PTNS arm (33 out of 49; 67%) and the sham arm (32 out of 38; 84%) reported no change in its use throughout the trial. Equal proportions in each arm (4% in PTNS vs. 5% in sham) reported increasing loperamide use. The proportion of patients who were able to reduce their loperamide use was higher in the PTNS arm than in the sham arm (29% vs. 11%); however, this difference was found not to be significant ($p = 0.06$).

Serious adverse events

There were four serious adverse events during the trial; however, none was related to the trial treatment and all were resolved.

Conclusions

The CONFIDeNT (CONtrol of Faecal Incontinence using Distal NeuromodulaTion) study was an adequately powered, well-conducted, definitive trial, carried out to a high standard with an absence of any methodological flaws or serious breaches.

Percutaneous tibial nerve stimulation did not show significant benefit over sham electrical stimulation in the treatment of FI based on the proportions of patients who reported at least a 50% reduction in weekly FIEs. However, among patients who received PTNS, mean total weekly FIEs and mean urge weekly FIEs were significantly reduced, and patient-centered outcomes were significantly improved, compared with patients who received sham treatment.

Based on the evidence presented it would be hard to justify recommending this therapy for the patient population in the trial.

In view of the relatively low costs associated with this treatment and its high acceptability, there may be a justification in continuing to treat a subgroup of patients with troublesome urge FI symptoms in whom directed therapy may cause symptomatic improvement. Further studies of PTNS should be directed at those with urge FI to determine the clinical effectiveness.

Trial registration

This trial is registered as ISRCTN88559475.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background

Faecal incontinence (FI) poses a significant UK public health problem. Its prevalence is difficult to accurately assess, although the best studies estimate this at 11–15% in the adult population[1] and as high as 50% in care homes.[2,3] As prevalence and severity increase with age,[4] FI is expected to become a greater problem in an increasingly aged population. It is known to be an under-reported problem, with many symptomatic patients suffering in silence.[5–8] FI has a significant impact on quality of life, causing social and psychological disability,[9,10] and often leads to people suffering from stigmatisation and social exclusion.[5,11,12] The attendant socioeconomic burden of FI is high not only because of the cost of health-care utilisation, but also because of job absenteeism.[13,14]

Management of faecal incontinence

Management of FI is challenging because of a widespread lack of expertise, high prevalence and multiple aetiologies. Initial management involves a tailored stepwise approach, beginning with more conservative strategies (diet, toilet training and medications) and moving on to appropriate nurse-led bowel retraining programmes and psychosocial support. Combinations of these treatments often prove effective;[15,16] however, many patients suffer refractory symptoms, for which the National Institute for Health and Care Excellence recommends moving to more invasive measures.[17] Depending on local expertise, surgery – for example sphincter repair, artificial sphincter, dynamic graciloplasty or a permanent stoma – may be the only option for these patients. Surgical procedures are invasive and have, at best, variable success rates with significant risk of morbidity.[18–21]

Neuromodulation is a relatively new treatment modality for FI which is bridging the gap between conservative strategies and invasive surgery in centres where expertise exists. It is based on recruitment of residual anorectal neuromuscular function pertinent to continence by electrical stimulation of the peripheral nerve supply, without the need for surgery to the anus itself.

Sacral nerve stimulation (SNS) employs direct electrical stimulation to the sacral nerve roots (mainly the S3 nerve root) and is a safe, effective treatment for FI, with short-, medium- and long-term median success rates reported as 63% (range 33–66%), 58% (range 52–81%) and 54% (range 50–58%) respectively.[22–28] SNS has become the first-line surgical treatment option for FI.[17] Despite largely favourable data, SNS requires two operations and is not without risk of morbidity.[29] Although it is cost-effective compared with other surgical options,[30] SNS does have high associated costs, recently estimated as £20,484 for the first 10 years of a patient's treatment,[31,32] because of the combination of equipment, hospital admission and ongoing care.

Tibial nerve stimulation in faecal incontinence

Tibial nerve stimulation is a minimally invasive neuromodulatory modality. The tibial nerve contains afferent and efferent fibres originating from the fourth and fifth lumbar and first, second and third sacral nerves. Thus, stimulation of the tibial nerve is thought to lead to similar changes in anorectal neuromuscular function as observed with SNS (owing to shared sacral root effects) but without the need for a permanent surgically implanted device. Tibial nerve stimulation (TNS) is an outpatient treatment, which can be delivered by any trained health-care professional, and is consequently much cheaper than SNS. Initially

described for urinary incontinence,[33] TNS was first used for FI in 2003.[34] Since then, there have been several publications regarding the use of TNS to treat FI. Two main delivery methods are described:

1. Percutaneous tibial nerve stimulation (PTNS) involves electrical stimulation via a needle placed adjacent to the tibial nerve just above the ankle. This is delivered via the Urgent® PC neuromodulation system (Uroplasty Limited, Manchester, UK). Treatment is typically delivered as 12 30-minute treatments, given either weekly for 12 weeks or twice-weekly for 6 weeks.
2. Transcutaneous tibial nerve stimulation (TTNS) involves electrical stimulation which is delivered via two-pad electrodes placed over the tibial nerve just above the ankle. This is usually delivered via a transcutaneous electrical nerve stimulation (TENS) machine. Treatment regimens vary considerably, although administration is usually in 20- to 30-minute sessions over a period of weeks or months.

The main advantage of PTNS over TTNS is the proximity of the needle to the tibial nerve, enabling higher treatment amplitude to be delivered while avoiding the painful skin sensations associated with transcutaneous treatment.

Evidence for percutaneous tibial nerve stimulation in faecal incontinence

Published studies of PTNS include nine case series[34–42] (one study[34] included a 'control' group for comparison), one small single-centre randomised single-blind trial (PTNS vs. TTNS vs. sham),[43] one comparative case-matched study (PTNS vs. SNS)[44] and one prospective clinical audit with a 'pseudo' case–control model (PTNS vs. SNS).[31] A recent review by the authors summarises the results.[45] Five publications are from the same institution and report results from an accumulating database. Interpretation and comparison of these studies is hampered by a lack of standardised and universally accepted outcome measures, observer and patient blinding, performance and interpretation bias and attrition bias.

When considering data from bowel diaries to assess treatment success (the most universally accepted method in the SNS literature), two studies[39,43] reported that 63% and 82% of patients had a $\geq 50\%$ reduction in the weekly number of faecal incontinence episodes (FIEs) immediately after treatment. Two studies reported longer-term follow-up, with 59% of patients experiencing treatment success after 1 year[39] and 53% at a median of 22 months,[42] based on the same outcome measure. When considering FIEs as a count, six studies[1–3,6,8,9] reported this outcome, with a median reduction from five episodes to one per week immediately following treatment (a statistically significant reduction in three of these studies[36,38,42]) and a median reduction from six episodes to one in the two studies that reported this outcome in the longer term (at 1 year[39] and at a median of 29 months[42]), which led to a statistically significant reduction in both.

The randomised single-centre study of PTNS versus TTNS versus sham treatment in 30 patients[43] reported that 82% of patients in the PTNS group, 45% of patients in the TTNS group and 13% of those in the sham group had $\geq 50\%$ reduction in the weekly number of FIEs immediately after treatment. This was statistically significant across all groups ($p = 0.035$).

In summary, the observational studies of PTNS showed improvements in most outcome measures (bowel diary, Cleveland Clinic Incontinence Score and quality-of-life measures) after treatment compared with baseline. A small three-arm RCT of PTNS versus TTNS versus sham showed effects of both treatments over sham, with PTNS appearing superior.[45]

It seems that PTNS may offer a low-cost (estimated at £5916 for the first 10 years based on 6-monthly 'top-up' sessions)[31] minimally invasive outpatient technique with almost no associated morbidity.[46] If this is true, and PTNS offers similar efficacy to SNS, PTNS may be considered as a genuinely new option in the pathway between conservative management and the more invasive surgical procedure of SNS.

Limitations of the current published evidence for percutaneous tibial nerve stimulation in faecal incontinence

To our knowledge, no double-blind placebo-controlled trial of PTNS in patients with FI has been performed. Thus, notably, the effect of PTNS in FI, over and above that of meetings with a nurse specialist alone, remains unknown. This is important because:

1. PTNS is available in several centres in the UK and, although much cheaper than SNS, there is still a cost associated with its use. Increasing numbers of centres are using it, but many are doing so with speculation that it is little more than an expensive form of acupuncture.
2. The possible placebo effect of PTNS should not be underestimated:

    i. High placebo responses are almost universally observed in trials of therapy for functional[47,48] and organic[48,49] colorectal diseases.
    ii. Therapeutic responses have been achieved by acupuncture alone in FI,[50] noting that the medial ankle is an established acupuncture site for the viscera ('sanyinjiao' or 'spleen 6').
    iii. Regular meetings with a specialist nurse may confer some benefit even without formal bowel retraining.[51]

3. The influence of unblinded observers, especially when interpreting bowel diary data, is also a potential source of bias.

Study aims

We aimed to assess the clinical effect of PTNS, compared with sham electrical stimulation, in the treatment of patients with significant FI in whom conservative management strategies have already failed.

We also planned to test the effect of PTNS versus sham electrical stimulation on:

1. improvements in validated incontinence scores
2. patient-centred FI-related symptoms
3. disease-specific and generic quality-of-life measures.

Hypothesis

A 12-week course of PTNS results in a clinical response rate of 55% compared with a sham response rate of 35%, with clinical response defined as a reduction in the weekly number of FIEs of $\geq 50\%$.

Chapter 2 Methods

Overview: study design

The CONFIDeNT (CONtrol of Faecal Incontinence using Distal NeuromodulaTion) study was a UK-based multicentre, pragmatic, parallel-arm, double-blind, randomised controlled trial comparing PTNS with sham electrical stimulation, with equal allocation, stratified by sex and centre, in the treatment of FI, and assessing outcomes following a standard 12-week treatment schedule. The detailed trial protocol is available to view online (www.nets.nihr.ac.uk). The study method is summarised in a flow diagram (see *Appendix 1*). Events occurring at each visit are detailed in *Appendix 2*. All case report forms used can be seen in *Appendix 3*.

Study outcomes

Clinical outcomes

These were assessed at baseline (prior to therapy) and 2 weeks following completion of a 12-week course of treatment. Clinical outcomes were derived from 2-week bowel diaries and a series of validated, investigator-administered questionnaires.

Primary

Responder versus non-responder: responder defined as a patient achieving ≥ 50% reduction in total FIEs per week, as recorded on a 2-week self-completed bowel diary.

Secondary

- Percentage change in FIEs per week (i.e. patients achieving ≥ 25%, ≥ 75% or 100% reduction in weekly FIEs).
- Change in FIEs per week as a continuous measure.
- Change in symptom severity score: St Mark's Continence Score (SMCS). A score from 0 (best) to 24 (worst) with > 5 indicating significant symptoms.[52]
- Change in disease-specific quality-of-life scores:
  - Gastrointestinal Quality of Life Index (GIQoL):[53] a score from 0 (worse) to 180 (best)
  - Faecal Incontinence Quality of Life Index (FIQoL):[54] a score with four domains scored from 1 (worst) to 4 (best).
- Change in general quality-of-life measures: Short Form Questionnaire-36 items (SF-36).[55] A score with eight domains with scores given as percentages.
- Change in patients' health status and overall health using European Quality of Life-5 Dimensions (EQ-5D)[56] questionnaire.
- Change in patient-centred outcomes questionnaire. A derivative of the International Consultation on Incontinence Modular Questionnaire – Bowel[57] with a score from 1 (best) to 80 (worst).
- Likert scale of patients' global impression of success (scale of 0–10).
- Qualitative data:
  - patient-perceived impression of change in use of incontinence pads and constipating medications
  - patient-perceived impression of change in urinary symptoms
  - patient impression of the treatment in general
  - patient-perceived allocation (PTNS or sham).

Other outcomes recorded at each visit:

- stimulation parameters
- adverse events and concomitant medications.

In addition to this, patients completed a bowel diary after six treatments and this formed a further secondary outcome.

Clinical centres

Centres with specialist expertise in FI, including nurse-led (or equivalent) incontinence services, were invited to participate in the study. Centres had to demonstrate experience with PTNS, having previously completed a full set of 12 treatments in a minimum of three patients. Each centre also required a minimum of two staff members to run the trial and ensure satisfactory blinding.

Study population

All adult patients attending the specialist continence or pelvic floor clinics at each of the centres were considered for participation in the study. This included patients with FI symptoms sufficiently severe to warrant intervention and in whom appropriate conservative therapies, such as diet, pelvic floor exercises, biofeedback and loperamide, had failed. Specialist investigations including structural and functional anorectal assessment were not mandatory, and anal sphincter injury was not a contraindication.

Inclusion criteria

- Faecal incontinence sufficiently severe to warrant intervention (as recommended by the principal investigator at each site).
- Failure of appropriate conservative therapies.
- Age $\geq$ 18 years.

Exclusion criteria

- Inability to provide informed consent for the research study.
- Inability to fill in the detailed bowel diaries required for outcome assessments (this will exclude participants who do not speak/read English).
- Neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (including any participant with painful peripheral neuropathy).
- Anatomical limitations that would prevent successful placement of needle electrode.
- Other medical conditions precluding stimulation, for example bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis.
- Congenital anorectal anomalies or absence of native rectum as a result of surgery.
- A cloacal defect.
- Present evidence of external full-thickness rectal prolapse.
- Previous rectal surgery (rectopexy/resection) done < 12 months prior to the study (24 months for cancer).
- Stoma in situ.
- Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea.
- Pregnancy or intention to become pregnant.
- Previous experience of SNS or PTNS.

Following in-depth discussion with the research ethics committee, it was decided that, as some of the outcome questionnaires had not been validated in languages other than English, we should exclude people who do not understand written or spoken English from the study.

Data collection

We planned that each patient should attend for 14 visits and the events that occurred at each visit were as follows.

Visit 1: interest – eligibility

At this appointment, or over the telephone, a local researcher trained in good clinical practice determined eligibility by interview on the basis of defined inclusion and exclusion criteria listed on case report form (CRF) 1. The participants' details were recorded on the screening log, and each participant was allocated a unique participant identifier number (see below). These data were used to complete the Consolidated Standard of Reporting Trials (CONSORT) flow chart and to generate reports on non-recruited patients for discussion at management group meetings.

Eligible subjects were provided with adequate explanation of the aims, methods, expected benefits and risks of participating in the study and given a patient information sheet containing this information. Participants were allowed 1 week to consider their participation (in accordance with good clinical practice). Participants who remained interested were provided with a bowel diary to complete over the next 2 weeks. Each participant was counselled on how to fill this diary in. Appointments were then booked for visits 2–14, with visit 2 being at least 2 weeks later to allow time for diary completion.

Unique participant identifier codes

Once a participant was registered on the screening log, he or she was allocated a unique participant identifier code. This consisted of six characters: three letters followed by three numbers. The letters denoted the study centre code, and the number was allocated on a consecutive basis, for example 001 for the first participant, and so on.

Visit 2: consent – confirm eligibility – baseline assessment – randomisation – first intervention

At this appointment, a member of the local team (trained in informed consent) answered any further questions and then asked the participant to sign the study consent form (also countersigned by the local researcher). All prospective participants were reminded of the need to be logistically able to complete the full protocol of 12 sessions at weekly intervals. Once the consent form was signed, the local investigator confirmed eligibility by recording data on CRF 1. If the participant was a female of childbearing potential, a urine pregnancy test was performed at this point.

The researcher then recorded all baseline data of FI history, past medical history and medication usage (using CRF 2 – initial assessment). The participant was asked to fill in the questionnaires (CRF 3) and to hand in the completed bowel diary, which was checked for completeness. Prior to randomisation the consent form, eligibility criteria (CRF 1) and initial assessment (CRF 2) were verified by another member of the research team.

Participants who failed to complete the bowel diary properly were given another 2-week bowel diary to complete and returned 2 weeks later for the trial to commence. If they failed a second attempt, they became a screen failure, and were withdrawn. Another participant was recruited in their place.

The researcher performed the randomisation, recorded this information on CRF 4 and (now unblinded) delivered the first 30-minute intervention (real PTNS or sham). Parameters of stimulation were recorded

(CRF 5). The participant's details were entered on the enrolment log, and a general practitioner (GP) letter, informing the GP of the participant's involvement in the trial, was sent out.

Visits 3–13: intervention – interim information

At appointments 3–13, an unblinded researcher (who might be the same person as in visit 2) delivered the 30-minute intervention, having checked CRF 4 to confirm randomisation allocation. They enquired about adverse events, concomitant medication usage and pad usage, and recorded these on CRF 5.

At visit 7, participants were given a 1-week interim bowel diary to complete between visits 7 and 8. This bowel diary was collected and checked at visit 8.

At visit 13, participants were given a 2-week bowel diary to complete prior to attending visit 14, 2 weeks later.

Visit 14: final study visit

The final study visit was performed by a blinded member of the research team (i.e. somebody who was not present at visits 2–13). At this appointment, the bowel diary was collected and checked for completeness. The participant was then asked to complete the questionnaire document (CRF 3) and the post-treatment questionnaire (CRF 6).

The researcher then ensured that all documents were present and filled in correctly, prior to the principal investigator completing and signing off CRF 7. The participant was then unblinded as to treatment allocation and further follow-up was arranged as necessary.

Participants who failed to complete the interim bowel diary between visits 7 and 8 attempted this again the following week, and this was recorded as a protocol deviation. Participants who failed to complete the final bowel diary were again asked to complete this after visit 14, and they returned for another final study visit 2 weeks later. This was also a protocol deviation.

After completion of trial

After visit 14, participants who received 'sham' stimulation were offered PTNS on an open-label basis. Participants who received real PTNS and who derived significant benefit were offered 'top-up' sessions as per local departmental protocols. Participants who received real PTNS but derived no significant benefit were offered further treatments on an 'open-label' basis, following local departmental protocols.

Study procedures: delivery of percutaneous tibial nerve stimulation or sham

Participants received PTNS or sham using the recommended standard of 12 weekly 30-minute outpatient stimulations. *Appendix 4* details exactly how PTNS and sham electrical stimulation were administered. Treatments were tailored to participants' needs but protocol tolerance stipulated a minimum of 10 treatments, no fewer than 5 days or greater than 10 days apart, to be completed in 13 weeks. Treatments given outside these windows were classed as a protocol deviation.

Percutaneous tibial nerve stimulation was delivered via the Urgent® PC neuromodulation system, a reusable external pulse generator that provides visual and auditory feedback. It has an adjustable current setting from 0 to 9 mA in pre-set 0.5-mA increments, a fixed-pulse frequency of 20 Hz and a pulse width of 200 microseconds.

Transcutaneous electrical nerve stimulation was used for the delivery of sham electrical stimulation (Biostim M7 TENS unit, Biomedical Life Systems, Vista, CA, USA). The sham treatment was a modification of that used and validated in the pivotal level I trial of Peters *et al.*[58] in overactive bladder (OAB) syndrome.[59]

However, this was improved upon by inserting (at the same site) the Urgent® PC needle in all subjects. In the Peters study, the Urgent PC® needle was used in the PTNS arm, but the sham arm employed an acupuncture technique using a Streitberger needle, which does not puncture the skin.

Treatments were always given in individual treatment rooms, with participants lying supine on a clinical couch. They were asked to remove clothing and shoes so as to bare legs from the knees downwards. A 'gardener's kneeling stool' was placed over both legs, just below the knees, and a sheet draped over this to hide the participant's feet from their view (*Figure 1*). Once the participant was comfortable, but prior to equipment set-up, each researcher read a standardised paragraph to the participant, informing them of what to expect. This read:

> *I am now going to start the nerve stimulation treatment. I will be inserting a small electrode needle, like an acupuncture needle, into your leg and putting sticky electrodes onto your foot. When I turn the machine on you will be asked when you can first feel an electrical sensation in your ankle or foot. I will carry on increasing the intensity of this until it is slightly uncomfortable, then I will turn it down a little if necessary. Occasionally you may also feel numbness or slight movement of your toes. This is normal. I will set the machine up and leave it running for 30 minutes. You may or may not continue to feel the stimulation during this time – this is normal also. After 30 minutes have elapsed I will remove the needle and sticky electrodes (the machine automatically turns off at this time). If the treatment becomes uncomfortable at any point please let me know and I will turn it down or stop the machine.*

All participants then had an Urgent® PC machine and a TENS machine set up on their right foot, unless there was a reason why the right foot could not be used, under which circumstances the left foot was used. In the true PTNS arm, the Urgent® PC was used as normal, and the TENS machine left turned off. In the sham arm, the TENS machine was used to provide the electrical stimulation and the Urgent® PC was turned on only to provide the auditory stimulus. Following satisfactory treatment commencement, the sheet was draped fully over the participant's feet, ensuring that accidental unblinding could not take place. The researcher then filled in the paperwork for this visit and left the room, returning after 30 minutes to remove the equipment.

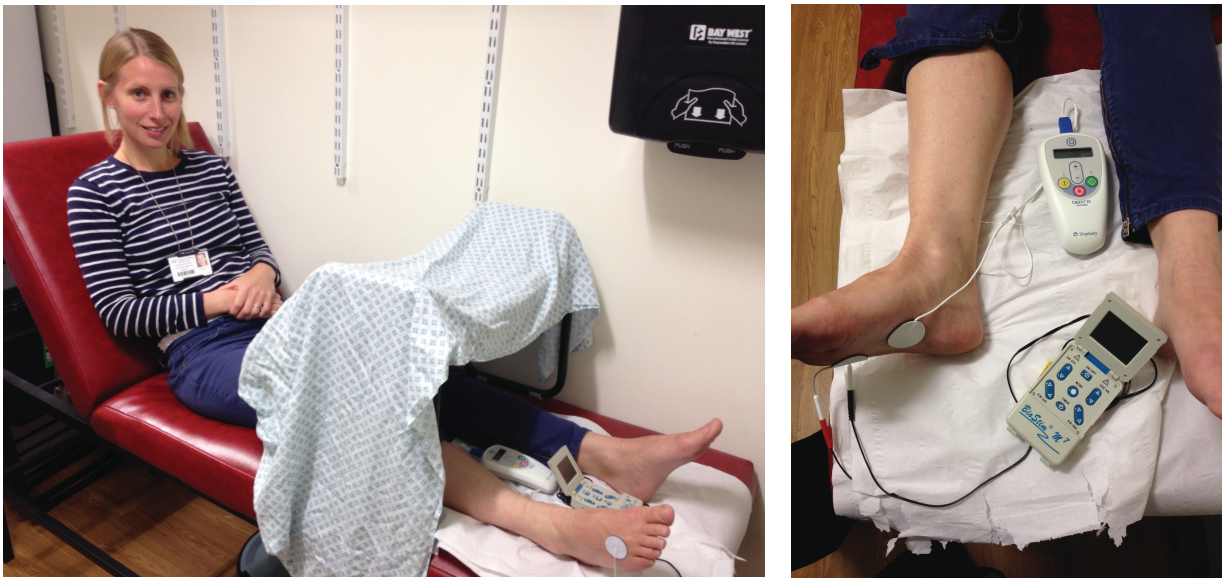

FIGURE 1 Photographs of equipment set-up.

Treatment arm

After checking equipment, which should have included the Urgent® PC machine, lead wire, alcohol wipe and electrode needle with tube assembly, the site of needle insertion was identified on the lower inner aspect of the right leg approximately three finger breadths (5 cm) cephalad to the medial malleolus and approximately one finger breadth (2 cm) posterior to the tibia. The area was cleaned with ethanol and the needle electrode–guide tube assembly placed over the identified insertion site at a 60° angle between electrode and ankle. The 34-gauge needle electrode was gently tapped to pierce the skin and thence advanced using a rotating motion approximately 2 cm. The lead wire was then connected to the stimulator and to the ipsilateral calcaneal reference electrode (*Figure 2a*). The lead wire was then taped to the participant's leg so that the PTNS participant experienced the same sensations as the sham participant. The TENS machine was connected to two electrodes, one placed under the little toe and one on top of the foot (*Figure 2b*). The TENS machine was not turned on. The setting for PTNS therapy was determined by increasing the current slowly while observing the participant's sensory response (appropriate response being in great toe or sole of foot) or motor response (plantar flexion of foot or great toe). Current was then reduced by one level for therapy, and continued for 30 minutes, at which point the electrode was removed.

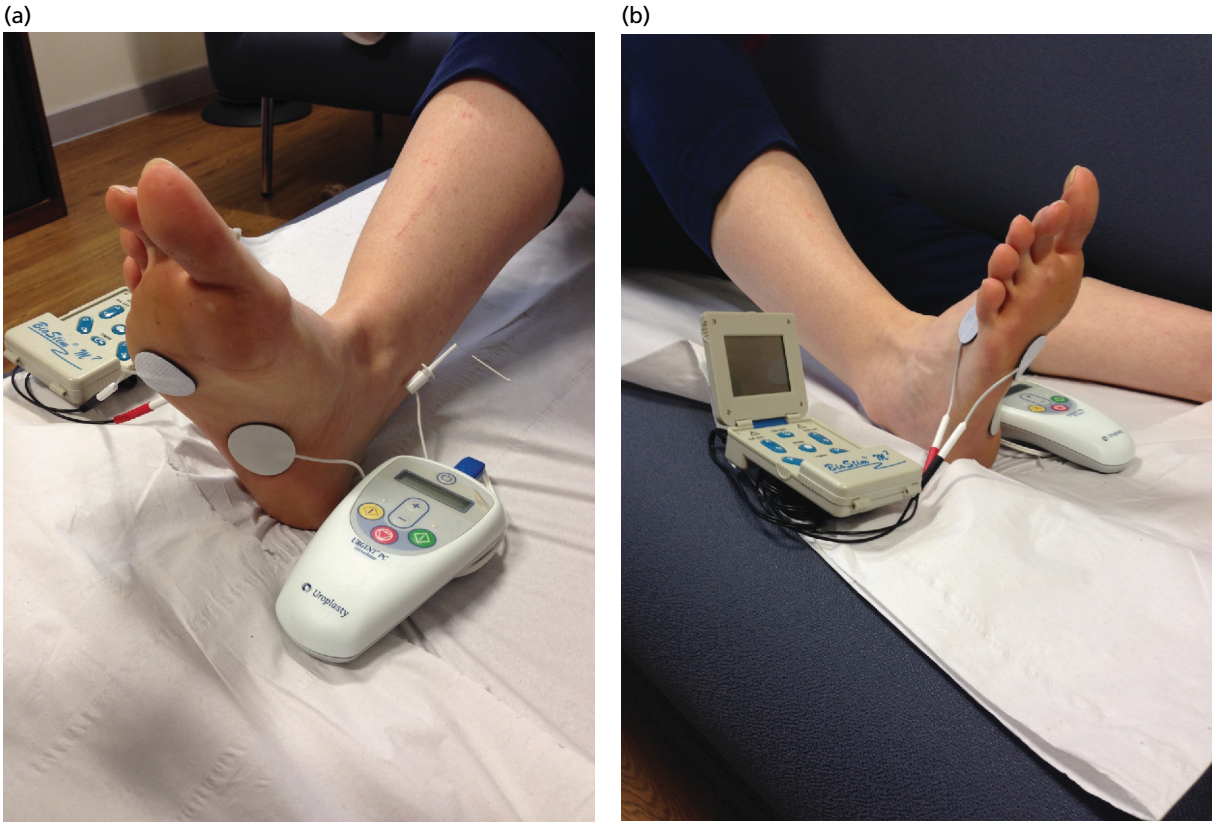

FIGURE 2 Equipment set-up. (a) PTNS needle and calcaneal electrode and (b) TENS surface electrode placements.

Sham arm

The same protocol was followed as for the treatment arm. The only difference was that the needle was inserted only 2 mm into the skin and subcutaneous tissue, that is just in far enough not to fall out and not deep enough to be close to the tibial nerve. The lead was then taped to the participant's leg near to, but not touching, the needle. The purpose of this was to prevent unblinding in the event of the participant inadvertently seeing the equipment. The PTNS surface electrode (see *Figure 2a*) on the calcaneus was also attached. The two active TENS surface electrodes were employed as shown in *Figure 2b*, with one placed under the little toe and one on top of the foot. Once all equipment was set up, the practitioner picked up both the Urgent® PC machine and the TENS machine, one in each hand. Both machines were turned on. The TENS machine was set to a pulse frequency of 10 Hz and a pulse width of 200 microseconds. Then, after pressing buttons simultaneously on the Urgent® PC machine and the TENS machine, the practitioner increased the adjustable current setting (which ranged from 0 to 10 mA in pre-set 1-mA increments on the TENS machine). The setting for therapy was determined in the usual way by observing the participant's sensory reactions or their foot for toe/ankle extensor motor responses, and if necessary the current was reduced by one level for therapy. The reason both machines were used together was so that the audible sounds produced by the Urgent® PC stimulator were the same in both the PTNS and the sham arms, to decrease auditory variation between the study arms.

This sham treatment was shown in a departmental pilot to be both more acceptable and more realistic than that described by Peters *et al.*,[58] which involved the placement of a Streitberger needle. We also confirmed that this sham, using TENS to deliver the electrical stimulation, does not stimulate the posterior tibial nerve (proven in a neurophysiological pilot by the consultant neurophysiologist).

Treatment quality control

The importance of quality control and standardisation of technique between individuals and centres was recognised. In order to keep the quality high, each researcher was taught and certified to give PTNS by a uroplasty-approved trainer. Each researcher also underwent a personal training session at the site initiation visit by the trial research fellow (EH) on how to deliver PTNS and sham according to the CONFIDeNT protocol. Each researcher was then observed delivering both treatments. Six-monthly site visits throughout the duration of the trial involved assessment of technique. Retraining was undertaken where necessary.

Withdrawal criteria

Participants were withdrawn from the treatment or the trial if they fulfilled any of the criteria below at any point following delivery of the first treatment.

Withdrawn from treatment only (follow-up data still collected)

- Participant no longer wished to be involved in trial treatments.
- Participant developed a medical condition listed in the exclusion criteria.
- Participant became pregnant or intended to become pregnant.
- Unblinding occurred.
- Participant had an intercurrent illness.

Withdrawn from the trial (no follow-up data collected)

- Participant was lost to follow-up (could not be contacted by telephone or other means).
- Participant no longer wished to be involved in the trial.
- Death.

Early withdrawal was documented carefully and all participants were followed up in the NHS in the usual way. In the case of each participant who withdrew, permission was sought to use the data that had already been collected.

Randomisation

Participants were randomised, with allocation concealment, using a bespoke web-based computer program held at Nottingham Clinical Trials Unit. Each centre randomised its own participants to receive either PTNS or sham following baseline data collection and immediately prior to delivery of the first treatment. The computer program required the researcher to input the unique participant identifier code, sex and date of birth, and immediate on-screen randomisation occurred. Allocation was on an equal basis with initial stratification by sex and then stratification of females by centre. Stratification by sex was used to reduce the potential confounding effects of variation in outcomes between male and female participants. As males represent only 10% of patients and only one or two male participants were expected from each centre (owing to differing pathophysiologies[60]), randomisation stratified on centre would increase the probability that all the males were allocated to PTNS or sham by chance. To avoid this situation, only females were stratified by centre, achieving a near balance of PTNS and sham arms and allowing comparability by centre.

Blinding

Blinding of participants

Participants were blinded to allocation, but had knowledge of the 50% chance of receiving sham treatment. For both PTNS and sham interventions (1) a standardised description of the technique was read from a card prior to each treatment, which described what the patient should expect – an electrical sensation variably in the ankle or foot with or without motor responses in the foot (note: there is significant variability in conscious sensation and motor responses even between participants undergoing only PTNS); (2) the lower extremity was draped from view, ensuring participants had no knowledge of equipment set-up; and (3) the audible sounds present during PTNS and sham treatments were identical.

Performance bias considerations

In order to avoid either arm receiving more advice or reassurance, the interaction of the administering researcher was standardised and limited to a general welcome, addressing any concerns (while recording adverse events) and answering questions regarding loperamide dosages and incontinence pad use (both recorded in outcome variables). The standardised description of the technique (as stated above) was read to the participant, the equipment set up and fully covered and then participant left to receive the 30-minute treatment.

Blinding of trial staff

At least two researchers were available at each site to run the study, one of whom performed the randomisation and all treatments, and was necessarily unblinded, while the other remained blinded and carried out the final data collection. Blinding and unblinding procedures are detailed in *Appendix 5*.

Sample size calculation

Data published at the time of sample size calculation[35,39,46,61] and our own data[36] on 50 patients suggested a 60% success rate for PTNS based on our chosen primary outcome measure. There were no RCT data for PTNS in FI; however, the pivotal level I SumiT trial of PTNS in OAB symptoms,[58] which used a similar global response assessment of urinary incontinence and intention-to-treat analysis, observed a moderate or marked improvement in symptoms in 55% in the PTNS arm and only 21% in the sham arm. On the basis that placebo responses are frequently higher for bowel than for bladder symptoms,[47–49] we selected a

sham response rate of 35% while keeping the more conservative estimate of treatment response of 55% (the difference of 20% we believe remains clinically important in relation to other therapies such as SNS). In total, 212 participants were required to detect this difference with 80% power at the 5% significance level. We expected to screen 235 participants at baseline to allow for a 10% failure to attend for randomisation, baseline data collection and first treatment.

Statistical methods

Statistical methods are detailed in the statistical analysis plan (see *Appendix 6*). This document was drawn up by the trial statisticians and reviewed by the Trial Steering Committee (TSC) and Data and Safety Monitoring Committee (DSMC), and received formal sign-off from both committees prior to unblinding and analysis.

The analysis was carried out using Stata version 12.1 (StataCorp LP, College Station, TX, USA), interfacing with Realcom Impute (2007, Centre for Multilevel Modelling, University of Bristol, Bristol, UK), which was used to multiply impute missing outcome and baseline covariate data.[62]

All patients randomised who received the first treatment were included in the intention-to-treat analysis of the primary end point. Those in whom post-treatment data were unavailable at 14 weeks for any reason (loss to follow-up or failure to complete treatment) had their outcome multiply imputed under the assumption of data missing at random using variables prognostic of outcome, such as measure of outcome made at baseline, and others predictive of 'missingness' (i.e. the reason it is missing) such as mean number of FIEs per week at baseline, age, sex and, where available, mid-study bowel diary data. The numbers of variables included in each imputation model were limited by the relatively small number of study centres. Multilevel multiple imputation was performed using the multivariate normal distribution in Realcom Impute, using treatment allocation, patient sex and allocation as auxiliary variables. After a burn-in of 1000 runs of the Monte Carlo Markov chain sampler, missing values were filled every 500th run to create a total of 10 completed data sets for analysis. The data were analysed in Stata and the results pooled by Rubin's rules.[62]

The final analysis was adjusted for variables that were selected prior to data extraction. A decision was made to fit fixed effects for sex, randomisation and baseline level of outcome and to fit a random effect for study centre. In order to handle potential clustering effects of patients within centre, the intracluster correlation coefficients (ICCs) and their 95% confidence intervals (CIs) for the outcomes by centre were estimated using the user-contributed Stata command *sea_obi*, which allows the ICC to be negative.[63] Random-effects models were fitted by restricted maximum likelihood estimation (e.g. *xtmixed*. . ., *reml*). For outcomes with a negative ICC, linear regression models were fitted (without clustering) using the *regress* command.

For binary outcomes, logistic mixed-effects models were used, adjusting for baseline mean number of FIEs per week and sex and with a random effect for study centre. Estimates from these models are presented as adjusted odds ratios with 95% CIs. For continuous outcomes, linear mixed-effects models were used, adjusting for baseline measure of outcome and sex, and with a random effect for study centre. Estimates from these models are presented as adjusted difference in means.

Per-protocol analysis was carried out for all outcome measures to include those patients who received a full course of treatment as per the protocol, that is at least 10 treatments in 13 weeks that were no fewer than 5 and no more than 10 days apart. Sensitivity analyses were performed for all outcome measures, excluding any patients who had reported no episodes of FI in their 14-day baseline bowel diary, and excluding those centres that had randomised fewer than five patients.

Subgroup analyses for the primary outcome, fitting an interaction term between the categorical variable defining the subgroups and the randomisation variable, were performed, as follows:

- males versus females
- severity of FI (those with ≥ 7 weekly FIEs vs. those with < 7 weekly FIEs)
- age (< 40 years, 40–60 years and > 60 years)
- type of FI (both urge and passive, urge only or passive only).

Ethical arrangements and research governance

This trial was granted ethical approval in June 2010 (Research Ethics Committee reference 10/H0703/25).

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996),[64] and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework for Health and Social Care,[65] trust and research office policies and procedures, and any subsequent amendments. The trial was compliant with the approved protocol and research ethics committee conditions of approval, and in line with good clinical practice guidelines.[66]

Information regarding study participants was kept confidential and managed by each study site in accordance with the Data Protection Act,[67] NHS Caldicott Guardian Agreements,[68] The Research Governance Framework for Health and Social Care[65] and research ethics committee approval.

Important changes to protocol after study commencement

Following study commencement, two amendments were made to the protocol, one major and one minor, but with no change to the study intervention. The following were amended:

- The post-treatment information questionnaire (CRF 6) was amended following recommendation by the TSC. It suggested that the recording of week-by-week incontinence pad and loperamide usage was neither satisfactory nor accurate, and that this information would be better captured by questionnaire at the end. Thus, two extra questions were added to the final questionnaire.
- Cleveland Clinic Incontinence Score was updated to the SMCS. This was used throughout but misnamed in the original protocol.
- Clarification was added to the protocol to include details of the per-protocol analysis criteria.
- Statistical analysis section was updated:
    - Multiple imputation method for handling missing outcome data rather than the last value carried forward method was included on recommendation from the Health Technology Assessment, as this is the widely accepted standard.
    - Regression models fitted to estimate treatment effect were changed from fixed centre effects to random centre effects.[69]
- Centre eligibility criteria were updated to remove the absolute requirement of a minimum of five participants recruited, following discussion with the TSC that this was an arbitrary and unnecessary requirement.

Trial oversight

The trial was under the auspices of the chief investigator and the pragmatic clinical trials unit at Barts and The London School of Medicine and Dentistry. The project was overseen by a TSC.

The TSC had an independent chairperson, and met every 6 months throughout to provide overall supervision and ensure the trial was conducted to the rigorous standards set out in the Medical Research Council's guidelines for good clinical practice.[66] Specifically, the TSC's role was to ensure:

1. that the views of users and carers were always taken into consideration
2. the scientific rigour of the study and adherence to protocol
3. that project milestones were met
4. that expertise/advice was provided to the Trial Management Group (TMG).

Membership of the TSC was:

- senior statistician – Sandra Eldridge
- independent chairperson – Professor Christine Norton, Professor of Nursing (King's College London)
- independent external member – Professor Ronan O'Connell, clinical and research expertise in lower gastrointestinal neuromodulation (University College Dublin)
- patient and public involvement representative – Deborah Gilbert, chief executive (Bowel & Cancer Research charity).

The TMG was responsible for day-to-day project delivery in each participating centre. It met monthly and was answerable to the TSC. The group was responsible for overseeing and managing:

1. trial recruitment and retention rates
2. site initiation, training, monitoring, compliance and correction/preventative actions
3. data management (collection, quality control, entry and query management)
4. adverse and serious adverse event (SAE) reporting
5. study milestones
6. study reporting
7. budget expenditure and accruals.

The TMG comprised:

- chief investigator – Charles Knowles
- academic clinical fellow – Emma Horrocks
- trial manager – Natasha Stevens
- trial statistician – Stephen Bremner.

A DSMC was appointed to monitor unblinded comparative data and make recommendations to the TSC. The DSMC initially met together with the TSC, and subsequently 2 weeks prior to the TSC to enable any findings/recommendations to be submitted to the TSC. DMSC meeting timings and conclusions can be seen in *Appendix 7*. A DAMOCLES DSMC charter[70] was adopted (see *Appendix 8*), and an independent pragmatic clinical trials unit statistician provided the DSMC with an unblinded comprehensive report prior to each meeting.

The DSMC comprised:

- independent lead – Professor Dion Morton, Professor of Surgery, University of Birmingham
- independent member – Professor Elaine Denny, Professor of Health Sociology, University of Birmingham
- independent statistician – Dr Daniel Altmann, Senior Lecturer in Medical Statistics, London School of Hygiene & Tropical Medicine, University of London.

Patient and public involvement

Patient and public involvement was considered at all stages of this trial from conception to dissemination. This is described in detail in *Appendix 9*.

Chapter 3 Results

Participant flow

The CONSORT diagram shows the flow of participants through the trial (*Figure 3*). Non-completing participants either withdrew from treatment (and remained in the trial) or withdrew from the trial (in which case no further data were collected from them). Permission was, however, sought to use the data that had already been collected.

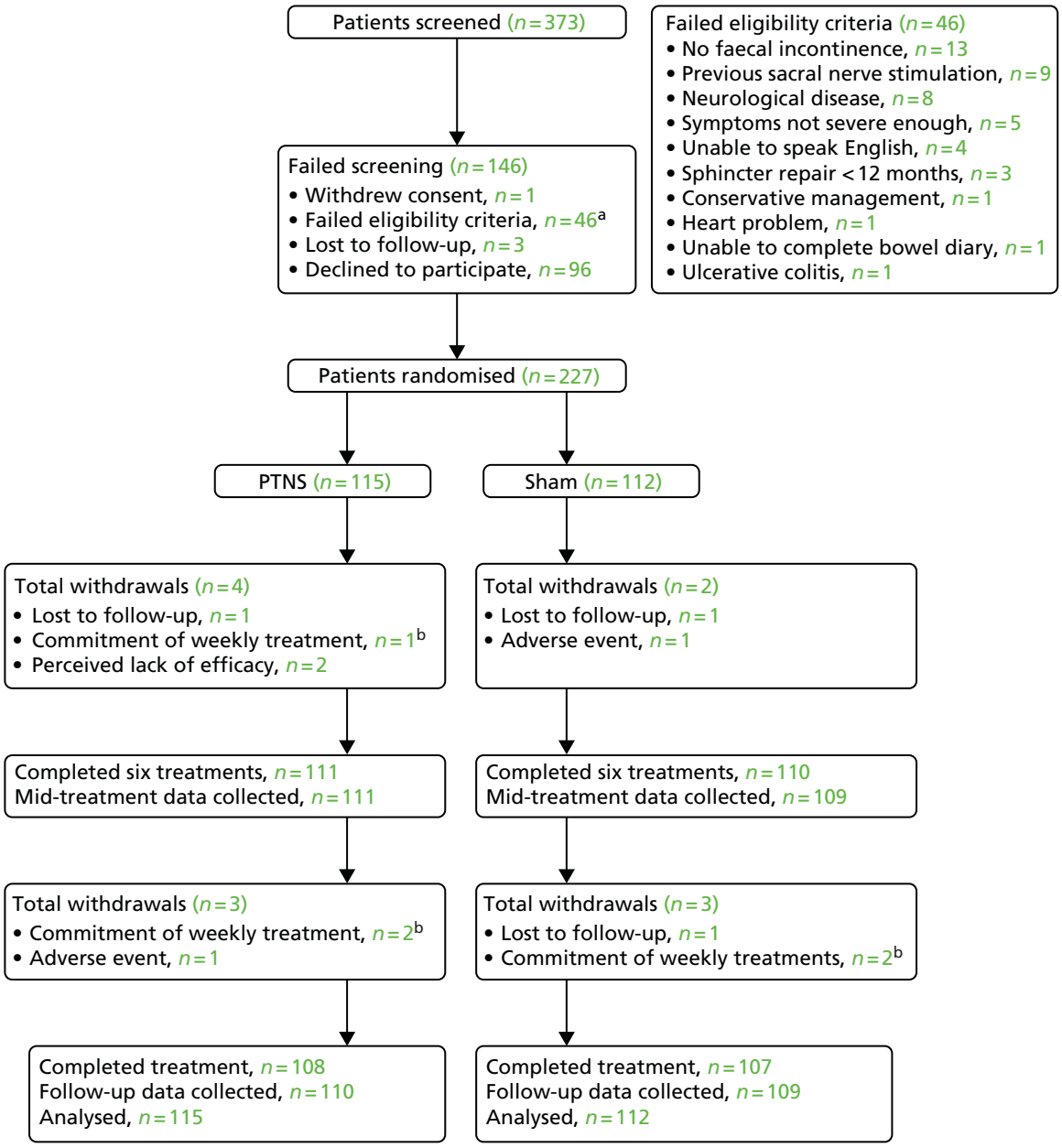

FIGURE 3 Flow of patients through the study. a, See eligibility criteria box; b, withdrawal from treatment only.

Trial recruitment

Seventeen of the 18 UK centres recruited participants for the trial between 23 January 2012 and 31 October 2013. The remaining centre was unable to participate because of staff shortages. Trial centres were Barts Health NHS Trust, London; Aintree University Hospitals NHS Foundation Trust, Liverpool; University Hospital Southampton NHS Foundation Trust, Southampton; Sandwell and West Birmingham NHS Trust, Birmingham; Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield; The Community Specialist Colorectal Clinic, Ching Way Medical Centre, London; Leicester General Infirmary, Leicester; Queen's Medical Centre, Nottingham; Castle Hill Hospital, Hull; University College Hospital, London; Bristol Royal Infirmary, Bristol; St Mark's Hospital, London; Guy's and St Thomas' Hospital, London; Poole Hospital NHS Foundation Trust, Poole; Leeds Royal Infirmary, Leeds; Pilgrim Hospital, Boston, Lincolnshire; and University Hospital of South Manchester, Wythenshawe. Centre recruitment rate is shown in *Figure 4*.

In total, 373 participants were screened and, of these, 227 (61%) were randomised. The overall recruitment rate is shown in *Figure 5*. The number of participants per site ranged from 1 to 45. There were 12 participant withdrawals: seven from the trial and five from treatment (see *Figure 3*).

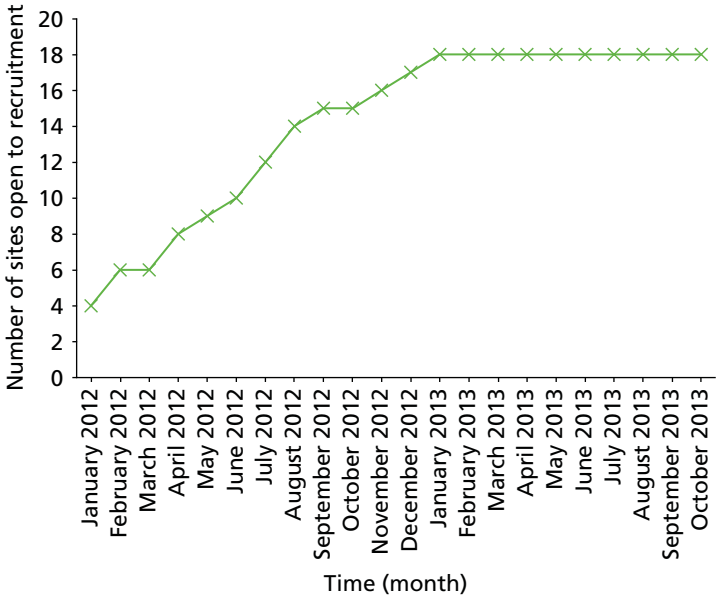

FIGURE 4 Recruitment of sites.

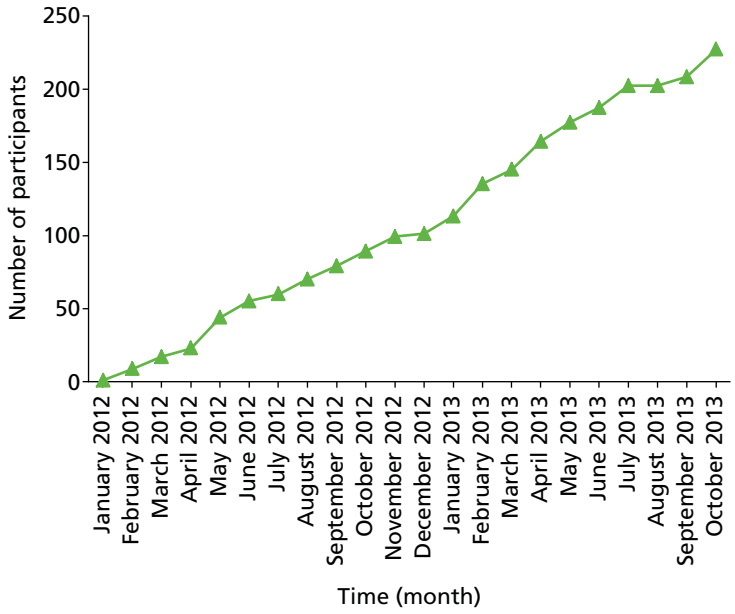

FIGURE 5 Participant recruitment.

Data quality

Data return was generally very high and quality was very good. Data from bowel diaries were 97.7% complete. This was probably a consequence of bowel diary training for each patient prior to completing the diary and the vigilant checking of bowel diaries on return. Questionnaire completion was also very good (mean 90.4%, range 77.6–100%). For all data, percentages were calculated from the corrected denominator; however, as data return was so high, individual values for number of patients for each outcome have not been recorded in the tables. These are available in *Appendix 10*.

Baseline data

In total, 227 participants were randomised: 115 to receive PTNS and 112 to receive sham electrical stimulation.

Baseline findings

Ninety per cent of participants were female, with a mean age of 57 years (range 20–85 years). Mean symptom duration was 8 years (range 5 months to 50 years). Baseline demographics and clinical data are summarised in *Table 1*. Previous treatments and relevant past medical history are summarised in *Tables 2* and *3* respectively. Complete lists of past medical history and regular medications are presented in *Appendices 11* and *12*. Demographics of the two arms were evenly matched for age and sex as per stratification. Of note, approximately 40% of participants appeared to have concomitant symptoms of FI and evacuatory difficulties (39% in PTNS arm and 44% in sham arm), and approximately 60% had concomitant urinary symptoms (61% in PTNS arm and 64% in sham arm).

TABLE 1 Baseline demographic and clinical data

Outcome	PTNS	Sham
Sex (female), *n* (%)	104 (90)	101 (90)
Age (years), median (IQR)	58 (50–67)	58 (48–65)
Duration of symptoms (months), median (IQR)	60 (24–168)	48 (24–108)
Obstetric history,[a] *n* (%)	95 (91)	96 (95)
Vaginal deliveries only,[a] *n* (%)	90 (95)	96 (100)
C-sections only,[a] *n* (%)	5 (5)	0 (0)
Episiotomies or tears,[a] *n* (%)	78 (87)	82 (85)
Passive FI, *n* (%)	88 (77)	86 (77)
Urge FI, *n* (%)	94 (82)	93 (83)
Flatus incontinence, *n* (%)	74 (64)	83 (74)
Evacuatory difficulties, *n* (%)	44 (39)	49 (44)
Straining, *n* (%)	34 (30)	37 (33)
Digitation, *n* (%)	12 (10)	15 (13)
Urinary symptoms, *n* (%)	70 (61)	72 (64)
Urinary urgency, *n* (%)	50 (43)	49 (44)
Urinary urge incontinence, *n* (%)	39 (34)	42 (38)

C-section, caesarean section; IQR, interquartile range.
a Females only (% calculated from females only).

TABLE 2 Previous treatments

Treatment	PTNS	Sham
Antidiarrhoeal medications, *n* (%)	77 (67)	67 (60)
Biofeedback, *n* (%)	56 (49)	59 (53)
Pelvic floor exercises, *n* (%)	37 (32)	36 (32)
Fibre supplementation, *n* (%)	18 (16)	30 (27)
Laxatives/suppositories/irrigation, *n* (%)	20 (17)	16 (14)
Anal sphincter repair, *n* (%)	4 (3)	4 (4)
Other anal surgery, *n* (%)	11 (10)	8 (7)
Defecatory advice, *n* (%)	9 (8)	7 (6)
Other, *n* (%)	5 (4)	8 (7)

TABLE 3 Past medical history

Outcome	PTNS	Sham
Hysterectomy,[a] *n* (%)	30 (29)	24 (24)
Vaginal operation,[a] *n* (%)	3 (3)	2 (2)
Pelvic operation,[a] *n* (%)	19 (18)	16 (16)
Abdominal operation, *n* (%)	28 (24)	30 (27)
Anal operation, *n* (%)	6 (5)	9 (8)
Neck or back pain, *n* (%)	15 (13)	21 (19)
OAB, *n* (%)	15 (13)	7 (6)
Diverticular disease, *n* (%)	4 (3)	6 (5)
Irritable bowel syndrome, *n* (%)	1 (1)	4 (4)

a Females only (% calculated from females only).

Bowel diary data at baseline

Baseline bowel diaries demonstrated a median of 6.0 FIEs per week in PTNS patients, comprising a median of 3.0 urge faecal incontinent episodes and a median of 2.0 passive episodes. In the sham arm there was a median of 6.9 FIEs per week, but with a slightly higher rate of passive FI (median 3.0 episodes) than urge episodes (median 2.5 episodes) (*Table 4*).

TABLE 4 Descriptive statistics of bowel diary data at baseline

Outcome	PTNS	Sham
FIEs per week		
Median (IQR)	6.0 (2.0–14.0)	6.9 (2.5–16.0)
Mean (SD)	9.9 (11.2)	10.4 (10.9)
Urge FIEs per week		
Median (IQR)	3.0 (0.9–8.0)	2.5 (0.5–7.0)
Mean (SD)	5.3 (7.2)	4.8 (5.9)
Passive FIEs per week		
Median (IQR)	2.0 (0.0–7.5)	3.0 (0.0–8.0)
Mean (SD)	4.6 (6.0)	5.7 (7.6)

IQR, interquartile range; SD, standard deviation.

Other baseline outcome measures

Baseline SMCSs were similar between the arms, with a mean score of 14.4 (standard deviation 3.7) in the PTNS arm and of 15.4 (standard deviation 4.1) in the sham arm. All 211 patients who completed their SMCS had significant FI on the basis of their score being > 5 (*Table 5*).

TABLE 5 Descriptive statistics of other outcome measures at baseline

Outcome	PTNS	Sham
SMCS[a]		
Median (IQR)	14.0 (12.0–17.0)	16.0 (13.0–18.0)
Mean (SD)	14.4 (3.7)	15.4 (4.1)
SMCS > 5, *n* (%)	110 (100)	101 (100)
FIQoL scores *Lifestyle*[b]		
Median (IQR)	2.7 (1.8–3.4)	2.5 (1.7–3.6)
Mean (SD)	2.6 (0.9)	2.6 (1.0)
Coping and behaviour[b]		
Median (IQR)	1.7 (1.2–2.3)	1.6 (1.1–2.6)
Mean (SD)	1.9 (0.7)	1.9 (0.9)
Depression and self-perception[b]		
Median (IQR)	3.1 (2.0–3.4)	2.6 (2.0–3.7)
Mean (SD)	2.8 (0.9)	2.7 (0.9)
Embarrassment[c]		
Median (IQR)	2.0 (1.7–2.7)	2.0 (1.3–2.7)
Mean (SD)	2.2 (0.8)	2.1 (0.8)
Patient-centred outcomes[d]		
Median (IQR)	8.9 (7.8–9.8)	9.2 (8.3–10.0)
Mean (SD)	8.5 (1.6)	8.7 (1.7)
GIQoL[e]		
Median (IQR)	130.0 (113.0–141.0)	126.5 (109.0–139.0)
Mean (SD)	126.7 (18.8)	123.8 (20.2)
SF-36 scores (%) *Physical functioning*		
Median (IQR)	70.0 (45.0–90.0)	65.0 (40.0–85.0)
Mean (SD)	65.7 (27.4)	61.4 (28.4)

TABLE 5 Descriptive statistics of other outcome measures at baseline (*continued*)

Outcome	PTNS	Sham
Role-physical		
Median (IQR)	50.0 (0.0–100.0)	25.0 (0.0–75.0)
Mean (SD)	46.4 (42.1)	36.4 (41.4)
Bodily pain		
Median (IQR)	60.0 (40.0–90.0)	57.5 (32.5–90.0)
Mean (SD)	61.3 (30.0)	58.2 (31.5)
General health		
Median (IQR)	50.0 (35.0–70.0)	50.0 (30.0–70.0)
Mean (SD)	51.2 (23.4)	50.3 (23.8)
Vitality		
Median (IQR)	45.0 (30.0–57.5)	50.0 (30.0–60.0)
Mean (SD)	43.9 (22.1)	42.7 (22.8)
Social functioning		
Median (IQR)	62.5 (37.5–75.0)	62.5 (37.5–87.5)
Mean (SD)	58.4 (28.8)	59.3 (31.6)
Role-emotional function		
Median (IQR)	66.7 (0.0–100.0)	33.3 (0.0–100.0)
Mean (SD)	58.4 (28.8)	59.3 (31.6)
Mental health		
Median (IQR)	60.0 (44.0–76.0)	64.0 (48.0–76.0)
Mean (SD)	60.3 (21.0)	60.8 (21.6)
EQ-5D index score[f]		
Median (IQR)	0.73 (0.62–0.85)	0.73 (0.62–0.85)
Mean (SD)	0.69 (0.27)	0.63 (0.34)

IQR, interquartile range; SD, standard deviation.
a 0 (best) to 24 (worst).
b 1 (best) to 4 (worst).
c 1 (best) to 4.4 (worst).
d 1 (best) to 10 (worst).
e 36 (worst) to 180 (best).
f –0.594 (worst) to 1 (best).

Primary outcome

The percentage of patients achieving a ≥ 50% reduction in weekly FIEs was similar in both arms at 38% (39 out of 103) for PTNS and 31% (32 out of 102) for sham treatment (unadjusted odds ratio 1.333; adjusted odds ratio 1.283, 95% CI 0.722 to 2.281; $p = 0.396$) (*Tables 6* and *7*).

TABLE 6 Results of intention-to-treat analysis ($n = 227$)

Outcome	Odds ratio	95% CI	*p*-value
≥ 50% reduction FIEs (primary outcome)	1.283	0.722 to 2.281	0.396
≥ 25% reduction in FIEs	1.264	0.730 to 2.190	0.404
≥ 75% reduction in FIEs	1.615	0.770 to 3.388	0.205
100% reduction in FIEs	1.635	0.592 to 4.514	0.344
	Difference in means		
Change in FIEs	–2.262	–4.185 to –0.339	0.021
Change in urge FIEs	–1.456	–2.693 to –0.219	0.021
Change in passive FIEs	–0.635	–1.668 to 0.397	0.228
FIQoL embarrassment	0.036	–0.151 to 0.223	0.706
FIQoL coping	0.013	–0.171 to 0.197	0.889
FIQoL lifestyle	0.086	–0.075 to 0.248	0.290
FIQoL depression	0.014	–0.297 to 0.324	0.927
SF-36 physical functioning	–1.854	–6.992 to 3.284	0.479
SF-36 role-physical	1.113	–8.866 to 11.092	0.826
SF-36 bodily pain	–1.026	–6.815 to 4.764	0.728
SF-36 general health	–0.158	–4.749 to 4.433	0.946
SF-36 vitality	–3.142	–8.129 to 1.845	0.215
SF-36 social functioning	5.209	–0.740 to 11.157	0.087
SF-36 role emotional	–4.815	14.802 to 5.171	0.343
SF-36 mental health	–0.509	–4.831 to 3.814	0.817
SMCS	–0.047	–1.033 to 0.939	0.925
Patient-centred outcomes	–0.545	–1.081 to –0.008	0.047
EQ-5D index score	–0.017	–0.078 to 0.044	0.583
GIQoL	–1.300	–5.168 to 2.568	0.506
Likert scale of success	0.808	–0.055 to 1.672	0.068

IQR, interquartile range; SD, standard deviation.

TABLE 7 Descriptive statistics for bowel diary outcomes at baseline and end of treatment

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
FIEs per week				
Median (IQR)	6.0 (2.0–14.0)	6.9 (2.5–16.0)	3.5 (1.0–10.0)	4.8 (1.5–12.8)
Mean (SD)	9.9 (11.2)	10.4 (10.9)	6.4 (7.6)	9.1 (10.7)
Urge FIEs per week				
Median (IQR)	3.0 (0.9–8.0)	2.5 (0.5–7.0)	1.5 (0.0–4.5)	1.5 (0.5–5.5)
Mean (SD)	5.3 (7.2)	4.8 (5.9)	3.0 (4.2)	4.4 (6.5)
Passive FIEs per week				
Median (IQR)	2.0 (0.0–7.5)	3.0 (0.0–8.0)	1.5 (0.0–5.0)	1.5 (0.0–6.5)
Mean (SD)	4.6 (6.0)	5.7 (7.6)	3.4 (4.6)	4.7 (6.6)

IQR, interquartile range; SD, standard deviation.

Secondary outcomes

Percentage change in faecal incontinence episodes

No significant difference was observed between the PTNS and sham arms in the number of participants achieving > 25%, > 75% and 100% reductions in weekly FIEs (see *Table 6* and *Figure 6*).

Change in faecal incontinence episodes as a continuous measure

There was a greater decrease in total number of FIEs per week in the PTNS than the sham arm (difference in means –2.3, 95% CI –4.2 to –0.3) episodes per week, and this difference was significant ($p = 0.02$). This comprised a reduction in urge FIEs (–1.5, 95% CI –2.7 to –0.2; $p = 0.02$) but not in passive FIEs (–0.64, 95% CI –1.67 to 0.40; $p = 0.23$) per week (see *Table 6* and *Figures 7* and *8*). There was very little continued improvement from mid-treatment to end of treatment (indicating that those who are likely to respond to treatment will have done this by week 6).

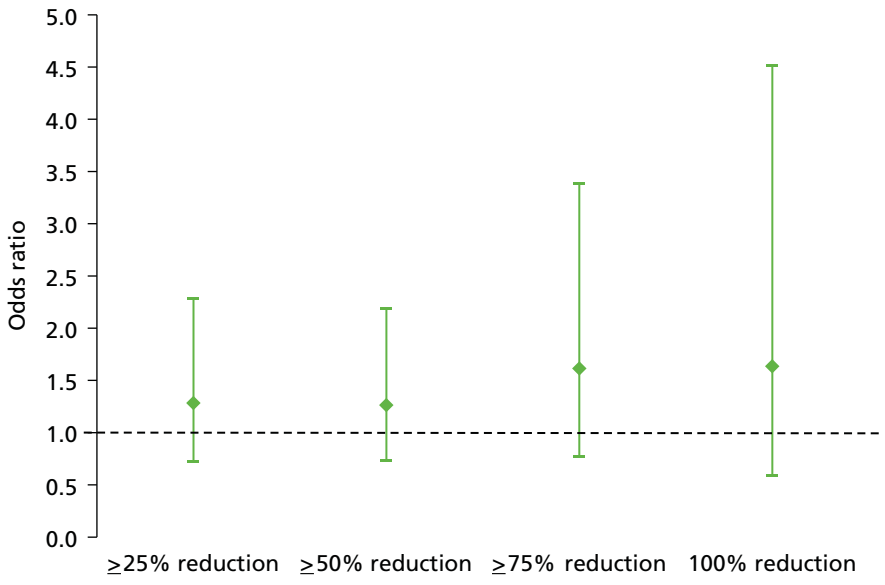

FIGURE 6 Adjusted odds ratios and 95% CIs of percentage reduction in FIEs: PTNS vs. sham.

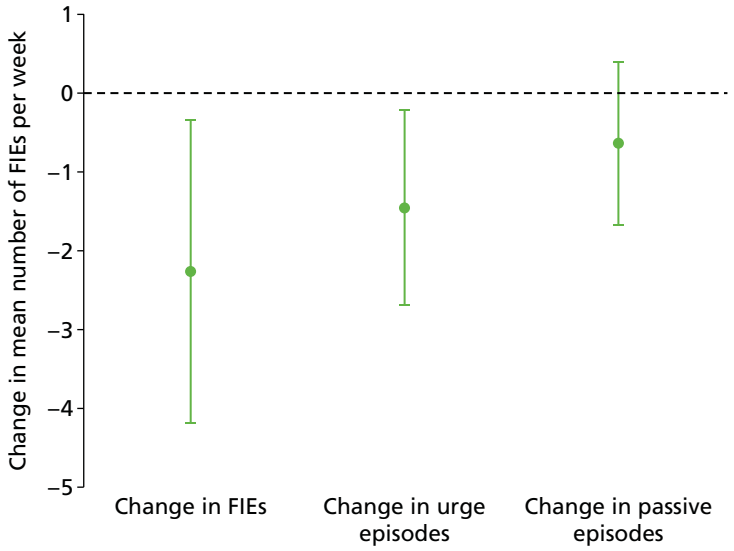

FIGURE 7 Adjusted difference in mean (95% CI) number of FIEs per week: PTNS vs. sham.

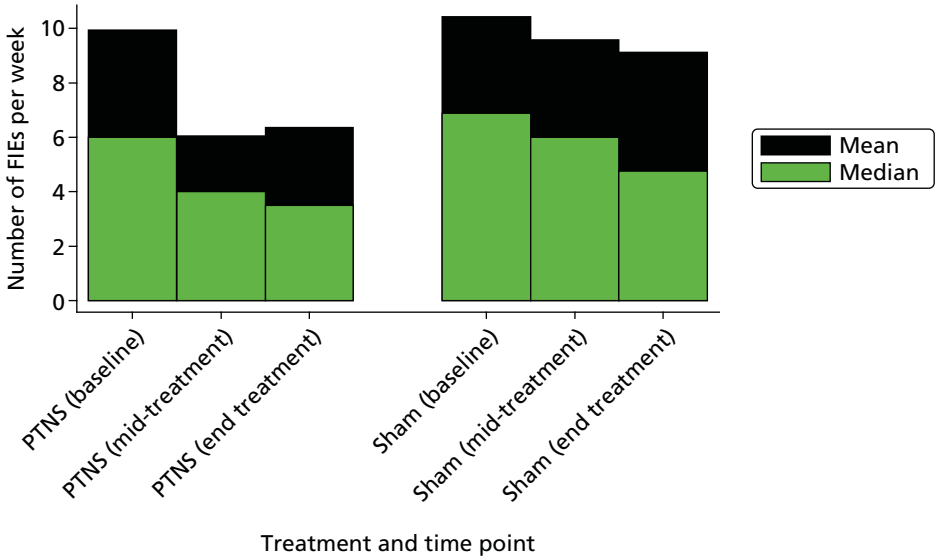

FIGURE 8 Faecal incontinence episodes per week by treatment arm and time point.

Change in symptom severity score: St Mark's Continence Score

No significant difference in SMCS was observed between the PTNS and sham arms following treatment (difference in means –0.047, 95% CI –1.033 to 0.939; $p = 0.93$) (*Table 8* and see *Table 6*).

Change in quality-of-life measures

No significant differences were seen in the disease-specific (FIQoL and GIQoL) or generic (SF-36) quality-of-life measures between the PTNS and sham arms following treatment (*Table 9* and *Figures 9* and *10*; see also *Table 6*).

TABLE 8 Descriptive statistics for SMCS at end of treatment

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
SMCS				
Median (IQR)	14.0 (12.0–17.0)	16.0 (13.0–18.0)	14.0 (11.0–17.0)	15.0 (11.0–18.0)
Mean (SD)	14.4 (3.7)	15.4 (4.1)	13.9 (4.3)	14.6 (4.6)
SMCS > 5				
n (%)	110 (100)	101 (100)	104 (100)	101 (100)

IQR, interquartile range; SD, standard deviation.

TABLE 9 Descriptive statistics for quality-of-life outcomes at baseline and end of treatment

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
FIQoL scores				
Lifestyle[a]				
Median (IQR)	2.7 (1.8–3.4)	2.5 (1.7–3.6)	3.0 (2.2–3.7)	2.9 (1.9–3.7)
Mean (SD)	2.6 (0.9)	2.6 (1.0)	2.8 (0.9)	2.8 (1.0)
Coping and behaviour[a]				
Median (IQR)	1.7 (1.2–2.3)	1.6 (1.1–2.6)	1.9 (1.3–2.6)	1.7 (1.2–2.9)
Mean (SD)	1.9 (0.7)	1.9 (0.9)	2.0 (0.8)	2.0 (1.0)
Depression and self-perception[a]				
Median (IQR)	3.1 (2.0–3.4)	2.6 (2.0–3.7)	3.1 (2.2–3.7)	2.6 (2.0–3.9)
Mean (SD)	2.8 (0.9)	2.7 (0.9)	2.9 (1.0)	2.8 (1.0)
Embarrassment[b]				
Median (IQR)	2.0 (1.7–2.7)	2.0 (1.3–2.7)	2.7 (1.7–3.0)	2.3 (1.7–3.0)
Mean (SD)	2.2 (0.8)	2.1 (0.8)	2.4 (0.8)	2.3 (0.9)
GIQoL scores[c]				
Median (IQR)	130.0 (113.0–141.0)	126.5 (109.0–139.0)	135.0 (115.0–148.0)	134.0 (120.0–146.0)
Mean (SD)	126.7 (18.8)	123.8 (20.2)	132.0 (20.6)	131.6 (20.5)
SF-36 scores (%)				
Physical functioning				
Median (IQR)	70.0 (45.0–90.0)	65.0 (40.0–85.0)	75.0 (47.5–90.0)	70.0 (45.0–90.0)
Mean (SD)	65.7 (27.4)	61.4 (28.4)	67.1 (27.7)	63.8 (29.0)

continued

TABLE 9 Descriptive statistics for quality-of-life outcomes at baseline and end of treatment (*continued*)

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
Role-physical				
Median (IQR)	50.0 (0.0–100.0)	25.0 (0.0–75.0)	62.5 (0.0–100.0)	25.0 (0.0–100.0)
Mean (SD)	46.4 (42.1)	36.4 (41.4)	54.4 (44.1)	46.2 (44.8)
Bodily pain				
Median (IQR)	60.0 (40.0–90.0)	57.5 (32.5–90.0)	67.5 (45.0–90.0)	67.5 (35.0–90.0)
Mean (SD)	61.3 (30.0)	58.2 (31.5)	64.3 (28.3)	62.1 (31.0)
General health				
Median (IQR)	50.0 (35.0–70.0)	50.0 (30.0–70.0)	55.0 (30.0–75.0)	50.0 (35.0–70.0)
Mean (SD)	51.2 (23.4)	50.3 (23.8)	52.8 (24.6)	50.6 (23.9)
Vitality				
Median (IQR)	45.0 (30.0–57.5)	50.0 (30.0–60.0)	50.0 (25.0–60.0)	50.0 (35.0–65.0)
Mean (SD)	43.9 (22.1)	42.7 (22.8)	45.6 (22.2)	46.7 (23.1)
Social functioning				
Median (IQR)	62.5 (37.5–75.0)	62.5 (37.5–87.5)	75.0 (50.0–87.5)	62.5 (37.5–87.5)
Mean (SD)	58.4 (28.8)	59.3 (31.6)	66.4 (28.6)	60.6 (31.7)
Role-emotional function				
Median (IQR)	66.7 (0.0–100.0)	33.3 (0.0–100.0)	100.0 (0.0–100.0)	83.3 (0.0–100.0)
Mean (SD)	58.4 (28.8)	59.3 (31.6)	61.7 (45.3)	60.2 (44.1)
Mental health				
Median (IQR)	60.0 (44.0–76.0)	64.0 (48.0–76.0)	64.0 (48.0–84.0)	64.0 (52.0–76.0)
Mean (SD)	60.3 (21.0)	60.8 (21.6)	62.7 (25.1)	63.0 (21.4)

IQR, interquartile range; SD, standard deviation.
a 1 (best) to 4 (worst).
b 1 (best) to 4.4 (worst).
c 36 (worst) to 180 (best).

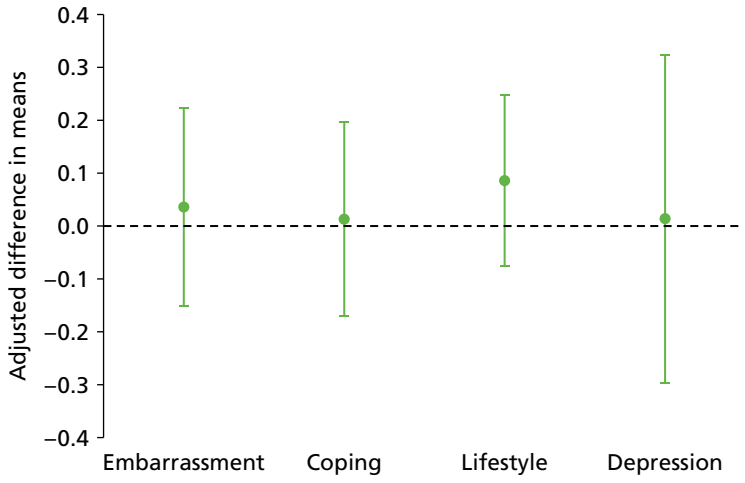

FIGURE 9 Adjusted difference in means (95% CI) for FIQoL: PTNS vs. sham.

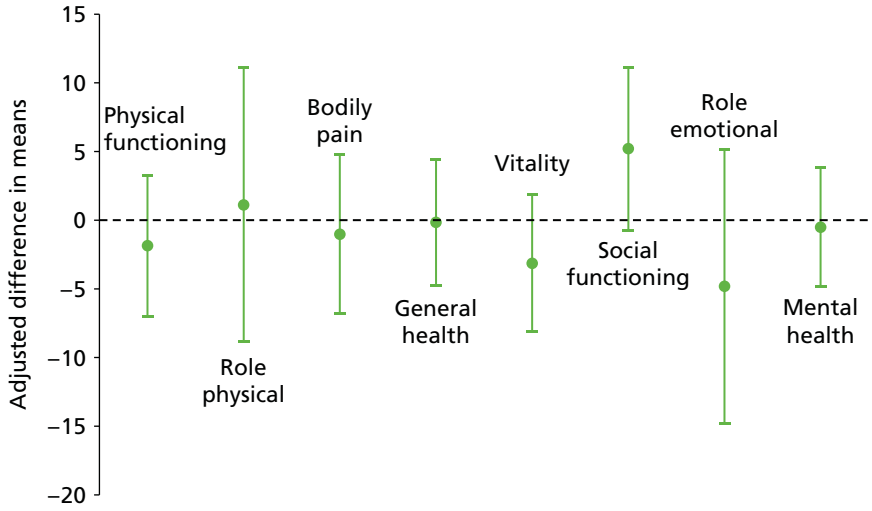

FIGURE 10 Adjusted difference in means (95% CI) for SF-36: PTNS vs. sham.

Change in patient-centred outcomes score

Improvement in patient-centred outcomes (i.e. a reduction in score) was significantly greater in the PTNS arm than in the sham arm (difference in means –0.545, 95% CI –1.081 to –0.008; $p = 0.047$) (*Table 10*; see also *Table 6*).

Likert scale of patients' global impression of success (scale 0–10)

No significant difference existed in patients' global impression of success between the PTNS and sham arms (difference in means 0.808, 95% CI –0.055 to 1.672; $p = 0.068$) (*Table 11*; see also *Table 6*).

European Quality of Life-5 Dimensions analysis

There were virtually no differences between the two arms either at baseline or after treatment in respect of EQ-5D index and visual analogue scale (VAS) scores, with scores on both scales remaining unchanged over time (*Table 12* and see *Table 6*). The full report can be viewed in *Appendix 13*.

TABLE 10 Descriptive statistics for patient-centred outcomes at end of treatment

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
Median (IQR)	8.9 (7.8–9.8)	9.2 (8.3–10.0)	8.4 (6.9–9.4)	9.3 (7.6–10.0)
Mean (SD)	8.5 (1.6)	8.7 (1.7)	7.8 (2.0)	8.4 (2.1)

IQR, interquartile range; SD, standard deviation.

TABLE 11 Descriptive statistics for Likert scale of success outcome at end of treatment

Outcome	PTNS	Sham
Median (IQR)	4.8 (0.0–6.8)	2.1 (0.0–4.9)
Mean (SD)	4.0 (3.3)	3.2 (3.1)

IQR, interquartile range; SD, standard deviation.

TABLE 12 Descriptive statistics for EQ-5D outcome at end of treatment

	Baseline		End of treatment	
Outcome	PTNS	Sham	PTNS	Sham
EQ-5D index, mean (SD)	0.69 (0.27)	0.63 (0.34)	0.68 (0.28)	0.65 (0.34)
EQ-5D VAS, mean (SD)	64.50 (21.72)	64.04 (21.24)	64.25 (22.32)	63.69 (23.66)

SD, standard deviation.

Other outcomes

In the PTNS arm, 57 out of 107 (54%) participants thought that they had received PTNS and 48 out of 107 (46%) thought that they had received sham treatment (*Figure 11*). In the sham arm, 32 out of 103 (31%) participants thought that they had received PTNS and 71 out of 103 (69%) participants thought that they had received sham treatment. Overall, 208 patients answered this question, of whom 62% perceived correctly and 38% perceived incorrectly.

Only 13% (8 out of 61) of patients in the PTNS arm experienced slight or substantial improvement in urinary symptoms and the figure in the sham arm was similar, at 11% (7 out of 64). Most symptomatic patients reported no effect: 39% in the PTNS arm and 50% in the sham arm. Indeed, more patients in the PTNS arm than in the sham arm reported a worsening of urinary symptoms (10% vs. 5%) (*Figure 12*).

Of participants who used loperamide at baseline, the majority in both the PTNS (33 out of 49 = 67%) and sham (32 out of 38 = 84%) arms reported no change in use throughout the trial. Similar percentages in each arm (4% in PTNS vs. 5% in sham) reported increasing loperamide use. A higher percentage of patients in the PTNS arm than in the sham arm reduced their loperamide use (29% vs. 11%) (*Figure 13*).

Other potentially relevant concomitant medication usage can be seen in *Appendix 14*. There has been minimal concomitant medication usage and this has not been considered significant.

Of the participants who used incontinence pads, the majority [56% (44 out of 79) in PTNS arm and 49% (35 out of 72) in sham arm] reported no change in use over the period of the trial. Similar percentages of participants reduced their pad usage through the course of the trial (15% in the PTNS arm and 14% in the sham arm), while 4% participants in the sham arm had to increase their pad usage compared with none in the PTNS arm (*Figure 14*).

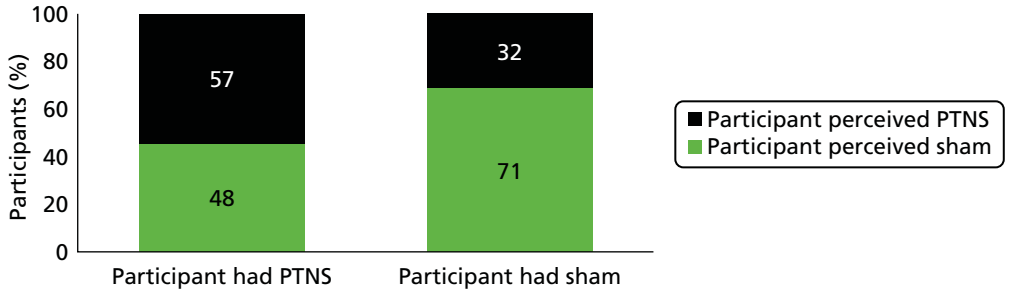

FIGURE 11 Participants' perception of treatment.

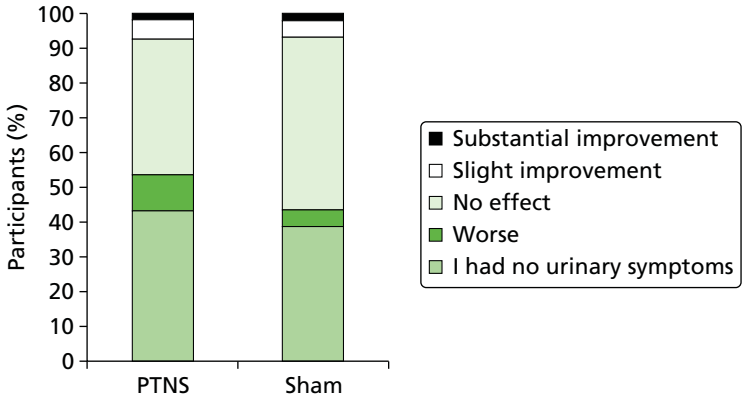

FIGURE 12 Effect of treatment on urinary symptoms.

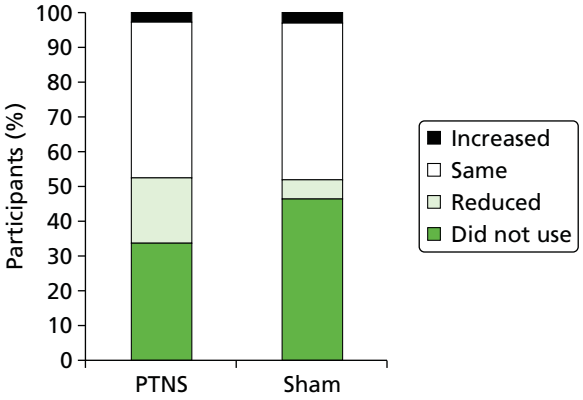

FIGURE 13 Effect of treatment on loperamide use.

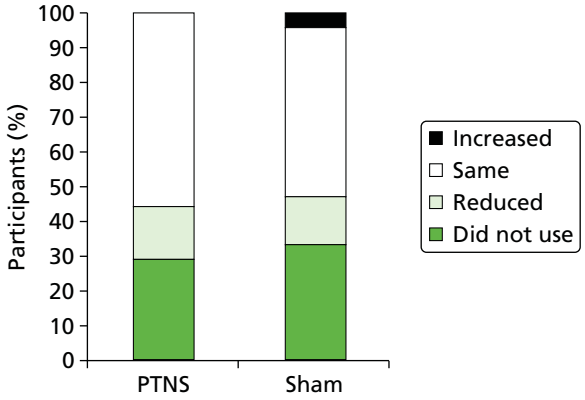

FIGURE 14 Effect of treatment on incontinence pad usage.

Per-protocol analysis

Per-protocol analysis was carried out subsequent to the intention-to-treat analysis. To be included in these analyses, patients were required to have at least 10 treatments within 13 weeks, with 10 treatments no fewer than 5 days and no more than 10 days apart. This was to ensure that patients attended for treatments regularly and in a time frame spread evenly throughout the treatment duration.

In total, 197 of the 227 patients completed the treatment per protocol. *Table 13* presents the results of the analysis of the primary outcome. The conclusion from this analysis remains unchanged and other important outcomes remain unchanged apart from the Likert scale of success, which shows that those in the PTNS arm were more likely than those in the sham arm to perceive that the treatment was successful; this difference was statistically significant.

TABLE 13 Results of per-protocol analysis ($n = 197$)

Outcome	Odds ratio	95% CI	*p*-value
≥ 50% reduction FIEs (primary outcome)	1.269	0.688 to 2.341	0.446
≥ 25% reduction in FIEs	1.247	0.698 to 2.228	0.456
≥ 75% reduction in FIEs	1.631	0.781 to 3.409	0.194
100% reduction in FIEs	1.658	0.590 to 4.655	0.338
	Difference in means		
Change in FIEs	–2.233	–4.275 to –0.191	0.032
Change in urge FIEs	–1.486	–2.778 to –0.194	0.024
Change in passive FIEs	–0.600	–1.663 to 0.463	0.268
SMCS	0.202	–0.855 to 1.258	0.708
GIQoL	–1.750	–5.864 to 2.364	0.401
FIQoL embarrassment	0.059	–0.141 to 0.260	0.563
FIQoL coping	–0.007	–0.211 to 0.196	0.944
FIQoL lifestyle	0.093	–0.079 to 0.266	0.286
FIQoL depression	0.030	–0.302 to 0.361	0.853
SF-36 physical functioning	–0.601	–5.964 to 4.761	0.826
SF-36 role-physical	1.562	–9.062 to 12.186	0.772
SF-36 bodily pain	–2.933	–8.975 to 3.108	0.341
SF-36 general health	0.612	–3.989 to 5.213	0.794
SF-36 vitality	–2.872	–7.967 to 2.224	0.268
SF-36 social functioning	5.665	–0.518 to 11.848	0.074
SF-36 role emotional	–6.562	–16.988 to 3.863	0.216
SF-36 mental health	–0.300	–4.633 to 4.033	0.892
Patient-centred outcomes	–0.593	–1.141 to –0.044	0.034
EQ-5D index score	–0.020	–0.082 to 0.042	0.524
Likert scale of success	0.934	0.037 to 1.831	0.042

Subgroup analyses

Preplanned subgroup analyses were performed for the primary outcome only. The following subgroups were selected:

- sex (male vs. female)
- FI severity (> 7 episodes per week vs. < 7 episodes per week on initial bowel diary)
- age (< 40 years, 40–60 years, > 60 years)
- both urge and passive incontinence, only urge, only passive.

The primary outcome was negative for each of these subgroup analyses (see *Appendix 15*).

Sensitivity analysis

Sensitivity analysis was carried out, removing the patients who scored 'zero' on their initial bowel diaries (see *Appendix 16*). This excluded 16 patients, nine from the PTNS arm and seven from the sham arm. The primary outcome was negative for this analysis (odds ratio 1.325, 95% CI 0.736 to 2.385; $p = 0.348$).

Further sensitivity analysis was carried out excluding patients who were recruited from poorly recruiting centres (defined as centres recruiting fewer than five patients) (see *Appendix 17*). This excluded four patients from two centres, two from each arm. The primary outcome was negative for this analysis (odds ratio 1.234, 95% CI 0.693 to 2.196; $p = 0.476$).

Centre effect

Data were analysed to allow for a centre effect, that is, outcomes among patients being treated by the same study centre may be correlated, indicating that treatment at some centres may be more effective. The ICC was very small (< 0.001 for most outcomes), indicating no significant centre effect. The only outcomes for which the ICC was substantial were ≥ 75% reduction (ICC = 0.222) in FIEs, 100% reduction in FIEs (ICC = 0.012), change in passive FIEs (ICC = 0.106), FIQoL coping (ICC = 0.104), SF-36 social functioning (ICC = 0.012), SF-36 mental health (ICC = 0.038), EQ-5D (ICC = 0.019) and the Likert scale of success (ICC = 0.02).

Serious adverse events

There were four SAEs during the trial (*Table 14*). None was related to the trial treatment and all were resolved.

Adverse events

A total of 204 adverse events were noted in the trial, 107 in the PTNS arm and 97 in the sham arm. *Table 15* reports severity by relatedness in each arm. There were seven mild related adverse events in each arm.

Related and possibly related adverse events can be seen in *Table 16*. A full list of all adverse events can be seen in *Appendix 18*.

TABLE 14 Serious adverse events

SAE	Allocation	Grade	Duration (days)	Action	Relatedness	Outcome
Flexible cystoscopy for botulinum toxin type A (Botox®, Allergan)	PTNS	Moderate	3	H	U	R
Sleeve gastrectomy	Sham	Severe	1	H	U	R
Pilonidal abscess	Sham	Moderate	26	H	U	R
Shoulder manipulation	PTNS	Severe	1	H	U	R

H, hospitalisation; R, resolved; U, unrelated.

TABLE 15 Adverse events: severity by relatedness

	PTNS				Sham			
Outcome	Related	Possibly related	Unrelated	Total	Related	Possibly related	Unrelated	Total
Mild	7	25	40	72	7	18	33	58
Moderate	0	13	17	30	0	14	21	35
Severe	0	4	1	5	0	1	3	4

TABLE 16 Related and possibly related adverse events

Outcome	Adverse event	PTNS	Sham
Related	Pain at needle site	4	3
	Bruising at needle site	2	1
	Altered sensation at needle site	1	0
	Bleeding at needle site	0	2
	Altered sensation in toe	0	1
Possibly related	Pain in abdomen	4	2
	Pain in back	1	0
	Pain in leg or foot	13	10
	Pain in perineum	0	1
	Altered sensation in leg or foot	4	0
	Altered sensation in perineum	0	1
	Weakness in leg	0	1
	Constipation	0	1
	Diarrhoea	8	3
	FI	0	1
	Urinary symptoms	0	4
	Headache/migraine	6	7
	Dizziness	5	0
	Nausea/vomiting	0	1
	Anxiety/depression	1	1
	Skin disorder	1	0

Chapter 4 Discussion

Although PTNS and sham electrical stimulation offer some improvement in FI symptoms by reducing weekly episodes, no clinically significant benefit of PTNS over sham was demonstrated. This was demonstrated by the primary outcome, with 38% of participants in the PTNS arm and 31% in the sham arm achieving at least a 50% reduction in FIEs.

Some of the secondary outcome variables, namely reduction in mean total weekly FIEs, reduction in mean urge FIEs and improvement on the patient-centred outcomes form (a derivative of the validated International Consultation on Incontinence Modular Questionnaire – Bowel), demonstrated a significant benefit of PTNS over sham treatment. However, the margin of clinical benefit must be considered small even though statistical significance was achieved, as this improvement was based on a reduction in weekly FIEs from a median of 6.0 (IQR 2.0–14.0) to a median of 3.5 (IQR 1.0–10.0), meaning that many participants still have significant FI. It is interesting to note that, if a treatment effect was going to occur, it would have done so by six treatments.

There was no significant improvement in the SMCS in the PTNS arm compared with the sham arm. Patients in the PTNS arm of the trial showed no significant improvement in any of the quality-of-life measures, compared with patients in the sham arm.

The results of this study may seem surprising when considered in the context of other published studies of PTNS from FI. The 12 published studies on PTNS, including 10 case series, one small randomised study and one comparative case-matched study of PTNS and SNS, allude to a 63–82% response rate using the same primary outcome, which is considerably higher than the 38% reported here. The results of this study are, however, closer to a recently conducted randomised study of PTNS compared with SNS, which found that 40% of patients in the PTNS arm reported treatment success at 3 months, again significantly lower than any other previously reported data.[71] Interestingly, a double-blind placebo-controlled randomised controlled trial of TTNS for FI in the literature shows no discernible benefit of TTNS over sham treatment in the treatment of FI.[72]

These findings highlight the necessity of conducting well-designed randomised controlled trials to answer clinical questions. The other previously published non-randomised studies are prone to significant bias, which may account for the difference in results.

Case series provide poor evidence and are open to significant bias. First and foremost, there is no control arm for comparison, leading to performance bias. There is no way of unpicking the effect of natural change in disease status over time or the well-recognised placebo effect of this nurse-led face-to-face intervention. Both of these issues can be ameliorated only by including a control arm. Selection bias in case series is a large problem unless subjects are truly selected consecutively. In addition to this, case series are often subject to attrition bias, as patients may be lost to follow-up or researchers may selectively report only subjects with positive findings. In case series, both the patient and the observer are often unblinded. This can introduce bias from both perspectives: patients may experience a high level of expectation, which may influence reporting; and, in addition to this, bias may be introduced from the observers' perspective, as clinicians often have a vested interest in treatment and publication. This problem is particularly important in trials of FI that involve bowel diary data, as diaries are notoriously poorly completed and open to interpretation.[73]

The only other RCTs of PTNS in the literature are those on OAB. Of these studies, two double-blinded RCTs that compare PTNS with sham electrical stimulation showed a statistically significant improvement in urinary frequency and urge urinary incontinence in the active PTNS arm compared with the sham arm (71% vs. 0% responders in the smaller study; $p < 0.001$;[74] and 54.5% vs. 24.9% in the larger pivotal trial;[58] $p < 0.001$). One had a significantly smaller sample size than the other ($n = 35$ and $n = 174$ respectively).

Both of these studies reported a higher treatment effect of PTNS than seen in the CONFIDeNT trial, and one that is significantly beneficial compared with sham. There could be a number of reasons for this. It could simply be a result of PTNS having efficacy in OAB but not FI. Alternatively, it could be a result of these studies selecting purely patients who had OAB, that is patients who experience bladder urgency (more akin to faecal urgency or urge FI), which may account for the CONFIDeNT trial showing no overall benefit in patients, but significant reductions in urge FIEs.

The disparity could also be a factor of primary outcome measure selection. Peters *et al.*[58] used a subjective primary end point involving number of patients who graded their overall bladder symptoms as moderately or markedly improved on a global response assessment. It is unclear whether or not this assessment tool has been validated. The smaller study chose an objective primary end point, equivalent to that used in the CONFIDeNT trial, of those patients who experienced a > 50% reduction in number of urge urinary incontinence episodes.

Both urological studies also reported a significantly lower treatment effect of the sham, or placebo. The placebo effect in trials of functional bowel disease is well acknowledged to be high; indeed, meta-analyses of 45 published trials estimate the placebo response rate in functional dyspepsia to be between 6% and 72%[75,76] and in 50 placebo-controlled irritable bowel syndrome trials it is estimated to be between 3% and 84%.[77–79] This may indicate that the 0% placebo effect in the Finazzi-Agro *et al.*[74] trial is a product of a small sample size, inadequate blinding or both. The apparently lower sham response in both studies may be a result of a less effective sham.

The sham stimulation used was different in both urological studies and also different from that used in the CONFIDeNT trial. In one study, the needle was placed in the medial head of gastrocnemius muscle and electrical stimulation activated for only 30 seconds prior to the stimulator being turned off;[74] in the other study, a Streitberger needle was used, which does not pierce the skin, and electrical stimulation was delivered via TENS. The sham chosen in the CONFIDeNT trial was designed to give a very similar feeling to that produced by the active treatment, by giving the sensation of the skin being pierced by the needle and by providing a constant electrical sensation.

The sham treatment in the CONFIDeNT trial was well conducted and blinding was maintained in each treatment session with no information revealed to patients. The trial team feel that this was an improvement on the sham used in the Peters *et al.*[58] study of OAB, as the sham treatment was carried out using the same needle as in the PTNS arm, and it did pierce the skin to give the same sensation as the PTNS arm, the only difference being that the needle was not advanced as far. The sham was shown not to stimulate the tibial nerve during neurophysiological testing.

Limitations

This study was generally conducted to a high standard and there were no major methodological flaws or protocol violations. The effect of sham stimulation was correctly predicted at 35%. It would have been difficult to predict such a marginal treatment effect based on the previous literature; however, the effect of treatment was still less than our conservative estimate of 55%. The data do not indicate that the sample size was inadequate, as the 95% CI of the primary outcome analysis precludes a clinically significant reduction in the odds of success.

The study did, however, have some limitations. As is the nature of FI, there was significant heterogeneity in the population of patients selected to take part in the trial. This may have affected the results, especially given that there may have been a treatment effect among those suffering with urge FI (akin to OAB).

Patients suffering with frequent loose stools, or those with significant constipation, may indicate different disease pathophysiologies, thus complicating the results with regard to efficacy of PTNS. As seen from the demographics, approximately 40% of patients in this study suffer with concomitant rectal evacuatory problems. Similarly, it could be argued that, based on the paper by Hoturas *et al.*,[80] which suggested that those with urge FI benefit more from PTNS, which would go along with a similar concept that PTNS works for OAB, the CONFIDeNT trial could have selected patients with pure urge FI. These stipulations would have added further complexity to the trial, requiring all patients to undergo anorectal physiology testing, and would have adversely affected recruitment by significantly reducing the number of patients eligible for the trial. Moreover, this was a pragmatic trial testing a treatment aimed as a first-line treatment for FI, for example in GP surgeries or nursing homes, where such patient selection would not be feasible or possible, and results are required to be generalisable.

Another limitation of this study, and one that widely affects studies of FI, is that there is no perfect or universally accepted outcome measure.[73] Weekly FIEs, as a count, has an overdispersed Poisson distribution, that is greater variability than expected. Therefore, attempting to define a clinically significant mean reduction in FIE per week in a population of patients with widely dispersed starting FI frequencies is very difficult. This study, along with many in the SNS literature, chose to counter this problem by adopting a categorical measure of percentage reductions, that is the proportion of patients who have a $\geq 50\%$ reduction in FIE per week, which is likely to be a much more realistic indication of success. Although subject to criticism, this was chosen as the primary outcome for the study not least because it has most often been used to assess SNS, thus allowing comparisons to be drawn between the two treatment modalities. Further, the 50% criterion has been applied as the primary end point in both of the pivotal trials of contemporary treatments in FI,[27,81] with these treatments subsequently reviewed favourably by the US Food and Drug Administration. It could be argued that a 50% reduction in FIEs is not life-changing because this may still signify significant FI; however, until another outcome measure is introduced into the literature this is the most widely accepted outcome for treatment comparison. It is also important to remember that bowel diary data were collected for only a 2-week period at the beginning and end of treatment, and a score of 'zero' on a bowel diary does not necessarily signify that a patient's incontinence is cured (a point ignored in previous literature, in which terms such as 'complete continence' are used to denote this eventuality).

Consideration has been given to the fact that, because the use of regular medications was not prohibited, a change in antidiarrhoeal medication (e.g. loperamide) may have reduced the effect size of PTNS. The decision was made not to limit the use of such medications, as it is likely that people would have continued to use the medications anyway. Instead, the decision was made to record patients' loperamide use throughout the trial. Patients were asked each week about loperamide use; however, following the first meeting of the TSC and DSMC, it was felt that this was not accurately recalled by patients and a decision was made that the best way to collect this information would be to ask at the end of the trial whether their usage had remained the same, increased or decreased. As this decision was made partway into the trial, this information was not collected from all patients. We did, however, feel that it important to attempt to quantify this because it is a potential confounder. The question on loperamide usage was answered by 144 out of 227 patients (64%), and this was in the main because 55 patients completed the trial prior to implementation of the new CRF. Those who did answer the question were evenly balanced between treatment arms. As can be seen from the results, of those who were taking loperamide, almost three times as many patients in the PTNS arm reduced this as in the sham arm. Simple chi-squared testing, however, found this difference to be non-significant ($p = 0.06$). This calculation should be interpreted with caution, as the numbers using loperamide at baseline were comparatively small and, because they are not the full randomised samples, may differ systematically (i.e. there may be confounding).

Another criticism of this study could be that patients were not excluded on the basis of having 'zero' FIEs reported on their baseline bowel diary, so long as the principal investigator was convinced that the participant had FI significant enough to warrant intervention. This decision was taken because FI is often a problem which happens in bouts and it is not impossible for a patient to experience two symptom-free

weeks by chance. The alternatives would have been either to exclude these patients, which might have seemed unfair given that they do have significant FI and should be entitled to try this treatment, or to give the patients another chance to complete the bowel diary. It was felt that these patients might well then fabricate the bowel diary if zero FIEs were to occur again, thus potentially confounding the results. Sensitivity analysis was done removing the 16 patients to whom this applied, who happened to be spread evenly across the two arms, and this made no difference to the overall results.

A further limitation of this study is the short follow-up period, as outcomes were assessed 2 weeks after the end of treatment. Many trials of this nature assess outcomes at 6 months; however, there are moves to extend this to 12 months following treatment [as per ROME IV (Rome Diagnostic Criteria for Functional Gastrointestinal Disorders); Professor Charles Knowles, unpublished data].

Finally, this trial could be criticised for lack of formal health economic analysis. This was not performed because of the lack of clinical effectiveness, and failure to demonstrate any changes in the EQ-5D questionnaire. The authors acknowledge that since then a potentially more sensitive five-level questionnaire has been developed, which might have yielded a different result.

Chapter 5 Conclusions

The CONFIDeNT study was a well-conducted, definitive trial, carried out to a high standard with an absence of any methodological flaws or serious breaches.

Percutaneous tibial nerve stimulation did not show significant clinical benefit over sham electrical stimulation in the treatment of FI based on the proportions of patients who reported at least a 50% reduction in weekly FIE. There was, however, a significant improvement in those patients who had PTNS in mean reduction in total weekly FIE, urge weekly FIE and patient-centred outcomes compared with those who had sham treatment.

Based on the evidence presented, it would be hard to justify recommending this therapy for the patient population in the trial.

In view of the relatively low costs associated with this treatment and its high acceptability, there may be a justification in continuing to treat a subgroup of patients with troublesome urge FI symptoms in whom directed therapy may cause symptomatic improvement. Further studies of PTNS should be directed at those with urge FI to determine whether or not this approach has value. Long-term follow-up of participants in the CONFIDeNT study will also be useful to further gauge response to treatment.

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Contributions of authors

Miss Emma J Horrocks (academic clinical fellow) contributed to the trial design, data collection, analysis and interpretation of the data, and drafting and submitting the final report.

Dr Stephen A Bremner (trial statistician) contributed to the trial design, data analysis and interpretation, and revising the final report.

Ms Natasha Stevens (trial manager) contributed to the trial design, data synthesis and revising the final report.

Professor Christine Norton (professor of nursing and chairperson of the TSC) contributed to modification of the study design, interpretation of the data and revising the final report.

Ms Deborah Gilbert (chief executive of Bowel & Cancer Research charity and patient and public involvement representative) contributed to the trial design, data interpretation and revising the final report.

Professor P Ronan O'Connell (professor of surgery and member of the TSC) contributed to the trial design, interpretation of the data and revision of the final report.

Professor Sandra Eldridge (professor of medical statistics and senior trial statistician) contributed to the acquisition of funding, trial design, supervision of the data analysis, data interpretation and revising the final report.

Professor Charles H Knowles (clinical professor of surgical research and chief investigator) contributed to the trial conception and design, the acquisition of funding, oversight of data collection, data interpretation, and revising and final approval of the final report.

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Data sharing statement

Data can be obtained from the corresponding author.

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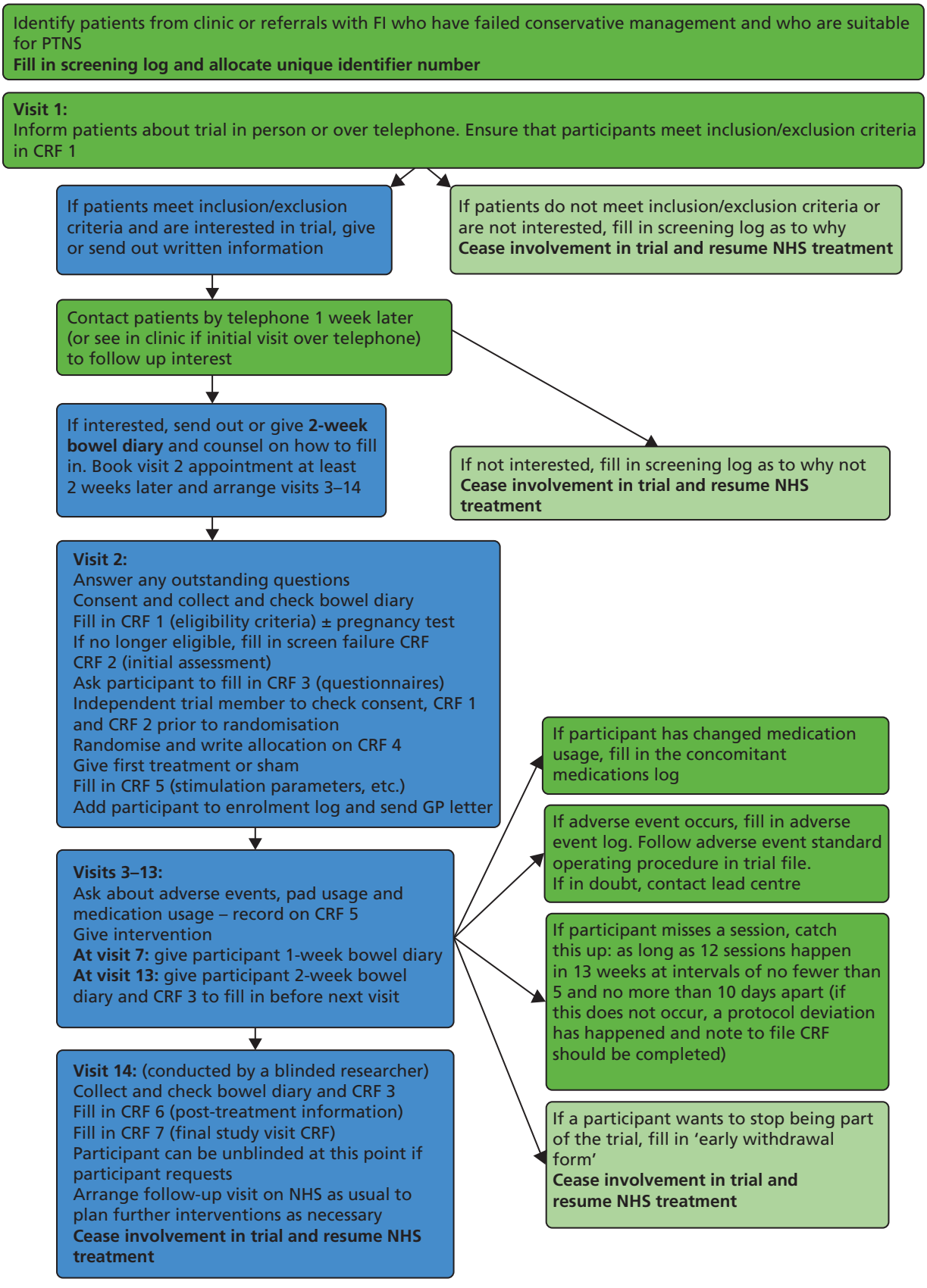
Appendix 1 Flow diagram of study



Appendix 2 Events at each visit

TABLE 17 Events at each visit

Event	Visit 1	Telephone conversation	Visit 2	Visits 3–13	Visit 14
Eligibility assessment	✗				
Bowel diary		✗		Visit 7–8	✗
Consent			✗		
Participant contact information sheet			✗		
Eligibility assessment (CRF 1)			✗		
Initial assessment (CRF 2)			✗		
Questionnaires (CRF 3)			✗		✗
Randomisation			✗		
Randomisation information (CRF 4)			✗		
Intervention			✗	✗	
Record stimulation parameters adverse events and medication/pad usage (CRF 5)			✗	✗	
Adverse events log			✗	✗	✗
Concomitant medications log			✗	✗	✗
Post-treatment information (CRF 6)					✗
Final study visit information (CRF 7)					✗

Appendix 3 Case report forms

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

CRF 1 – Eligibility Criteria

Inclusion Criteria	**Yes**	**No**
Faecal incontinence sufficiently severe enough to warrant intervention		
Failure of appropriate conservative therapies		
Age ≥18		

N.B. Appropriate specialist investigations including structural and functional anorectal assessment would be informative, although not mandatory.

If any of the above criteria are answered NO the participant is not eligible for the study. If the participant is excluded from the study, complete the Screening Log to explain why.

Exclusion Criteria	**Yes**	**No**
Inability to provide informed consent for the research study		
Inability to fill in the detailed bowel diaries required for outcome assessments (this will exclude participants who do not speak / read English)		
Neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (any participant with painful peripheral neuropathy)		
Anatomical limitations that would prevent successful placement of needle electrode		
Other medical conditions precluding stimulation: e.g. bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis		
Congenital anorectal anomalies or absence of native rectum due to surgery		
A cloacal defect		
Present evidence of external full thickness rectal prolapse		
Previous rectal surgery (rectopexy/resection)< 12 months ago (24 months for cancer)		
Stoma *in situ*		
Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea		
Pregnancy or intention to become pregnant*		
Previous experience of SNS or PTNS		

*If a female participant is of child bearing potential (e.g. pre-menopausal) this includes a discussion regarding appropriate forms of contraception, and the avoidance of becoming pregnant during the trial. If a participant does become pregnant during the trial, they must report this immediately to the research staff.

For females of child bearing potential at screening, please perform urinary pregnancy test.

Result: POSITIVE / NEGATIVE (PLEASE CIRCLE)

If any of the above criteria are answered YES the participant is not eligible for the study. If the participant is excluded from the study, complete the Screening Log to explain why.

DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

STORE IN PARTICIPANTS CRF FOLDER

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

CRF 2: INITIAL ASSESSMENT

CIRCLE YES OR NO AND PROVIDE DETAILS WHERE INDICATED.

DATE OF VISIT 1:	_ _ / _ _ _ / _ _ _ _ (DD/MMM/YYYY)	
DATE OF SCREENING (TODAY):	_ _ / _ _ _ / _ _ _ _ (DD/MMM/YYYY)	
CONSENT TAKEN: (If no, do not continue until obtained)	YES	NO
PARTICIPANT INFORMATION SHEET GIVEN TO PATIENT	YES	NO
SIGNED COPY OF CONSENT FORM GIVEN TO PATIENT	YES	NO

AGE OF PARTICIPANT :	YEARS	
SEX OF PARTICIPANT	MALE	FEMALE

HISTORY OF FAECAL INCONTINENCE - INCLUDING TYPE:

DURATION OF SYMPTOMS: Preceding event or occurrence :

FREQUENCY OF STOOL:	YES	NO	DETAILS:
URGE TO PASS STOOL:	YES	NO	DETAILS:
PASSIVE INCONTINENCE	YES	NO	DETAILS:
URGE INCONTINENCE	YES	NO	DETAILS:
FLATUS INCONTINENCE	YES	NO	DETAILS
EVACUATORY DIFFICULTIES	YES	NO	DETAILS:
STRAINING	YES	NO	DETAILS:
PROLAPSE	YES	NO	DETAILS:
SOILING OF UNDERWEAR	YES	NO	DETAILS:
USE OF PADS	YES	NO	DETAILS:
ABLE TO DEFER DEFECATION	YES	NO	HOW LONG FOR (IN MINUTES): _ _ _ MINUTES
ABLE TO DISTINGUISH FAECES FROM FLATUS	YES	NO	DETAILS:
SENSE OF BLOCK OR BULGE	YES	NO	DETAILS:
DIGITATION REQUIRED	YES	NO	DETAILS:
ANXIETY / PANIC	YES	NO	DETAILS:

URINARY SYMPTOM HISTORY:	YES	NO	
INCREASED FREQUENCY	YES	NO	DETAILS:

URGENCY	YES	NO	DETAILS:
STRESS INCONTINENCE:	YES	NO	DETAILS:
URGE INCONTINENCE:	YES	NO	DETAILS:
OTHER:	YES	NO	DETAILS:

PREVIOUS FAECAL INCONTINENCE TREATMENTS:				YES	NO
CONSERVATIVE MANAGEMENT:	YES	NO	DETAILS:		
BIOFEEDBACK:	YES	NO	DETAILS:		
SPHINCTER REPAIR:	YES	NO	DETAILS:		
OTHER?	YES	NO	DETAILS:		

ALLERGIES:	YES	NO	DETAILS:

MEDICATIONS:

	YES	NO	DETAILS BELOW
MEDICATION	DOSE/FREQUENCY		INDICATION

PAST MEDICAL HISTORY: **[_] NONE**

DATE DIAGNOSIS: (DD/MMM/YYYY)	CONDITION	ONGOING	
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO
		YES	NO

PAST OBSTETRIC HISTORY:	YES	NO	DETAILS:				
VAGINAL DELIVERIES:	0	1	2	3	4	5	6
EPISIOTOMY/TEARS:	YES	NO	DETAILS:				

ANO-RECTAL PHYSIOLOGY RESULTS (PLEASE ATTACH COPY):		
DIGITAL RECTAL EXAMINATION (IF NO PHYSIOLOGY):		
IF IMPACTED – GIVE DISIMPACTION MEDICATION – GIVEN	YES	NO

FILE THE ORIGINAL, SIGNED AND DATED CONSENT FORM IN THE PARTICIPANTS' 'CONSENT FORM FOLDER' WITH THE CONTACT INFORMATION SHEET.

GIVE ONE COPY OF CONSENT FORM TO THE PARTICIPANT AND FILE ANOTHER COPY IN PATIENT NOTES.

PLEASE ATTACH ANO-RECTAL PHYSIOLOGY RESULTS

STORE IN PARTICIPANTS CRF FOLDER

DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

Completed by: _ _ _ Verified by: _ _ _

Data entry by: _ _ _

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

CRF 3

Please fill in the following document.

It comprises 6 questionnaires which we ask you to fill in before and after treatment, to help to assess how successful your treatment has been.

Many thanks for your co-operation and help in our trial

Unique patient identifier: _ _ _ / _ _ _

Pre-treatment / post treatment (Delete as appropriate)

Date today: _ _ / _ _ _ / _ _ _ _ (dd / mmm / yyyy)

STORE IN PARTICIPANTS CRF FOLDER

Gastrointestinal Quality of Life Index

These questions ask about the effect of bowel symptoms on your quality of life.
Please tick one for each question.

Q1. How often during the past 2 weeks have you had pain in the abdomen?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q2. How often in the past 2 weeks have you had a feeling of fullness in the upper abdomen?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q3. How often in the last 2 weeks have you had bloating (sensation of too much gas in the abdomen)?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q4. How often during the past 2 weeks have you been troubled by excessive passage of gas through the back passage?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q5. How often during the past 2 weeks have you been troubled by strong burping or belching?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q6. How often during the past 2 weeks have you been troubled by gurgling noises from the abdomen?

1) Never
2) A little of the time

3) Some of the time
4) Most of the time
5) All of the time

Q7. How often during the past 2 weeks have you been troubled by frequent bowel movements?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q8. How often during the past 2 weeks have you found eating to be a pleasure?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q9. Because of your disorder, to what extent have you restricted the kinds of foods that you eat?

1) Not at all
2) A little
3) Somewhat
4) Much
5) Very much

Q10. During the past 2 weeks, how well have you been able to cope with everyday stresses?

1) Extremely poorly
2) Poorly
3) Moderately well
4) Well
5) Extremely well

Q11. How often during the past 2 weeks have you been sad about being ill?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q12. How often during the past 2 weeks have you been nervous or anxious about your disorder?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time

5) Never

Q13. How often during the past 2 weeks have you been happy with life in general?
1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q14. How often during the past 2 weeks have you been frustrated about your disorder?
1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q15. How often during the past 2 weeks have you been tired or fatigued?
1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q16. How often during the past 2 weeks have you felt unwell?
1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q17. Over the past week, have you woken up in the night?
1) Every night
2) 5-6 nights
3) 3-4 nights
4) 1-2 nights
5) Never

Q18. Since your disorder started, have you been troubled by changes in your appearance?
1) Not at all
2) A little bit
3) Somewhat
4) A moderate amount
5) A great deal

Q19. Because of your disorder, how much physical strength have you lost?

1) A great deal
2) A moderate amount
3) Somewhat
4) A little bit
5) Not at all

Q20. Because of your disorder, to what extend have you lost your endurance?

1) Not at all
2) A little bit
3) Somewhat
4) A moderate amount
5) A great deal

Q21. Because of your disorder, to what extent do you feel unfit?

1) Extremely unfit
2) Moderately unfit
3) Somewhat unfit
4) A little unfit
5) Fit

Q22. During the past 2 weeks how often have you been able to complete your normal daily activities? (school, work, household)

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q23. During the past 2 weeks how often have you been able to take part in your usual patterns of leisure or recreational activities?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q24. During the past 2 weeks, how much have you been troubled by the treatment for your disorder?

1) Not at all
2) A little
3) Somewhat
4) Much
5) Very much

Q25. To what extend have your personal relations with people close to you (family or friends) worsened because of your disorder?

1) Very much
2) Much
3) Somewhat
4) A little
5) Not at all

Q26. To what extent has your sex life been impaired (harmed) because of your disorder?

1) Not at all
2) A little
3) Somewhat
4) Much
5) Very much

Q27. How often during the past 2 weeks have you been troubled by fluid or food coming up into your mouth (regurgitation)?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q28. How often during the past 2 weeks have you felt uncomfortable because of your slow speed of eating?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q29. How often during the past 2 weeks have you had trouble swallowing your food?

1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q30. How often during the past 2 weeks have you been troubled by urgent bowel movements?

1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q31. How often during the past 2 weeks have you been troubled by diarrhoea?
1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q32. How often during the past 2 weeks have you been troubled by constipation?
1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q33. How often during the past 2 weeks have you been troubled by nausea?
1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q34. How often during the past 2 weeks have you been troubled by blood in the stools?
1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Q35. How often during the past 2 weeks have you been troubled by heartburn?
1) All of the time
2) Most of the time
3) Some of the time
4) A little of the time
5) Never

Q36. How often during the past 2 weeks have you been troubled by uncontrolled stools?
1) Never
2) A little of the time
3) Some of the time
4) Most of the time
5) All of the time

Patient Centered Outcomes Form

Recent studies show that patients with bowel incontinence think the following issues are the most important.
For each, please indicate *how* important *you* think they are for you **TODAY** using a scale from zero to ten with:

1 Not important at all ..... 10 being vitally important

Q1. Unpredictability of when bowel accidents may happen:

1 2 3 4 5 6 7 8 9 10

Q2. Always needing to know toilet locations:

1 2 3 4 5 6 7 8 9 10

Q3. Hygiene and odors:

1 2 3 4 5 6 7 8 9 10

Q4. Effect on social life:

1 2 3 4 5 6 7 8 9 10

Q5. Effect on employment:

1 2 3 4 5 6 7 8 9 10

Q6. Strategies to help you cope with symptoms:

1 2 3 4 5 6 7 8 9 10

Q7. Embarrassment:

1 2 3 4 5 6 7 8 9 10

Q8. Fear of bowel accidents:

1 2 3 4 5 6 7 8 9 10

SF-36 Health Survey

INSTRUCTIONS: This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Q1 In general, would you say your health is:

1) Excellent	1
2) Very good	2
3) Good	3
4) Fair	4
5) Poor	5

Q2 Compared to one year ago, how would you rate your health in general now?

1) Much better now than one year ago	1
2) Somewhat better than one year ago	2
3) About the same as one year ago	3
4) Somewhat worse than one year ago	4
5) Much worse now than one year ago	5

Q3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	Yes, limited a lot	Yes, limited a little	No, not Limited at all
Vigorous activities such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playir golf.	1	2	3
Lifting or carrying groceries.	1	2	3
Climbing several flights of stairs.	1	2	3
Climbing one flight of stairs.	1	2	3
Bending, kneeling or stooping.	1	2	3
Walking more than a mile.	1	2	3
Walking half a mile.	1	2	3
Walking one hundred yards.	1	2	3
Bathing or dressing yourself.	1	2	3

Q4 During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the kind of work or other activities	1	2
Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

Q5 During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplish less than you would like	1	2
Didn't do work or other activities as carefully as usual	1	2

Q6 During the past 4 weeks, to what extend has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?

1) Not at all 1
2) Slightly 2
3) Moderately 3
4) Quite a bit 4
5) Extremely 5

Q7 How much bodily pain have you had during the past 4 weeks?

1) None 1
2) Very mild 2
3) Mild 3
4) Moderate 4
5) Severe 5
6) Very severe 6

Q8 During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)?

1) Not at all 1
2) A little bit 2
3) Moderately 3
4) Quite a bit 4
5) Extremely 5

Q9 These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling.
How much of the time during the past 4 weeks ….

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dump that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

Q10 During the past 4 weeks, how much time has your physical health of emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

1) All of the time	1
2) Most of the time	2
3) Some of the time	3
4) A little of the time	4
5) None of the time	5

Q11 How TRUE or FALSE is each of the following statements to you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get ill more easily than other people					
I am as healthy as anybody I know					
I expect my health to get worse					
My health is excellent					

Quality of Life Scale for Faecal Incontinence

Q1. In general, would you say your health is:

1) Excellent
2) Very good
3) Good
4) Fair
5) Poor

Q2. For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage. (If it is a concern for you for reasons other than accidental bowel leakage then tick the box under Not Applicable (N/A).

Due to accidental bowel leakage:

	Most of The time	Some of the time	A little of the time	None of the time	
a) I am afraid to go out	1	2	3	4	N/A
b) I avoid visiting friends	1	2	3	4	N/A
c) I avoid staying the night away from home	1	2	3	4	N/A
d) It is difficult for me to get out and do social things	1	2	3	4	N/A
e) I cut down on how much I eat before I go out	1	2	3	4	N/A
f) Whenever I am away from home I try to stay near a toilet as much as possible	1	2	3	4	N/A
g) It is important to plan my schedule (daily activities) around my bowel pattern	1	2	3	4	N/A
h) I avoid traveling	1	2	3	4	N/A
i) I worry about not being able to get to the toilet in time	1	2	3	4	N/A
j) I feel I have no control over my bowels	1	2	3	4	N/A
k) I cant hold my bowel movement long enough to get to the bathroom	1	2	3	4	N/A
l) I leak stool without even knowing it	1	2	3	4	N/A
m) I try to prevent accidents by staying near a bathroom	1	2	3	4	N/A

Q3. Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items. (If it is a concern for you for reasons other than accidental bowel leakage then check the box under Not applicable N/A)

Due to accidental bowel leakage:

	Most of The time	Some of the time	A little of the time	None of the time	
a) I feel ashamed	1	2	3	4	N/A
b) I do not do any of the things I want to do	1	2	3	4	N/A
c) I worry about bowel accidents	1	2	3	4	N/A
d) I feel depressed	1	2	3	4	N/A
e) I worry about others smelling stool on me	1	2	3	4	N/A
f) I feel like I am not a healthy person	1	2	3	4	N/A
g) I enjoy life less	1	2	3	4	N/A
h) I have sex less often than I would like to	1	2	3	4	N/A
i) I feel different from other people	1	2	3	4	N/A
j) The possibility of bowel accidents is always on my mind	1	2	3	4	N/A
k) I am afraid to have sex	1	2	3	4	N/A
l) I avoid traveling by plane or train	1	2	3	4	N/A
m) I avoid going out to eat	1	2	3	4	N/A
n) Whenever I go to a new place, I specifically seek out the bathrooms	1	2	3	4	N/A

Q4. During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

1) Extremely so – to the point that I have just about given up
2) Very much so
3) Quite a bit
4) Some - enough to bother me
5) A little bit
6) Not at all

Cleveland Clinic Faecal Incontinence Score

Please tick the ONE statement that you think most closely apply to you in each section:

Q1. How often did you loose control of solid bowel motions?

1) Never
2) Rarely (less than once a month)
3) Sometimes (once a month or more)
4) Weekly
5) Daily

Q2. How often did you loose control of liquid bowel motions?

1) Never
2) Rarely (less than once a month)
3) Sometimes (once a month or more)
4) Weekly
5) Daily

Q3. How often did you loose control of wind?

1) Never
2) Rarely (less than once a month)
3) Sometimes (once a month or more)
4) Weekly
5) Daily

Q4. How often did leakage of bowel motion or wind cause you to alter your lifestyle or avoid your usual activities?

1) Never
2) Rarely (less than once a month)
3) Sometimes (once a month or more)
4) Weekly
5) Daily

Q5. Do you wear a pad or plug because of leakage of bowel motion?

1) Yes
2) No

Q6. Do you use any medicines to help slow the bowel down (e.g. immodium or codeine)?

1) Yes
2) No

Q7. If there was no toilet nearby, could you delay a bowel motion for 15 minutes?

1) Yes
2) No

EQ-5D Health Questionnaire (EuroQoL Group 1990)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Q1. **Mobility**

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

Q2. **Self-Care**

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Q3. **Usual activities** (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

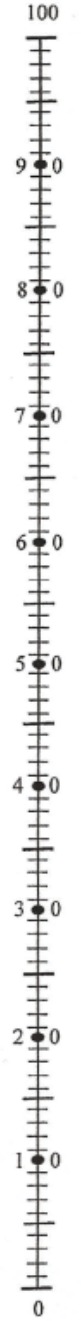
Q4. **Pain/Discomfort**

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

Q5. **Anxiety/Depression**

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

Q6. To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.
We would like you to indicate on this scale how good or bad your own health is today, in your opinion.
Please do this by drawing a line on the scale that indicates how good or bad your health state is today.



Many thanks for completing this questionnaire.

DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

Completed by: Participant / Interviewer _ _ _ Date: _ _ / _ _ _ / _ _ _ _ _ / _ _ _ _	Verified by: _ _ _ Date: _ _ / _ _ _ / _ _ _ _	Data Entry by: Date: _ _ / _ _

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

RANDOMISATION INFORMATION - CRF 4

UNIQUE PARTICIPANT IDENTIFIER: _ _ _ / _ _ _

DATE OF RANDOMISATION (TODAY): _ _ / _ _ _ / _ _ _ _ (dd / mmm / yyyy)

ALLOCATION AT RANDOMISATION: PTNS / SHAM (DELETE AS APPROPRIATE)

FILE IN THE RANDOMISATION FILE

IN A SECURE AND LOCKED CABINET SEPARATE TO ALL OTHER PARTICIPANT INFORMATION AND CRF'S TO BE ACCESSABLE ONLY TO UNBLINDED RESEARCH STAFF.

DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

DOCUMENTATION FOR VISITS 2-13 (CRF 5)

No	Date	PTNS: Setting and response (S = sensory; m = motor)	Adverse events (If yes fill in AE log)	Pad usage (Any change? Y/N)	Medication use - Any change? (If yes fill in con meds log)	Recorded By* (signature)	Verified By (initials)
1	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
2	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
3	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
4	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
5	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
6	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _

No	Date	PTNS: Setting and response (S = sensory; m = motor)	Adverse events (If yes fill in AE log)	Pad usage (Any change? Y/N)	Medication use - Any change? (If yes fill in con meds log)	Recorded By (initials)	Verified By (initials)
7	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
8	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
9	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
10	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
11	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _
12	_ _ / _ _ _/ _ _ _ _	mA: _ _ Response: S / M Location: Side: L / R	YES / NO	YES / NO Details:	YES / NO	_ _ _	_ _ _

DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

POST TREATMENT INFORMATION - CRF 6

VISIT 14: DATE TODAY: _ _ / _ _ _ / _ _ _ _ (dd / mmm / yyyy)

1. DO YOU THINK YOU RECEIVED 'REAL' PTNS STIMULATION OR THE 'SHAM' STIMULATION?

   REAL PTNS **SHAM STIMULATION** (Please circle)

2. DID YOU SUFFER ANY SIDE EFFECTS OR ADVERSE EVENTS FROM THE TREATMENT?

   YES **NO** (Please circle)

   If yes, please give details:

3. DID THE TREATMENT HAVE ANY EFFECT ON YOUR URINARY SYMPTOMS?

   I DID NOT HAVE ANY URINARY SYMPTOMS (Please circle)

   MADE SYMPTOMS WORSE

   NO EFFECT

   MILD IMPROVEMENT

   SIGNIFICANT IMPROVEMENT

   SYMPTOMS CURED

   Additional Comments regarding urinary symptoms please:

4. DID THE TREATMENT HAVE ANY EFFECT ON THE AMOUNT OF LOPERAMIDE (IMMODIUM) OR CODEINE YOU USE?

   USE HAS INCREASED

   USE HAS REMAINED THE SAME

   USE HAS DECREASED

   Not applicable - I DID NOT USE THESE MEDICATIONS THROUGHOUT THE STUDY

5. DID THE TREATMENT HAVE ANY EFFECT ON YOUR USE OF INCONTINENCE PADS?

   USE HAS INCREASED

   USE HAS REMAINED THE SAME

   USE HAS DECREASED

   Not applicable - I DID NOT USE INCONTINENCE PADS THROUGOUT THE STUDY

6. ARE THERE ANY OTHER COMMENTS YOU WOULD LIKE TO MAKE ABOUT THE TREATMENT OR THIS TRIAL?

7. CAN YOU DESCRIBE HOW YOU FELT PRIOR TO YOUR TREATMENT?

8. CAN YOU DESCRIBE HOW YOU FELT DURING YOUR TREATMENT?

9. CAN YOU DESCRIBE HOW YOU FEEL NOW, FOLLOWING YOUR TREATMENT?

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)
FINAL STUDY VISIT - CRF 7

DATE TODAY: _ _ / _ _ _ / _ _ _ _ (dd / mmm / yyyy)

PLEASE INDICATE WHICH APPLIES TO PATIENT DURING THEIR LAST STUDY VISIT:

☐ PATIENT WITHDREW EARLY FROM STUDY (ENSURE 'EARLY WITHDRAWAL FROM STUDY' CRF IS COMPLETED)

☐ PATIENT COMPLETED STUDY AND ALL THE FOLLOWING DOCUMENTATION IS COMPLETE:

- ☐ CRF 1
- ☐ CRF 2
- ☐ CRF 3– PRE-TREATMENT
- ☐ CRF 3– POST-TREATMENT
- ☐ CRF 4
- ☐ CRF 5
- ☐ CRF 6
- ☐ BOWEL DIARY – PRE-TREATMENT
- ☐ BOWEL DIARY – POST-TREATMENT
- ☐ ADDITIONAL CRFS AS NECESSARY

I CONFIRM THAT THIS PARTICIPANT HAS COMPLETED THE TRIAL IN ACCORDANCE WITH THE APPROVED PROTOCOL, REC CONDITIONS OF APPROVAL AND IN LINE WITH GOOD CLINICAL PRACTICE GUIDELINES.

Principal Investigator Signature: _____

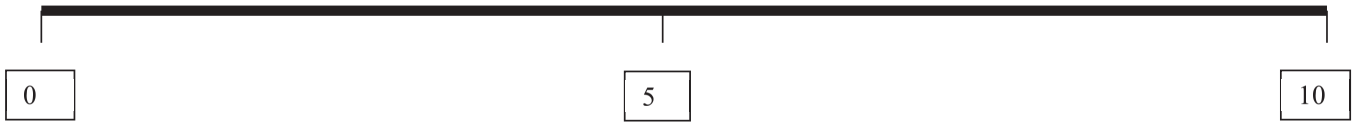
Name: _____ Date: _ _ / _ _ _ / _ _ _ _

STORE IN PARTICIPANTS CRF FOLDER

LIKERT SCALE OF SUCCESS

PLEASE INDICATE ON THE SCALE BELOW HOW SUCCESSFUL YOU FEEL YOUR FAECAL INCONTINENCE TREATMENT IN THIS TRIAL HAS BEEN.

0=COMPLETELY UNSUCCESSFUL TO 10 = COMPLETELY SUCCESSFUL



DECLARATION: I have reviewed this Case Report Form and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant.

Completed by: Participant/Interviewer
Date: _ _/_ _ _/_ _ _ _

Verified by: _ _ _
Date: _ _/_ _ _/_ _ _ _

Data Entry by: _ _ _
Date: _ _/_ _ _/_ _ _ _

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Controlled bowel movements (no incontinence: underwear, pads or pants remained clean)														
How many times did you go to the toilet (controlled)?														
Uncontrolled bowel movements (incontinence: underwear, pads or pants got dirty)														
How many times did you NOT make it in time to toilet (rush)?														
How many times did you not feel the bowel movement but only afterwards (passive leakage)?														
Staining/ minor soiling of underwear														
Did you stain/soil your underwear, pants or pad(s) today?	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no
Pad usage/Enema/ Suppository														
Pad(s) used for	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no

incontinence?														
Enema Suppository administrated?	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no
Social functioning														
Did your (faecal) incontinence limit you in your daily activities (e.g. leaving the house, shopping etc)?	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no	Yes /no
Stool consistency														
What was your stool consistency today? (Circle one)	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid	Solid/ mushy / liquid

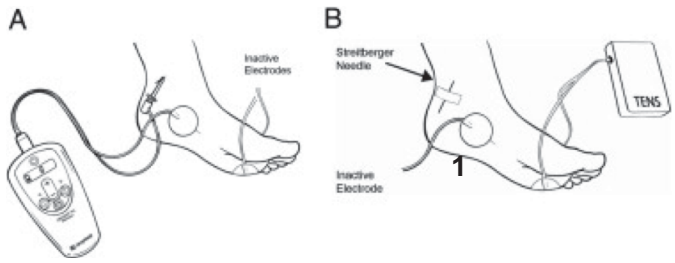
Appendix 4 Standardised percutaneous tibial nerve stimulation and sham

CONtrol of **F**aecal **I**ncontinence using **D**istal **N**euromodula**T**ion (CONFIDeNT)

Standardised PTNS and Sham

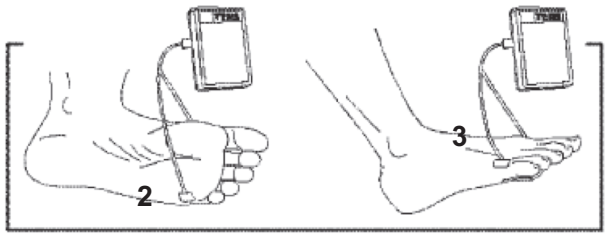
EQUIPMENT SET UP

Figure 1



1. Just distal to calcaneus on sole of foot in midline (active for PTNS)
2. Bottom of foot just proximal to smallest toe
3. Top of foot just above smallest toe

Figure 2



Sham

PTNS: Urgent ® PC neuromodulation system (Uroplasty Ltd., Manchester, UK).

- Needle: Lower inner aspect of the RIGHT leg - three finger breaths (5 cm) cephalad to the medial malleolus and approximately one fingerbreadth (2 cm) posterior to the tibia. 60-degree angle between electrode and ankle.
- Electrode: Ipsilateral calcaneus.

TENS: Biostim M7 TENS unit, Biomedical Life Systems, Vista, California

- Electrodes: Right foot, one under the little toe and one on top of the foot.

FOR PTNS:

- Set up both machines.
- Place tape over wire connected to PTNS needle (so appearance is identical to sham).
- Only turn on PTNS machine - fixed-pulse frequency of 20Hz and a pulse width of 200 microseconds
- Continue treatment as usual – increasing amplitude until a sensory or motor response – reduce.
- DO NOT ALLOW PARTICIPANT TO ALTER SETTINGS THEMSELVES

FOR SHAM:

- Set up both machines. With PTNS, DO NOT CONNECT LEAD TO PTNS NEEDLE.
- Instead, tape lead near needle so it is not possible to tell at a glance if connected or not.
- Pick up both the TENS and PTNS machines
- Check TENS settings **pulse frequency 10Hz and pulse width 200 microseconds.**
- Press buttons simultaneously on PTNS and TENS machines to increase Amplitude (participant will only feel TENS as PTNS machine is not properly connected). THE PARTICIPANT WILL THEN HEAR THE BEEPS FROM THE PTNS MACHINE AS IN THE PTNS ARM.
- When a significant sensory or motor response is observed, turn down one setting.
- **Press timer button twice – 30 mins will count down on TENS display**
- Leave the participant as usual for the 30 minute treatment.
- DO NOT ALLOW PARTICIPANT TO ALTER SETTINGS THEMSELVES

VERBAL EXPLANATION TO PARTICIPANT

"I am now going to start the nerve stimulation treatment. I will be inserting a small electrode needle, like an acupuncture needle, into your leg and putting sticky electrodes onto your foot. When I turn the machine on you will be asked when you can first feel an electrical sensation in your ankle or foot. I will carry on increasing the intensity of this until it is slightly uncomfortable, then I will turn it down a little if necessary. Occasionally you may also feel numbness or slight movement of your toes. This is normal. I will set the machine up and leave it running for 30 minutes. You may or may not continue to feel the stimulation during this time – this is normal also. After 30 minutes have elapsed I will remove the needle and sticky electrodes (the machine automatically turns off at this time). If the treatment becomes uncomfortable at any point please let me know and I will turn it down or stop the machine."

Appendix 5 Standard operating procedures

Standard Operating Procedures (SOP) for: Randomisation and Unblinding Procedure for the CONFIDeNT Study			
SOP Number:	**5**	Version Number:	**1**
Effective Date:	**5 JAN 2012**	Review Date:	**5 JAN 2015**

Author:	**Emma Horrocks, Clinical Research Fellow**

Authorisation:	
Name / Position	**Professor Charles Knowles/ Chief Investigator**
Signature	**XXXX**
Date	**4/1/12**

Staff signatures: I have read, understood and will comply with this SOP		
Name (please print)	Signature	Date

Purpose and Objective:
To define the procedure for randomisation of study participants for the CONFIDeNT Study.

SOP Text

	Responsibility	Activity
1.	Research Team	**Performing Randomisation:** On visit 2, participants will be randomised, using a web-based computer program, to receive either PTNS or sham. Prior to allocation, the participant must have provided informed consent. CRF 1 and CRF 2 (Eligibility Criteria and Initial Assessment) must have been completed and checked by another member of the research team. CRF 3 (Questionnaires) must also have been completed. These documents should be completed.in accordance with SOP 10 – Document Completion. Details of the randomisation website are as follows: `https://ctu4.nottingham.ac.uk/1141/login.asp` The randomisation programme is a bespoke system designed and held at the Nottingham Clinical Trials Unit (NCTU) and run by the NCTU data manager. The system is fully tested by the trial team and PCTU statistician. The research nurse/researcher at each site will log on using a site specific username and password, which will be provided by the Research Fellow during the Site Initiation Visit. Following successful log on the researcher will select their site from the drop-down menu (the only other choice being the test site). They will then select 'Enrol new participant' from the list of options. The screen automatically appears which requires input of the unique participant identifier, sex, date of birth and initials of participant. Once these are entered, 'click submit'. The next screen allows the researcher to check the details are correct, and if not, to amend them, or if they are correct, click 'next form'. The next page requires the researcher to again check the details, and if incorrect, click 'prev form' to go back to the previous form and amend the details. If the details are correct, the researcher is asked to check two boxes, one agreeing that the data entered is correct, and the other agreeing that the participant meets the entry criteria for the CONFIDeNT Trial, as outlined in the Protocol. If these two boxes are checked, the researcher can then press the 'randomise' button. This will allow immediate on-screen randomisation with the allocation showing on the next screen. The researcher will then fill in the randomisation information on CRF 4. This CRF will be held in a 'Randomisation File' in each site, which contains only CRF 4. Each participant's CRF 4 will be kept in a concealed envelope within this Randomisation File to prevent accidental unblinding to researchers not completing

		treatment for this participant.. This ensures that prior to each treatment the unblinded researcher performing the treatment can check the randomisation allocation, but it will not be in the participants CRF folder to avoid accidental unblinding of other site researchers. The participants Unique Participant Identifier is made up of 3 letters followed by 3 numbers. The letters are unique to each site and are documented in the CONFIDeNT trial protocol(Appendix A). The numbers are allocated at each site and are allocated sequentially to each participant during screening for the trial, beginning with 001. The allocation will be known by the researcher carrying out the first treatment. Thereafter, at each visit, the participant will receive the PTNS or sham as identified by the randomisation CRF 4. Once the randomisation has been performed, an automated, blinded, pseudo-anonymised email will be sent to the PI at that site, informing them that the randomisation has taken place. An automated, unblinded, pseudo -anonymised email will also be sent to the Trial Manager, Natasha Stevens, in order to keep a centralised trial randomisation log. Each site will be able to log on to the randomisation tool and view the participants that have been randomised at their site. This can be done by logging on to the website, and selecting 'View a summary of randomisations performed' from the list. This will show details of the participants randomised but will NOT show randomisation allocation, in order to prevent unblinding. If CRF 4 containing the randomisation allocation is not completed immediately following on screen randomisation, it will not be possible for the research sites to access information about the allocation. If this occurs, the site should contact the Trial Manager, Natasha Stevens, contact details below, who will be able to access the allocation for all participants.
2.	PI/ Research Team	**Procedure if Randomisation Tool not working:** If, for any reason, a site is unable to perform a randomisation using the online tool, in the first instance the site should contact the Research Fellow Emma Horrocks, or Trial Manager, Natasha Stevens (see details below). Assistance can be given over the phone regarding the use of the online randomisation tool. If the website or internet is not working at a particular site, Natasha Stevens, Trial Manager, can perform randomisation on behalf of the site, and relay the randomisation to the site over the phone and via a pseudo-anonymised email. Failing this, if the website is not functioning at any site, the Nottingham Clinical Trial Unit should be contacted to conduct randomisation. Contact details:

		Dan Simpkins IT/Data Manager Nottingham Clinical Trials Unit Office 2009, C Floor, South Block Queen's Medical Centre Tel: XXXX Email: XXXX
3.	PI/Research Team	**Unblinding:** If, for any reason, un-blinding is required, in the first instance the permission of the Local Principal Investigator should be sought. If they are unavailable, or this is not possible, the Academic Clinical Fellow, Emma Horrocks, or the Chief Investigator, Charles Knowles should be contacted. Emma Horrocks Email: XXXX Tel: XXXX Charles Knowles: Email: XXXX Tel: XXXX Once permission is sort, the local investigator can break the randomisation code by looking at CRF 4 for the appropriate participant. If this is not possible, because the information is unavailable out of hours, the lead site should be contacted. In the first instance the Trial Manager can be contacted, who can access the randomisation code by the computer programme, and if she is unavailable the Data Manager, Sandy Smith, should be contacted. Only the trial manager and data manager will have access to the randomisation data within the database. Natasha Stevens (Trial Manager) Email: XXXX Tel: XXXX Sandy Smith (Data Manager) Email: XXXX Tel: XXXX

Version	Reason for Change	Date Approved
1.0		
2.0		

Appendix 6 Statistical analysis plan

CONFIDeNT

Statistical Analysis Plan

Version: 1.0
Date: 19/Jun/2014

Person(s) contributing to the analysis plan	
Name(s) and position(s)	Dr Stephen Bremner, trial statistician Prof Sandra Eldridge, director of PCTU Prof Charles Knowles, chief investigator Emma Horrocks, trial coordinator
Authorisation	
Position	**Chief or principal investigator**
Name	Prof Charles Knowles
Signature	
Date	DD/MMM/YYYY
Position	**Senior trial statistician**
Name	Prof. Sandra Eldridge
Signature	
Date	DD/MMM/YYYY

1. INTRODUCTION

Purpose of statistical analysis plan

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the CONFIDeNT trial. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post hoc or unplanned analyses will be clearly identified in the respective study analysis report.
The structure and content of this document provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation (ICH) and the PCTU SOP (PCTU/07).
The following were reviewed in preparation for writing this document:
Trial application submitted 04/01/2011
ICH E9 Guidance on statistical principals for clinical trials
ICH E3 Structure and content of clinical study reports
CONSORT guidelines for the reporting of randomised trials

Members of the writing committee

Stephen Bremner (SB) and Sandra Eldridge (SE) were primarily responsible for writing the Statistical Analysis Strategy with SB responsible for writing the computer code implementing the analysis strategy and implementing the strategy at the point of analysis. Emma Horrocks and Prof Charles Knowles helped refine outcome definitions and choose variables for the multiple imputation. This document was developed prior to examination of unblinded trial data and will not be implemented prior to final approval.

Summary

DESIGN: Pragmatic multi-centre, double-blinded, placebo-controlled trial of 227 patients randomised to receive the intervention (PTNS) or sham (needle insertion and electrical stimulation). All patients follow an assessment period, recruitment, allocation, standard 3 month treatment protocol (one 30. min session per week for 12 weeks) with trial outcomes determined at 14 weeks.
SETTING: 19 UK centres providing specialist nurse-led treatment for pelvic floor disorders.
TARGET POPULATION: Patients aged > 18 years with faecal incontinence (FI) who have failed conservative treatments and whose symptoms are sufficiently severe to merit further intervention (80-90% female based on departmental data).
HEALTH TECHNOLOGIES BEING ASSESSED: PTNS (Urgent ® PC neuromodulation system) is produced by a single manufacturer (Uroplasty ®). The equipment includes a hand held pulse generator unit, single use leads and fine needle electrodes. Needle insertion is performed in a sitting position in an outpatient setting on either leg adhering to the manufacturer's protocol (and specialist training). Treatment is for 30 mins. weekly for a duration of 12 weeks. Validated sham stimulation - insertion of the Urgent PC needle subcutaneously at the same site with electrical stimulation delivered to the distal foot using TENS.

MEASUREMENT OF COSTS AND OUTCOMES: Primary outcome variable: change in weekly FI episodes (calculated from bowel diaries) expressed as proportion of patients achieving ≥ 50% reduction in FI episodes per week; Secondary outcomes: (1) percentage change in FI episodes per week, (2) change in mean number of FI episodes per week, (3) validated patient-rated quantitative outcomes including symptom severity score (St Mark's score), disease-specific: FI-QOL, and generic: EQ-5D QOL measures, and SF-36, (4) FI-specific patient-centred outcomes (5 validated key issues), (5) Likert scales of patient's global impression of success (0-10), (6) Short urinary symptom assessment. Adverse events and anti-diarrhoeal drug usage will also be recorded. Economic analysis will measure direct NHS costs with utilities derived from the EQ-5D. The proposed HE analysis will be detailed in a separate document.

Changes from planned analysis in the protocol

We decided to fit random centre effects rather than fixed effects on the basis of findings by Kahan & Morris (Kahan & Morris, 2013). We also decided to multiply impute the data and remove any reference to last observation carried forward.

STUDY OBJECTIVES AND ENDPOINTS

Study objectives

Primary objectives

To determine the effectiveness of PTNS versus sham electrical stimulation based on changes in the number of weekly FI episodes from baseline (bowel diary completed over two week period prior to first intervention) to end of treatment (bowel diary completed for weeks 12 and 13)

Secondary objectives

To determine the effectiveness of PTNS versus sham electrical stimulation (TENS) based on changes in validated incontinence scores, patient-centred FI-related symptoms and disease-specific and generic quality of life measures from baseline (bowel diary completed over two week period prior to first intervention) to end of treatment (bowel diary completed for weeks 12 and 13)

Exploratory objectives

None

Outcome measures

Primary outcome

Change in weekly FI episodes expressed as proportion of patients achieving ≥ 50% reduction in FI episodes per week. The change is measured between pre- and post-treatment bowel diaries.

The number of FI episodes per day are the sum of episodes in Q2a (rush) and Q2b (passive leakage) of the bowel diary. The average number per week is the sum of all 14 days, divided by 2.

%change = 100% × (#FI(baseline) - #FI(end of intervention)) / #FI(baseline)

Where #FI is the average number of episodes of FI per week. Where %change is negative, this represents an increase in FI episodes; where it is positive, this represents a decrease in FI episodes.

A patient achieving a ≥ 50% reduction will be classed as a treatment success, otherwise the patient is classed as a treatment failure.

Secondary outcomes

Percentage change in FI episodes per week, from baseline (the two-week period just before the 1st treatment) to end of treatment i.e. bowel diary for two weeks after the 12th treatment; for three additional cut offs: an improvement ≥ 25% vs. less, an improvement ≥ 75% vs. less and an improvement of 100% vs. less

Continuous change in FI episodes per week; i.e. average number of FI episodes per week for the two weeks post-treatment, minus average number of FI episodes per week at baseline (from pre-treatment two-week bowel diary).

Continuous change in FI episodes per week (rush and passive leakage as two separate outcomes); i.e. average number of episodes per week for the two weeks post-treatment, minus average number of episodes per week at baseline (from pre-treatment two-week bowel diary).

St Mark's incontinence score (Vaizey et al. 1999)

Likert scale of patient's global impression of success

Patient-centred FI-related symptoms

Disease specific and generic quality of life measures

- EQ-5D

- SF-36 (8 domains)

- Faecal incontinence quality of life score- four domains: coping, embarrassment, lifestyle and depression

- Gastro-intestinal quality of life score

Short urinary symptom assessment (descriptive)

Change in medication use: has pad usage/loperamide usage decreased/remained the same/increased? (descriptive)

Safety outcomes

None

STUDY METHODS

Overall study design and plan

Target for analysis: 106 intervention and 106 sham participants
Actual number randomised: 227
Date of first randomisation: 21/01/2012
Date of last randomisation: 31/10/2013
Trial design: individually randomised, parallel group
Blinding: See section 3.4
Randomised Interventions: PTNS vs. sham
Allocation ratio: 1:1

Selection of study population

Inclusion Criteria

Faecal incontinence sufficiently severe enough to warrant intervention

Failure of appropriate conservative therapies

Age ≥ 18 years

Exclusion Criteria

Inability to provide informed consent for the research study

Inability to fill in the detailed bowel diaries required for outcome assessments (this will exclude participants who do not speak / read English)

Neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (any participant with painful peripheral neuropathy)

Anatomical limitations that would prevent successful placement of needle electrode

Other medical conditions precluding stimulation: e.g. bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis

Congenital anorectal anomalies or absence of native rectum due to surgery

A cloacal defect

Present evidence of external full thickness rectal prolapse

Previous rectal surgery (rectopexy / resection) done < 12 months ago (24 months for cancer),

Stoma *in situ*

Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea

Pregnancy or intention to become pregnant

Previous experience of SNS or PTNS

Method of treatment assignment and randomisation

Participants were randomised, with allocation concealment, at a ratio of 1:1 at visit 2 using a web-based computer programme to receive either PTNS or sham. This was performed by the Nottingham Clinical Trials Unit Study. Centres inputted the sex of the participant. Sex was used to reduce the potential confounding effects of variation in outcomes between male and female participants. Males represent approximately 10% of patients and have differing pelvic physiology and often disease aetiology (e.g. post anal surgery rather than childbirth). As only 1 or 2 male patients were expected to be enrolled from each centre, randomisation was first stratified on sex, and then within females only, further stratified on centre reducing the possibility that all the males are allocated to PTNS by chance. Randomly permuted blocks of length randomly varying 2, 4 and 6 will be used to ensure near balance between PTNS and sham arms.

Treatment masking (Blinding)

Blinding of patients: For both interventions: (1) a standardised description of the techniques were read from a card. This described an electrical sensation variably in the ankle or foot with or without motor responses in the foot (note: there is significant variability in conscious sensation and motor responses even between patients undergoing only PTNS); (2) the equipment (identical for both interventions) was shown to the patient; (3) the lower extremity was be draped from view; and (4) the audible sounds produced by the Urgent PC unit identical.
Performance bias considerations: Since the sham group might be expected to seek more advice than the treatment arm (if the hypothesis that PTNS is more effective than placebo is correct), the interaction of the administering nurse/physician was standardised so that general supportive advice given at consultations was identical for all participants. This was limited to a general welcome, answers to any concerns (whilst recording adverse events), advice on loperamide dosages and pad use (both recorded in outcome variables).
Blinding of trial staff: two members of staff were available at each site to run the study. Randomisation into the treatment or placebo arm of the study occurred at Visit 2, after all the documentation had been completed. At this point, the member of staff carrying out the PTNS or sham was unblinded. That same staff member carried out all 12 treatments for the patient. Following the final treatment the member of staff who remained blinded collected all of the final data, before allowing the patient to find out if they were in the sham or treatment arm. In this way, the staff member conducting the final meeting with the patient remained blinded until the end.

Sample size determination

Research into treatment of FI is currently hampered by the lack of a valid and reliable tool that allows standardisation of outcomes. There are advantages and disadvantages of the numerous possible quantitative outcome variables e.g. individual symptoms and composite scores, and generally poor correlation of either with disease specific or generic quality of life measures. Of possible outcomes, the most frequently used and

probably least affected by subjective reporting differences is number of FI episodes per unit time (usually per week). This outcome, obtained directly from the mean of 2 week bowel diary frequencies has been employed in almost all contemporary studies of FI interventions including recent SNS studies. The problem with this variable is that, being a count, it has a Poisson distribution and is over-dispersed i.e. has greater variability than expected. This raises major difficulties in defining a *clinically significant* mean reduction in FI episodes per week in a population of patients with widely dispersed starting FI frequencies. To counter this problem, almost all contemporary studies have adopted a primary outcome using a categorical measure of percentage reductions i.e. the proportion of patients who have a 50% or greater reduction in faecal incontinence episodes per week. We justify this approach on the following basis:

The most important inferred outcome of this study will be the comparison of PTNS outcomes with that of other interventional treatments especially those of SNS. Since the primary outcome of nearly all studies of SNS has been based on the $\geq$ 50% reduction in FI episodes rule, the continued use of this outcome will better inform bodies such as NICE. Indeed, this outcome was used in the NICE ruling on sacral nerve stimulation; it was also the primary outcome in the 16-site multicentre FDA investigational device exemption (IDE) trial of sacral nerve stimulation in 120 patients with FI.

This outcome has also been the approach of choice for urinary incontinence episodes in the only pivotal trial of PTNS in the urology literature and also for NICE commissioned systematic reviews.

Baseline and post treatment FI episodes expressed as continuous variables yield data from over-dispersed Poisson distributions. The arithmetic means of these variables are very difficult to correlate with significant clinical effect e.g. a mean change of 5 FI episodes per week is not possible in patients with starting frequencies of four or fewer and is of little or no benefit to a patient with a starting frequency of 50. The change variable will however remain a secondary outcome.

Previous publications and our own data on 50 patients suggest a 60% success rate for PTNS on the basis of above justified primary outcome measure. There are no RCT data for PTNS in FI. However the pivotal level I SUmiT trial of PTNS in overactive bladder symptoms (OAB) which used a similar global response assessment of urinary incontinence and an intention to treat analysis, observed a moderate or marked improvement in symptoms in 55% PTNS group and only 21% sham group. On the basis that placebo responses are frequently higher for bowel rather than bladder symptoms we have selected a sham response rate of 35% whilst keeping this more conservative estimate of treatment response of 55%. We believe this difference remains clinically important. Two hundred and twelve patients are required to detect this difference with 80% power at the 5% significance level. We aimed recruit 235 patients at baseline to allow for a 10% failure to attend the 2nd visit (allocation and first intervention).

DATA COLLECTION

Baseline

Age, sex, history of faecal incontinence (including type), urinary symptom history, previous faecal incontinence treatments, medications, past medical history, past obstetric history. (see CRF 2 v5 for items)
Bowel diary (14 consecutive days)
Gastrointestinal quality of life index, patient centred FI symptoms, SF-36 Health Survey, QoL scale for faecal incontinence, St. Mark's faecal incontinence score, EQ-5D health questionnaire (see CRF 3 v3 for detail)

Follow up

Visits 2-13: PTNS or tens machine settings and response (sensory or motor), adverse events, any change in pad usage, any changes in medication use? (see CRF 5 v3)
Week 7: bowel diary over 7 consecutive days
Final visit (post treatment) (week 14): which treatment did patient think they were on? Any effect on urinary symptoms? Any change in loperamide or codeine use? Any change in pad use? How patient felt before, during and after treatment, Likert scale of success.
Bowel diary over 14 consecutive days
CRF 3 v3

Timing of data collection

Event	Visit 1	Telephone Conversation	Visit 2	Visits 3-13	Visit 14
Eligibility assessment	X				
Bowel Diary		X		Visit 7-8	X
Consent			X		
Participant Contact Information Sheet			X		
Eligibility assessment (CRF1)			X		
Initial assessment (CRF2)			X		
Questionnaires (CRF3)			X		X
Randomisation			X		
Randomisation information (CRF4)			X		
Intervention			X	X	
Record stimulation parameters adverse events and medication / pad usage (CRF5)			X	X	
Adverse Events Log			X	X	X
Concomitant Medications Log			X	X	X
Post treatment Information (CRF6)					X
Final Study Visit Information (CRF7)					X

GENERAL ISSUES FOR STATISTICAL ANALYSIS

All analyses will be conducted two sided and significance interpreted at the 5% level.

Blinding of the statistical analysis

The trial statistician will remain blind to allocation until this analysis plan was signed off

Analysis populations

Intent-to-treat population
The intention-to-treat (ITT) sample is defined for this trial as all participants randomised into the trial, *who received at least their first treatment*, included in the intervention group to which they were randomised.

Available-case population
N/A

Per protocol population
Patients attending at least 10 treatment sessions in 13 weeks will be classed as treatment completers.

Safety population
N/A
Other populations
N/A

Database

Description

Data were entered by the trial manager, clinical academic fellow and data entry clerks onto a Microsoft Access 2010 database held on the Barts Cancer Institute secure server. Data was entered at QMUL.

Data quality

Completeness of data was checked each time a report was generated for data monitoring committee meetings, and prior to final analysis. All eligibility and primary outcome data were checked by a member of the trial team other than the person who entered it. This was done in batches, as and when time permitted. A 10% random sample of CRFs for secondary outcomes were checked and the overall error rate was found to be below the 2% error rate that would have necessitated a 100% check of the secondary outcomes data.

Database freeze and lock

Once the trial team completed all data entry and checking, the data date stamped and frozen for transfer to Stata version 12.1 using the *odbc* facility in Stata. The statistician responsible for the analysis conducted additional data checks. These range

checks, logical and consistency checks which may not have been picked up by checks performed at the individual level.
Discrepancies were dealt with by the trial manager checking the paper CRFs, and the database was locked for analysis i.e. it was transferred to a read only location.

Analysis software

The analysis will be carried out using Stata version 12.1, interfacing with Realcom Impute which will be used to multiply impute missing outcome and baseline covariate data.

Methods for withdrawals, loss to follow-up and missing data

All patients randomised who receive the first treatment will be included in the intention-to-treat analysis of primary endpoint. Prior to the first treatment, it was anticipated that some patients (up to 10%) would fail to attend after eligibility was assessed due to a failure of compliance with the travel and attendance needs of the treatment course or study. These were not counted as study recruits. Those in whom post-treatment data are unavailable at 14 weeks for any reason (loss to follow up, failure to complete treatment) will have their outcome multiply imputed under the assumption of missing at random (MAR) using variables prognostic of outcome, such as measure of outcome made at baseline, and others that are predictive of missingness such as mean number of FI episodes per week at baseline, age, sex, and where available, mid-study bowel diary data. See appendix (b) for details. Multilevel multiple imputation will be performed using the multivariate normal distribution in Realcom Impute, using treatment allocation, patient sex and allocation as auxiliary variables. After a burn in of 1,000 runs of the MCMC sampler, missing values will be filled every 500th run to create a total of 10 completed datasets for analysis. The data will be analysed in Stata and the results pooled by Rubin's rules.

Method for handling centre effects

Study centre will be included as a random effect

Method for handling randomisation stratification or minimisation factors

Patient sex will be included as a fixed effect, study centre as a random effect

Method for handling clustering effects

The intracluster correlation coefficients (ICC) and their 95% confidence intervals for the outcomes by centre (level 2) will be estimated using the user-contributed Stata command *sea_obi* which allows the ICC to be negative. Random effects models will be fitted by restricted maximum likelihood estimation (e.g. *xtmixed ..., reml*). However, should these fail due to the between centre variance being close to zero, random effects models will be fitted by generalised least squares (e.g. *xtregress*). If ICCs are estimated as ≤ 0 then we will use similar regression models without adjusting for clustering.

Method for selecting other variables that will be adjusted for

This was agreed by consensus prior to any data extraction and the decision was: fit fixed effects for sex, randomisation and baseline level of outcome.

Multiple comparisons and multiplicity

No adjustments to p-values planned

Method for handling non-adherence

All patients randomised who receive the first treatment will be included in the intention-to-treat analysis of primary endpoint.

Method for handling time-varying interventions
N/A

Method for handling outliers and influential points
N/A

Data from external sources
N/A

Derived and computed variables

In the bowel diary, participant's record:
Controlled bowel motions: No incontinence – pads or pants remained clean

2. Uncontrolled bowel movements: Incontinence – underwear, pads or pants got dirty.
Within this section patients are asked how many of those times they:
a. Didn't make it in time to the toilet (rush)

b. Didn't feel the bowel movement until after it had happened (passive leakage)
The FI episodes will be calculated from those of 'Uncontrolled bowel Movements', whether this be 'rush' or 'passive leakage', by adding the two together.

DESCRIPTIVE ANALYSES

NB To help identify problems with missing data, outlying values, or other errors, full descriptive statistics MUST be produced for all variables in the database(s)

Participant flow

Participant throughput will be summarised in a CONSORT diagram.

Representativeness of sample
N/A

Baseline comparability of randomised groups

<u>Demographics</u>
Age and sex distributions will be described, by trial arm

<u>Prior and concurrent medications</u>
Proportion of patients taking loperamide and/or codeine

<u>Baseline and screening conditions</u>
Severity of FI symptoms according to bowel diary (i.e. mean number of episodes per week, recorded over a 14 day period)

Baseline medical history
Previous treatment for FI, and obstetric history. These are binary variables, except for number of previous vaginal deliveries (0, 1, 2, 3, 4, 5 or 6), and will be reported as number and percentage.

Baseline physical exam
N/A

Cluster characteristics if cluster randomised
N/A

Characteristics of care providers where applicable
N/A

Comparison of losses to follow-up

The proportion of patients withdrawing will be compared descriptively by arm

Comparison of compliance to treatment and protocol

The proportion of patients attending one or more treatment sessions will be compared descriptively.
The distribution of the proportion of treatment sessions attended per patient will be compared descriptively by arm. Participants who receive ≥ 10 treatments in 13 weeks will be considered to have received a full set of treatments for the per protocol analysis.

Emergency or accidental unblinding of randomised treatment

It was hard to envisage any necessity to break the randomisation code. We specified that should this be required, in the first instance the permission of the Local Principal Investigator should be sought. If they were unavailable, or this was not possible, the Academic Clinical Fellow, Emma Horrocks, of the Chief Investigator, Charles Knowles should be contacted.
Once permission had been sought, the local investigator could break the randomisation code by looking at CRF 4 for the appropriate participant. If this was not possible, because the information was unavailable out of hours, the lead centre should be contacted. In the first instance the Trial Manager could be contacted, who could break the randomisation code by the computer programme, and if she was unavailable the Daniel Simpkins at Nottingham Clinical Trials Unit should be contacted. Only the trial manager, independent statistician and Nottingham representative had access to the randomisation data within the database.

INTERIM ANALYSES AND SAFETY MONITORING ANALYSES

Purpose of interim analyses

None were planned

ANALYSIS OF PRIMARY OUTCOME

Definition of outcome measure

Responder vs. non-responder: Defined as a 50% or greater reduction in FI episodes per week, comparing end of intervention bowel diary with baseline). i.e.
If 100% × (#FI(baseline) - #FI(end of intervention))/#FI(baseline) ≥ 50%, class as responder
Where #FI stands for the average number of FI episodes per week. Where %change is negative, this represents an increase in FI episodes; where it is positive, this represents a decrease in FI episodes.

Descriptive statistics for outcome measure

Number and proportion of responders (as defined above) in each arm

Primary analysis

A logistic regression, adjusting for mean number of FI episodes at baseline, with a fixed effect for treatment arm, and sex, will be fitted using the Stata command *xtmelogit*, specifying study centre as a random effect

Assumption checks and actions to be taken if they do not hold
None

Other analysis supporting the primary (inc. sensitivity analyses)
N/A

ANALYSIS OF SECONDARY OUTCOMES

Definition of outcome measures
Percentage reduction in FI episodes per week for three additional cut offs: an improvement of ≥ 25% vs. less, an improvement of ≥ 75% vs. less and an improvement of 100% vs. less

Mean reduction in FI episodes per week (continuous); i.e. average number of FI episodes per week for the two weeks post-treatment, minus average number of FI episodes per week at baseline (from pre-treatment two-week bowel diary)

Mean reduction in (a) uncontrolled rush FI episodes per week and (b) uncontrolled passive leakage FI episodes i.e. average number of FI episodes per week for the two weeks post-treatment, minus average number of FI episodes per week at baseline (from pre-treatment two-week bowel diary)

Patient centred outcomes (continuous)

St Mark's score (continuous)

FI-QOL (continuous) [the four domains will be handled as outcomes in four separate models]

EQ-5D (continuous)

SF-36 (continuous) [the eight domains will be handled as outcomes in eight separate models]

Likert scale of patient's global impression of success (0-10). (continuous)

Short urinary symptom assessment (ordered categorical)

Descriptive statistics for outcome measure
Mean and SD for symmetric continuous variables
Median, 10th & 90th centiles for skewed continuous variables
Number and % for binary and other categorical variables

Secondary analysis
Continuous outcomes will be modelled using a mixed effects linear regression with the command *xtmixed*, adjusting for the baseline level of the outcome, sex and including a random effect for study centre. It should be noted that for outcome (2), analysis of change in FI episodes as the outcome is less efficient than ANCOVA i.e. end of intervention mean number of episodes as outcome, adjusted for baseline mean number of episodes. In this case the outcome variable will be mean number of FI episodes per week at end of treatment adjusting for the covariate, baseline measure of the outcome. Binary outcomes will be modelled using a mixed effects logistic regression *xtmelogit*, adjusting for the baseline measure of the outcome, sex and including a random effect for study centre. Urinary symptoms (outcome 9) will not be modelled.

Assumption checks and actions to be taken if assumptions do not hold.
Normality and homoscedasticity of residuals (*xtmixed* only), normality of random effects

Other analysis supporting the secondary (inc. sensitivity analyses)
N/A

SAFETY AND TOLERABILITY ANALYSES

Intervention exposure
N/A

All adverse events
The PTNS treatment and sham have no recognised significant adverse effects. However, at each weekly visit each patient will be asked if they have suffered any side effects or adverse effects of the treatment. These will be documented and in the study database and reported to the data monitoring committee prior to each meeting with them.

Adverse events leading to withdrawal

Serious adverse events

Clinical laboratory evaluations

SUBGROUP ANALYSES

Definition of outcome measure

Definition of subgroups

Primary outcome –
Sex (male vs. female)
FI severity (< or ≥ 7 episodes/wk)

Secondary outcomes –
age (<40 years, 40 to 60 years, 60+ years),

Sample size justification for the subgroup analysis
None

Descriptive analysis for subgroups

Method of analysis

An interaction term will be defined by multiplying the sub group dummy variables by the treatment assignment variable. For age, a global test of the two interaction terms will be performed using a likelihood ratio test.

AMENDMENTS TO VERSION 1.0

The pre-planned subgroup analysis 'urge versus passive FI episodes' had been inadvertently left out of version 1.0.

- Further, the sub-group analyses were to be conducted only on the primary outcome and not on the secondary outcomes as previously written.

- The Stata code listed in appendix 14(a) was refined during the analysis to correctly handle patients with fewer than 7 days of bowel diary data and the new code has replaced that previously in 14(a). The code to define stool consistency outcomes was not included in version 1.0 and was developed during the analysis.

- The listing of variables used in the multilevel multiple imputations was updated during the analysis to include more detail and also the imputation model for the four binary outcomes (primary (>= 50% reduction in FI) and three secondary (>=25%, >=75%, 100%)).

REFERENCES

Kahan BC & Morris TP. Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? Statist. Med 2013, 32 1136–1149

Vaizey CJ, Carapeti E, Cahill JA, et al. Prospective comparison of faecal incontinence grading systems *Gut* 1999 44: 77-80 doi: 10.1136/gut.44.1.77

APPENDICES

Stata code for creating outcome variables

```
*** Bowel diary data

forvalues i = 1(1)14 {
replace Q3_`i' = "" if Q3_`i' == "."
encode Q3_`i', generate(x)
drop Q3_`i'
rename x Q3_`i'
recode Q3_`i' (1=0)(2=1)
label variable Q3_`i' YN

replace Q4a_`i'="" if Q4a_`i' == "."
encode Q4a_`i', generate(x)
drop Q4a_`i'
rename x Q4a_`i'
recode Q4a_`i' (1=0)(2=1)
label variable Q4a_`i' YN

replace Q4b_`i'="" if Q4b_`i' == "."
encode Q4b_`i', generate(x)
drop Q4b_`i'
rencode x Q4b_`i'
recode Q4b_`i' (1=0)(2=1)
label variable Q4b_`i' YN

replace Q5_`i'="" if Q5_`i' == "."
encode Q5_`i', generate(x)
drop Q5_`i'
rencode x Q5_`i'
recode Q5_`i' (1=0)(2=1)
label variable Q5_`i' YN

generate x=real(Q1_`i')
drop Q1_`i'
rencode x Q1_`i'
generate x=real(Q2a_`i')
drop Q2a_`i'
rencode x Q2a_`i'
generate x=real(Q2b_`i')
drop Q2b_`i'
rencode x Q2b_`i'

encode Q6_`i', generate(x)
drop Q6_`i'
rencode x Q6_`i'
recode Q6_`i' (1=.)(6=0)(5=1)(4=2)
label variable Q6_`i' consist
```

```
}
sort PIN
compress

egen controlled = rowtotal(Q1_1 Q1_2 Q1_3 Q1_4 Q1_5 Q1_6 Q1_7 Q1_8
Q1_9 Q1_10 Q1_11 Q1_12 Q1_13 Q1_14), missing
egen uncontrolled_a = rowtotal(Q2a_1 Q2a_2 Q2a_3 Q2a_4 Q2a_5 Q2a_6
Q2a_7 Q2a_8 Q2a_9 Q2a_10 Q2a_11 Q2a_12 Q2a_13 Q2a_14), missing
egen uncontrolled_b = rowtotal(Q2b_1 Q2b_2 Q2b_3 Q2b_4 Q2b_5 Q2b_6
Q2b_7 Q2b_8 Q2b_9 Q2b_10 Q2b_11 Q2b_12 Q2b_13 Q2b_14), missing

egen staining = rowtotal(Q3_1 Q3_2 Q3_3 Q3_4 Q3_5 Q3_6 Q3_7 Q3_8 Q3_9
Q3_10 Q3_11 Q3_12 Q3_13 Q3_14), missing
egen pads = rowtotal(Q4a_1 Q4a_2 Q4a_3 Q4a_4 Q4a_5 Q4a_6 Q4a_7 Q4a_8
Q4a_9 Q4a_10 Q4a_11 Q4a_12 Q4a_13 Q4a_14), missing
egen enema = rowtotal(Q4b_1 Q4b_2 Q4b_3 Q4b_4 Q4b_5 Q4b_6 Q4b_7 Q4b_8
Q4b_9 Q4b_10 Q4b_11 Q4b_12 Q4b_13 Q4b_14), missing
egen social = rowtotal(Q5_1 Q5_2 Q5_3 Q5_4 Q5_5 Q5_6 Q5_7 Q5_8 Q5_9
Q5_10 Q5_11 Q5_12 Q5_13 Q5_14), missing
egen stool = rowtotal(Q6_1 Q6_2 Q6_3 Q6_4 Q6_5 Q6_6 Q6_7 Q6_8 Q6_9
Q6_10 Q6_11 Q6_12 Q6_13 Q6_14), missing

egen m_unc_a = rowmiss(Q2a_1 Q2a_2 Q2a_3 Q2a_4 Q2a_5 Q2a_6 Q2a_7)
egen m_unc_b = rowmiss(Q2b_1 Q2b_2 Q2b_3 Q2b_4 Q2b_5 Q2b_6 Q2b_7)

generate FI_episodes = uncontrolled_a + uncontrolled_b
generate FI_epi_pw = FI_episodes/2


*** primary outcome

generate Responder_50 = 1 if FI_epi_pw2/FI_epi_pw0<=.5
replace Responder_50 = 0 if FI_epi_pw2/FI_epi_pw0>.5 &
!missing(FI_epi_pw2) & !missing(FI_epi_pw0)

*** binary secondary outcomes: 25%, 75%, 100% improvement
generate Responder_25 = 1 if FI_epi_pw2/FI_epi_pw0<=.75
replace Responder_25 = 0 if FI_epi_pw2/FI_epi_pw0>.75 &
!missing(FI_epi_pw2) & !missing(FI_epi_pw0)

generate Responder_75 = 1 if FI_epi_pw2/FI_epi_pw0<=.25
replace Responder_25 = 0 if FI_epi_pw2/FI_epi_pw0>.25 &
!missing(FI_epi_pw2) & !missing(FI_epi_pw0)

generate Responder_100 = 1 if FI_epi_pw2==0
replace Responder_100 = 0 if FI_epi_pw2>0 & !missing(FI_epi_pw2)


*** Gastrointestinal quality of life

renpfix x_

foreach var of varlist GI2 GI4 GI6 GI8 GI9 GI11 GI12 GI13 GI14 GI16
GI18 GI20 GI22 GI24 GI26 GI28 GI30 GI32 GI34 GI36 {
*** reverse scoring
g x_`var'=1 if `var'==5
replace x_`var'=2 if `var'==4
replace x_`var'=3 if `var'==3
replace x_`var'=4 if `var'==2
replace x_`var'=5 if `var'==1
drop `var'
```

```
}

renpfix x_
order GI1 GI2 GI3 GI4 GI5 GI6 GI7 GI8 GI9 GI10 GI11 GI12 GI13 GI14
GI15 GI16 GI17 GI18 GI19 GI20 GI21 GI22 GI23 GI24 GI25 GI26 GI27 GI28
GI29 ///
  GI30 GI31 GI32 GI33 GI34 GI35 GI36
egen GIQoL_tot=rowtotal(GI1-GI36), missing
egen mGIQoL = rowmiss(GI1-GI36)
replace GIQoL_tot =. if mGIQoL ~= 0


*** EQ-5D

rename EQ1 mob
rename EQ2 self
rename EQ3 usual
rename EQ4 pain
rename EQ5 mood
rename EQ6 VAS

gen EuroQol = 1
replace EuroQol = 1-.069 if mob == 2
replace EuroQol = 1-.314 if mob == 3
replace EuroQol = EuroQol-.104 if self == 2
replace EuroQol = EuroQol-.214 if self == 3
replace EuroQol = EuroQol-.036 if usual == 2
replace EuroQol = EuroQol-.094 if usual == 3
replace EuroQol = EuroQol-.123 if pain == 2
replace EuroQol = EuroQol-.386 if pain == 3
replace EuroQol = EuroQol-.071 if mood == 2
replace EuroQol = EuroQol-.236 if mood == 3
replace EuroQol = EuroQol-.081 if (mob ~= 1 |self ~= 1|usual ~=
1|pain ~= 1|mood ~= 1)&(mob ~= . & self ~= . & usual ~= . & pain ~= .
& mood ~= .)
replace EuroQol = EuroQol - .269 if mob == 3|self ==3 |usual ==3
|pain == 3|mood == 3
replace EuroQol=. if mob == .|self == .|usual == .|pain == .|mood ==
.
egen itemEuro = rownonmiss(mob self usual pain mood)
generate invalidEuro = 1 if itemEuro > 0 & itemEuro < 5
replace invalidEuro = 0 if itemEuro == 5
egen mEuroQol = rowmiss(mob self usual pain mood)



*** Patient Centred Outcomes
egen PC_tot=rowtotal(PC1 PC2 PC3 PC4 PC5 PC6 PC7 PC8), missing
egen PC_mean=rowmean(PC1 PC2 PC3 PC4 PC5 PC6 PC7 PC8)
egen mPC = rowmiss(PC1 PC2 PC3 PC4 PC5 PC6 PC7 PC8)
replace PC_mean=. if mPC ~= 0

*** St. Mark's FI scale
recode CC1-CC4 (1=0)(2=1)(3=2)(4=3)(5=4)
recode CC5 CC6 (1=0)
recode CC7 (1=0)(2=4)
egen CC_tot=rowtotal(CC1 CC2 CC3 CC4 CC5 CC6 CC7), missing
egen mCC = rowmiss(CC1 CC2 CC3 CC4 CC5 CC6 CC7)
replace CC_tot = . if mCC ~= 0
```

```
*** SF-36
rename SF1 q1
rename SF2 q2
rename SF3a q3
rename SF3b q4
rename SF3c q5
rename SF3d q6
rename SF3e q7
rename SF3f q8
rename SF3g q9
rename SF3h q10
rename SF3i q11
rename SF3j q12
rename SF4a q13
rename SF4b q14
rename SF4c q15
rename SF4d q16
rename SF5a q17
rename SF5b q18
rename SF5c q19
rename SF6 q20
rename SF7 q21
rename SF8 q22
rename SF9a q23
rename SF9b q24
rename SF9c q25
rename SF9d q26
rename SF9e q27
rename SF9f q28
rename SF9g q29
rename SF9h q30
rename SF9i q31
rename SF10 q32
rename SF11a q33
rename SF11b q34
rename SF11c q35
rename SF11d q36

foreach var of varlist q1 q2 q20 q22 q34 q36 {
generate `var'_value=100 if `var'==1
replace `var'_value=75 if `var'==2
replace `var'_value=50 if `var'==3
replace `var'_value=25 if `var'==4
replace `var'_value=0 if `var'==5
}

foreach var of varlist q3-q12 {
generate `var'_value=0 if `var'==1
replace `var'_value=50 if `var'==2
replace `var'_value=100 if `var'==3
}

foreach var of varlist q13-q19 {
generate `var'_value=0 if `var'==1
replace `var'_value=100 if `var'==2
}

foreach var of varlist q21 q23 q26 q27 q30 {
generate `var'_value=100 if `var'==1
replace `var'_value=80 if `var'==2
replace `var'_value=60 if `var'==3
```

```
replace `var'_value=40 if `var'==4
replace `var'_value=20 if `var'==5
replace `var'_value=0 if `var'==6
}

foreach var of varlist q24 q25 q28 q29 q31 {
generate `var'_value=0 if `var'==1
replace `var'_value=20 if `var'==2
replace `var'_value=40 if `var'==3
replace `var'_value=60 if `var'==4
replace `var'_value=80 if `var'==5
replace `var'_value=100 if `var'==6
}

foreach var of varlist q32 q33 q35 {
generate `var'_value=0 if `var'==1
replace `var'_value=25 if `var'==2
replace `var'_value=50 if `var'==3
replace `var'_value=75 if `var'==4
replace `var'_value=100 if `var'==5
}

drop q1-q36

egen SF36_PF = rowmean(q3_value q4_value q5_value q6_value q7_value
q8_value q9_value q10_value q11_value q12_value)
egen SF36_RLPH = rowmean(q13_value q14_value q15_value q16_value)
egen SF36_RLEM = rowmean(q17_value q18_value q19_value)
egen SF36_EF = rowmean(q23_value q27_value q29_value q31_value)
egen SF36_EM = rowmean(q24_value q25_value q26_value q28_value
q30_value)
egen SF36_SF = rowmean(q20_value q32_value)
egen SF36_P = rowmean(q21_value q22_value)
egen SF36_GH = rowmean(q1_value q33_value q34_value q35_value
q36_value)


*** QoL FI scale

generate FI1_rev=1 if FI1==5
replace FI1_rev=2 if FI1==4
replace FI1_rev=3 if FI1==3
replace FI1_rev=4 if FI1==2
replace FI1_rev=5 if FI1==1

egen FIQoL_lif = rowmean(FI2a FI2b FI2c FI2d FI2e FI2g FI2h FI3b FI3l
FI3m)
egen FIQoL_cop = rowmean(FI2f FI2i FI2j FI2k FI2m FI3c FI3h FI3j
FI3n)
egen FIQoL_dep = rowmean(FI1_rev FI3d FI3f FI3g FI3i FI3k FI4)
egen FIQoL_emb = rowmean(FI2l FI3a FI3e)

egen mFIQoL_lif = rowmiss(FI2a FI2b FI2c FI2d FI2e FI2g FI2h FI3b
FI3l FI3m)
egen mFIQoL_cop = rowmiss(FI2f FI2i FI2j FI2k FI2m FI3c FI3h FI3j
FI3n)
egen mFIQoL_dep = rowmiss(FI1_rev FI3d FI3f FI3g FI3i FI3k FI4)
egen mFIQoL_emb = rowmiss(FI2l FI3a FI3e)

replace FIQoL_lif =. if mFIQoL_lif ~= 0
replace FIQoL_cop =. if mFIQoL_cop ~= 0
```

```
replace FIQoL_dep =. if mFIQoL_dep ~= 0
replace FIQoL_emb =. if mFIQoL_emb ~= 0
```

Variables to be used in the multilevel multiple imputation

Outcomes that are reported as a group of domains will be imputed together where possible. Baseline measures, mid-treatment (bowel diary data only) and end of treatment outcomes will be included together in the multivariate response. Centre is the only level 2 variable (random intercepts)

	Imputation Variables	
Outcomes	To include in multivariate response	Auxillary variables
Mean number of FI episodes per week	Mean number of FI episodes per week, St Mark's Continence Score, Likert	Age, Sex and random allocation
GI QOL Index (reported as total score	Mean number of FI episodes per week, St Mark's Continence Score, GI QOL	Age, Sex and random allocation
Patient centered outcomes form	Patient centered outcomes form	Age, Sex and random allocation
SF-36 (eight domains)	SF-36 (4 domains at a time)	Age, Sex and random allocation
Quality of life scale for FI (four domains)	QOL for FI	Age, Sex and random allocation
St Marks Continence Score	Mean number of FI episodes per week, St Mark's Continence Score	Age, Sex and random allocation
EQ-5D	EQ-5D	Age, Sex and random allocation

List of case report forms (see statistics master file for detail)

☐ CRF 1 – Eligibility assessment

☐ CRF 2 – Initial assessment

☐ CRF 3 – PRE-TREATMENT questionnaires

☐ CRF 3 – POST-TREATMENT questionnaires

☐ CRF 4 – Randomisation

☐ CRF 5 – Record stimulation parameters adverse events and medication / pad usage

☐ CRF 6 – Post-treatment information

☐ CRF 7 – Final study visit information

☐ BOWEL DIARY – PRE-TREATMENT (14 days)

☐ BOWEL DIARY – MID-TREATMENT (7 days)

☐ BOWEL DIARY – POST-TREATMENT (14 days)

Appendix 7 Data and Safety Monitoring Committee input

Data Safety and Monitoring Committee meeting timings and conclusions

Meeting 1: 6 February 2012

Conclusions

The DSMC agreed to meet at least 3 weeks prior to each TSC to enable sufficient time for analysis and interpretation of data prior to reporting to the TSC. It was also recognised that safety was not really an issue (owing to the nature of the treatment) and therefore the DSMC would concentrate on the ethical basis of the trial, assessing whether or not it was being conducted according to the protocol and whether or not it was able to answer the clinical question being asked. The timelines for future meetings were agreed, with the next scheduled for 5 months later to enable sufficient data to be collected. The remaining meetings would be at 4-monthly intervals. The author and format of the DSMC charter was agreed and the method of providing unblinded data by an independent statistician was confirmed. The trial statistician also agreed to draft the statistical analysis plan in time for the next DSMC meeting.

At subsequent meetings, the trial manager and trial statistician presented reports on the trial progress to date and reviewed the open data report, with the DSMC making clarifications or further elaborating as required. The DSMC then conducted their review of the unblinded report at a closed meeting and reported their recommendations and conclusions to the TSC in writing.

Meeting 2: 24 October 2012

Recommendations

The covariates for analysis were discussed and the per protocol analysis definitions agreed. The DSMC recommended that concomitant medications usage be presented by treatment arm but also by relevance and irrelevance to the treatment of FI. The DSMC was concerned there might be a significant difference in the drop-out rate between arms and agreed to monitor this and centre effects closely. The format of the report was discussed, with recommendations made for presenting the data. It was requested that the stratification factors for randomisation be included in the next report so that the DSMC could assess balance in the randomisation. It was also requested that AEs and SAEs by allocation be included in the next report.

Conclusions

The DSMC concluded that its remit should be to assure patient safety (although not a major concern in this trial), to ensure that the treatment is not futile, to assess whether or not the outcomes are sensitive enough to measure change and to ensure that the statistical analysis plan is fair and appropriate. The committee was delighted with the general progress of the trial, noting that centres were opening rapidly and recruitment increasing appropriately. For a challenging invasive functional bowel disease trial, the CRF returns also seemed satisfactory. Review of the unblinded data revealed no specific concerns and the DSMC was happy for the trial to progress.

Meeting 3: 18 March 2013

Recommendations

The DSMC made several recommendations for the formatting and presentation of data, particularly with regard to outcome data, AEs and withdrawals. The committee was interested in the data provided for the use of constipating agents and the use of bowel medication. The DSMC recommended providing an additional two tables: the first table to show 'use of bowel medication' at baseline and at end of treatment; the second table to show the numbers of people who increased their intake of constipating agents or decreased their intake of constipating agents, and the same for bowel medication, for each of the two groups. Finally, the DSMC suggested meeting again in 6 months before database lock, so that a final review of the data set could be performed and so the committee could contribute to the final report.

Conclusions

The DSMC was delighted with the conduct and the progress in the trial. Recruitment was running close to target and the trial was likely to close in the summer of 2013. The DSMC was pleased to see that the completeness of the data collection was good and no concerns were raised at the open meeting.

Meeting 4: 25 November 2013

Recommendations

The DSMC recommended that SAEs needed to be categorised into probably related and unrelated. The committee suggested analysing men separately as well as together with women, owing to the small number of men in the study. It was also noted that urinary symptoms in men and women were very different and these should also be analysed separately because of different physiological processes. The committee also recommended including data from centres where fewer than five patients had been recruited and analysing with and without these data, conducting sensitivity analysis if required. The committee expected that there was unlikely to be any centre effect.

Conclusions

The committee reviewed the confidential report and had no concerns over the data. The committee congratulated the team on a very successful trial. The committee did not consider another meeting to be necessary; however, the chairperson offered to look over the final data set.

Appendix 8 Data and Safety Monitoring Committee Charter

CHARTER FOR DATA MONITORING COMMITTEE FOR THE CONFIdeNT STUDY

DRAFT FOR APPROVAL

Introduction

Study name
CONFIDeNT: CONtrol of Faecal Incontinence using Distal NeuromodulaTion.

Study registration
ISRCTN88559475.

Objectives of the study
To determine the effectiveness of PTNS versus sham electrical stimulation, based on (primary outcome) reductions in weekly FIEs and on (secondary outcomes) improvements in validated incontinence scores and other symptoms and quality-of-life measures.

Purpose of charter
The purpose of this document is to describe the roles and responsibilities of the independent Data and Monitoring Ethics Committee (DMEC) for the CONFIDeNT study, including the timing of meetings, methods of providing information to and from the TSC, frequency and format of meetings and statistical issues.

Roles and responsibilities of the Data Monitoring and Ethics Committee

Broad statement of aim of committee
To protect and serve study participants (especially regarding safety) and to assist and advise the chief investigator so as to protect the validity and credibility of the trial.

Terms of reference
The DMEC will receive and review interim results of the study.

The DMEC is responsible to the TSC of the study. Although it may choose to communicate interim results or make recommendations, the final decisions about the study rest with the TSC.

During the period of recruitment to the study, data will be supplied to the Chair of the DMEC as frequently as is requested. Meetings of the committee, either in person or by phone, will be arranged periodically, as considered appropriate by the Chair.

In the light of the interim data, the DMEC will inform the TSC if, in their view, there is proof beyond reasonable doubt that the data indicate that the treatment under investigation is either clearly indicated or clearly contraindicated.

If the DMEC does choose to inform the TSC that in their view the situation described above pertains, the TSC will consider modifying or stopping intake into the study. Unless modification or cessation is

recommended by the DMEC, however, the TSC, collaborators and administrative staff (except staff who produce the confidential analyses) will remain ignorant of the interim results.

Collaborators, and all others associated with the study, may write directly to the Chair of the DMEC, to draw attention to any concern they may have about the possibility of harm arising from the use of the treatment under study, or about any other matters that may be relevant.

Specific roles of Data Monitoring and Ethics Committee

These will include interim reviews of the trial's progress including:

- updated figures on recruitment and losses to follow-up
- data quality, including completeness and adherence to protocol by participants and investigators
- evidence for treatment harm, for example safety data and adverse events
- advice on any protocol modifications suggested by investigators or sponsors.

Before or early in the trial

Before the start of recruitment, the TSC met with the DMEC to discuss various aspects of the trial and protocol. All DMEC members had the opportunity to see the study protocol, and will have the opportunity to comment on the contents of this charter.

Among the points raised, it was suggested that a draft statistical analysis plan be drafted for the next DMEC meeting. Other points raised, relevant to the DMEC, are mentioned later in this document.

Composition of Data Monitoring and Ethics Committee and relationship to trial steering committee

Membership and size

The members are independent of the trial, and include a clinician and a statistician.

The members of the CONFIDeNT DMEC are:

Professor Dion Morton (chair)
Professor of Surgery
Academic Department of Surgery
University of Birmingham
Queen Elizabeth Hospital
Mindelsohn Way
Edgebaston
Birmingham, B15 2WB
E-mail: XX

Professor Elaine Denny (independent member)
Professor of Health Sociology
Birmingham City University
City North Campus
Birmingham, B42 2SU
E-mail: XX

Dr Dan Altmann (independent statistician)
Senior Lecturer in Medical Statistics
Department of Medical Statistics
London School of Hygiene & Tropical Medicine
Keppel Street
London, WC1E 7HT
E-mail: XX

The responsibilities of the trial statistician

The trial statistician, Dr Stephen Bremner, in consultation with the senior trialstatistician Professor Sandra Eldridge, will organise the interim reports to the DMEC. These reports will contain unblinded data, although the trial statistician will not see the unblinded version. It is not expected that the trial statistician will need to participate in DMEC meetings, but he should be available to respond to any queries arising from the interim reports.

Payment to Data Monitoring and Ethics Committee members

Members will be reimbursed for travel to and from DMEC meetings if required.

Competing interests

Data Monitoring and Ethics Committee members should disclose to the TSC any competing interests, not restricting to financial matters. DMEC members will respect the confidentiality of the interim reports, and will not use interim results to influence or inform financial trading. The format for a short competing interests form is given in *Annex 1*, and should be completed by DMEC members and returned to the chief investigator [CI].

Organisation of Data Monitoring and Ethics Committee meetings

Timing of data monitoring and ethics committee meetings

The first DMEC meeting should be at 5 months, and will be held in Birmingham; subsequently meetings will be held 3 to 4 weeks prior to planned TSC meetings. The format of subsequent DMEC meetings will be decided by DMEC.

Trial documentation and procedures to ensure confidentiality and proper communication

It is anticipated that the first interim report for DMEC, organised by the trial statistician, should contain data presented, where possible, by unblinded trial allocation group, to include (1) recruitment flow chart (showing attendance at scheduled visits and any reported non-adherence and withdrawal from the trial); (2) primary and secondary outcomes; and (3) adverse events and any other safety-related data. A dummy report before the first DMEC meeting, although helpful, is not necessary. Changes to format or content may be requested by DMEC for subsequent DMEC meetings.

Access to the accumulating data and interim results

Data and Safety Monitoring Committee members do not have the right to share confidential information with anyone outside the DMEC, including the CI and named applicants.

Responsibility for identifying and circulating external evidence

Identification and circulation of external evidence (e.g. from other trials/systematic reviews) is not the responsibility of the DMEC members. The TSC will usually collate any such information if appropriate.

To whom the data monitoring and ethics committee will communicate the decisions/recommendations that are reached

The DMEC will report its recommendations in writing to the TSC, copying to the trial statistician, in time for consideration at the next TSC meeting. It is hoped and anticipated that, routinely, if the trial is to continue largely unchanged, then a note from the DMEC Chair back to TSC along the lines given in *Annex 2* will be sufficient response.

Ensuring safety of confidential papers

The DMEC members should store interim report papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMEC members should destroy all interim reports.

Decision-making

What decisions/recommendations will be open to the Data Monitoring and Ethics Committee?

Possible recommendations could include:

- no action needed, trial continues as planned
- early stopping as a result, for example, of clear benefit or harm of a treatment, futility or external evidence
- extending recruitment (based on actual control arm response rates being different to predicted) or extending follow-up
- sanctioning and/or proposing protocol changes.

Statistical methods

Any planned interim analyses should be tabled by the trial statistician before the first DMEC meeting for discussion and agreement.

How decisions or recommendations will be reached within the Data Monitoring and Ethics Committee

Data Monitoring and Ethics Committee members must agree on a process of decision-making, including whether or not there will be voting or other formal or informal methods of achieving consensus.

Every effort should be made by the DMEC to reach a unanimous decision. If the DMEC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC, as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.

When the Data Monitoring and Ethics Committee is quorate for decision-making

Owing to the relatively small size of the DMEC, decisions should involve all three members, but not necessarily at a face-to-face meeting: teleconference or e-mail contact may be sufficient. DMEC members who will not be able to attend a planned face-to-face meeting may pass comments to the DMEC Chair for consideration during any discussions.

Reporting

Minutes of meetings

Separate minutes of DMEC meetings will be taken by the Chair of the DMEC. The DMEC Chair must sign off all minutes.

What will be done if there is disagreement between the Data Monitoring and Ethics Committee and the trial steering committee?

If the DMEC has serious problems or concerns with the TSC decision, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the TSC or an external expert who is not directly involved with the trial. The funder may be invited to such meetings.

After the trial

Publication of results

At the end of the trial there will be a meeting to allow the DMEC to discuss the final data with the chief investigator and give advice about data interpretation.

The information about the Data Monitoring and Ethics Committee that will be included in published trial reports

Data Monitoring and Ethics Committee members will be named and their affiliations listed in the main trial report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMEC meetings should be included in the body of this paper.

Will the Data Monitoring and Ethics Committee have the opportunity to comment on publications before submission?

The DMEC will be given an opportunity to read and comment on any publication before it is submitted.

Constraints on Data and Safety Monitoring Committee members divulging information about their deliberations after the trial has been published

The DMEC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published.

Annex 1 Competing interests form

Potential competing interests of DMEC members for CONFIDeNT, ISRCTN88559475.

The avoidance of any perception that members of a DMEC may be biased in some fashion is important for the credibility of the decisions made by the DMEC and for the integrity of the CONFIDeNT study. Possible competing interests should be disclosed: in many cases simple disclosure should be sufficient. Otherwise, the DMEC member should remove the conflict or stop participating in the DMEC. *Table 18* lists potential competing interests.

Please complete the following section and return to the Chief Investigator.

_____ **No**, I have no competing interests to declare

_____ **Yes**, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

Name: _____

Signed: _____ Date: _____

TABLE 18 Potential competing interests

Stock ownership in any commercial companies involved
Stock transaction in any commercial company involved (if previously holding stock)
Consulting arrangements with the sponsor
Frequent speaking engagements on behalf of the intervention
Career tied up in a product or technique assessed by trial
Hands-on participation in the trial
Involvement in the running of the trial
Emotional involvement in the trial
Intellectual conflict, for example strong prior belief in the trial's experimental arm
Involvement in regulatory issues relevant to the trial procedures
Investment (financial or intellectual) in competing products
Involvement in the publication

Annex 2 Suggested report from the Data Monitoring and Ethics Committee to the Trial Steering Committee where no recommendations are being made

BOX 1 Suggested report from the DMEC to the TSC where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear [Chair of Trial Steering Committee]

The Data Monitoring and Ethics Committee (DMEC) for the [insert trial name] trial met on [meeting date] to review its progress and interim accumulating data. [List members] attended the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [specify protocol version number and date] with no changes.

We shall next review the progress and data [provide approximate timing]

Yours sincerely,

[Name of meeting Chair]

Chair of Data Monitoring and Ethics Committee

On behalf of the DMEC (all members listed below)

DMEC members:

(1) [Insert name and role]

(2) [Insert name and role]

(3) [Insert name and role]

Appendix 9 Patient and public involvement

The CONFIDeNT trial has had active collaboration with the Bowel & Cancer Research charity from the early stages of the trial and throughout trial implementation and dissemination of results. The chief executive of this charity has been a lay representative on the TSC and has been influential in portraying the lay understanding and interpretation of trial materials, reviewing the trial protocol and patient information material, and aiding in the production of a lay summary of trial results for dissemination to patients and user groups, a copy of which will be published on the Bowel & Cancer Research charity website.

The researchers recognise that there was limited patient and public involvement in the development of the research question, in the grant application and in the review of patient materials because of the lack of an established patient and public involvement network at the time of trial design. Through linking with the Bowel & Cancer Research charity, and in collaboration with the National Centre for Bowel Research and Surgical Innovation, we have strengthened our patient and public involvement position for future trials by establishing a patient and public involvement group and now have an established patient and public involvement group with over 70 members. This group is specifically interested in areas of bowel research being conducted in the centre, including FI and constipation, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, bowel cancer and stomas. Now that this database of patient and public involvement members has been established, we are able to consult members for feedback on surveys and questionnaires, on trial design and acceptability and on acceptability of documentation developed for patients, including advertising materials, patient information sheets, diaries and questionnaires, as well as able to invite members for inclusion in TSCs and attendance at meetings and workshops.

This collaboration held a highly successful event at Barts and the London School of Medicine and Dentistry in December 2012 to showcase the research being undertaken within the centre. Members of the PPI group were invited to attend and patient representatives were also invited to speak about experience participating in research. A similar event was run in April 2015, which involved more interactive workshops to aid understanding of what it means to be involved in a patient and public involvement group and deliver training on the various tasks that may be undertaken as a patient and public involvement member.

Finally, should HTA funding be agreed, we plan to develop a 'pod' and live science show at the Centre of the Cell. This is a centre for public engagement which 'combines an award-winning interactive science centre plus live science shows, workshops, debates, science talks and a widening participation for East London and beyond'.[82] We have been in initial discussions with the Centre of the Cell, and have come up with some fantastic ideas on how to disseminate the results of this trial while raising awareness of bowel problems such as FI and try to improve education about the healthy bowel. As part of this, we plan to develop a high-tech, multimedia, interactive pod show for children. This will provide longevity in disseminating the message of preventing bowel disease from an early age and also educate children on the type of medical research undertaken to help prevent and treat bowel disease.

The following text is a lay summary of the CONFIDeNT trial results, which has been edited by our patient and public involvement group and will be sent out to all trial participants:

> *Thank you very much for participating in this important research project.*
>
> *The aim of the study was to assess the effectiveness of PTNS (percutaneous tibial nerve stimulation) compared to placebo or sham (pretend) electrical stimulation treatment in reducing FIEs.*
>
> *In total, 227 patients from 17 NHS hospitals across the UK were involved in the study. Half of the patients had PTNS treatment and half had sham treatment, each undergoing a course of 12 treatments over 12 weeks. We recorded your faecal incontinence episodes before treatment*

commencement, after 6 treatments and at the end of 12 treatments. Your treatment was deemed successful if you experienced a 50% or more reduction in faecal incontinence episodes as recorded on bowel diaries. We also measured changes in your quality of life from questionnaires.

This study is now complete and we write to you to share the results. There was no significant difference between the number of patients in each group who experienced a 50% or more reduction in faecal incontinence episodes. In the PTNS group, 38% of patients had successful treatment and in the sham group 31% of patients had successful treatment. This does not amount to a significant difference between the two groups. There was also no difference in improvement in quality of life between the group that received real PTNS and those that received sham treatment.

Further analysis did however show that patients experienced a significant reduction in the overall number of faecal incontinence episodes in the PTNS group, and this did not happen in the sham group. This seemed to be a reduction in the 'rush' type episodes rather than the 'no warning' type episodes. This could be important for tailoring future treatment and further research into this area is required.

The results of this study will be shared with doctors and other medical practitioners through national and international conferences in a detailed scientific report.

If you would like to read more about these findings, please refer to the lay summary of results on the Bowel & Cancer Research Charity website www.bowelcancerresearch.org. A full detailed report will be available on the funder's website, National Institute of Health Research www.nihr.ac.uk.

Once again thank you for your participation, without which we could not have completed the study. We enclose with this letter an invitation for your continued involvement in our patient and public involvement group (PPI group) and do hope you may be interested in working with us in the future to promote public awareness and engagement with research, particularly in the area of bowel diseases.

Appendix 10 Raw data

TABLE 19 Main bowel diary outcomes at baseline and at end of treatment

Outcome	PTNS	Sham	Total
Total weekly FIEs at baseline			
n	111	108	219
Mean (SD)	9.9 (11.2)	10.4 (10.9)	10.2 (11.0)
Median (IQR)	6.0 (2.0–14.0)	6.9 (2.5–16.0)	6.5 (2.0–14.6)
Minimum to maximum	0.0 to 57.0	0.0 to 71.0	0.0 to 71.0
Urge FIEs per week at baseline			
n	114	109	223
Mean (SD)	5.3 (7.2)	4.8 (5.9)	5.1 (6.6)
Median (IQR)	3.0 (0.9–8.0)	2.5 (0.5–7.0)	3.0 (0.5–7.0)
Minimum to maximum	0.0 to 42.5	0.0 to 41.0	0.0 to 42.5
Passive FIEs per week at baseline			
n	112	108	220
Mean (SD)	4.6 (6.0)	5.7 (7.6)	5.2 (6.8)
Median (IQR)	2.0 (0.0–7.5)	3.0 (0.0–8.0)	2.5 (0.0–7.5)
Minimum to maximum	0.0 to 27.0	0.0 to 43.0	0.0 to 43.0
Total weekly FIEs after treatment			
n	105	104	209
Mean (SD)	6.4 (7.6)	9.1 (10.7)	7.7 (9.3)
Median (IQR)	3.5 (1.0–10.0)	4.8 (1.5–12.8)	4.0 (1.0–11.0)
Minimum to maximum	0.0 to 44.5	0.0 to 43.5	0.0 to 44.5
Urge FIEs per week after treatment			
n	106	105	211
Mean (SD)	3.0 (4.2)	4.4 (6.5)	3.7 (5.5)
Median (IQR)	1.5 (0.0–4.5)	1.5 (0.5–5.5)	1.5 (0.0–4.5)
Minimum to maximum	0.0 to 23.5	0.0 to 35.5	0.0 to 35.5
Passive FIEs per week after treatment			
n	105	105	210
Mean (SD)	3.4 (4.6)	4.7 (6.6)	4.0 (5.8)
Median (IQR)	1.5 (0.0–5.0)	1.5 (0.0–6.5)	1.5 (0.0–5.5)
Minimum to maximum	0.0 to 21.0	0.0 to 33.5	0.0 to 33.5

IQR, interquartile range; SD, standard deviation.

TABLE 20 St Mark's Continence Scores (baseline and end of treatment)

Outcome	PTNS	Sham	Total
SMCS at baseline			
n	110	101	211
Mean (SD)	14.4 (3.7)	15.4 (4.1)	14.9 (3.9)
Median (IQR)	14.0 (12.0–17.0)	16.0 (13.0–18.0)	15.0 (13.0–18.0)
Minimum to maximum	5.0 to 22.0	5.0 to 24.0	5.0 to 24.0
SMCS after treatment			
n	104	101	205
Mean (SD)	13.9 (4.3)	14.6 (4.6)	14.3 (4.4)
Median (IQR)	14.0 (11.0–17.0)	15.0 (11.0–18.0)	14.0 (11.0–18.0)
Minimum to maximum	6.0 to 23.0	5.0 to 24.0	5.0 to 24.0

IQR, interquartile range; SD, standard deviation.

TABLE 21 Patient characteristics and past medical history

Outcome	PTNS (*N* = 115)	Sham (*N* = 112)	Total (*N* = 227)
Sex			
Male	11 (10%)	11 (10%)	22 (10%)
Female	104 (90%)	101 (90%)	205 (90%)
Age (years)			
n	115	112	227
Mean (SD)	57.8 (12.4)	56.5 (12.1)	57.2 (12.2)
Median (IQR)	58.0 (50.0–67.0)	58.0 (48.0–65.0)	58.0 (49.0–66.0)
Minimum to maximum	20.0 to 85.0	23.0 to 79.0	20.0 to 85.0
Duration of symptoms (months)			
n	112	110	222
Mean (SD)	112.6 (117.5)	79.7 (88.4)	96.3 (105.2)
Median (IQR)	60.0 (24.0–168.0)	48.0 (24.0–108.0)	60.0 (24.0–120.0)
Minimum to maximum	5.0 to 600.0	6.0 to 540.0	5.0 to 600.0
Number of vaginal deliveries			
n	90	96	186
Mean (SD)	2.3 (1.2)	2.4 (1.1)	2.4 (1.2)
Median (IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
Minimum to maximum	1.0 to 7.0	1.0 to 7.0	1.0 to 7.0
Caesarean deliveries			
No, *n* (%)	90 (95)	96 (100)	186 (97)
Yes, *n* (%)	5 (5)	0 (0)	5 (3)

TABLE 21 Patient characteristics and past medical history (*continued*)

Outcome	PTNS (*N* = 115)	Sham (*N* = 112)	Total (*N* = 227)
Obstetric history			
No, *n* (%)	9 (9)	5 (5)	14 (7)
Yes, *n* (%)	95 (91)	96 (95)	191 (93)
Episiotomy/tear			
No, *n* (%)	12 (13)	14 (15)	26 (14)
Yes, *n* (%)	78 (87)	82 (85)	160 (86)
Previous biofeedback			
No, *n* (%)	56 (50)	48 (45)	104 (47)
Yes, *n* (%)	56 (50)	59 (55)	115 (53)
Previous sphincter repair			
No, *n* (%)	101 (91)	101 (94)	202 (92)
Yes, *n* (%)	10 (9)	7 (6)	17 (8)
Previous treatment (other), *n* (%)	18 (17)	21 (21)	39 (19)
Increased stool frequency, *n* (%)	69 (61)	69 (62)	138 (62)
Urgency to pass stool, *n* (%)	99 (90)	99 (88)	198 (89)
Passive FI, *n* (%)	88 (77)	86 (77)	174 (77)
Urge FI, *n* (%)	94 (82)	93 (83)	187 (82)
Flatus incontinence, *n* (%)	74 (64)	83 (74)	157 (69)
Evacuatory difficulties, *n* (%)	44 (39)	49 (44)	93 (41)
Straining, *n* (%)	34 (30)	37 (33)	71 (31)
Prolapse, *n* (%)	4 (4)	8 (7)	12 (5)
Soils underwear, *n* (%)	104 (91)	103 (92)	207 (92)
Use pads, *n* (%)	77 (67)	73 (65)	150 (66)
Unable to defer defecation, *n* (%)	52 (47)	43 (41)	95 (44)
Unable to distinguish faeces from flatus, *n* (%)	44 (38)	38 (35)	82 (36)
Sense of rectal blockage or bulge, *n* (%)	21 (18)	22 (20)	43 (19)
Digitation required, *n* (%)	12 (10)	15 (13)	27 (12)
Anxiety/panic, *n* (%)	75 (65)	84 (75)	159 (70)
Urinary symptom history, *n* (%)	70 (61)	72 (64)	142 (63)
Increased frequency of urine, *n* (%)	44 (38)	43 (38)	87 (38)
Urinary urgency, *n* (%)	50 (43)	49 (44)	99 (44)
Urinary stress incontinence, *n* (%)	43 (37)	42 (38)	85 (37)
Urinary urge incontinence, *n* (%)	39 (34)	42 (38)	81 (36)
Other urinary symptoms, *n* (%)	15 (14)	12 (12)	27 (13)

IQR, interquartile range; SD, standard deviation.

TABLE 22 Bowel diary data at baseline

Outcome	PTNS (*N* = 115)	Sham (*N* = 111)	Total (*N* = 226)
Total weekly FIEs at baseline			
n	111	108	219
Mean (SD)	9.9 (11.2)	10.4 (10.9)	10.2 (11.0)
Median (IQR)	6.0 (2.0–14.0)	6.9 (2.5–16.0)	6.5 (2.0–14.6)
Minimum to maximum	0.0 to 57.0	0.0 to 71.0	0.0 to 71.0
Urge FIEs per week at baseline			
n	114	109	223
Mean (SD)	5.3 (7.2)	4.8 (5.9)	5.1 (6.6)
Median (IQR)	3.0 (0.9–8.0)	2.5 (0.5–7.0)	3.0 (0.5–7.0)
Minimum to maximum	0.0 to 42.5	0.0 to 41.0	0.0 to 42.5
Passive FIEs per week at baseline			
n	112	108	220
Mean (SD)	4.6 (6.0)	5.7 (7.6)	5.2 (6.8)
Median (IQR)	2.0 (0.0–7.5)	3.0 (0.0–8.0)	2.5 (0.0–7.5)
Minimum to maximum	0.0 to 27.0	0.0 to 43.0	0.0 to 43.0
Controlled defecations per week at baseline			
n	115	111	226
Mean (SD)	13.2 (12.2)	12.4 (9.5)	12.8 (11.0)
Median (IQR)	11.0 (4.7–17.5)	10.5 (6.5–17.0)	11.0 (6.0–17.0)
Minimum to maximum	0.0 to 83.5	0.0 to 51.5	0.0 to 83.5
Days of underwear staining per week at baseline			
n	114	110	224
Mean (SD)	3.8 (2.2)	4.0 (2.4)	3.9 (2.3)
Median (IQR)	3.7 (2.0–6.0)	4.5 (2.0–6.0)	4.0 (2.0–6.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days using pad per week at baseline			
n	112	106	218
Mean (SD)	3.6 (3.2)	3.7 (3.3)	3.6 (3.3)
Median (IQR)	4.5 (0.0–7.0)	4.3 (0.0–7.0)	4.5 (0.0–7.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days with an enema per week at baseline			
n	112	107	219
Mean (SD)	0.3 (1.1)	0.2 (0.7)	0.2 (0.9)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0

TABLE 22 Bowel diary data at baseline (*continued*)

Outcome	PTNS (*N* = 115)	Sham (*N* = 111)	Total (*N* = 226)
Days per week stool was mostly solid at baseline			
n	108	109	217
Mean (SD)	2.6 (2.5)	2.6 (2.2)	2.6 (2.3)
Median (IQR)	2.0 (0.0–4.8)	2.3 (0.5–3.8)	2.0 (0.5–4.2)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly mushy at baseline			
n	108	109	217
Mean (SD)	0.8 (1.4)	1.0 (1.4)	0.9 (1.4)
Median (IQR)	0.0 (0.0–1.2)	0.0 (0.0–1.5)	0.0 (0.0–1.4)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly liquid at baseline			
n	108	109	217
Mean (SD)	3.5 (2.3)	3.4 (2.1)	3.5 (2.2)
Median (IQR)	3.5 (1.8–5.5)	3.5 (2.0–5.0)	3.5 (1.9–5.3)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0

IQR, interquartile range; SD, standard deviation.
Patients must have at least 7 days of data for a bowel diary outcome to be computed at baseline.

TABLE 23 Other secondary outcomes at baseline

Outcome	PTNS (*N* = 115)	Sham (*N* = 112)	Total (*N* = 227)
GIQoL at baseline			
n	98	98	196
Mean (SD)	126.7 (18.8)	123.8 (20.2)	125.3 (19.5)
Median (IQR)	130.0 (113.0–41.0)	126.5 (109.0–139.0)	128.0 (112.0–140.0)
Minimum to maximum	78.0 to 162.0	68.0 to 160.0	68.0 to 162.0
EQ-5D at baseline			
n	115	109	224
Mean (SD)	0.69 (0.27)	0.63 (0.34)	0.66 (0.31)
Median (IQR)	0.73 (0.62–0.85)	0.73 (0.62–0.85)	0.73 (0.62–0.85)
Minimum to maximum	–0.18 to 1.00	–0.24 to 1.00	–0.24 to 1.00
SMCS at baseline			
n	110	101	211
Mean (SD)	14.4 (3.7)	15.4 (4.1)	14.9 (3.9)
Median (IQR)	14.0 (12.0–17.0)	16.0 (13.0–18.0)	15.0 (13.0–18.0)
Minimum to maximum	5.0 to 22.0	5.0 to 24.0	5.0 to 24.0

continued

TABLE 23 Other secondary outcomes at baseline (*continued*)

Outcome	PTNS (*N* = 115)	Sham (*N* = 112)	Total (*N* = 227)
Patient-centred outcomes at baseline			
n	100	92	192
Mean (SD)	8.5 (1.6)	8.7 (1.7)	8.6 (1.7)
Median (IQR)	8.9 (7.8–9.8)	9.2 (8.3–10.0)	9.0 (8.0–9.9)
Minimum to maximum	1.9 to 10.0	1.6 to 10.0	1.6 to 10.0
SF-36 physical functioning at baseline			
n	108	107	215
Mean (SD)	65.7 (27.4)	61.4 (28.4)	63.6 (27.9)
Median (IQR)	70.0 (45.0–90.0)	65.0 (40.0–85.0)	70.0 (40.0–85.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 role-physical at baseline			
n	111	107	218
Mean (SD)	46.4 (42.1)	36.4 (41.4)	41.5 (41.9)
Median (IQR)	50.0 (0.0–100.0)	25.0 (0.0–75.0)	25.0 (0.0–100.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 bodily pain at baseline			
n	113	112	225
Mean (SD)	61.3 (30.0)	58.2 (31.5)	59.8 (30.7)
Median (IQR)	60.0 (40.0–90.0)	57.5 (32.5–90.0)	57.5 (32.5–90.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 general health at baseline			
n	114	108	222
Mean (SD)	51.2 (23.4)	50.3 (23.8)	50.8 (23.6)
Median (IQR)	50.0 (35.0–70.0)	50.0 (30.0–70.0)	50.0 (35.0–70.0)
Minimum to maximum	0.0 to 100.0	0.0 to 95.0	0.0 to 100.0
SF-36 vitality at baseline			
n	108	104	212
Mean (SD)	43.9 (22.1)	42.7 (22.8)	43.3 (22.4)
Median (IQR)	45.0 (30.0–57.5)	50.0 (30.0–60.0)	50.0 (30.0–60.0)
Minimum to maximum	0.0 to 85.0	0.0 to 95.0	0.0 to 95.0
SF-36 social functioning at baseline			
n	115	112	227
Mean (SD)	58.4 (28.8)	59.3 (31.6)	58.8 (30.1)
Median (IQR)	62.5 (37.5–75.0)	62.5 (37.5–87.5)	62.5 (37.5–87.5)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0

TABLE 23 Other secondary outcomes at baseline (*continued*)

Outcome	PTNS (*N* = 115)	Sham (*N* = 112)	Total (*N* = 227)
SF-36 role-emotional function at baseline			
n	113	111	224
Mean (SD)	56.3 (43.0)	48.9 (44.2)	52.7 (43.7)
Median (IQR)	66.7 (0.0–100.0)	33.3 (0.0–100.0)	66.7 (0.0–100.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 mental health at baseline			
n	109	106	215
Mean (SD)	60.3 (21.0)	60.8 (21.6)	60.6 (21.3)
Median (IQR)	60.0 (44.0–76.0)	64.0 (48.0–76.0)	64.0 (44.0–76.0)
Minimum to maximum	12.0 to 100.0	0.0 to 96.0	0.0 to 100.0
FIQoL lifestyle at baseline			
n	93	92	185
Mean (SD)	2.6 (0.9)	2.6 (1.0)	2.6 (1.0)
Median (IQR)	2.7 (1.8–3.4)	2.5 (1.7–3.6)	2.7 (1.7–3.5)
Minimum to maximum	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0
FIQoL coping at baseline			
n	79	77	156
Mean (SD)	1.9 (0.7)	1.9 (0.9)	1.9 (0.8)
Median (IQR)	1.7 (1.2–2.3)	1.6 (1.1–2.6)	1.7 (1.2–2.4)
Minimum to maximum	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0
FIQoL depression at baseline			
n	75	81	156
Mean (SD)	2.8 (0.9)	2.7 (0.9)	2.8 (0.9)
Median (IQR)	3.1 (2.0–3.4)	2.6 (2.0–3.7)	2.9 (2.0–3.6)
Minimum to maximum	1.1 to 4.1	1.0 to 4.1	1.0 to 4.1
FIQoL embarrassment at baseline			
n	110	106	216
Mean (SD)	2.2 (0.8)	2.1 (0.8)	2.1 (0.8)
Median (IQR)	2.0 (1.7–2.7)	2.0 (1.3–2.7)	2.0 (1.3–2.7)
Minimum to maximum	1.0 to 4.0	1.0 to 3.7	1.0 to 4.0

IQR, interquartile range; SD, standard deviation.

TABLE 24 Bowel diary data mid-treatment

Outcome	PTNS (*N* = 110)	Sham (*N* = 110)	Total (*N* = 220)
Total weekly FIEs mid-treatment			
n	97	99	196
Mean (SD)	6.1 (7.6)	9.6 (11.5)	7.8 (9.9)
Median (IQR)	4.0 (1.0–9.0)	6.0 (1.0–14.0)	4.0 (1.0–10.0)
Minimum to maximum	0.0 to 46.0	0.0 to 51.0	0.0 to 51.0
Urge FIEs per week mid-treatment			
n	102	102	204
Mean (SD)	3.3 (4.3)	4.4 (6.3)	3.9 (5.4)
Median (IQR)	2.0 (0.0–5.0)	2.0 (0.0–7.0)	2.0 (0.0–6.0)
Minimum to maximum	0.0 to 25.0	0.0 to 29.0	0.0 to 29.0
Passive FIEs per week mid-treatment			
n	100	102	202
Mean (SD)	3.0 (4.6)	5.0 (7.3)	4.0 (6.2)
Median (IQR)	1.0 (0.0–4.5)	1.0 (0.0–8.0)	1.0 (0.0–6.0)
Minimum to maximum	0.0 to 24.0	0.0 to 37.0	0.0 to 37.0
Controlled defecations per week mid-treatment			
n	104	102	206
Mean (SD)	13.0 (11.5)	11.4 (7.6)	12.2 (9.8)
Median (IQR)	11.0 (6.0–15.5)	10.0 (7.0–15.0)	10.0 (7.0–15.0)
Minimum to maximum	0.0 to 84.0	0.0 to 44.0	0.0 to 84.0
Days of underwear staining per week mid-treatment			
n	99	97	196
Mean (SD)	3.3 (2.3)	3.4 (2.6)	3.4 (2.5)
Median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days using pad per week mid-treatment			
n	99	99	198
Mean (SD)	3.7 (3.2)	3.8 (3.4)	3.8 (3.3)
Median (IQR)	4.0 (0.0–7.0)	7.0 (0.0–7.0)	5.5 (0.0–7.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days using an enema per week mid-treatment			
n	95	97	192
Mean (SD)	0.2 (0.7)	0.2 (0.8)	0.2 (0.8)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Minimum to maximum	0.0 to 4.0	0.0 to 7.0	0.0 to 7.0

TABLE 24 Bowel diary data mid-treatment (*continued*)

Outcome	PTNS (*N* = 110)	Sham (*N* = 110)	Total (*N* = 220)
Days per week stool was mostly solid mid-treatment			
n	65	70	135
Mean (SD)	3.2 (2.3)	3.2 (2.4)	3.2 (2.3)
Median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–5.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly mushy mid-treatment			
n	65	70	135
Mean (SD)	0.5 (1.0)	1.0 (1.7)	0.8 (1.4)
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–1.0)
Minimum to maximum	0.0 to 4.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly liquid mid-treatment			
n	65	70	135
Mean (SD)	3.3 (2.4)	2.8 (2.6)	3.1 (2.5)
Median (IQR)	3.0 (2.0–5.0)	2.5 (0.0–5.0)	3.0 (0.0–5.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0

IQR, interquartile range; SD, standard deviation.
Patients must have complete data on an outcome, that is 7 days, for the outcome to be computed.

TABLE 25 Bowel diary data at end of treatment

Outcome	PTNS (*N* = 109)	Sham (*N* = 108)	Total (*N* = 217)
Primary outcome			
≥ 50% reduction in FIEs, *n* (%)	39 (38)	32 (31)	71 (35)
≥ 25% reduction in FIEs, *n* (%)	51 (50)	46 (45)	97 (47)
≥ 75% reduction in FIEs, *n* (%)	26 (25)	17 (17)	43 (21)
100% reduction in FIEs, *n* (%)	11 (11)	7 (7)	18 (9)
Total weekly FIEs after treatment			
n	105	104	209
Mean (SD)	6.4 (7.6)	9.1 (10.7)	7.7 (9.3)
Median (IQR)	3.5 (1.0–10.0)	4.8 (1.5–12.8)	4.0 (1.0–11.0)
Minimum to maximum	0.0 to 44.5	0.0 to 43.5	0.0 to 44.5
Urge FIEs per week after treatment			
n	106	105	211
Mean (SD)	3.0 (4.2)	4.4 (6.5)	3.7 (5.5)
Median (IQR)	1.5 (0.0–4.5)	1.5 (0.5–5.5)	1.5 (0.0–4.5)
Minimum to maximum	0.0 to 23.5	0.0 to 35.5	0.0 to 35.5

continued

TABLE 25 Bowel diary data at end of treatment (*continued*)

Outcome	PTNS (*N* = 109)	Sham (*N* = 108)	Total (*N* = 217)
Passive FIEs per week after treatment			
n	105	105	210
Mean (SD)	3.4 (4.6)	4.7 (6.6)	4.0 (5.8)
Median (IQR)	1.5 (0.0–5.0)	1.5 (0.0–6.5)	1.5 (0.0–5.5)
Minimum to maximum	0.0 to 21.0	0.0 to 33.5	0.0 to 33.5
Controlled defecations per week after treatment			
n	104	107	211
Mean (SD)	13.0 (9.9)	11.6 (9.2)	12.3 (9.6)
Median (IQR)	11.0 (7.0–16.3)	10.5 (5.5–15.5)	11.0 (6.5–16.0)
Minimum to maximum	0.0 to 67.0	0.0 to 68.5	0.0 to 68.5
Days of underwear staining per week after treatment			
n	106	106	212
Mean (SD)	3.1 (2.2)	3.3 (2.5)	3.2 (2.4)
Median (IQR)	2.5 (1.0–4.5)	3.0 (1.0–6.0)	2.8 (1.0–5.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days using pad per week after treatment			
n	103	103	206
Mean (SD)	3.6 (3.2)	3.6 (3.3)	3.6 (3.3)
Median (IQR)	4.0 (0.0–7.0)	4.5 (0.0–7.0)	4.3 (0.0–7.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days using an enema per week after treatment			
n	103	102	205
Mean (SD)	0.4 (1.3)	0.2 (0.9)	0.3 (1.1)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly solid after treatment			
n	100	106	206
Mean (SD)	3.6 (2.4)	3.0 (2.4)	3.3 (2.4)
Median (IQR)	3.5 (1.7–5.5)	3.0 (0.5–5.1)	3.2 (1.0–5.4)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly mushy after treatment			
n	100	106	206
Mean (SD)	0.7 (1.3)	0.9 (1.5)	0.8 (1.4)
Median (IQR)	0.0 (0.0–0.8)	0.0 (0.0–1.1)	0.0 (0.0–1.0)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0
Days per week stool was mostly liquid after treatment			
n	100	106	206
Mean (SD)	2.7 (2.1)	3.1 (2.1)	2.9 (2.1)
Median (IQR)	2.5 (1.1–4.0)	3.0 (1.5–4.5)	2.9 (1.4–4.5)
Minimum to maximum	0.0 to 7.0	0.0 to 7.0	0.0 to 7.0

IQR, interquartile range; SD, standard deviation.
Patients must have at least 7 days of data for a bowel diary outcome to be computed at end of treatment.

TABLE 26 Other secondary outcomes after treatment

Outcome	PTNS (*N* = 107)	Sham (*N* = 107)	Total (*N* = 214)
GIQoL after treatment			
n	95	91	186
Mean (SD)	132.0 (20.6)	131.6 (20.5)	131.8 (20.5)
Median (IQR)	135.0 (115.0–48.0)	134.0 (120.0–146.0)	134.5 (118.0–148.0)
Minimum to maximum	86.0 to 167.0	74.0 to 171.0	74.0 to 171.0
EQ-5D after treatment			
n	108	106	214
Mean (SD)	0.68 (0.28)	0.65 (0.34)	0.67 (0.31)
Median (IQR)	0.76 (0.62–0.85)	0.73 (0.56–0.85)	0.73 (0.62–0.85)
Minimum to maximum	–0.02 to 1.00	–0.24 to 1.00	–0.24 to 1.00
Patient-centred outcomes after treatment			
n	87	85	172
Mean (SD)	7.8 (2.0)	8.4 (2.1)	8.1 (2.1)
Median (IQR)	8.4 (6.9–9.4)	9.3 (7.6–10.0)	8.8 (7.0–9.8)
Minimum to maximum	1.0 to 10.0	1.0 to 10.0	1.0 to 10.0
SMCS after treatment			
n	104	101	205
Mean (SD)	13.9 (4.3)	14.6 (4.6)	14.3 (4.4)
Median (IQR)	14.0 (11.0–17.0)	15.0 (11.0–18.0)	14.0 (11.0–18.0)
Minimum to maximum	6.0 to 23.0	5.0 to 24.0	5.0 to 24.0
SF-36 physical functioning after treatment			
n	96	105	201
Mean (SD)	67.1 (27.7)	63.8 (29.0)	65.4 (28.4)
Median (IQR)	75.0 (47.5–90.0)	70.0 (45.0–90.0)	70.0 (45.0–90.0)
Minimum to maximum	5.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 role-physical after treatment			
n	108	106	214
Mean (SD)	54.4 (44.1)	46.2 (44.8)	50.4 (44.6)
Median (IQR)	62.5 (0.0–100.0)	25.0 (0.0–100.0)	50.0 (0.0–100.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 bodily pain after treatment			
n	109	109	218
Mean (SD)	64.3 (28.3)	62.1 (31.0)	63.2 (29.6)
Median (IQR)	67.5 (45.0–90.0)	67.5 (35.0–90.0)	67.5 (37.5–90.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0

continued

TABLE 26 Other secondary outcomes after treatment (*continued*)

Outcome	PTNS (*N* = 107)	Sham (*N* = 107)	Total (*N* = 214)
SF-36 general health after treatment			
n	107	105	212
Mean (SD)	52.8 (24.6)	50.6 (23.9)	51.7 (24.2)
Median (IQR)	55.0 (30.0–75.0)	50.0 (35.0–70.0)	50.0 (30.0–70.0)
Minimum to maximum	0.0 to 100.0	0.0 to 95.0	0.0 to 100.0
SF-36 vitality after treatment			
n	105	104	209
Mean (SD)	45.6 (22.2)	46.7 (23.1)	46.1 (22.6)
Median (IQR)	50.0 (25.0–60.0)	50.0 (35.0–65.0)	50.0 (30.0–60.0)
Minimum to maximum	0.0 to 100.0	0.0 to 95.0	0.0 to 100.0
SF-36 social functioning after treatment			
n	109	109	218
Mean (SD)	66.4 (28.6)	60.6 (31.7)	63.5 (30.3)
Median (IQR)	75.0 (50.0–87.5)	62.5 (37.5–87.5)	62.5 (37.5–87.5)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 role-emotional after treatment			
n	108	108	216
Mean (SD)	61.7 (45.3)	60.2 (44.1)	61.0 (44.6)
Median (IQR)	100.0 (0.0–100.0)	83.3 (0.0–100.0)	100.0 (0.0–100.0)
Minimum to maximum	0.0 to 100.0	0.0 to 100.0	0.0 to 100.0
SF-36 mental health after treatment			
n	101	107	208
Mean (SD)	62.7 (25.1)	63.0 (21.4)	62.8 (23.2)
Median (IQR)	64.0 (48.0–84.0)	64.0 (52.0–76.0)	64.0 (52.0–84.0)
Minimum to maximum	4.0 to 100.0	0.0 to 100.0	0.0 to 100.0
FIQoL lifestyle after treatment			
n	90	88	178
Mean (SD)	2.8 (0.9)	2.8 (1.0)	2.8 (1.0)
Median (IQR)	3.0 (2.2–3.7)	2.9 (1.9–3.7)	2.9 (2.0–3.7)
Minimum to maximum	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0
FIQoL coping after treatment			
n	68	71	139
Mean (SD)	2.0 (0.8)	2.0 (1.0)	2.0 (0.9)
Median (IQR)	1.9 (1.3–2.6)	1.7 (1.2–2.9)	1.8 (1.2–2.9)
Minimum to maximum	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0

TABLE 26 Other secondary outcomes after treatment (*continued*)

Outcome	PTNS (*N* = 107)	Sham (*N* = 107)	Total (*N* = 214)
FIQoL depression after treatment			
n	64	64	128
Mean (SD)	2.9 (1.0)	2.8 (1.0)	2.9 (1.0)
Median (IQR)	3.1 (2.2–3.7)	2.6 (2.0–3.9)	2.9 (2.1–3.9)
Minimum to maximum	1.0 to 4.4	1.1 to 4.4	1.0 to 4.4
FIQoL embarrassment after treatment			
n	102	102	204
Mean (SD)	2.4 (0.8)	2.3 (0.9)	2.3 (0.9)
Median (IQR)	2.7 (1.7–3.0)	2.3 (1.7–3.0)	2.3 (1.7–3.0)
Minimum to maximum	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0
Likert scale of success after treatment			
n	110	107	217
Mean (SD)	4.0 (3.3)	3.2 (3.1)	3.6 (3.2)
Median (IQR)	4.8 (0.0–6.8)	2.1 (0.0–4.9)	3.4 (0.0–6.0)
Minimum to maximum	0.0 to 10.0	0.0 to 10.0	0.0 to 10.0
Do you think you had PTNS or sham?			
Sham, *n* (%)	48 (46)	71 (69)	119 (57)
PTNS, *n* (%)	57 (54)	32 (31)	89 (43)
Did you have any adverse events?			
No, *n* (%)	95 (87)	88 (81)	183 (84)
Yes, *n* (%)	14 (13)	20 (19)	34 (16)
Was there any effect on urinary symptoms?			
No urinary incontinence, *n* (%)	47 (44)	41 (39)	88 (41)
Made it worse, *n* (%)	11 (10)	5 (5)	16 (8)
No effect, *n* (%)	42 (39)	52 (50)	94 (44)
Slight improvement, *n* (%)	6 (6)	5 (5)	11 (5)
Substantial improvement, *n* (%)	2 (2)	2 (2)	4 (2)
What was your loperamide use?			
Did not use, *n* (%)	25 (34)	33 (46)	58 (40)
Decreased, *n* (%)	14 (19)	4 (6)	18 (12)
Same, *n* (%)	33 (45)	32 (45)	65 (45)
Increased, *n* (%)	2 (3)	2 (3)	4 (3)
What was your pad use?			
Did not use, *n* (%)	23 (29)	24 (33)	47 (31)
Decreased, *n* (%)	12 (15)	10 (14)	22 (15)
Same, *n* (%)	44 (56)	35 (49)	79 (52)
Increased, *n* (%)	0 (0)	3 (4)	3 (2)

IQR, interquartile range; SD, standard deviation.

Appendix 11 Past medical history

TABLE 27 Numbers of patients with relevant past medical history

Outcome	PTNS	Sham
Hysterectomy	30	24
Vaginal operation	3	2
Pelvic operation	19	16
Abdominal operation	28	30
Anal operation	6	9
Sphincter repair	4	4
Neck or back pain or back problem	15	21
OAB or bladder incontinence	15	7
Constipation	1	0
Diarrhoea	1	0
Diverticular disease	4	6
FI	8	11
Irritable bowel syndrome	1	4
Crohn's disease/proctitis	1	1
Abdominal problem	3	2
Perianal or anal problem	4	3
Anxiety/depression/psychiatric illness	22	24
Breast problem or cancer	8	2
Cardiovascular problem	34	27
ENT problem	7	5
Eye problem or operation	11	7
Fatigue/fibromyalgia/myalgic encephalopathy	6	4
Gynaecological problem	6	9
Haematological disorder	6	3
Headache/migraine	4	6
HIV infection or infectious disease	1	2
Metabolic disorder	0	4
Minor operation	1	5
Neurological problem	5	4
Orthopaedic problem	23	16
Respiratory problem	14	22
Rheumatological problem (other than back or neck pain)	22	16
Rhinitis or hay fever	3	7
Skin disorder	7	9
Thoracic operation	0	1
Upper GI reflux	20	18

ENT, ear, nose, throat; GI, gastrointestinal; HIV, human immunodeficiency virus.

Appendix 12 Regular medications

TABLE 28 Numbers of patients receiving regular medication

Medication	PTNS	Sham
Codeine phosphate	5	4
Laxative	5	11
Loperamide	30	30
Analgesia	20	26
Antimalarial	0	1
Antibiotic/antiviral/antifungal	3	3
Antidepressant/antianxiety/psychological medication	34	24
Antihistamine	5	8
Autoimmune condition medication	2	3
Cardiovascular medication	31	24
Chemotherapy	2	0
Cold or flu remedy	0	0
Eye medication	8	4
Gynaecological medication	2	0
Metabolic medication	0	0
Neurological condition medication	4	6
Other GI medications	0	0
Respiratory medication	13	22
Skin condition medication	4	5
Urinary incontinence/OAB medication	7	7
Vaccine	0	0

GI, gastrointestinal.

Appendix 13 European Quality of Life-5 Dimensions summary

ANALYSIS OF EUROPEAN QUALITY OF LIFE-5 DIMENSIONS DATA FROM THE CONFIDeNT TRIAL

Background

European Quality of Life-5 Dimensions data have been collected as part of the CONFIDeNT trial comparing PTNS against a sham treatment (TENS) alongside other patient-reported outcome (PRO) measures, symptom diaries and clinical outcomes.

York Health Economics Consortium has been requested by Queen Mary, University of London to conduct a basic statistical analysis of the EQ-5D (Option 1).

Methods and results

Methods

A Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) data file containing the data was provided by Queen Mary, University of London. The data were anonymised and comprised a unique study code for each patient, the group (PTNS or sham) to which the patients had been allocated, the EQ-5D data for two time points (week 2 baseline and week 14 end of study), that is the raw scores for mobility, self-care, usual activities, pain/discomfort, anxiety/depression, the EQ-5D VAS score and the EQ-5D index score. The data were analysed using Stata 12.1 software. The descriptive statistics were derived for the EQ-5D VAS score and EQ-5D index score, that is the average VAS scores and index scores for each arm of the trial at the two time points and the differences between the two arms, as well as the standard deviations, 95% CIs and the average change and standard deviation of change. Descriptive statistics were also derived for the categorical (ordinal) data (EQ-5D raw scores), consisting of the category frequencies at the two time points, as well as a cross-tabulation to highlight changes over time in EQ-5D scores.

Results

Data were available from 227 patients: 115 in the PTNS arm and 112 in the sham arm. The mean scores by group (arm) over time are shown in *Table 29*.

It may be seen that there were virtually no differences between the two arms either at week 2 (baseline) or at week 14 in respect of both the EQ-5D VAS scores and the EQ-5D index scores, with scores on both scales remaining unchanged over time.

The mean change from baseline (difference between week 14 and week 2) is shown in *Table 30*, for the EQ-5D VAS and the EQ-5D index scores. It may be seen that there was a slight decrease in EQ-5D VAS and EQ-5D index scores for the PTNS from baseline. For the sham treatment, VAS score increased slightly from baseline, whereas the index score remained almost unchanged.

The mean differences between the two groups are shown in *Table 31*. As may be seen from *Table 31*, although the PTNS were marginally higher at each point, the differences in scores between the two groups were minimal.

The cross-tabulations for the individual EQ-5D domains are shown in *Table 32*. Few changes were observed for the mobility and self-care domains both over time and between the two groups, that is the

TABLE 29 Mean scores by time point and group

Variable	Group	*n*	Mean	SD	Minimum	Maximum	LCL	UCL
VAS week 2	PTNS	114	64.50	21.72	5.00	100	60.51	68.49
VAS week 2	Sham	112	64.04	21.24	20.00	100	60.10	67.97
VAS week 14	PTNS	109	64.25	22.32	8.00	100	60.06	68.44
VAS week 14	Sham	109	63.69	23.66	10.00	100	59.25	68.13
Index week 2	PTNS	115	0.69	0.27	–0.18	1	0.64	0.74
Index week 2	Sham	109	0.63	0.34	–0.24	1	0.57	0.70
Index week 14	PTNS	108	0.68	0.28	–0.02	1	0.63	0.74
Index week 14	Sham	106	0.65	0.34	–0.24	1	0.59	0.72

LCL, lower confidence limit; SD, standard deviation; UCL, upper confidence limit.

TABLE 30 Mean change from baseline by group

Variable	Group	*n*	Mean	SD
VAS	PTNS	108	–0.67	18.88
VAS	Sham	109	0.32	23.74
Index	PTNS	108	–0.01	0.23
Index	Sham	105	0.02	0.25

SD, standard deviation.

TABLE 31 Mean differences between groups over time

Variable	Mean difference	SE	LCL	UCL
VAS week 2	0.46	2.86	–5.17	6.10
VAS week 14	0.56	3.12	–5.58	6.70
Index week 2	0.05	0.04	–0.03	0.13
Index week 14	0.03	0.04	–0.05	0.12

LCL, lower confidence limit; SE, standard error; UCL, upper confidence limit.

TABLE 32 Cross-tabulation of individual EQ-5D domains between the two time points

	Mobility week 14							
	PTNS				Sham			
Mobility week 2	1	2	3	Total	1	2	3	Total
1	69	4	0	73	63	9	0	72
2	7	29	0	36	6	29	0	35
3	0	0	0	0	0	0	0	0
Total	76	33	0	109	69	38	0	107
	Self-care week 14							
	PTNS				Sham			
Self-care week 2	1	2	3	Total	1	2	3	Total
1	92	3	0	95	90	5	0	95
2	7	7	0	14	0	10	0	10
3	0	0	0	0	0	1	0	1
Total	99	10	0	109	90	16	0	106
	Usual activities week 14							
	PTNS				Sham			
Usual activities week 2	1	2	3	Total	1	2	3	Total
1	48	7	0	55	42	15	0	57
2	16	31	0	47	13	27	1	41
3	0	5	2	7	3	3	3	9
Total	64	43	2	109	58	45	4	107
	Pain/discomfort week 14							
	PTNS				Sham			
Pain/discomfort week 2	1	2	3	Total	1	2	3	Total
1	28	13	2	43	26	8	0	34
2	12	43	3	58	14	38	4	56
3	0	3	4	7	1	5	9	15
Total	40	59	9	108	41	51	13	105
	Anxiety/depression week 14							
	PTNS				Sham			
Anxiety/depression week 2	1	2	3	Total	1	2	3	Total
1	34	13	0	47	37	12	0	49
2	14	33	8	55	11	25	7	43
3	0	5	2	7	1	7	7	15
Total	48	51	10	109	49	44	14	107

The numbers in the column and row headings represent the raw scores on the individual EQ-5D domains.

vast majority of patients did not record any change for these two domains. These domains were also the only two for which patients did not record the more severe scores.

A greater number of changes were recorded for the other three domains. For usual activities, 26% and 32% of scores changed from week 2 to week 14 for the PTNS and sham arms respectively; for pain/discomfort the figures were 31% for both arms; and for anxiety/depression they were 28% and 35% respectively.

For anxiety/depression there was an almost equal percentage change observed for improvement (e.g. a change from 3 to 2, or 2 to 1) and deterioration in scores (e.g. 1 to 2, or 2 to 3) between the PTNS and sham arms. For improvement in scores, the percentage changes were 17% and 18% respectively (PTNS and sham), and 19% and 18% for deterioration in scores. For usual activities, the percentage change in improvement was virtually the same between groups: 19% for PTNS and 18% for sham. However, there was a greater percentage of deterioration in usual activities for the sham group: 6% for PTNS and 15% for sham. This pattern was reversed for pain/discomfort: 14% (PTNS) and 19% (sham) for improvement and 17% and 11% for deterioration.

Conclusions

The results demonstrated that there were no differences between the two arms, PTNS and sham, in terms of patients' overall health (EQ-5D VAS) or their health status (EQ-5D index score). Furthermore, there were no changes in the overall scores on these two measures over time. Differences were observed for the individual domains of the EQ-5D, particularly for usual activities, pain/discomfort and anxiety/depression. Patients in the sham arm experienced a greater degree of deterioration in their usual activities than those in the PTNS arm. However, in contrast to this, those patients in the PTNS arm reported a greater degree of pain/discomfort, whereas those in the sham arm noted an improvement in their levels of pain/discomfort.

These results should be interpreted in the context of the other outcome measures derived in the study, and with the caveat that the EQ-5D may not be sensitive to change in this patient population; however, the results suggest that the PTNS treatment – although it may not have an impact on overall quality of life – may improve patients' usual activities, but perhaps at the cost of an increased degree of pain or discomfort.

Appendix 14 Concomitant medications

TABLE 33 Concomitant medications

Allocation	Medication	Indication	Duration (days)	Ongoing
PTNS	Cocodamol	Arm pain	4	No
PTNS	Cocodamol	Headache	1	No
PTNS	Codydramol	Leg pain	1	No
PTNS	Coproxamol	Pain	n/a	Yes
PTNS	Coproxamol	Neck pain	2	No
Sham	Coproxamol	Dental pain	n/a	Yes
Sham	Cocodamol	Leg pain	3	No
Sham	Morphine	Osteoarthritis and fibromyalgia	n/a	Yes
Sham	Tramadol	Fractured coccyx	14	No
Sham	Tramadol	Abdominal pain	n/a	Yes
Sham	Tramadol	Knee pain	n/a	Yes
Sham	Tramadol	Chest pain	n/a	Yes
PTNS	Ispaghula husk (Fybogel®, Reckitt Benckiser)	Unknown	Unknown	Unknown
PTNS	Ispaghula husk (Fybogel®, Reckitt Benckiser)	Diarrhoea	2	Yes
PTNS	Klean-Prep® (Norgine, Helsinn-Birex Pharmaceuticals Ltd)	Preparation for colonoscopy	1	No
PTNS	Klean-Prep® (Norgine, Helsinn-Birex Pharmaceuticals Ltd)	Preparation for colonoscopy	1	No
PTNS	Sodium picosulfate with magnesium citrate (Picolax®, Ferring)	Preparation for colonoscopy	1	No
Sham	Ispaghula husk (Fybogel®, Reckitt Benckiser)	Constipation	7	No
Sham	Lactulose	Post surgery	8	No
Sham	Lactulose	Constipation	Unknown	No

n/a, not applicable.

Appendix 15 Subgroup analyses

TABLE 34 Results of subgroups analysis on primary outcome ($n = 227$)

Outcome	Main treatment effect			Interaction term(s)				Interaction term global *p*-value
	PTNS vs. sham, OR	95% CI	*p*-value	Interaction term 1, OR		Interaction term 2, OR	95% CI	
Moderator				Male vs. female	95% CI			
Sex (male vs. female)	1.143	0.629 to 2.078	0.661	5.418	0.451 to 65.065	n/a	n/a	0.183
≥ 7 FIEs per week base vs. < 7	1.177	0.535 to 2.590	0.686	1.212	0.389 to 3.776	n/a	n/a	0.740
Age groups (years)				40–60 vs. < 40	> 60 vs. < 40			
< 40, 40–60, > 60	1.575	0.205 to 12.106	0.662	0.745	0.075 to 7.371	0.857	0.088 to 8.385	0.957
Type of incontinence				Urge only vs. urge and passive	Passive only vs. urge and passive			
Urge or passive or both	1.589	0.730 to 3.456	0.243	0.824	0.185 to 3.675	0.424	0.090 to 1.995	0.554

n/a, not applicable; OR, odds ratio.
Odds ratio corresponds to the adjusted OR for PTNS vs. sham from a logistic mixed-effects model, adjusted for baseline mean FIEs per week and sex, and includes a random effect for study centre. Missing data were multiply imputed using multilevel multiple imputation to create 10 complete data sets for analysis, the results of which were combined using Rubin's rules.

Appendix 16 Sensitivity analysis 1

TABLE 35 Results of sensitivity analysis (excludes 16 patients with no FIEs in baseline bowel diary)

Outcome	Type	*n*	Estimate	LCL	UCL	*p*-value	Model-based ICC
≥ 50% reduction in FIEs (primary outcome)	OR	211	1.325	0.736	2.385	0.348	< 0.001
≥ 25% reduction in FIEs	OR	211	1.314	0.747	2.311	0.344	< 0.001
≥ 75% reduction in FIEs	OR	211	1.643	0.775	3.484	0.195	0.212
100% reduction in FIEs	OR	211	1.670	0.596	4.674	0.330	0.008
Change in FIEs	Beta	211	–2.468	–4.533	–0.403	0.019	< 0.001
Change in rush FIEs	Beta	211	–1.557	–2.881	–0.232	0.021	< 0.001
Change in passive leakage FIEs	Beta	211	–0.736	–1.850	0.378	0.195	0.1
FIQoL embarrassment	Beta	211	0.049	–0.149	0.247	0.630	< 0.001
FIQoL coping	Beta	211	0.021	–0.172	0.214	0.831	0.116
FIQoL lifestyle	Beta	211	0.105	–0.070	0.280	0.236	< 0.001
FIQoL depression	Beta	211	0.025	–0.294	0.344	0.873	< 0.001
SF-36 physical functioning	Beta	211	–2.025	–7.515	3.464	0.469	< 0.001
SF-36 role-physical	Beta	211	1.646	–8.860	12.152	0.758	n/a
SF-36 bodily pain	Beta	211	–1.039	–7.114	5.036	0.737	< 0.001
SF-36 general health	Beta	211	0.159	–4.759	5.076	0.949	< 0.001
SF-36 vitality	Beta	211	–2.930	–8.194	2.334	0.273	n/a
SF-36 social functioning	Beta	211	6.343	0.010	12.676	0.051	0.017
SF-36 role emotional	Beta	211	–5.461	–15.881	4.959	0.302	n/a
SF-36 mental health	Beta	211	0.031	–4.477	4.540	0.989	0.065
SMCS	Beta	211	–0.139	–1.163	0.885	0.790	< 0.001
Patient-centred outcomes	Beta	211	–0.562	–1.123	–0.001	0.050	< 0.001
EQ-5D index score	Beta	211	–0.017	–0.081	0.048	0.610	0.019
GIQoL	Beta	211	–1.558	–5.566	2.449	0.442	n/a
Likert scale of success	Beta	211	0.786	–0.123	1.694	0.091	0.009

LCL, lower confidence limit; n/a, not applicable; OR, odds ratio; UCL, upper confidence limit.
Odds ratio corresponds to the adjusted OR for PTNS vs. sham from a logistic mixed-effects model, adjusted for baseline mean FIEs per week and sex, and includes a random effect for study centre. Beta corresponds to the adjusted difference in means for PTNS vs. sham from a linear mixed-effects model, adjusted for baseline level of outcome (except Likert scale of success) and sex, and includes a random effect for study centre. n/a indicates that the unconditional ICC was < 0 and the corresponding outcomes were modelled using linear regression without an adjustment for study centre. Missing data were multiply imputed using multilevel multiple imputation to create 10 complete data sets for analysis, the results of which were combined using Rubin's rules.

Appendix 17 Sensitivity analysis 2

TABLE 36 Results of sensitivity analysis excluding centres that recruited fewer than five patients (two centres, four patients)

Outcome	Type	*n*	Estimate	LCL	UCL	*p*-value	Model-based ICC
≥ 50% reduction in FIEs (primary outcome)	OR	223	1.234	0.693	2.196	0.476	< 0.001
≥ 25% reduction in FIEs	OR	223	1.220	0.698	2.132	0.485	< 0.001
≥ 75% reduction in FIEs	OR	223	1.634	0.776	3.438	0.196	0.214
100% reduction in FIEs	OR	223	1.690	0.609	4.693	0.315	0.006
Change in FIEs	Beta	223	–2.158	–4.034	–0.283	0.024	< 0.001
Change in rush FIEs	Beta	223	–1.501	–2.752	–0.25	0.019	< 0.001
Change in passive leakage FIEs	Beta	223	–0.592	–1.637	0.453	0.267	0.094
FIQoL embarrassment	Beta	223	0.020	–0.166	0.206	0.83	< 0.001
FIQoL coping	Beta	223	0.017	–0.168	0.203	0.855	0.1
FIQoL lifestyle	Beta	223	0.092	–0.072	0.257	0.27	< 0.001
FIQoL depression	Beta	223	0.010	–0.301	0.321	0.945	< 0.001
SF-36 physical functioning	Beta	223	–1.479	–6.674	3.717	0.576	< 0.001
SF-36 role-physical	Beta	223	1.462	–8.684	11.608	0.777	n/a
SF-36 bodily pain	Beta	223	–0.844	–6.712	5.024	0.778	< 0.001
SF-36 general health	Beta	223	–0.021	–4.676	4.634	0.993	< 0.001
SF-36 vitality	Beta	223	–3.857	–8.875	1.161	0.131	n/a
SF-36 social functioning	Beta	223	5.419	–0.585	11.423	0.078	0.012
SF-36 role emotional	Beta	223	–5.297	–15.405	4.811	0.303	n/a
SF-36 mental health	Beta	223	–0.877	–5.237	3.483	0.693	0.031
SMCS	Beta	223	0.052	–0.928	1.032	0.917	< 0.001
Patient-centred outcomes	Beta	223	–0.575	–1.121	–0.029	0.039	< 0.001
EQ-5D index score	Beta	223	–0.020	–0.082	0.042	0.524	0.017
GIQoL	Beta	223	–1.269	–5.182	2.643	0.521	n/a
Likert scale of success	Beta	223	0.856	–0.016	1.728	0.055	0.02

LCL, lower confidence limit; n/a, not applicable; OR, odds ratio; UCL, upper confidence limit.
Odds ratio corresponds to the adjusted OR for PTNS vs. sham from a logistic mixed-effects model, adjusted for baseline mean FIEs per week, sex and includes a random effect for study centre. Beta corresponds to the adjusted difference in means for PTNS vs. sham from a linear mixed-effects model, adjusted for baseline level of outcome (except Likert scale of success), sex and includes a random effect for study centre. n/a indicates that the unconditional ICC was < 0 and the corresponding outcomes were modelled using linear regression without an adjustment for study centre. Missing data were multiply imputed using multilevel multiple imputation to create 10 complete data sets for analysis, the results of which were combined using Rubin's rules.

Appendix 18 Adverse events

TABLE 37 All adverse events in PTNS patients

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
ANT002	Orthopaedic injury	–	Unrelated	73	Moderate	Other	Resolved
ANT007	Bleeding	Rectal	Unrelated	1	Mild	Other	Resolved
ANT007	Cough/cold/flu	–	Unrelated	–	Mild	Concomitant medication given	Unresolved
ANT011	Fall	–	Unrelated	1	Mild	No action taken	Resolved
ANT011	Fall	–	Unrelated	1	Mild	No action taken	Resolved
ANT019	Breast lump	–	Unrelated	–	Mild	No action taken	Unknown
ANT019	Vomiting/nausea	–	Unrelated	2	Mild	No action taken	Resolved
ANT028	Cough/cold/flu	–	Unrelated	4	Mild	No action taken	Resolved
ANT040	Pain	Back	Unrelated	8	Moderate	No action taken	Resolved
BLT002	Headache/migraine	–	Possible	8	Moderate	Concomitant medication given	Resolved
BLT002	Infection	Chest	Unrelated	8	Moderate	Concomitant medication given	Resolved
BLT002	Pain	Arm	Unrelated	3	Mild	No action taken	Resolved
BLT002	Pain	Back	Unrelated	2	Moderate	Concomitant medication given	Resolved
BLT003	Allergic reaction	–	Unrelated	25	Mild	Concomitant medication given	Resolved
BLT003	Dizziness	–	Possible	1	Mild	No action taken	Resolved
BLT003	Infection	Tooth/gum	Unrelated	6	Mild	Concomitant medication given	Resolved
BLT005	Diarrhoea	–	Possible	3	Mild	No action taken	Resolved
BLT005	Infection	Skin	Unrelated	14	Mild	No action taken	Resolved

continued

TABLE 37 All adverse events in PTNS patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
BLT005	Infection	Urinary tract	Unrelated	9	Mild	Concomitant medication given	Resolved
BLT005	Pain	Leg	Unrelated	14	Mild	No action taken	Resolved
BLT018	Dizziness	–	Possible	23	Mild	No action taken	Resolved
BLT018	Infection	Tooth/ gum	Unrelated	32	Mild	Concomitant medication given	Resolved
BLT041	Bruising	Needle site	Related	14	Mild	No action taken	Resolved
BLT041	Cough/cold/flu	–	Unrelated	7	Mild	No action taken	Resolved
BLT041	Cough/cold/flu	–	Unrelated	12	Mild	No action taken	Resolved
BLT041	Infection	Ear	Unrelated	19	Mild	Concomitant medication given	Resolved
BLT042	Cough/cold/flu	–	Unrelated	5	Mild	Concomitant medication given	Unresolved
BLT042	Cough/cold/flu	–	Unrelated	17	Mild	Concomitant medication given	Resolved
BLT053	Cough/cold/flu	–	Unrelated	8	Mild	Concomitant medication given	Resolved
BLT053	Pain	Leg	Possible	1	Severe	No action taken	Resolved
BLT053	Pain	Leg	Possible	–	Moderate	Concomitant medication given	Unresolved
BLT066	Orthopaedic injury	–	Unrelated	48	Moderate	No action taken	Resolved
BLT068	Pain	Back	Unrelated	17	Moderate	No action taken	Resolved
BLT074	Headache/migraine	–	Possible	2	Moderate	Concomitant medication given	Resolved
BLT074	Infection	Urinary tract	Unrelated	15	Moderate	No action taken	Resolved
BLT074	Pain	Leg	Possible	3	Moderate	No action taken	Resolved
BLT074	Pain	Foot	Possible	21	Severe	No action taken	Resolved
BLT074	Pain	Leg	Possible	1	Moderate	No action taken	Resolved

TABLE 37 All adverse events in PTNS patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
BLT074	Skin disorder	–	Possible	9	Mild	No action taken	Resolved
CHH006	Pain	Arm	Unrelated	5	Mild	Concomitant medication given	Resolving
GST003	Pain	Leg	Possible	10	Mild	No action taken	Resolved
LGI003	Dizziness	–	Possible	–	Mild	Other	Unresolved
PHT003	Altered sensation	Leg	Possible	–	Mild	No action taken	Unresolved
PHT003	Altered sensation	Leg	Possible	–	Mild	No action taken	Unresolved
PHT003	Fall	–	Unrelated	–	Mild	No action taken	Unresolved
PHT004	Cough/cold/flu	–	Unrelated	21	Moderate	No action taken	Resolved
PHT004	Rheumatoid arthritis	–	Unrelated	–	Moderate	Concomitant medication given	Unresolved
PHT008	Anxiety/ depression/ psychiatric illness	–	Possible	–	Mild	Concomitant medication given	Resolving
PHT009	Altered sensation	Foot	Possible	1	Mild	No action taken	Resolved
PHT009	Altered sensation	Foot	Possible	1	Mild	No action taken	Resolved
PHT009	Dizziness	–	Possible	1	Mild	No action taken	Resolved
PHT009	Pain	Back	Possible		Mild	No action taken	Unresolved
QMC002	Pain	Needle site	Related	16	Mild	Other	Resolved
QMC003	Diarrhoea	–	Possible	5	Moderate	No action taken	Resolved
QMC003	Pain	Needle site	Related	22	Mild	Other	Resolved
SMH001	Cough/cold/flu	–	Unrelated	26	Mild	Concomitant medication given	Resolved
SMH001	Headache/migraine	–	Possible	3	Mild	Concomitant medication given	Resolved
SMH001	Pain	Neck	Unrelated	6	Mild	Concomitant medication given	Resolved

continued

TABLE 37 All adverse events in PTNS patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
SMH010	Bruising	Needle site	Related	8	Mild	No action taken	Resolved
SMH010	Dizziness	–	Possible	1	Mild	No action taken	Resolved
SMH010	Pain	Abdomen	Possible	9	Moderate	No action taken	Resolved
SOT005	Diarrhoea	–	Possible	3	Mild	Concomitant medication given	Resolved
SOT009	Vomiting/nausea	–	Unrelated	–	Mild	Concomitant medication given	Resolving
STH002	Headache/migraine	–	Possible	–	Severe	Concomitant medication given	Resolved
STH006	Altered sensation	Needle site	Related	1	Mild	No action taken	Resolved
STH007	Cough/cold/flu	–	Unrelated	8	Mild	Concomitant medication given	Resolved
STH007	Cough/cold/flu	–	Unrelated	8	Mild	Concomitant medication given	Resolved
STH013	Pain	Needle site	Related	–	Mild	No action taken	Unknown
SWB002	Vitamin D deficiency	–	Unrelated	–	Mild	Concomitant medication given	Unresolved
SWB010	Renal problem	–	Unrelated	–	Mild	Concomitant medication given	Unresolved
SWB021	Diarrhoea	–	Possible	6	Mild	No action taken	Resolved
SWB022	Pain	Toe	Possible	–	Mild	No action taken	Unknown
SWB022	Vomiting/nausea	–	Unrelated	3	Moderate	No action taken	Resolved
SWB023	Pain	Heel	Possible	2	Mild	No action taken	Resolved
UCL004	Infection	Chest	Unrelated	–	Mild	No action taken	Resolving
UCL008	Headache/migraine	–	Possible	2	Moderate	No action taken	Resolved
UCL013	Pain	Leg	Possible	2	Mild	No action taken	Resolved
UCL016	Pain	Leg	Possible	2	Moderate	Concomitant medication given	Resolved

TABLE 37 All adverse events in PTNS patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
UCL016	Pain	Needle site	Related	2	Mild	No action taken	Resolved
UCL016	Vomiting/nausea	–	Unrelated	1	Mild	No action taken	Resolved
ULH003	Pain	Breast	Unrelated	–	Mild	Concomitant medication given	Unresolved
ULH003	Upper GI reflux	–	Unrelated	64	Moderate	Concomitant medication given	Resolved
ULH011	Bleeding	Rectal	Unrelated	1	Moderate	No action taken	Resolved
ULH014	Operative procedure/ hospital procedure	–	Unrelated	3	Moderate	Hospitalisation	Resolved
USM005	Diarrhoea	–	Possible	4	Mild	No action taken	Resolved
USM023	Skin disorder	–	Unrelated	9	Mild	Other	Resolved
USM025	Infection	Tooth/ gum	Unrelated	–	Mild	Concomitant medication given	Unknown
USM026	Fall	–	Unrelated	1	Mild	No action taken	Resolving
USM030	Pain	Heel	Possible	–	Moderate	No action taken	Unresolved
WCU001	Pain	Abdomen	Possible	3	Mild	No action taken	Resolved
WCU004	Altered sensation	Arm	Unrelated	1	Moderate	No action taken	Resolved
WCU004	Infection	Urinary tract	Unrelated	6	Mild	Concomitant medication given	Resolved
WCU004	Pain	Toe	Possible	1	Moderate	No action taken	Resolved
WCU004	Pain	Leg	Possible	1	Moderate	No action taken	Resolved
WCU010	Diarrhoea	–	Possible	2	Mild	No action taken	Resolved
WCU011	Bleeding	Rectal	Unrelated	1	Moderate	Concomitant medication given	Unresolved
WCU011	Pain	Abdomen	Possible	4	Mild	No action taken	Resolved
WCU012	Pain	Abdomen	Possible	–	Mild	No action taken	Unresolved

continued

TABLE 37 All adverse events in PTNS patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
WCU014	Infection	Chest	Unrelated	6	Mild	Concomitant medication given	Resolved
WCU021	Infection	Urinary tract	Unrelated	11	Mild	Concomitant medication given	Unknown
WCU021	Vomiting/nausea	–	Unrelated	2	Mild	No action taken	Resolved
WCU033	Diarrhoea	–	Possible	1	Severe	Concomitant medication given	Unknown
WCU033	Operative procedure/hospital procedure	–	Unrelated	1	Severe	Hospitalisation	Resolved
WCU038	Headache/migraine	–	Possible	2	Moderate	Concomitant medication given	Resolved
WCU038	Skin disorder	–	Unrelated	4	Mild	No action taken	Resolved
WCU043	Pain	Groin	Unrelated	1	Moderate	No action taken	Resolved
WCU043	Pain	Ear	Unrelated	3	Moderate	No action taken	Resolved
WCU049	Diarrhoea	–	Possible	–	Mild	No action taken	Resolved

GI, gastrointestinal.

TABLE 38 All adverse events in sham patients

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
ANT001	Skin disorder	–	Unrelated	–	Moderate	No action taken	Unknown
ANT008	Pain	Leg	Possible	70	Mild	No action taken	Resolved
ANT014	Operative procedure/ hospital procedure	–	Unrelated	1	Mild	Concomitant medication given	Resolved
ANT018	Altered sensation	Toe	Related	1	Mild	No action taken	Resolved
ANT038	Operative procedure/ hospital procedure	–	Unrelated	8	Moderate	No action taken	Resolved

TABLE 38 All adverse events in sham patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
ANT041	Infection	Chest	Unrelated	8	Mild	Concomitant medication given	Resolved
ANT041	Orthopaedic injury	–	Unrelated	15	Moderate	Concomitant medication given	Resolved
ANT044	Upper GI reflux	–	Unrelated	–	Moderate	Concomitant medication given	Resolving
BLT001	Cough/cold/flu	–	Unrelated	3	Mild	Concomitant medication given	Resolved
BLT001	Diarrhoea	–	Possible	2	Moderate	No action taken	Resolved
BLT013	Bruising	Needle site	Related	5	Mild	No action taken	Resolved
BLT013	Infection	Chest	Unrelated	19	Moderate	Concomitant medication given	Resolved
BLT013	Pain	Ankle	Possible	8	Mild	No action taken	Resolved
BLT019	Altered sensation	Perineum	Possible	1	Mild	No action taken	Resolved
BLT019	Altered sensation	Perineum	Possible	1	Mild	No action taken	Resolved
BLT019	Operative procedure/ hospital procedure	–	Unrelated	1	Moderate	No action taken	Resolved
BLT019	Orthopaedic injury	–	Unrelated	3	Mild	No action taken	Resolved
BLT019	Pain	Shoulder	Unrelated	2	Mild	Concomitant medication given	Resolved
BLT026	Cough/cold/flu	–	Unrelated	14	Moderate	Concomitant medication given	Resolved
BLT026	Cough/cold/flu	–	Unrelated	4	Mild	Concomitant medication given	Resolved
BLT026	Urinary symptoms	–	Possible	1	Mild	No action taken	Resolved
BLT031	Headache/ migraine	–	Possible	3	Mild	No action taken	Resolved
BLT031	Pain	Back	Unrelated	–	Moderate	Concomitant medication given	Unresolved

continued

TABLE 38 All adverse events in sham patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
BLT046	Cough/cold/flu	–	Unrelated	7	Mild	No action taken	Resolved
BLT046	Diarrhoea	–	Possible	2	Mild	No action taken	Resolved
BLT046	Pain	Abdomen	Possible	13	Mild	No action taken	Resolved
BLT046	Pain	Abdomen	Possible	22	Mild	No action taken	Resolved
BLT046	Urinary symptoms	–	Possible	–	Moderate	No action taken	Resolving
BLT051	Cough/cold/flu	–	Unrelated	5	Mild	Concomitant medication given	Resolved
BLT051	Headache/ migraine	–	Possible	1	Moderate	No action taken	Resolved
BLT058	Altered sensation	Lip	Unrelated	8	Mild	No action taken	Resolved
CHH002	Diarrhoea	–	Possible	1	Mild	No action taken	Resolved
CHH004	Infection	Tooth/gum	Unrelated	8	Mild	Concomitant medication given	Resolving
LRI002	Pain	Leg	Possible	3	Mild	Concomitant medication given	Resolved
LRI002	Skin disorder	–	Unrelated	3	Moderate	Concomitant medication given	Resolved
LRI006	Anxiety/ depression/ psychiatric illness	–	Possible	–	Moderate	Other	Unresolved
LRI007	Headache/ migraine	–	Possible	5	Moderate	Concomitant medication given	Resolved
PHT005	Upper GI reflux	–	Unrelated	–	Moderate	Concomitant medication given	Unresolved
PHT006	Bleeding	Rectal	Unrelated	2	Mild	No action taken	Resolved
PHT010	Pain	Back	Unrelated	1	Mild	No action taken	Resolving
QMC001	Infection	Skin	Unrelated	8	Mild	No action taken	Resolved
QMC001	Pain	Needle site	Related	–	Mild	No action taken	Resolved
QMC001	Pain	Needle site	Related	30	Mild	No action taken	Resolved

TABLE 38 All adverse events in sham patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
QMC004	Infection	Chest	Unrelated	9	Mild	Concomitant medication given	Resolved
SMH007	Cough/cold/flu	–	Unrelated	156	Mild	Concomitant medication given	Resolved
SMH007	Urinary symptoms	–	Possible	–	Mild	No action taken	Unknown
SMH013	Pain	Leg	Possible	11	Moderate	Concomitant medication given	Unresolved
SOT002	Infection	Chest	Unrelated	6	Moderate	Concomitant medication given	Resolved
STH012	Pain	Leg	Possible	–	Moderate	No action taken	Unknown
SWB016	Infection	Chest	Unrelated	7	Mild	Concomitant medication given	Resolved
SWB020	Headache/ migraine	–	Possible	6	Severe	Concomitant medication given	Resolved
SWB020	Headache/ migraine	–	Possible	–	Mild	No action taken	Unknown
UCL002	Infection	Chest	Unrelated	8	Mild	Concomitant medication given	Resolving
UCL006	Infection	Chest	Unrelated	4	Moderate	Concomitant medication given	Resolving
UCL006	Infection	Cold sores	Unrelated	6	Mild	Concomitant medication given	Resolving
UCL010	Cough/cold/flu	–	Unrelated	9	Mild	Concomitant medication given	Resolved
UCL012	Skin disorder	–	Unrelated	8	Mild	No action taken	Unresolved
ULH001	Infection	Urinary tract	Unrelated	6	Moderate	Concomitant medication given	Resolved
ULH001	Infection	Chest	Unrelated	7	Moderate	Concomitant medication given	Resolved
ULH006	Infection	Urinary tract	Unrelated	8	Moderate	Concomitant medication given	Resolved

continued

TABLE 38 All adverse events in sham patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
ULH007	Infection	Chest	Unrelated	8	Moderate	Concomitant medication given	Resolved
ULH009	Bleeding	Rectal	Unrelated	3	Mild	No action taken	Resolved
ULH013	Water retention	–	Unrelated	–	Mild	No action taken	Resolved
ULH018	Operative procedure/ hospital procedure	–	Unrelated	1	Mild	No action taken	Unknown
ULH018	Operative procedure/ hospital procedure	–	Unrelated	1	Moderate	No action taken	Unknown
ULH018	Operative procedure/ hospital procedure	–	Unrelated	3	Mild	No action taken	Unknown
ULH022	Bleeding	Needle site	Related	4	Mild	No action taken	Resolved
USM019	Upper GI reflux	–	Unrelated	–	Mild	Concomitant medication given	Resolving
USM022	Infection	Urinary tract	Unrelated	8	Mild	Concomitant medication given	Resolved
USM022	Upper GI reflux	–	Unrelated	–	Moderate	Concomitant medication given	Unknown
USM028	Fall	–	Unrelated	1	Moderate	No action taken	Resolved
USM028	Pain	Leg	Possible	11	Moderate	No action taken	Resolved
USM028	Vomiting/nausea	–	Possible	6	Moderate	No action taken	Resolved
USM032	Infection	Diverticulitis	Unrelated	14	Moderate	Concomitant medication given	Resolved
WCU003	Weakness	Leg	Possible	1	Moderate	No action taken	Resolved
WCU006	FI	–	Possible	4	Mild	No action taken	Resolved
WCU006	Infection	Skin	Unrelated		Mild	Other	Unknown
WCU006	Skin disorder	–	Unrelated	1	Mild	No action taken	Resolved
WCU008	Infection	Skin	Unrelated	26	Moderate	Hospitalisation	Resolved
WCU008	Operative procedure/ hospital procedure	–	Unrelated	1	Severe	Hospitalisation	Resolved

TABLE 38 All adverse events in sham patients (*continued*)

Personal information number	Adverse event	Site	Related	Duration (days)	Grade	Action taken	Outcome
WCU008	Vomiting/nausea	–	Unrelated	2	Mild	No action taken	Resolved
WCU017	Pain	Rib	Unrelated	1	Severe	Concomitant medication given	Resolving
WCU017	Pain	Rib	Unrelated	–	Severe	Concomitant medication given	Resolving
WCU018	Constipation	–	Possible	–	Mild	Concomitant medication given	Unresolved
WCU018	Headache/ migraine	–	Possible	2	Mild	Concomitant medication given	Resolved
WCU018	Pain	Perineum	Possible	2	Moderate	No action taken	Resolved
WCU018	Pain	Leg	Possible	1	Moderate	No action taken	Resolved
WCU018	Pain	Leg	Possible	1	Moderate	No action taken	Resolved
WCU029	Infection	Urinary tract	Unrelated	–	Mild	Concomitant medication given	Unresolved
WCU029	Infection	Urinary tract	Unrelated		Mild	No action taken	Unresolved
WCU029	Pain	Ankle	Possible	1	Moderate	No action taken	Resolved
WCU029	Pain	Needle site	Related	1	Mild	No action taken	Resolved
WCU035	Pain	Foot	Possible	1	Moderate	No action taken	Resolved
WCU041	Bleeding	Needle site	Related	1	Mild	No action taken	Resolved
WCU041	Cough/cold/flu	–	Unrelated	9	Mild	Concomitant medication given	Resolved
WCU041	Headache/ migraine	–	Possible	67	Mild	Concomitant medication given	Resolved
WCU047	Infection	Urinary tract	Unrelated	6	Mild	Concomitant medication given	Resolved
WCU047	Urinary symptoms	–	Possible	–	Mild	No action taken	Unresolved

GI, gastrointestinal.

EME
HS&DR
HTA
PGfAR
PHR

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