NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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PROTOCOL DOCUMENT

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

Phase III Trial

REC Reference: 10/H0703/25

CONFIDeNT Group

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Glossary of Terms

PTNS	Percutaneous Tibial Nerve Stimulation
SNS	Sacral Nerve Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
PCTU	Pragmatic Clinical Trials Unit
NICE	National Institute for Clinical Excellence
RCT	Randomised Controlled Trial
OAB	Overactive Bladder
GCP	Good Clinical Practice
CNS	Colorectal Specialist Nurse
CRF	Case Report Form
AE	Adverse Event
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
TMG	Trial Management Group
DSMC	Data Safety Monitoring Committee

Contents

Other participating centres

Thirteen other specialist centres with multidisciplinary expertise in the management of pelvic floor disorders have already met recruitment criteria:

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Mr Dermot Burke
Mr Paul Carter
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Mr Graeme Duthie
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Lay summary

Faecal incontinence occurs when a person passes faeces (stools) without the usual control. It is a distressing condition that is actually very common although under-reported because of embarrassment. Milder symptoms may be managed by treatments such as dietary change, drugs and bowel retraining, but many patients still resort to surgery to improve symptoms. Although several operations exist to treat incontinence e.g. those aiming to repair damaged anal sphincter muscles, it is now clear that these often have poor results.

Two relatively new treatments called sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS) involve sending pulses of electricity to the nerves controlling the bowel and muscles of the anus (anal sphincter).

SNS does this by inserting electrodes in the lower back just above the tailbone and connecting them to an implanted electrical stimulator which is buried in the buttock and acts a bit like a heart pacemaker. SNS is a relatively well-established treatment in specialist centres, which has been used for over 10 years. It has been shown in studies to be successful for faecal incontinence achieving some improvement in at least three quarters of patients. In Europe, this procedure is fast becoming first treatment offered when non-surgical treatments fail. Nevertheless, SNS is not a miracle cure for all, requiring 2 operations, with potential complications and expensive equipment (> £10,000 approx).

PTNS is a newer treatment, which involves electrically stimulating a nerve at the ankle, using a very small needle, as an outpatient (a bit like acupuncture). This sends signals back to the spine region to try and improve symptoms of faecal incontinence. Since this is a newer treatment, fewer studies have been performed to quantify how successful it is, but early results of PTNS suggest that it may be as good as SNS. If this is true, this is very important because it is much less invasive and considerably cheaper than SNS (equipment £500 per patient).

This project will for the first time determine how effective PTNS is in the treatment of patients with faecal incontinence, by comparing it to sham (fake stimulation). This study is a properly designed clinical trial of 212 patients in at least 14 UK Specialist Centres.. The results of this trial will lead to direct benefits for patients and the NHS.

Scientific Summary

DESIGN: Pragmatic multi-centre, double-blinded, placebo-controlled trial of 212 participants randomized to receive the intervention (PTNS) or sham (needle insertion and electrical stimulation). All participants follow an assessment period, recruitment, allocation, standard 3 month treatment protocol (one 30 min session per week) with trial outcomes determined at 7 and 14 weeks.

SETTING: 14 UK centres providing specialist nurse-led treatment for pelvic floor disorders. The fully registered Pragmatic Clinical Trials Unit (PCTU) at Barts and the London School of Medicine and Dentistry will be the coordinating CTU.

TARGET POPULATION: Participants aged > 18 years with FI who have failed conservative treatments and whose symptoms are sufficiently severe to merit further intervention (80-90% female based on dept. data).

HEALTH TECHNOLOGIES BEING ASSESSED: PTNS (Urgent PC) is produced by a single manufacturer (Uroplasty ®). The equipment includes a hand held pulse generator unit and single use leads and fine needle electrodes. Needle insertion is performed in a sitting position in an outpatient setting on the right leg adhering to the manufacturers 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 participants achieving ≥ 50% reduction in FI episodes per week; Secondary outcomes: (1) percentage change FI episodes per week, (2) numeric decrease in FI episodes per week, (3) validated patient-rated quantitative outcomes including symptom severity score (Cleveland Clinic Score), disease-specific: FI-QOL, and generic: EQ-5D QOL measures, (4) FI-specific patient-centered outcomes (5 validated key issues), (5) Likert scales of patients 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.

Background

The problem of faecal incontinence

Faecal incontinence (FI) is a major public health problem with varying degrees of severity reported by approximately 1-15% of UK adults outside nursing institutions [1,2]. Furthermore, because symptoms are under-reported due to embarrassment, only 15-45% seek treatment [3,4]. Since prevalence and severity increase with age [2,3] FI is anticipated to become a greater problem in an increasingly aged population. Although FI is not life threatening, it is a cause of significant social and psychological disability [5]. People with FI often experience stigmatisation and social exclusion [6-8]. The socio-economic combined cost of healthcare utilisation and job absenteeism [9] related to FI is indicative of the unmet clinical need in this area with attendant high economic costs to both patients and the NHS [10]. It is estimated that combined urinary and FI in adults account for 2% of the total UK healthcare budget with an annual NHS spend in excess of £500 million [10].

Management of FI is a major problem due not only to high prevalence but also to lack of widespread expertise. In general, a step-wise approach is undertaken with first line conservative treatment such as dietary advice, drugs, nurse-led bowel re-training programs +/- focused biofeedback and psychosocial support. Although these treatments may improve symptoms in more than half of patients, they are not universally successful [11,12,13]. Thus, patients with intractable symptoms and impaired QOL, may be offered a surgical solution e.g. sphincter repair, artificial sphincter, dynamic graciloplasty or stoma. These procedures are invasive, irreversible, and have at best variable success rates with significant risk of morbidity [14-16].

Neuromodulation for FI

Neuromodulation is a new treatment modality for FI based on recruitment of residual anorectal neuromuscular function pertinent to continence by electrical stimulation of the peripheral nerve supply, without the need for potentially hazardous surgery to the anus itself.

Sacral nerve stimulation (SNS)

SNS was the first such neuromodulatory modality, involving direct electrical stimulation of the sacral nerve roots. It is a safe and effective treatment, offering a less invasive therapeutic option for most patients failing non-interventional therapies for FI, regardless of aetiology e.g. sphincter injury, neurological impairment [17-22]. Review data suggest complete continence following SNS in 41-75%, and > 50% decrease in symptoms in 75-100% of patients [20,23]. Sustained functional benefit has been shown in studies by key groups to be up to 10 years. [11, 20, 24, 25, 26, 27, 28] Despite such favourable data, SNS is not a ‘cure all’ treatment with the following considerations:

(1) SNS requires 2 operations that despite advances in technology and technique may still lead to complications [29]. SNS, although cost effective compared to other surgical options [30], does have high equipment costs (approx. £10,000 pp) and costs associated with ongoing management [31]. Estimated recurrent costs of implementing NICE (2007) guidelines on FI are £7.327 million of which £3.746 million is for SNS [32].

(2) Although rightly the first line 'invasive' therapy for FI on the basis of published data, in practice, outcomes may be more modest, especially if correctly expressed on a basis of intention to treat [30]. Indeed a recent paper from one of the leading centres in Europe reported a successful outcome in only 42% of patients (103/245) on an intention to treat basis [33].

(3) The outcome measure of "success" in such studies has been defined as a ≥ 50% reduction in FI episodes per week and can thus be recorded in patients who are still significantly incontinent. The need for more meaningful patient-centred outcomes has been identified by NICE with some recently published [8].

Percutaneous tibial nerve stimulation (PTNS)

More recently, another neuromodulatory modality has become available. PTNS offers an alternative treatment, which delivers electrical stimulation to the nerves that control bowel function by their branches that go to the ankle (tibial nerve). The technique was first trialled for urinary incontinence [34] (as was the case with SNS) with some evidence of long term effectiveness[35]. However limited case series also show 60-70% success rates in FI [36-38]. PTNS may be considered as a genuinely new option in the pathway between conservative management and the more invasive surgical procedure of SNS.PTNS is a repeatable, low cost (approx. £500 pp) minimally invasive outpatient technique with almost no associated morbidity [39].

Current published evidence for PTNS

1. Three small case series of PTNS [36-38] indicate success rates (based on 50% reduction of weekly FI episodes) of 60-70% in keeping with our own recent published [40] and pilot data on 50 patients.
2. There are no published placebo-controlled or treatment comparison trials of PTNS in patients with FI.
3. The effect of PTNS over and above that of attendance (advice / support) and / or needle insertion alone is thus still unknown in FI. This is important because:
    a. the possible placebo effect of PTNS cannot be underestimated
    b. although PTNS is much cheaper than SNS, the single use leads and needles still cost approximately £500 pp for a standard course of 12 weeks treatment.
4. The effectiveness of PTNS over placebo (sham stimulation) has been confirmed for a urinary indication by the recent publication of the first RCT of PTNS (SumiT trial) [41]. This pivotal level I study of PTNS in overactive bladder symptoms (OAB) included patients whose main symptom was urinary incontinence. Using a global response assessment and intention to treat design, a moderate or marked improvement in symptoms was observed in 55% PTNS group and only 21% sham group using the Streitburger needle and TENS.
5. Sustainability of response to PTNS at one year has only been reported in one study to date of FI (of only 14 patients) [38] but has been better documented in the adult [42] and paediatric [35] urology literature. This is important because it is unclear from our own experience whether PTNS produces a more permanent reprogramming of defaecatory behaviour (such as is said to occur with biofeedback [43]) or a temporary fix that wanes some time after treatment has ceased, thus requiring long-term maintenance treatments.
6. There are no cost analysis or effectiveness data for PTNS in FI.

Placebo responses cannot be underestimated

1. High placebo responses are almost universally observed in trials of therapy for functional (range 3-84%, mean 40% for IBS based on 50 studies [43,44]), and even organic (e.g. ulcerative colitis: mean > 30%) [44,45] colorectal diseases;
2. Therapeutic responses have recently been achieved by acupuncture alone in FI [46], noting that the medial ankle is an established acupuncture site for the viscera ("sanyinjiao" or "spleen 6"). High placebo responses have been observed even with sham acupuncture using techniques such as the Streitberger needle in studies of IBS [47];
3. Regular attendance with a specialist nurse may confer some benefit even without formal bowel retraining [48].

Competing studies

1. A French study (A-M Leroi, Rouen) was added in error to the clinicaltrials.gov website Sept 15th 2009 (NCT00977652) but will not be progressed (personal communication from PI);
2. A recently funded study (RfPb PB-PG-0909-20150) commenced recruitment in March 2011. It will determine estimates of cost and acceptability of sacral nerve stimulation in comparison with PTNS whilst also determining estimates of effectiveness. The study has only 17 patients in each arm and uses a combination of quantitative and qualitative (interview) methods. It is strictly a pilot comparison study rather than a definitive trial and is concerned with providing estimates were a definitive trial of PTNS and SNS to be conducted in the future. This is a single-centre study whose population is derived only from those patients considered for SNS (strict NICE criteria based on symptom severity etc.). It has in our view no potential conflict with the current application. To our knowledge, there are no ongoing HTA or other NIHR activities in this area.

Importance

The Interventional Procedures Programme (NICE) last year issued (Nov 2010) a request for specialist advice through the Interventional Procedures Advisory Committee to develop guidance on PTNS for bowel dysfunction and faecal incontinence (ref 877/1). The main requirement for this evaluation is that of a definitive placebo-controlled RCT.

Knowledge of the effectiveness of PTNS is paramount to informing NHS (NICE) policy on the management of patients with FI. Recently published supplementary NICE guidelines (May 2011) state that PTNS is a safe procedure with limited evidence of effectiveness in a limited number of patients, and that it should be used with special arrangements in place for clinical governance, consent and audit or research.

How will the proposed trial address this need

There is an urgent general need to improve the evidence base for device-based therapies with a paucity of well-conducted studies in the surgical literature [49]. It is thought, from very limited data, that PTNS may have similar effectiveness to SNS, but no RCT for PTNS in FI has ever been conducted. There is considerable scepticism regarding the legitimacy of effects of PTNS leading to a national position of genuine equipoise i.e. an increasing number of centres are using it but many are doing so with

speculation that it is little more than an expensive form of acupuncture. It is therefore essential to conduct a suitably powered placebo controlled trial to resolve this matter one way or the other.

The proposed RCT will provide valid outcome data for PTNS in the treatment of FI. With this a reasoned comparison with the more invasive and much more costly intervention of SNS can be made. The results will have enormous relevance to patients both within the NHS and internationally with the broad national population mix (North-South, ethnic minorities) permitting some generalisability of results to other populations. Benefits to patients will be realisable in the medium term in the UK. Specifically, the adoption of PTNS would have the potential to:

- Expand treatment choice for patients
- Enable treatment of patient groups currently marginalised from interventional therapy e.g. the very elderly
- Reduce need for operative surgery
- Reduce need for inpatient stays
- Reduce operative morbidity including hospital acquired infections
- Reduce waiting times for treatment

Such information has the potential to change the current algorithm of management of FI and thus impact on future NHS resource utilization; PTNS could thus become the routine first 'invasive' intervention in patients with FI failing prior conservative physician- and nurse-led approaches. SNS would only thence be employed for PTNS failures or for those requiring an unacceptable level of continued PTNS maintenance therapy. Furthermore, PTNS could be relatively easily implemented throughout the NHS, requiring modest training and expertise, and little financial outlay on specialist equipment. Similarly, failure to show benefit would abolish this line of research association.

Preliminary data

Data from 50 patients completing PTNS with median 6 months follow up at Barts and The London Trust suggest a success rate at of 60% with no complications (table 1). Over the 18 month period, only 3 (6%) patients started therapy but did not complete it (2 due to pregnancy and one due to dissatisfaction) in keeping with the data from the OAB trial [41].

Table 1: Preliminary data on 50 patients (Barts & The London Trust: Jan 2008 – Sept 2009)

N = 50 (of 53 starting therapy)
Age: median 59, range 30-77 years
Sex: 45 female, 5 male

	Before PTNS (med, range)	After 3 month treatment (med, range)	Difference (mean, SD)
FI episodes per week	6, 0-39*	1, 0-39	-5.3, 7.5
FI score (Cleveland clinic) [50]	16, 5-24	10, 0-24	-3.2, 4.4

Responders (> 50% dec. FI episodes): 30/50 = 60% (only 1/5 males successful)

* the zero in this range reflects real life conditions i.e. that a minority of patients recorded no episode of FI in the particular 2 weeks of the baseline bowel diary

Study Aims

To determine the effectiveness of PTNS versus sham electrical stimulation based on:

1. reductions in weekly FI episodes (primary outcome) and,

2. improvements in validated incontinence scores, patient-centred FI-related symptoms and disease-specific and generic quality of life measures (secondary outcomes);

Design

The proposed study is a UK based multi-centre (at least 14 centres) double-blinded, placebo-controlled trial of 212 participants randomised to receive the intervention (PTNS) or sham (needle insertion and TENS): 106 in each arm. All participants follow an assessment period, recruitment, allocation, standard 3 month treatment protocol (one 30 min session per week) with primary outcome determined at 14 weeks on an intention to treat basis.

The following pragmatic considerations were included in study design:

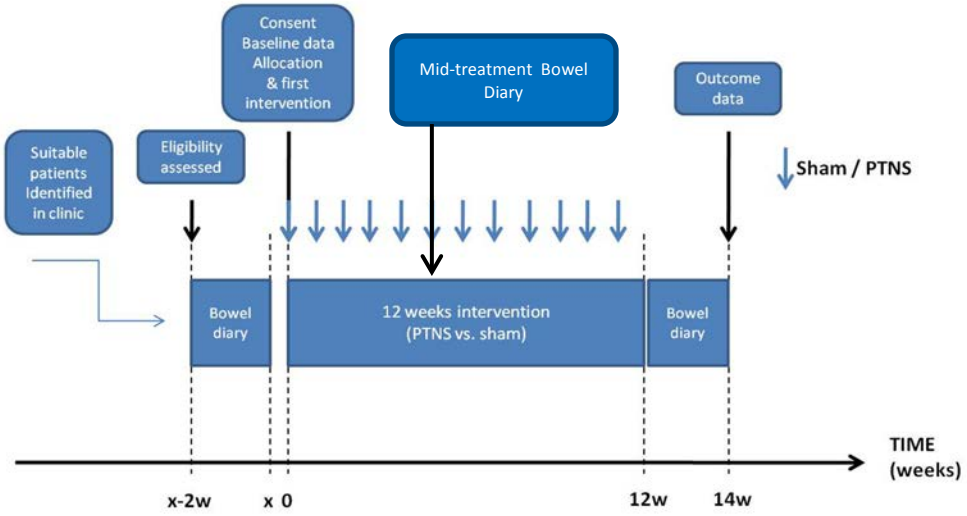
1. All participants randomised who receive the first treatment will be included in the intention-to-treat analysis of primary endpoint. Those in whom post-treatment data are unavailable at 14 weeks for any reason (loss to follow up, failure to complete treatment) will have their outcomes defined using the interim bowel diary data collected between treatments 6 and 7 (Visits 7 and 8). Those who do not have this data available (again due to loss to follow up or failure to complete treatment) will be defined as non-responders and their 14 week outcome imputed from their baseline FI frequency. Prior to the first treatment, it is anticipated that some participants (up to 10%) will fail to attend after eligibility is assessed due to a failure of compliance with the travel and attendance needs of the treatment course or study. These will not count as study recruits. Based on our own department's data and supported by the study of Peters et al., [41] it is anticipated that the dropout rate after the first intervention is complete will be 6%. This level is acceptable to analyse secondary endpoints using available case analysis. The reason for this interim bowel diary assessment is two-fold;
    a. to gauge response to a short course of treatment (since some people believe a 12 week course is not necessary);
    b. to allow us to collect 'real' data regarding those participants who do not complete the full 12 week course of treatment, in an attempt to judge whether this was due to objective lack of response.

2. We have elected not to implement 'ideal' trial conditions by dictating the cessation of all other medications during the RCT (with prescribed breakthrough medication protocols). It was felt that compliance would be low with such an instruction and that the effect size could be thus reduced by undocumented greater use in the sham arm. It was deemed preferable instead to permit *ad libitum* use of medications e.g. loperamide or fibre supplements but record this at each appointment as a potential confounder which could be subsequently included as a covariate in the analysis. In any case, the majority of participants have already failed using simple medications so regular usage is expected to be low.

3. It is accepted that the sham stimulation could be described as an 'alternative treatment' rather than a placebo. Although sham effects may result from both 'true' placebo responses [42,44], acupuncture [47] or 'electro-acupuncture' [51], the aim of this study is to determine the specific (perhaps additive)

effects of episodic low frequency electrical stimulation of the posterior tibial nerve as per the manufacturer's protocol.

Figure 1: trial protocol



Study centre eligibility

Participating centres have been selected from specialist clinics with nurse-led incontinence services. Only those centres with experience of PTNS will be eligible to participate. The applicants have already had interest from over 20 centres. However only those who at the time of the study commencement have received both specialist training under the guidance of the manufacturer and lead specialist nurse, and who have completed a minimum of 3 complete participant treatments i.e. 36 individual 30 minute treatments will be deemed eligible. Each centre will require a minimum of 2 staff with GCP training: one to perform baseline assessments, consent, allocation and intervention, and one to perform outcome assessments. Each centre is also required to input a minimum of 5 participants into the trial.

Participant recruitment

In general, participants with FI are seen by a specialist as a result of secondary or tertiary referral to a coloproctologist (usually colorectal surgeon). The patient is then referred to the pelvic floor service led usually by a colorectal specialist nurse +/- physiotherapist. Maximal conservative measures are undertaken (diet, lifestyle, pharmacological, defaecatory dynamics) and the patient followed up at intervals accordingly. If these are unsuccessful, suitable patients will start PTNS in the centres where this technique is available. At any time, most centres have a waiting list of such patients who are continuing with conservative therapies whilst awaiting PTNS (because of service constraints). For the trial, such patients will be sequentially identified and offered participation. Thus the arrangement at all sites is that the CNS / physiotherapist will identify patients retrospectively (some centres have > 20 such patients at any time) from those already within the pelvic floor service and prospectively as new patients are referred.

These patients will be locally referred to the local lead investigator who will formally determine general eligibility from the case notes.

Events at each visit

Visit 1: Interest - eligibility: At this appointment, or over the telephone, a GCP-trained local investigator will determine eligibility by interview on the basis of defined inclusion and exclusion listed on case report form 1 (CRF1). The participants details will be recorded on the screening log, and each participant will be allocated a Unique Participant Identifier number (see below).

Eligible subjects will be provided with adequate explanation of the aims, methods, anticipated benefits and hazards of the study and will take away, or be sent, a patient information sheet containing this information.

Following this appointment, participants will be telephoned one week later (or given an appointment one week later if initially contacted over the telephone) to allow ample time for them to consider their participation (in accord with GCP guidance).

If participants remain interested in participating in the study they will be sent or given a bowel diary, to complete over the next 2 weeks. Each participant will be counselled on how to fill this diary in. Appointments will then be booked for Visits 2-14, with Visit 2 being at least 2 weeks hence.

Unique Participant Identifier Codes

Once a participant is enrolled on the screening log, they will be allocated a Unique Participant Identifier Code. This will consist of 6 digits, three letters and three numbers. The letters will denote the study centre code, and the number will be allocated on a consecutive basis, e.g. 001 for the first participant and so on. (See Appendix 1 for study centre codes).

Visit 2: Consent – confirm eligibility - baseline assessment – randomisation – first intervention: At this appointment, a member of the local team (trained in informed consent) will answer any outstanding questions and thence ask participants to sign the study consent form.

All prospective participants will be reminded of the need to be logistically able to complete the full protocol of 12 sessions at weekly intervals.

Once the consent form is signed, the local investigator will confirm eligibility by recording data on CRF 1**.** If the participant is a female of childbearing potential, a urine pregnancy test will be performed at this point.

Providing the participant remains eligible for the study, the Participant Contact Information Sheet will then be filled in. The researcher will then record all baseline data using CRF2 (initial assessment) and CRF3 (questionnaires) and also collect and check the completed bowel diary. The bowel diary will then be checked for completeness.

Prior to randomisation, the consent form, eligibility criteria (CRF 1) and initial assessment (CRF 2) will be verified by another member of the research team.

If the participant has failed to complete the bowel diary properly, they will be given another 2 week bowel diary to complete. They will return again 2 weeks later to clinic, where the treatments will commence. If,

however, they fail at the second attempt to complete the bowel diary, they will become a 'Screen Failure', and be withdrawn, and the Screen Failure CRF should be filled in. Another participant will be recruited in their place.

The researcher will then perform the randomisation and record this information on CRF 4. This researcher will now be un-blinded to treatment allocation. The participant will then undergo the first 30 min intervention by the same researcher and following this, the researcher will complete CRF 5. Participants' details will now be entered on the enrolment log. The GP letter, informing the GP of the participants involvement in the trial, will be sent out following this visit.

Visit 3-13: intervention – interim information: At appointments 3-13, a member of the local team (which may be the same member as in Visit 2) will deliver the 30 minute intervention. They will check on CRF 4, prior to commencement, to make sure of the randomisation allocation, either PTNS or sham.

During this appointment with the participant, the researcher will enquire about adverse events, concomitant medication usage and pad usage, and record these on CRF 5.

At Visit 7, participants will be given a one week interim bowel diary to fill in between Visits 7 and 8. This bowel diary will then be collected and checked at Visit 8. Intervention parameters will also be entered on CRF 5.

At Visit 13, participants will also be given a two week bowel diary and CRF 3 questionnaire document to complete prior to attending Visit 14, two weeks later.

Visit 14: final study visit: The final study visit will be performed by a blinded member of the research team (i.e. somebody who has not been present at visits 2-13).

At this appointment, the bowel diary and CRF 3 questionnaire document will be collected and checked for completeness. The participant will then be asked to complete CRF 6, the post treatment questionnaire.

The research member will then ensure all documents are present and filled in correctly, and then ask the PI to complete and sign CRF 7. Once this has all been completed, the participant can be unblinded as to their treatment allocation if they wish. This is the final study visit, so further follow up should be arranged at this visit.

If participants have failed to complete the Interim Bowel Diary between Visits 7 and 8, this should be attempted again the following week. This is a Protocol Deviation, and therefore a 'Note to File CRF' should be completed to explain this. If participants fail to complete the Final Bowel Diary, again this should be attempted again after Visit 14, and participants brought back to collect this. This is also a Protocol Deviation, and should be documented in a 'Note to File CRF'.

After completion of trial: After Visit 14, participants who received 'sham' stimulation will be offered PTNS at this time, if they wish.

Participants who received real PTNS who derived significant benefit, will be offered 'top-up' sessions on an ad hoc basis, and will be followed up in NHS clinics in the usual way.

Participants who received real PTNS who derived no significant benefit will be offered further treatments on an 'open-label' basis, following local step-wise management protocols.

Table 2: Events at each visit

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

Inclusion and exclusion criteria

Broadly, eligibility will be failure of appropriate conservative therapies in patients with symptoms that are sufficiently severe to warrant intervention. It is expected that many patients will have had NICE-recommended appropriate specialist investigations including structural and functional anorectal assessment although these are not mandatory. Anal sphincter injury is not a contra-indication [32].

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

* Following in depth discussion with the Research Ethics Committee, it was decided that, since some of the outcome questionnaires had not been validated in languages other than English, we should exclude from the study people who do not understand written or spoken English.

Interventions

Participants will receive PTNS or sham using the recommended standard of 12 weekly 30 minute outpatient stimulations [Figure 1]. The stimulation protocol is based on that currently recommended by the manufacturer, NICE guidelines and used by most centres treating urinary disorders (including OAB SUMMIT trial) and FI [41].

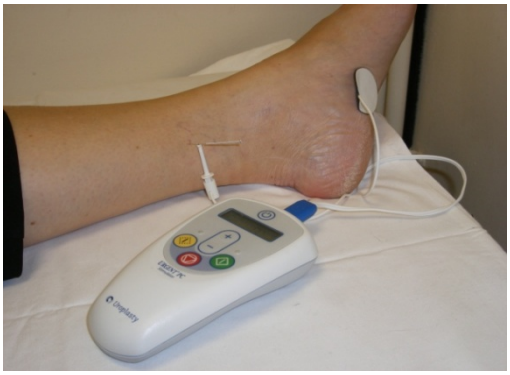
The sham arm will use a modification of that used in the pivotal level I trial of Peters *et al*., [41] in overactive bladder syndrome and previously validated by this group [52]. The main difference is that the sham proposed in the current study improves on that used by Peters by actually inserting (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 employed an acupuncture technique using a Streitburger needle, which does not puncture the skin. (A legitimate concern regarding sham validity).

In the CONFIDeNT study, all participants will have a PTNS machine and a TENS machine set up on their RIGHT foot, as shown below. (Unless there is a reason why the right foot cannot be used, in which case this should be documented). In the true PTNS arm, the PTNS machine will be utilised as normal, and the TENS machine left turned off. In the sham arm, the Urgent PC ® needle will be placed subcutaneously, and not connected to the machine, and the electrical stimulation delivered to the distal foot using TENS. All subjects have a needle and 3 surface electrode pads placed as shown in figure 3 (A, B & C) to standardize the perception of the intervention between the 2 arms. Electrode A is used for the treatment and B & C for the sham. See Appendix 2.

This sham has been shown in a departmental pilot to be both more acceptable and more realistic than that described by Peters et al, involving placement of a Streitberger needle. We have 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 Consultant Neurophysiologist). Further, it has been trialled successfully at both road show meetings and is easily learnt.

Figure 2: Images of percutaneous tibial nerve stimulation



Needle in place at left ankle attached to portable stimulator unit (urgent PC ®)

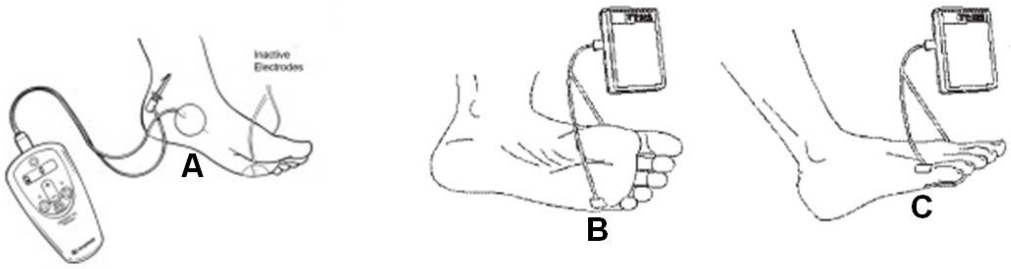
Patient undergoing outpatient stimulation

Treatment arm: This uses the Urgent ® PC neuromodulation system (Uroplasty Ltd., Manchester, UK) [39-41]. After checking equipment including battery level, the site of insertion is identified at a location on the lower inner aspect of the RIGHT leg approximately three finger breaths (5 cm) cephalad to the medial malleolus and approximately one fingerbreadth (2 cm) posterior to the tibia. The area is cleaned with ethanol and the needle electrode-guide tube assembly placed over the identified insertion site at a 60-degree angle between electrode and ankle. The 34 gauge needle electrode is gently tapped to pierce the skin and thence advanced using a rotating motion approximately 2cm. The lead wire is then connected to the stimulator and to the ipsilateral calcaneal reference electrode (A. in figure 3) (as standard practice). The lead wire is then taped to the participants leg in order that the PTNS participant will experience the same sensations as the sham participant (see below). The inactive electrodes (B & C) are attached as shown and connected to the TENS machine (Biostim M7 TENS unit, Biomedical Life Systems, Vista, California). The TENS machine is not turned on.

The PTNS stimulator is a reusable external pulse generator that provides visual and auditory feedback. It has an adjustable current setting from 0-9mA in preset 0.5 mA increments, a fixed-pulse frequency of 20Hz and a pulse width of 200 microseconds. After determining the setting for therapy by increasing the current slowly whilst observing the participant's sensory or foot for toe / ankle extensor motor responses, the current is reduced by one level for therapy. Therapy is continued for 30mins and thence the electrode removed. Treatment is repeated for 12 sessions within the three-month duration exact intervals tailored to participant's needs but must comply with study requirements: Requirements – 12 treatments within 13 weeks, no two treatments less than 5 days or greater than 10 days apart). Side effects include occasional tenderness at the site of needle insertion [39,40].

Sham arm: the same protocol is followed as above. The only difference is that the needle will be inserted only 2mm into the skin and subcutaneous tissue i.e. just in far enough to not fall out and not deep enough to be close to the posterior tibial nerve. The lead will then be taped to the participants leg near to, but not touching the needle. The purpose of this is to prevent unbinding in the event of the participant inadvertently seeing the equipment. The PTNS surface electrode (A) on the calcaneous is also attached as above. The two active TENS surface electrodes (B & C) are employed as demonstrated below, with one under the little toe and one on top of the foot. Once all equipment is set up, the practitioner picks up both the Urgent PC machine and the TENS machine, one in each hand. Both machines are turned on. The TENS machine should be set to a pulse frequency of 10Hz and a pulse width of 200 microseconds. Then, pressing buttons simultaneously on the Urgent PC and the TENS machine, the practitioner should increase the adjustable current setting (which ranges from 0-10mA in preset 1mA increments on the TENS machine) and in the usual way determine the setting for therapy by observing the participant's sensory or foot for toe / ankle extensor motor responses, the current is reduced by one level for therapy. The reason both machines are picked up together is so that the audible sounds produced by the Urgent PC stimulator are the same in both the PTNS and sham arms, to decrease auditory variation between the study arms.

Figure 3: PTNS needle and surface electrode (A). TENS surface electrode placements (B & C). Note: The PTNS and TENS electrodes are inserted / connected on all subjects identically.



Randomisation

Participants will be randomised, with allocation concealment, at visit 2 using a web-based computer program to receive either PTNS or sham. This will be performed using a bespoke programme designed and held at the Nottingham Clinical Trials Unit. Study centres will input the unique participant identifier and gender of the participant and immediate on-screen randomisation will occur. This information should immediately be recorded on CRF 4 (randomisation information), which is stored separately from the other CRFs.

Stratification will occur in the following way; strata 1 = men; then women will be stratified by centre. Stratification by gender will be 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 participants are expected to be enrolled from each centre, randomisation stratified on centre would allow the possibility that all the males are allocated to PTNS by chance. To avoid this scenario, we will therefore only stratify women by centre, so achieving near balance of PTNS and sham arms and ensuring comparability by centre.

Allocation concealment

Blinding of participants: For both interventions: (1) a standardised description of the techniques will be read from a card (See Appendix 2). This will describe 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 will be draped from view; and (3) the audible sounds produced by the Urgent PC unit will be 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 will be standardised so that general supportive advice given at consultations is identical for all participants. This will be 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: At least two researchers will be available at each site to run the study. Randomisation into the treatment or placebo arm of the study will occur at Visit 2, after all the documentation has been completed. At this point, the researcher carrying out the PTNS or sham will be unblinded. That same researcher will carry out all 12 treatments for the participant (with a spare researcher available in the event of illness or holiday).. Following the final treatment the member of staff who remains blinded will collect all of the final data, before allowing the participant to find out if they were in the sham or treatment arm. In this way, the staff member conducting the final meeting with the participant will remain blinded until the end.

Breaking Randomisation Code

It is hard to envisage any necessity to break the randomisation code. If however, for any reason, this 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, of the Chief Investigator, Charles Knowles should be contacted.

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 centre should be contacted. In the first instance the Trial Manager can be contacted, who can break 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.

Trial outcomes

The overall objective is to determine the effectiveness of PTNS in patients with faecal incontinence (FI). Specifically, the effectiveness of PTNS vs. sham electrical stimulation will be determined after a standard 3 month treatment course using:

1. primary outcome:
    a. Change in weekly FI episodes expressed as proportion of patients achieving ≥ 50% reduction in FI episodes per week.
2. secondary outcomes:
    a. Percentage change FI episodes per week;
    b. Numeric continuous change in FI episodes per week;
    c. Validated incontinence scores;
    d. Patient-centred FI-related symptoms;
    e. Likert scale of patients global impression of success
    f. Disease specific and generic quality of life measures;
    g. Short urinary symptom assessment

Clinical outcomes

These will be assessed using bowel diaries and investigator-administered questionnaires. Bowel diary data will be collected at week -2 to 0 where 0 is start of treatment and -2 is baseline pre-randomisation, and at 14 weeks for the 2 preceding weeks post intervention i.e. weeks 12-14. There will also be a 1 week bowel diary collected between Visits 7 and 8, half way through the treatment duration. This is when participants usually start to perceive benefit. This will help to improve the quality of data on participants who withdraw from the study as outcomes will be analysed using the last available data on those participants who do not complete the final 2 week bowel diary. In those patients who withdraw from the study prior to completing the final study visit no secondary outcome data will be available for analysis. The bowel diaries will record number and type of incontinence episodes per week (and associated symptoms). An episode of faecal incontinence is defined as 'any episode considered significant enough by the participant to include on their bowel diary'.

Primary:
Responder vs. non-responder: Defined as a 50% or greater reduction in FI episodes per week (on intention–to-treat).

Secondary:
a. Percentage reduction in FI episodes per week – in addition to informing the primary outcome, this will give a confidence interval of effect and permit calculation of the proportions of patients who achieve complete continence or no change / deterioration (used in one Cochrane review of surgery for FI: [53]).
b. Mean reduction in FI episodes per week. The confidence interval of this measure will be important for clinical interpretation of effect.
c. Validated and reliable patient-rated quantitative outcomes including symptom severity scores (Cleveland Clinic Score) [50], validated disease-specific: FI-QOL [24] and generic: EQ-5D [54] quality of life measures will be employed.

d. Recently-described patient-centred qualitative outcome tools have identified 5 key issues [8]. These will be employed as suggested by NICE (2007) research recommendations [32] and are anticipated to provide more clinically meaningful outcomes.
e. Likert scales of patients global impression of success (0-10). These have been employed infrequently in the FI literature but will help to validate the primary outcome (a).
f. Short urinary symptom assessment. As many patients have combined FI and urinary incontinence symptoms – it will be of value to assess both.

Other recorded variables:

g. Adverse events are rare with PTNS but any will be recorded at each visit.
h. The level (amplitude) of stimulation, reported sensory and observed motor responses (present, absent, site) will be recorded at each visit
i. Medication usage: as noted above in trial design considerations, antidiarrhoeal and other medication such as fibre supplements will not be controlled during the study. Drugs and dosage will however be recorded at each appointment in case they become a confounding variable. The use of pads is recorded in the Cleveland Clinic Score.
j. The participant's perceived allocation (treatment or sham) will be recorded at the final visit. The purpose of this is to help interpret the final result in terms of re-ensuring the validity of the sham in light of the small changes made to it from that previously validated in the SUMMIT OAB trial.

Calculating weekly FI episodes

The bowel diary is divided into:

1. 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.

Patients will be counselled on how to fill in the form before they do

Health economic outcomes

Health economic analysis will estimate the direct NHS costs incurred by participants in undertaking the treatment. Data on resource-using activities during treatment; e.g. time using PTNS, consultations, diagnostic tests can largely be derived from the clinical information recorded at the study sites. Utilities will be derived from the EQ-5D outcomes using the national matrix of health state valuations [56].

The economic analysis will be based on the trial, but will draw on external data [28] for comparison with non-PTNS interventions as a sham PTNS is being used as the control. A more sophisticated comparison involving decision-modelling may be performed as a follow up if separate funding can be sought.

Adverse events

An AE is any untoward medical occurrence in a participant to whom an intervention has been performed, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporarily associated with study activities.

The PTNS treatment and placebo have no recognised significant adverse effects. However, at each weekly visit each participant will be asked if they have had any new symptoms or medical conditions since their last visit. This will be documented on CRF 5. If any Aes have occurred, the AE will be recorded on the AE Log.

Serious Adverse Events are defined as follows:

- Fatal – results in death (NOTE: death is an outcome, not an event)
- Life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Investigators Assessment

Seriousness

The Chief/Principal Investigator responsible for the care of the participant, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given above.

Causality

The Investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definition given.

Expectedness

The investigator must assess the expectedness of all SAEs according to the definition given. If the SAE is unexpected and related, then it needs reporting.

Severity

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on participant/event outcome criteria.

- Mild: Some discomfort noted but without disruption of daily life
- Moderate: Discomfort enough to affect/reduce normal activity
- Severe: Complete inability to perform daily activities and lead a normal life

Reporting

If the event is classified as SERIOUS, the CI will be informed immediately, and will report all SAEs that are RELATED to the study and are UNEXPECTED to the main research ethics committee (REC) using the NRES non-trials SAE form and SOP within 15 days of the CI being made aware of the event.

The SAE will be recorded in the participants' CRF folder and the participant followed up with regular phone calls and at the following appointment the following week. The SAE form is scanned and emailed or faxed to the sponsor. The email address the form should be sent to at the Joint R&D Office (JRO) is: ResearchSafety@bartsandthelondon.nhs.uk

The fax number is: 0207 882 7276

There are no SAEs expected to occur in this population. Therefore, all related SAE's are reportable as outlined above.

Withdrawal Criteria

Participants will be withdrawn from the trial if they fulfil any of the criteria below at any point following delivery of the first treatment.

- Participant no-longer wishes to be involved in trial
- Participant develops medical condition which fulfils part of the exclusion criteria
- Participant becomes pregnant
- If, for any reason, the participant has to be unblinded
- Participant lost to follow up (could not be contacted by telephone or other means)
- Intercurrent illness
- Death

When a participant is withdrawn from the study, the Early Withdrawal from Study CRF will be filled in by a researcher. In order to ensure clarity of each participants outcome, the researcher should also complete the final study visit (CRF 7).

Once a participant has withdrawn from the trial, they will be followed up on the NHS in the usual way, and progress down the usual treatment protocol.

Proposed sample size

Previous publications [36-39] and our own data [40] 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) [41] which used a similar global response assessment of urinary incontinence and intention to treat design, 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 [43-45] 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 in relation to other therapies such as SNS. 212 participants are required to detect this difference with 80% power at the 5%

significance level. We will recruit 235 participants at baseline to allow for a 10% failure to attend the 2nd visit (allocation and first intervention).

Feasibility

Fourteen UK centres (including the lead centre) providing specialist nurse-led treatment for pelvic floor disorders that meet the centre inclusion criteria have agreed to participate in the study. These centres provide sufficient geographical (Durham to Bristol), urban and rural, as well as ethnic diversity. The sample size of 235 will be recruited over a period of 18 months. The 14 centres each treat between 20-40 broadly eligible patients per annum currently with PTNS (e.g. 75 patients have undergone PTNS at BLT over the last 2 years). Even if only 20 of these agreed to participate, this would allow for 25 per centre over 15 months = 280 total in 15 months. In addition, expertise in PTNS is expanding nationally. We have had significant further interest in this study and have identified further 'reserve' centres that could be included on the advice of the study steering group if interim recruitment rates (see milestones below) are unsatisfactory. Because funding will follow the participant this would not result in increased trial funding requirements.

Primary Outcome Choice

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 [17-25]. 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 [17-25]. We justify this approach on the following basis:

1. 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 ≥ 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 [NICE IPG99]; 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.

2. This outcome has also been the approach of choice for urinary incontinence episodes in the only pivotal trial of PTNS in the urology literature [41] and also for NICE commissioned systematic reviews [23].

3. Baseline, post treatment and change FI episodes expressed as continuous variables all 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. This variable will however remain a secondary outcome.

Plan of Statistical Analysis

Outcomes will take the form of binary (success or failure: primary outcome measure), count (change in number of FI episodes), ordinal (patient's global impression of success) and continuous (GIQOL, SF36, FI score, and EQ-5D) data. Regression models, with a fixed effect for centre, appropriate to the outcome data types will be fitted to estimate the treatment effect, adjusting for baseline values (when appropriate), sex, and loperamide use/fibre supplements as potential confounders (the dose and frequency of these will be recorded at all visits). Analysis will be performed using proprietary software (Stata version 10.1, Stata Corp. Texas) by the PCTU study statistician (Stephen Bremner). $P < 0.05$ will be taken to indicate statistical significance. Given the stability of FI over a short period of time, where follow-up scores are missing, these will be imputed using the baseline scores, or interim bowel diary scores if available**.** The rationale for this is that primary outcome would, in the absence of any intervention, be expected to remain stable over the relatively short time span of the trial. Any changes or deviations from the original statistical plan will be described and justified in the Clinical Study report. Every attempt will be made to avoid any deviations from the original statistical plan.

Ethical approval

PTNS is CE-marked and clinically established in the NHS. A favourable ethical opinion has been given (ELCHA REC 10/H0703/25 June 2010); Amendment 1 approved 19th Oct 2010 and Amendment 2 approved 6th June 2011.

PTNS treatment and placebo have no recognised significant adverse effects. Although the trial necessarily delays 'real' treatment of participants in the sham arm, this time has been limited to just over 3 months (discussed with Professor Richard Ashcroft, Prof of Bioethics and Law, QMUL). PTNS or an alternative treatment e.g. SNS can be offered immediately thereafter. We believe that the importance of the research question with subsequent major implications to NHS service delivery merits this modest delay. The trial will not affect prompt delivery of PTNS or other NHS treatments to non-trial patients.

Early Termination of Study

The Sponsor, Cheif Investigator, Research Ethics Committee (REC) and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Sponsor where practical. In the occurrence of premature trial termination or suspension, the above mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the sponsors responsibility for notifying the Regulatory Authorities). After such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects interest. The investigator must review all participating subjects as soon as practical and complete all required records.

Data Handling & Record Keeping

Confidentiality

Information with regards to study participants will be kept confidential and managed by each study site in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Trial documentation will be made available to suitably qualified study staff, auditors and inspectors representing the Sponsor and the regulatory authorities.

The participants will be anonymised with regards to any future publications relating to this study.

Required Study Documents for each site

- A signed protocol and any subsequent amendments
- PTCU self-monitoring template
- Current/Superseded Patient Information Sheets
- Current/Superseded Consent Forms
- Current/Superseded GP Information letters
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Delegation log
- Staff training log
- Screening log
- Enrolment log
- Participant Signed Consent Forms
- Completed Case Report Forms and Randomisation
- Participant Contact Information Sheets
- Study Reports
- Monitoring visit log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE documentation and reporting plan for the study
- Standard Operating Procedures (SOPs)

Case Report Forms

Source data will be recorded directly to CRF. The responsibility of completion of CRF's is detailed on the site delegation log and completed as per CRF instruction sheet.

Identifiable data will be recorded on the Participant Contact Information Sheet. This will be stored with the Participant Consent Form in the 'Consent Form Folder', separately from the other CRFs. All other CRFs will contain no identifiable data, but will contain Unique Participant Identifier (as detailed above), so can be stored together in the CRF Folder for each individual. All Randomisation Information CRFs (CRF 4), should be kept separately from the other CRFs, in the 'Randomisation Folder' containing CRF 4s for all

participants at that centre. This folder can thus be referred to prior to each treatment, but it will not be stored with the other CRFs to prevent inadvertent unblinding.

The following Case Report Forms are to be completed:

CRF 1: Eligibility Assessment – to be completed by research member prior to randomisation

CRF 2: Initial Assessment - – to be completed by research member prior to randomisation

CRF 3: Questionnaires – to be completed by participant prior to randomisation (with help from research member as required)

GI Quality of Life Index
Patient Centred Outcomes Form
SF-36
Quality of Life Scale for Faecal Incontinence
Cleveland Clinic Faecal Incontinence Score
EQ -5D Health Questionnaire

CRF 4: Randomisation Information – to be completed by unblinded researcher

CRF 5: Documentation for Visits 2-13 – to be completed by unblinded researcher

CRF 6: Post Treatment Information – to be completed by blinded researcher and participant

CRF 7: Final Study Visit Information – to be completed by PI

Additional CRFs: - all to be completed by research member

Adverse Events Log
Concomitant Medications Log
Early Withdrawal from Study
Serious Adverse Event form
Screen Failure CRF
Unscheduled Visit CRF
Note to File CRF

Other Information Recorded

Bowel Diary: Each participant will also complete a 2 week bowel diary prior to commencement of the treatment and following treatment and a 1 week bowel diary between visits 7 and 8. This is not outside normal NHS practice, and this information will be analysed alongside trial data.

Participant Contact Information Sheet: Each participant will provide personal details, contact details and GP details. This will be the only identifiable data kept on each participant, and will be kept separately from the non-identifiable CRFs.

Transport of Trial Data

All trial data will be collected from each participating site either in person by the Trial Manager or Academic Clinical Fellow in a locked bag, or sent by special courier, and transported back to the Lead Centre, Barts and the London NHS Trust, for data entry onto the trial database. No identifiable data will be removed from any site. The Participant Contact Information Sheet and Consent form for all participants will remain in each centre, as will the randomisation information (CRF 4).Data on randomisation of participants will therefore only be inputted onto the trial database after all other CRF

information has been entered. This information will be gained directly from the online randomisation tool, and will be carried out by the Trial Manager, in order to ensure blinding remains.

Record Retention and Archiving

Is a requirement of the Research Governance Framework and Trust Policy that the research data are kept for 20 years. Barts and the London NHS Trust have an approved repository for this long-term storage at the Trust Modern Records Centre which is based at 9 Prescot Street.

Each site will be responsible for archiving their site files and participants identifiable data (consent form, contact information and randomisation) at their own archive facility for a period of 20 years.

At the end of the 20 year retention period, the Records Management team will alert R&D that the records are due for disposal. The Principal Investigator and sponsor will be informed and the full agreement of everyone concerned will be obtained before any records are destroyed.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments. The trial will be carried out in compliance with the approved protocol and REC conditions of approval, and in line with Good Clinical Practice Guidelines.

Non Compliance

Non-compliances with the protocol, SOP's or regulatory guidelines will be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. Any serious breaches will be reported to the sponsor as outlined in the sponsors SOP.

Data monitoring

The project will be under the auspices of the Chief Investigator and the PCTU, Barts and The London School of Medicine and Dentistry. The project will be overseen by a Trial Steering Committee (TSC).

The TSC will meet at 3 months and either meet or teleconference every 6 months thereafter throughout the lifetime of the project. The role of the TSC is to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. Specifically, the TSC will ensure:

1) that views of users and carers are always taken into consideration;

2) the scientific rigour of the study and adherence to protocol;

3) that project milestones are met;

4) expertise / advice are provided to the Trial Management Group (TMG).

Membership of the TSC will be in accordance with HTA guidance:

- Charles Knowles – Chief Investigator
- Sandra Eldridge – Senior Statistician
- Independent Chair: Prof Christine Norton, Professor of Nursing (Imperial College and Bucks New University),
- Independent external members: Professor Ronan O'Connell (University College, Dublin: clinical and research expertise in lower GI neuromodulation) and Professor Paul Enck (University of Tuebingen, Germany: International opinion leader on acupuncture and placebo responses),
- Patient representative and a public involvement representative: Deborah Gilbert, Bowel & Cancer Research Charity Secretary
- Representatives of the Trial Sponsor and the Trial Funder will be invited to all TSC meetings.

A Trial Management Group (TMG) will be responsible for day to day project delivery in each participating centre. It will meet monthly and include the local lead, study nursing leads and relevant research staff. This group will answer to the TSC.

At Barts and the London NHS Trust, the TMG consists of:

- Charles Knowles – Chief Investigator
- Emma Horrocks – Academic Clinical Fellow
- Natasha Stevens – Trial Manager
- Stephen Bremner – Trial Statistician

A data and safety monitoring committee (DSMC) will be appointed to monitor un-blinded comparative data and make recommendations to the TSC. The DSMC will meet together with the TSC for an initial meeting and subsequently two weeks prior to the TSC to enable any findings / recommendations to be fed to the TSC to whom they report.

The DSMC comprises:

- Independent lead: Professor Dion Morton, Professor of Surgery, University of Birmingham,
- Professor Elaine Denny: Professor of Health Sociology, University of Birmingham
- Dr Duolao Wang: Senior Lecturer in Medical Statistics, London School of Hygiene & Tropical Medicine, University of London

A DMEC charter will be adopted, and the project team should provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC and follow guidelines set out in the charter.

The trial manager, Ms Natasha Stevens, will monitor trial activity at each site. This will include keeping a record of trial recruitment to inform the trial management group who will monitor the recruitment rate at each site and implement procedures to increase recruitment or minimise withdrawals as required. The recruitment rates will be uploaded to UKCRN monthly as required. The trial manager will also keep a record of all serious adverse events for reporting to the DSMC, REC and the sponsor as required. The trial manager will also ensure that all site staff have been supplied with the current versions of all trial documentation and have sufficient training in trial related SOP's and arrange re-training where necessary. Each site will require site initiation and training prior to commencing the study.

The PCTU will train trial staff in PCTU Standard Operating Procedures (SOPs) as relevant to the trial, review and advise on all trial specific SOPs, set up a trial master file and carry out audits of the trial master file for ongoing quality assurance. They will also ensure compliance with GCP regulations and advise on staff GCP requirements, clinical trial regulatory requirements, adverse event reporting and pharmacovigilance, as well as delivering risk assessment and trial monitoring plans and advising on any other PCTU support available.

The study site will perform remote trial monitoring according to the agreed PCTU trial monitoring plan and self-monitoring template. The frequency and intensity will be determined by the PCTU monitoring plan and risk assessment. Trial monitoring will include source data verification checks on informed consent forms and eligibility for randomisation and a sample set of CRF's. The remote monitoring reports reviewed by the PCTU and all findings will be followed up and actioned as per trial monitoring plan

The PCTU will perform regular 6 monthly audits and will also carry out triggered audits as determined by risk assessment or through findings identified via the remote monitoring reports. In addition, the sponsor may also carry out an audit throughout the duration of the trial.

Project Timetable

A Gantt chart of the project is shown in figure 4. We propose a total study duration of 24 months. Our proposed study milestones (also on chart) will be:

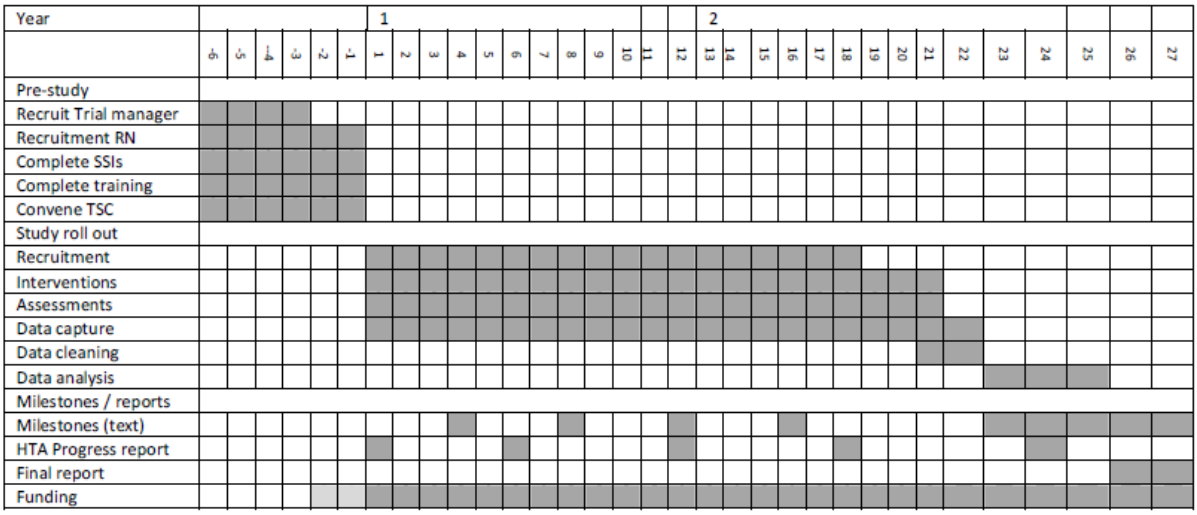
End month -3: Appoint trial manager
End month -1: Completion of all SSIs, staff recruitment and training. Data systems in place
Start month 1: First recruitment and baseline assessments
End month 1: Start first study intervention
End month 4: End first study intervention
End month 18: Last study recruitment

End month 21: Last study intervention
End month 21: Last study assessment
End month 25: Finish data analysis
End month 27: Submit final study report

Recruitment rates

It is essential to meet recruitment targets. Recruitment rates will monitored by the Trial Manager, and assessed at the end of months 4, 8, 12 and 16. Targets of 48, 96, 144 and 192 participants respectively, based on a mean recruitment rate of 12 per month, are expected. If we are failing to meet these recruitment targets as the study progresses, we will recruit further centres from those on the 'reserve list'. All centres will of course have to pass the criteria for inclusion with appropriate training.

Figure 4: Gantt Chart of study



Publication plan

Following completion of the study, the authors will use all reasonable endeavours to ensure the appropriate publication or other dissemination of the conclusions of the study.

The authors plan to submit this pivotal level I trial for publication in The Lancet circa Feb 2014. Authorship will be limited to the core trial personnel and two researchers per site, who have contributed significantly at all stages in the trial, who will be included as 'The CONFIDeNT Trial Group' and named individually.

Other sites shall not publish or otherwise disseminate the conclusions of the study, including all or any part of the results of the study without the prior written consent of the Chief Investigator and Sponsor, such consent not to be unreasonably withheld or delayed.

Any publication or other dissemination of the conclusions of the study by any of the other sites shall not occur until the lead site has published the conclusions of the study.

Funder

The project will be funded by the National Institute for Health Research Health Technology Assessment Programme – 09/104/16

Conflict of Interest

This project is independently funded by the NIHR HTA Programme. There are no conflicts of interest regarding the protocol of this study and its potential implications.

Appendix 1: Study Centre Codes

Aintree University Hospitals NHS Foundation Trust	ANT
Barts and the London NHS Trust	BLT
United Hospitals Bristol NHS Foundation Trust - Bristol Royal Infirmary	BRI
University Hospital of North Durham	CDD
Hull and East Yorkshire Hospitals NHS Trust - Castle Hill Hospital	CHH
Homerton University NHS Foundation Trust	HNT
South London Healthcare NHS Trust - Queen Elizabeth Hospital, Woolwich	QEH
Nottingham University Hospitals NHS Trust - Queen's Medical Centre	QMC
St Marks Hospital, Northwick Park	SMH
Salford Royal NHS Foundation Trust, Manchester	SRH
Sheffield Teaching Hospitals NHS Foundation Trust	STH
Sandwell and West Birmingham NHS Trust	SWB
University College London Hospitals	UCL
University Hospitals of Leicester - Leicester General Infirmary	LGI
University Hospital Southampton NHS Foundation Trust	SOT
Whipps Cross University Hospital, London	WCU
University Hospital of South Manchester, Wythenshawe Hospital	USM
University Lincolnshire Hospital Trust - Pilgrim Hospital	ULH
Glan Clywd Hospital, Rhyl	GCH
Guy's and St Thomas' Hospital NHS Trust	GST
Leeds Teaching Hospitals NHS Trust - Leeds Royal Infirmary	LRI
Mid Yorkshire Hospitals NHS Trust	MYH
Northern Lincolnshire & Goole Hospitals NHS Trust	NLG
Rotherham Hospital NHS Foundation Trust	RHT
The Royal Liverpool and Broadgreen University Hospitals NHS Trust	RLU
Taunton & Somerset NHS Trust	TST
Poole NHS Foundation Trust	PHT

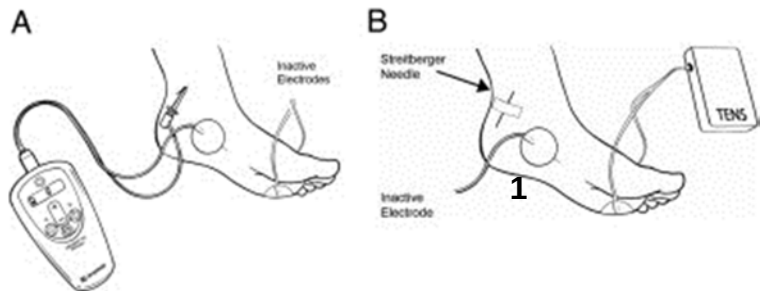
Appendix 2: Standardised PTNS and Sham

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

Standardised PTNS and Sham

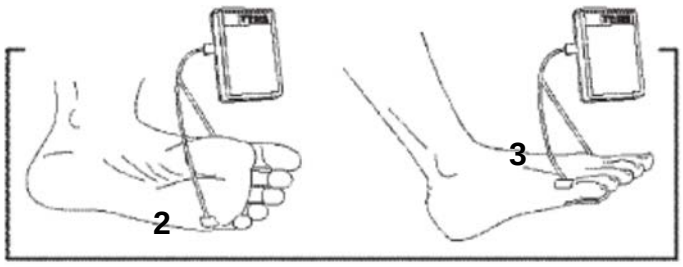
EQUIPMENT SET UP

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 fell 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 of 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 you will be asked when you can first feel an electrical sensation in your ankle or foot. 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."

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Chief Investigator Signature page

PROTOCOL DOCUMENT

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

The clinical study as detailed within this research protocol **(Version 11, dated 16th July 2012)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name:

Chief Investigator Site:

Signature and Date:

Statistician Signature page

PROTOCOL DOCUMENT

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

The clinical study as detailed within this research protocol **(Version 11, dated 16th July 2012)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Statistician Name:

Statistician Site:

Signature and Date:

Principle Investigator Signature page

PROTOCOL DOCUMENT

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

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Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

Addendum to Protocol: Inclusion of 1 year follow-up study.

Rationale

The aim of the CONFIDeNT Study is to ascertain efficacy of PTNS vs sham stimulation in patients with faecal incontinence. This study is pivotal in developing the most effective treatment protocol for patients with FI. It does not however examine the long-term effectiveness of PTNS, which could be easily ascertained with a further observational follow-up study. Upon completion of the CONFIDeNT Study, following up both PTNS and sham patients for 1 year would provide useful data regarding 'disease-free survival', requirement and timing of top-up treatments, effects on quality of life, acceptability of PTNS and health economic analysis.

Aims

This 1-year observational study will follow up all CONFIDeNT Trial participants to inform about long-term effectiveness of PTNS treatment and requirement for 'top-up' treatments. It will also inform regarding the outcome of sham patients. All participants would be contacted at 6 months and 1 year after their final PTNS or sham treatment. Further, participants who had successful PTNS treatment will contact their CONFIDeNT centre if and when they perceive loss of efficacy, and time to this loss of efficacy will be documented.

Design

All participants who completed the CONFIDeNT Trial will be followed up by the lead centre, Queen Mary University London, at 6 months and 1 year following PTNS or sham treatment by post/email and telephone. Follow up will consist of questionnaire data and bowel diaries.

The bowel diary will be that used in the CONFIDeNT Study. The questionnaire is entitled the 'CONFIDeNT Study follow-up Questionnaire, and includes the Cleveland Clinic Faecal Incontinence Score and the EQ-5D questionnaire.

In addition, patients will be able to contact their local centre in the intervening time if they perceive loss of efficacy of successful PTNS or sham treatment. At this time, length of efficacy of treatment will be recorded for each patient. Patients are free to have further 'top-up' PTNS sessions or any other treatment for FI during this study.

Eligible participants

All participants who complete the CONFIDeNT Trial will be eligible for inclusion into the follow-up study.

Events

Visit 13 CONFIDeNT Study: Participants will be invited be involved in the follow-up study and given a Participant Information Sheet at this visit if interested.

Visit 14 CONFIDeNT Study: At Visit 14, two weeks later, a member of the local team (trained in informed consent) will answer any outstanding questions and thence ask participants to sign the study consent form. The local study team member will then re-confirm the participants contact details, and register the participant on the enrolment log for the follow-up study. Each participant will give consent for his or her contact details to be securely passed on to the lead centre where the follow-up study will be co-ordinated.

After CONFIDeNT Study Visit 14: Contact details of those participants enrolled on the follow-up study will be passed on to the lead centre in the same way as for the CONFIDeNT Study as detailed above 'All trial data will be collected from each participating site either in person by the Academic Clinical Fellow in a locked bag, or sent by special courier, and transported back to the Lead Centre, Barts and the London NHS Trust'.

6-months following CONFIDeNT Study completion: Participants will be contacted by telephone to confirm that 6 months have passed since completion of the study. They will be asked how they wish to complete the follow-up questionnaires; either by telephone interview with the Academic Clinical Fellow, via email or by post. Questionnaires and a 2 week bowel diary will be completed appropriately and collated at the Lead Centre.

12-months following CONFIDeNT Study completion: Participants will be again contacted by telephone to confirm that 1 year has passed since completion of the study. They will be asked how they wish to complete the follow-up questionnaires; either by telephone interview with the Academic Clinical Fellow, via email or by post. Questionnaires and a 2 week bowel diary will be completed appropriately and collated at the Lead Centre. Involvement in the study will then cease.

At any time following enrolment in Follow-up Study: Patients who perceive a deterioration in the efficacy of successful PTNS will contact their local study centre for follow-up. The time to this deterioration will be documented in each study centre.

Loss to follow-up

Three attempts will be made to contact each participant at 6-months and 1-year by telephone and post/email. If these are unsuccessful, the patients will be presumed lost to follow-up.

Withdrawal from study

If participants wish to withdraw from this follow-up study, they will be free to do so at any time without giving a reason.

Trial outcomes

The pragmatic primary outcome of this 1 year observational follow-up study is continued efficacy i.e. a binary outcome of whether PTNS (or sham) has continued perceived efficacy by the patient, or not.

The following secondary outcomes will be studied:

1. Requirement and timing of PTNS 'top-up' treatments
2. Requirement for other treatments or surgery for FI
3. Acceptability of PTNS treatment
4. Effect on FI measures and quality of life
5. Formal assessment of health utilisation

Plan of statistical analysis

The primary outcome will take the form of binary category (on-going success or failure of treatment) vs. time. Secondary outcomes include counts (change in number of FI episodes), ordinal (patient's global impression of success) and continuous (Wexner score, EQ-5D) data. Appropriate analytical methods will be used to compare PTNS to sham and gain a measure of disease-free post-treatment survival (time series, censored for loss of follow up) and cost effectiveness over time (using EQ-5D).

Analysis will be performed using proprietary software (Stata version 10.1, Stata Corp. Texas) by the study statistician. $P < 0.05$ will be taken to indicate statistical significance.

Project timetable

We propose a total study duration of 24 months. Our proposed study milestones will be:

September 2012:	Recruit first patient to CONFIDeNT follow up study
August 2013:	Last patient recruited to CONFIDeNT Study
October 2013:	Last patient recruited to follow-up study
October 2014:	Last follow up from CONFIDeNT follow up study.

Funding

Full funding has been secured for this study from Uroplasty Ltd.