Full Title: 14/144/08: RANDOMISED DOUBLE-BLIND EFFICACY AND MECHANISM STUDY OF SUB-SENSORY SACRAL (OPTIMISED) NEUROMODULATION IN ADULTS WITH FAECAL INCONTINENCE

Short Title/Acronym	SUBsensory Sacral Neuromodulation for InContinence - SUBSoNIC
Sponsor	Queen Mary, University of London

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UK Sites

- Barts Health NHS Trust (Knowles)
- Sandwell and West Birmingham NHS Trust (Gill; George)
- University Hospital Birmingham NHS Trust (Bagul)
- University College Hospitals NHS Foundation Trust (Emmanuel)
- University Hospital Southampton NHS Foundation Trust (Dudding)
- University Hospital of South Manchester NHS Foundation Trust (Telford)
- Manchester University NHS Foundation Trust, Manchester Royal Infirmary (Curran)
- Cambridge University Hospitals NHS Foundation Trust (Powar)
- NHS Lothian, Western General Hospital, Edinburgh (Collie)
- University Hospitals of Leicester NHS Trust (Miller; Ho)
- Plymouth Hospitals NHS Trust (Lai; Oppong)
- Ashford and St Peter's NHS Trust (Nisar; Thomas)
- University Hospitals of North Midlands NHS Trust [Farmer]
- St Marks Hospital at The North West Hospitals NHS Trust (Vaizey)
- Sheffield Teaching Hospitals NHS Foundation Trust (Kelly)
- Wingate Institute, Queen Mary University of London (Scott)
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European Sites

- St Vincent's Hospital, Dublin (O'Connell; Hanly)
- University of Erlangen, Germany (Matzel)

Contents

1 GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
EC	European Commission
EQ-5D-5L	EuroQol Health Outcome Measure
FI	Faecal Incontinence
FI QoL	Faecal Incontinence Quality of Life Score
HRA	Health Research Authority
ICF	Informed Consent Form
JRMO	Joint Research Management Office
LPLV	Last Patient Last Visit
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
NICE	The National Institute for Clinical Excellence
OAB Q	Assessment of OverActive Bladder symptoms
PCTU	Pragmatic Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PPIG	Patient and Public Involvement Group
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research & Development
SAE	Serious Adverse Event
SDV	Source Document Verification

SF-ICQ-B	International Consultation on Incontinence Bowel Questionnaire
SIV	Site Initiation Visit
SNM	Sacral Neuromodulation
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSAR	Transient Anal Sphincter Relaxations
TSC	Trial Steering Committee

2 SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 8, dated 12 Nov 2020)**, 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), ICH Good Clinical Practice Guidelines (1996) and the current applicable local regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Prof Charles Knowles

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:

05/01/2021

Statistician Agreement Page (as applicable)

The clinical study as detailed within this research protocol (Version 8, dated 12 Nov 2020), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current local regulatory requirements.

Statistician Name: **Richard Hooper**

Signature and Date:

05/01/2021

Principal Investigator Agreement *(if different from Chief investigator)*

The clinical study as detailed within this research protocol **(Version 8, dated 12 Nov 2020)**, 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), ICH Good Clinical Practice Guidelines (1996) and the current applicable local regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

3 SUMMARY/SYNOPSIS

Short Title	SUBsensory Sacral Neuromodulation for InContinence (*SUBSoNIC)*
Methodology	Randomised double-blind crossover trial of sub-sensory sacral neuromodulation (SNM) and cohort follow up
Research Sites	NHS Trusts in U.K. and selected European sites with surgical expertise in SNM, and trial oversight by Pragmatic Clinical Trials Unit, Queen Mary, University of London
Objectives/Aims	*Primary Clinical Objectives* To determine clinical efficacy of sub-sensory sacral neuromodulation (SNM) compared to sham *Secondary Clinical Objectives* • To obtain 1 year clinical outcomes of SNM using 2016 optimised therapy (with standardised lead placement). • Validate a new electronic outcome measures and a device to record them. • To improve knowledge of the kinetics of effects of SNM *Mechanistic Objectives* • To identify the biological effect of sub-sensory SNM on underlying anorectal afferent neuronal pathophysiology. • To improve the general understanding of the pathophysiology of FI
Number of Participants/Patients	N = 90 (1:1 allocation ratio) Group 1 (45): SNM/SHAM Group 2 (45): SHAM/SNM Randomised to two equal arms after SNM implantation. Both arms will receive 16 weeks with stimulator set to sub-sensory level (SNM) (T0-T16 or T16-T32) and 16 weeks with stimulator set to zero volts (SHAM)(T16-T32 or T0-T16). All patients will then be followed up to the 1 year time-point (T32-T58) with stimulators set to patient decisive stimulation level (supra- or sub-sensory) (open label).
Main Inclusion Criteria	Adults aged between 18-80 meeting Rome III and ICI definitions of FI (recurrent involuntary loss of faecal material that is a social or hygienic problem and not a consequence of an acute diarrhoeal illness), have failed non-surgical treatments to the NICE standard with minimum severity criteria of 8 FI or faecal urgency episodes without incontinence (a minimum of 4 FI episodes is required) in a 4 week screening period and clinically suitable for SNM.
Statistical Methodology and Analysis (if applicable)	*Primary clinical outcome*: • Frequency of FI episodes per unit time using a paper diary (based on 4 weeks reporting) *Secondary clinical outcomes* • Panel of validated FI clinical instruments • Digital real-time event recording and novel outcomes *Mechanistic outcomes* • Advanced anorectal physiology • Anocortical neurophysiology *Procedural data*

	• Electrode placement and settings, • sensory and motor thresholds
Proposed Start Date	01.09.2017
Proposed End Date	31.11.2021
Study Duration	51 Months

4 INTRODUCTION

4.1 Background

Faecal incontinence (FI) is defined as the recurrent involuntary loss of faecal material leading to a social or hygienic problem (International Consultation on Incontinence: ICI)[1] and not related to an acute diarrhoeal illness (Rome III). While variations exist regarding prevalence due to differences in survey methods, screening questions, reference timeframe, definition and population studied, few could argue that FI is not a substantial health problem. Population studies suggest prevalence ranging from 3-15% in community-dwelling women, 15% in community dwelling older people, 18-33% in hospitals, 38% in home health, and up to 50-70% in nursing homes[2]. A clear relationship with advancing age suggests that it will remain a problem within the developing Western population demographic[2].

FI leads to substantive effects on quality of life in terms of physical and emotional health; to stigmatization and social isolation; and in older people, admission to residential care. Societal costs incurred by lost work productivity and absenteeism can be added to significant direct and indirect medical costs attributable to drug and pad usage, to specialist care, and particularly to nursing costs in older patients. Such estimates probably under-reflect the full impact of FI due to under-reporting[3]. It is estimated that treatment of urinary and FI account for at least 2% of the total UK healthcare budget[4].

Initial treatments of FI include pharmacological and behavioural therapies, the latter generally incorporating some form of biofeedback. Whilst anecdotally these treatments appear to improve continence in a significant number of patients there is little high quality evidence to support this[5]. Traditionally surgical treatments focusing on anal sphincter function are offered when conservative measures fail. These can be classified into reconstructive (sphincteroplasty), augmentation (bulking agents) and neosphincter procedures (artificial sphincters, graciloplasty). These procedures are invasive, irreversible, and balance variable success rates against some risk of significant morbidity. A stoma is the final option.

Neuromodulation is one of the fastest growing areas of medicine: technologies now address diverse disease areas including epilepsy, Parkinson's disease and tremor, chronic pain and deafness. The application of neuromodulation to the problem of FI has significantly changed the treatment paradigm for many patients over the past 20 years. Chronic stimulation of the sacral nerve roots using an implanted electrode and generator – sacral neuromodulation (SNM) is now considered the first-line surgical treatment option for the majority of adults with FI in whom non-operative therapies have failed to alleviate symptoms (NICE 2007[4]) especially as it is the least invasive procedure. However, despite having regulatory approval from the NICE and the U.S. Food and Drug Administration (FDA), SNM remains an expensive intervention with a limited high quality evidence base for either mechanism of action or efficacy.

<u>Evidence of SNM efficacy</u>

Numerous observational studies [systematically reviewed by the applicants in 2013][6] show that SNM leads to a substantial health gain for adults with FI with low levels of operative morbidity compared to alternative surgical strategies. Reduced FI episodes correlate with objective QoL improvements[7] and SNM has been shown to be cost effective with an ICER of

£25,070 per QALY lying within the threshold recommended by the NICE as an effective use of NHS resources[7]. This systematic review however also highlighted the generally poor methodological quality of included studies which were almost universally single centre retrospective or prospective clinical case series with unblinded observers and failure to report outcomes on an intention to treat basis. The latter point is especially important since significant attrition bias undermines nearly all studies even including the higher quality pivotal trial for FDA approval (a prospective multi-centre US case series of 120 patients[8, 9]). Two independent recent publications from Europe that have reported large patient series using the ITT principle have shown less encouraging results (circa 45% long-term success)[10, 11].

The lead applicant has recently reviewed available randomised trial data for SNM in FI[12]. A total of 6 included studies comprised 4 crossover designs and two parallel group RCTs. One crossover included only 2 patients[13]; a further study published only in abstract form reported mainly mechanistic outcomes in only 7 patients[14]. The remaining two crossover studies included the widely cited study by Leroi *et al*.[15], which enrolled 34 patients pre-selected on the basis of a successful prior SNM implantation. Only 27 participated in the crossover and only 24 completed the study (10 excluded patients included 4 explantations due to adverse events and others due to lack of efficacy or protocol violations). Although the majority (18 / 24) of analysed patients preferred 'ON' vs. 'OFF' at the end of study, the study failed to show a clinically meaningful reduction of symptoms between ON and OFF periods e.g. difference in median FI episodes per week of only one episode. This was suggested to result in part from a short washout period (1 week) and a carry-over effect. A second very recently published crossover study[16] employed an identical trial design but with smaller numbers of patients, randomising only 16 of 31 preselected implanted patients and thence only for two 3 week crossover periods. In contrast to the earlier study, significant decreases in FI episodes and summative symptom scores were observed in the ON vs. OFF periods despite having no washout. In an unblinded RCT by Tjandra and colleagues[17] 53 participants with severe faecal incontinence in the SNM group experienced fewer episodes of faecal incontinence compared to the control group who received optimal medical therapy (MD -5.20, 95% CI -9.15 to -1.25 at 3 months; MD -6.30, 95% CI -10.34 to -2.26 at 12 months). The recently published (by the applicants) NIHR-funded observer-blinded RCT of SNM vs. a less invasive form of neuromodulation: percutaneous tibial nerve stimulation (PTNS)[18] demonstrated a within group effect size that was greater for SNM than PTNS. While pilot in design and with small numbers (n = 40 total), this effect was modest compared to most observational case series.

Evidence of SNM mechanism

Traditional understanding of the pathophysiology and surgical management of FI held that sphincter 'barrier' had primacy. It is now clear that whilst sphincter disruption is still relevant to the development of FI in many patients e.g. obstetric injuries, it is only one factor in complex defaecatory dysfunction that involves alteration in unconscious anorectal and pelvic reflexes and conscious modulation by the central nervous system (CNS). SNM was developed for FI with the view that it would augment defective sphincteric function[19]. It is now well appreciated that patients with FI resulting from pathophysiology other than primary sphincter dysfunction also benefit from treatment[20]. The importance of sensory dysfunction on both urinary and bowel control is being increasingly appreciated and there is strong evolving evidence (including our own pilot data in humans and experimental animals [covered in specific study rationale below]) that the mechanism of action of SNM results primarily from modulation of afferent nerve activity.

Implications for current study proposal

Pulling the above evidence together it is clear that the clinical efficacy of SNM has never been rigorously determined in a trial setting. There is therefore a need for a well-designed study of SNM that seeks to determine definitive proof of clinical effect size and which notably improves on the small number of existing randomised studies and observational data. Such a study has the opportunity to embed a hypothesis-led mechanistic study.

Clinical relevance and impact

SNM is the pre-eminent therapy for bladder and bowel indications and has already impacted on patients, carers and the NHS. However UK and global uptake is actually small compared to the magnitude of clinical need (currently approx. 1 / 1000 adults with FI have received SNM in the USA). Barriers to greater adoption include cost and continued physician uncertainty regarding efficacy. Upfront device costs of approx. £9,000 must be added to the need for specialist service development to monitor, re-programme and replace devices[21]. It is estimated that half the total costs of implementing NICE 2007 FI guidelines can be attributed to adoption of SNM[4].

The reported benefits of SNM (and regulatory approvals: NICE & FDA) have been based on observational data (see above). Further, NICE technology guidance (IPG99) was based on a few early small case series which employed a now redundant open surgical technique to implant the electrode. The current percutaneous approach has reduced the morbidity rate but may have worse therapeutic outcomes. SNM is thus an example of a new technology introduced into clinical practice without objective and rigorous evaluation of efficacy due to factors such as intrinsic clinical appeal in a market devoid at the time of much competition. We maintain that while trial evidence at this late stage may be insufficient to curtail the dominance of SNM, it is still important, not least for the comparison with numerous other technologies at earlier stages of market penetration that are subject to the 'stop them starting' rather than 'start them stopping' mantra. In an austere era when health providers must increasingly justify the use of high value devices, key clinical opinion leaders acknowledge the need to now 'go back' and produce the evidence that will be required to expand, maintain or refute the central position of SNM in the paradigm of FI specialist management.

Timeliness

The proposed study is timely because: (1) NICE is due to reconvene in 2018 to revise the guidelines for SNM and its role in the treatment of FI: last 2007[4]; (2) SNM therapy has undergone significant optimisation in 2014-2016. The CI (Knowles) has been instrumental in this process that involves improved technology and improved procedural steps. The outcomes of this 'optimised' SNM for FI have not yet been studies in any trial; (3) the planned research will generate important knowledge regarding mechanism of action. This has potential to aid patient selection, technology and procedural optimization that could focus therapy, improve outcomes and reduce healthcare costs. The findings will also lead to a substantial advance in scientific knowledge and understanding of fundamental biological mechanisms of FI in humans. Embedded technology developments for continuously recording time-indexed symptom episodes and other novel outcome measures also represent an innovation in their own right.

Medtronic engages in continuously increasing evidence on its neuromodulation therapies and is supportive of this study.

4.2 Specific rationale

4.2.1 Double blind efficacy study

A double-blind randomised crossover design is appropriate to experimentally assess clinical effect size and to study mechanism. The crossover will compare sub-sensory chronic sacral root stimulation against sham stimulation with the well-acknowledged advantage of statistical efficiency. It is however also acknowledged that such a study MUST improve on the previous 4 attempts at crossover studies to provide useful efficacy data. The proposed design will address the main criticisms of previous studies:

1. Adequate intervention periods to adequately assess response. We will have two 16 week periods (SNM and SHAM) in comparison with previous studies (maximum 1 month[15])
2. Adequate washout period and reduced risk of carryover effects. While the duration of carry over effects of SNM is unknown, the current study design allows for almost 3 months washout before outcomes are assessed, compared to a maximum in previous studies of 1 week[15]. Clinical experience suggests that this duration is adequate but we will nevertheless continuously monitor the kinetics of therapy and washout throughout the study using the newly developed e-recording tools.
3. Adequate statistical power, we propose a completed crossover of 80 patients compared to previous maximum of 24[15]
4. Reduced selection bias. Although the crossover design does not permit full adherence to an intent to treat principle i.e. from start of trial therapy with test stimulation, we will randomise all newly implanted patients rather than patients who have already been selected on the basis of successful chronic therapy. Selected patients will thus be naïve to chronic stimulation and ALL consenting implanted patients will be randomised.
5. Reduced attrition bias. We will continue assessments on all participants provided the patient has not withdrawn consent. Patients who become unblinded to intervention would not however contribute data to analysis.
6. Improved patient blinding. We will use the experience gained from the Durham-based NIHR RfPB TiLTS-CC study (Knowles co-applicant) to maintain blinding.
7. Improved assessment methods [e.g. Diaries are collected for a longer period. As well as a paper diary an electronic simple touch screen device will also be trialled]

We do however accept that the choice of design has some limitations:

1. Although it is acknowledged that a small proportion of patients prefer supra-sensory stimulation (about 10% in our clinical practice), especially in the short term, for double-blinding it is clearly necessary to mandate sub-sensory stimulation and we acknowledge that this is in effect an experimental variant of the therapy used in 'real life'. We will however comply with routine clinical practice by having a reprogramming session at 6 weeks in each arm regardless of intervention status i.e. in the SHAM arm this will be a 'pseudo-reprogramming' event. For the FI indication, a recent randomised observer-blinded comparison showed no difference in effects of supra and sub-sensory stimulation[22] building on a small study that showed that therapeutic response threshold was significantly lower than sensitivity threshold[23]. However we acknowledge that some differences in physiological results have been recorded for sub- and supra-sensory stimulation in the patients with slow-transit constipation[24] and this is acknowledged in the study title.

2. We acknowledge that it is difficult (and labour intensive) to blind patients to SNM in crossover designs particularly for patients who receive the intervention first and then have it switched OFF. This proved a problem in a recent study of irritable bowel syndrome[25] in which 75% patients correctly identified that the stimulator was ON or OFF across all crossover phases. This noted, previous crossover studies of FI (accepting limitations in published documentation) have successfully blinded participants. This remains a risk for any placebo-controlled intervention where the number needed to treat is relatively small i.e. the majority of patients can identify their stimulation status by the effect it has on their symptoms. This noted, the effect size of SNM vs sham remains uncertain (a reason for performing the study).
3. The study does not address the long-term clinical effectiveness, cost-effectiveness and safety of SNM.

4.2.2 Cohort follow up study

The primary study (double blind cross-over) will provide a robust estimate of experimental efficacy. The cohort of thus recruited patients however also provide an opportunity to study the outcome at a later time point with patient decisive stimulation (sub- or supra-sensory) as would be normal for routine clinical practice. On this basis, patients will be followed up for a further 6 months to a total therefore of just over one year post implant (2 x 16 + 26 = 58) and outcomes recorded between 54-58 weeks (+/- 1 week). Such data will provide the first estimate of the outcome of optimised lead placement[26] in adults with FI and also do so with the scientific rigor mandated by a prospective randomised study managed by a CTU (even if the intervention by this stage is 'open label'). It is acknowledged that patients will only have actually had 36 weeks of stimulation (continuous or discontinuous depending on crossover sequence) however published data indicate that outcomes at 6 months are almost identical to those at later time-points[8] (accepting data censorship in some cohort studies).

4.2.3 Mechanistic study

With new technologies emerging, stratification of therapy for patients with FI will become increasingly important to direct the right treatment to the right patient. In the absence of proof of mechanism or biomarkers of therapeutic success, provision of SNM is currently based on severity metrics and failure of conservative treatments (NICE 2007). There is international unanimity (expert panels including applicants: Brussels March 2014 and Geneva May 2014) that SNM mechanistic studies are now a research priority. New knowledge makes this possible: (1) published and pilot data from the applicants in rodents[27] and human[28, 29] indicate the central role of afferent neuronal dysfunction in the pathophysiology of FI and its modulation by SNM (supported by more developed data from the urology field[30]); (2) technological developments for which the applicants have been pioneers[31, 32].

<u>4.2.3.1 Pilot data: anorectal function</u>

Although acute sphincteric motor responses are recorded during implantation, chronic SNM has no consistent effect on basic anal motor function (contractile force) but may modulate resting tone[22] and the afferent limb of local and spinal reflexes that participate in transient anal sphincter relaxations (TASRs) and thus sampling i.e. intermittent relaxation of the anal canal to discriminate rectal contents. Twenty-one healthy volunteers (HVs) and 10 patients with FI underwent prolonged high-resolution anorectal manometry (HRAM)[31]. The study was performed in the sitting position for 45 minutes pre- and post-consumption of a standardized meal (828kcal; 48g fat). Participants reported perception of gastrointestinal/anorectal sensations in real-time. TASRs were defined as an equalization of rectal and anal pressures involving ≥20% of the anal canal. In health, TASRs occurred more frequently following meal

consumption (median 3 [IQR 1–6] post-prandially vs. 0 [0–1] pre-prandially, P=0.01). Median TASR duration was 23 seconds [IQR: 19-27] and was temporally-associated with a 44% reduction in average anal canal pressure (65 mmHg [53–81] before vs. 36 [28-44] during; P=0.0001) accompanied by a 45% increase in rectal pressure (18 mmHg [15–23] before vs. 25 [19–33] during; P=0.001). TASR characteristics in the FI group were similar to those found in HV however these were very infrequent events (pre: median 0.0 [IQR 0-0] vs. post-prandially: median 0.5 [IQR 0-3]). TASRs were commonly perceived by HV (56% temporally associated with gastrointestinal/anorectal sensations, most commonly the urge to pass wind [74% perceived events]) however only a single TASR was perceived in the FI group. TASR frequency increased in all of 4 patients studied with prolonged HRAM before and after SNM (e.g. post-prandial: median 1 [IQR 0-1] to 3 [IQR 1-4] events).

FI patients have subjective disturbed call to stool which is rapidly restored after SNM[33]. Pilot studies using detailed viscerosensory bowel diaries confirm this clinical observation. At baseline, 30 FI patients had an abnormal quality, site and intensity of defaecatory urge compared to 44 healthy female controls. In a small number (n = 6) undergoing SNM, many of these variables normalized. These changes were accompanied in 4/6 patients by normalisation of anal electrical sensitivity which was abnormal in approx. 50% patients with FI at baseline [data at 1cm from anal verge: FI: n = 13: mean 9.1 (SD 4.3) vs. HV: n = 29: mean 4.6 (SD 1.9); P = 0.004]. In a separate RCT performed by the applicants taking patients with baseline blunted rectal sensation, SNM also largely normalized thresholds to volumetric distension[29]. These data have now been replicated by others[34] are in keeping with the observations on perception of TASRs.

4.2.3.2 Pilot data: anocortical function

The association between impaired recto-anal sensitivity and FI has been noted above. Our studies in an animal model of obstetric injury suggest neuronal injury is manifest as dysfunction in central somatosensory pathways[35, 36]. Acute SNM potentiated EPs in healthy rats[27, 37] while restoring previously inhibited evoked potentials (EPs) in injured animals [Evers NGM 2016] APPENDIX II: figure (1)]. In humans, anal evoked potentials (AEPs) were recorded in response to motor threshold stimulation with a bipolar electrode 1cm from the anal verge. Dual observer analysis of cortical recordings taken from Cz'-Fz and Cz-A1 channels showed that 26/30 (87%) healthy volunteers had recordable AEPs of excellent or good quality compared to only 1/13 (8%) of those with FI, p<0.001. Hierarchical regression demonstrated that FI, advancing age, female sex and parity were associated with poor AEP quality. Unlike the rodent model, acute (2 weeks temporary) SNM only restored inhibited AEPs in 1/8 patients with FI. This suggests that brain areas other than the primary somatosensory cortex may be recruited through compensatory plasticity underlying restoration of conscious anorectal sensory function or that this process requires more prolonged (chronic) therapy. The former point is supported by unpublished rodent data demonstrating a cortical layer change in the distribution of a molecular marker of synaptic plasticity [APPENDIX II: figure (2)]. The appearance of this marker in layer 2 of the cortex after SNM suggests that there is altered activity in ipsilateral cortical projection pathways (i.e. the processing area for anorectal function is now processed somewhere else distant, but ipsilateral to the primary sensory cortex).

Magnetoencephalography (MEG) is a non-invasive clinical tool which measures and maps the magnetic field mainly generated by neurons tangentially orientated to the skull. It has advantages over several other methods of functional neuroimaging for patients with SNM who for instance cannot undergo MRI assessment and has been extensively used by the

applicants[38, 39] to assess central pathways from the pharynx, a structure which has similar structure and function to the anus. Pharyngeal function can be restored following neural injury by brain plasticity occurring in motor and non-motor cortical regions in response to therapeutic neuromodulation and measured by functional brain imaging[32, 40, 41]. Changes in brainstem, thalamic and cortical activities have been observed in urological studies of SNM using several functional imaging modalities[42, 43] including at sub-sensory stimulation levels[44], but are unstudied in FI.

4.3 Risks / benefits

4.3.1 Study related risks

The study poses no major risk to participants above the standard risk of SNM therapy. SNM is an established therapy whose main attraction is non-invasiveness and safety compared to other surgical procedures. The small period (3 months) without active therapy imposed by the crossover design is not deemed 'harmful' for a chronic and stable condition by the time surgical intervention is considered.

Taking the average natural background radiation in the UK to be 2.3 mSv per annum, then an effective dose of 1.6 mSv for this study is approximately equal to eight months of natural background radiation exposure. X-ray examination involves exposure to ionising radiation and carries a risk of induction of excess cancers which may not be expressed for many years after exposure. Using the adult population lifetime risk coefficient of 5% per Sievert gives a lifetime risk of cancer of approximately 1 in 12,500. The Public Health England Radiation Protection Division describes risks of this magnitude as very low.

Some of the questionnaires contain personal questions about bowel problems and the effect of these on quality of life and psycho-behavioural functioning, however all have been used in studies of similar patients previously.

4.3.2 Mechanistic study related risks

4.3.2.1 Risks associated with MEG/MRI

For anocortical tests, the patient must be able to submit for a pre-study registration MRI, have a plug anal electrode inserted and sit in the MEG scanner for a total of about 45 minutes; the patient must attend 3 times. These tests are non-invasive and only confer mild discomfort due to insertion of anal catheter. No ionising radiation is employed by any tests.

4.3.2.2 Risks associated with anal manometry

For the anorectal tests, the main difference from routine clinical evaluation of anorectal function is the addition of prolonged high resolution anorectal manometry. This test is not performed routinely and has a longer duration than standard studies (about 110 minutes); the patient must attend twice. These tests are non-invasive and only confer mild discomfort due to insertion of anal catheter. No ionising radiation is employed by any tests.

4.3.3 Study Benefits

Participants will receive a high standard of surgery using the latest technical optimisation and monitored care as consequence of the protocol. All participants will receive SNM therapy due to the crossover design. Participation will add to the knowledge base for treating adults with FI. Reasonable travel expenses will be reimbursed.

4.3.4 Mechanistic benefits
Participation will add to the knowledge base for determining the pathophysiology of disease and treating sub-groups of adults with FI. Travel will be reimbursed and refreshments provided.

The risk benefit ratio of the proposed protocol design is considered acceptable to warrant trial participation and investigations.

5 TRIAL OBJECTIVES

5.1 Overall study aim

To determine clinical efficacy of sub-sensory chronic low voltage electrical sacral nerve-root stimulation: sacral neuromodulation (SNM) using a commercially-available implantable device, Medtronic Interstim ® in adults with FI failing conservative treatment.

The study combines clinical and mechanistic objectives.

5.2 Clinical objectives

Primary clinical objectives:

- To determine whether chronic sub-sensory SNM leads to a minimum clinically-relevant reduction in frequency of total FI episodes compared to sham stimulation?
    - *Hypothesis: SNM reduces frequency of total FI episodes by a mean of 30% compared to sham stimulation in the third month of chronic stimulation*.
- To determine the effect size of sub-sensory SNM on a range of clinical outcomes compared to sham stimulation?
    - *Hypothesis: sub-sensory SNM leads to significant and clinically-beneficial changes in a range of established and novel innovative outcome measures in the third month of chronic stimulation.*

Secondary clinical objectives: The study will generate important new knowledge by:

- Providing 12 month clinical outcome data for SNM using optimised therapy (standardised lead placement): cohort follow up study.
- Validating new electronically recorded outcome measures for future FI trials (and a new device to record them);
- Providing data on the kinetics of response and carryover effects;
- Providing data on predictive value of baseline characteristics and operative factors as covariates of response (especially on optimised lead placement);
- Increasing general understanding of the basic pathophysiology of FI in a well-characterised patient cohort.

5.3 Mechanistic objectives:

- To determine the effect of sub-sensory SNM on anorectal sensorimotor reflex function?
    - *Hypotheses: (a) SNM but not sham increases frequencies of fasting and fed perceived and unperceived transient anal sphincter relaxations (based on prolonged high resolution anorectal manometry recordings) to levels observed in healthy individuals; (b) SNM but not sham increases conscious sensation of defaecatory urge based on symptom reporting and objective measures of anorectal sensory function;*
- To determine the effect of SNM on ano-cortical afferent function?
    - *Hypothesis: SNM leads to brain plasticity (based on magnetoencephalography) in motor and non-motor cortical and sub-cortical regions.*

6 METHODOLOGY

6.1 Inclusion Criteria

- Adults aged 18-80.
- Meet Rome III and ICI definitions of FI (recurrent involuntary loss of faecal material that is a social or hygienic problem and not a consequence of an acute diarrhoeal illness).
- Failure of non-surgical treatments to the NICE standard[I]
- Minimum severity criteria of 8 FI or faecal urgency episodes (including a minimum of 4 FI episodes) in a 4 week screening period (this is important to exclude patients who might thence have zero FI episodes during baseline evaluations).
- Ability to understand written and spoken English or relevant language in European centres (due to questionnaire validity).
- Ability and willingness to give informed consent.

[I] Minimum NICE standard includes; diet, bowel habit and toilet access addressed. Medication e.g. loperamide, advice on incontinence products, pelvic floor muscle training, biofeedback and rectal irrigation should be offered if appropriate[4].

All patients will have been determined as clinically suitable for SNM based on clinical evaluation and subsequent multidisciplinary team discussion (as mandated by NHS England specialist commissioning guidance) or equivalent guidance in other participating EU countries.

6.2 Exclusion Criteria

A standard list of exclusions (disease variants; surgical fitness, specific contra-indications to implantation) will be used[18]. Note that these are routine clinical exclusions to the use of SNM rather than participation in the research. For completion:

- Known communication between the anal and vaginal tracts.
- Prior diagnosis of congenital anorectal malformations.

- Previous rectal surgery (rectopexy / resection) performed < 12 months ago (24 months for cancer).
- Present evidence of full thickness rectal prolapse or a high grade intussusception.
- Prior diagnosis of chronic inflammatory bowel diseases.
- Displays symptoms of chronic constipation with over-flow incontinence.
- Structural abnormality of the pelvic floor leading to clear evidence of obstructed defaecation based on examination and/or imaging.
- Presence of active perianal sepsis (including pilonidal sinus).
- Defunctioning loop or end stoma *in situ.*
- Diagnosed with neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease.
- Current or future need for MR imaging based on clinical history
- Complete or partial spinal cord injury.
- Bleeding disorders E.g. Haemophiliac, warfarin therapy.
- Pregnancy or intention to become pregnant during the study period.
- Not fit for preferred method of anaesthesia.
- Anatomical limitations that would prevent successful placement of an electrode including congenital abnormalities.
- Psychiatric or physical inability to comply with the study protocol (inc. e-diary assessments) at investigator discretion.
- Is required to drive for long periods of time for example lorry drivers, taxi drivers and delivery drivers.

6.3 Study Design

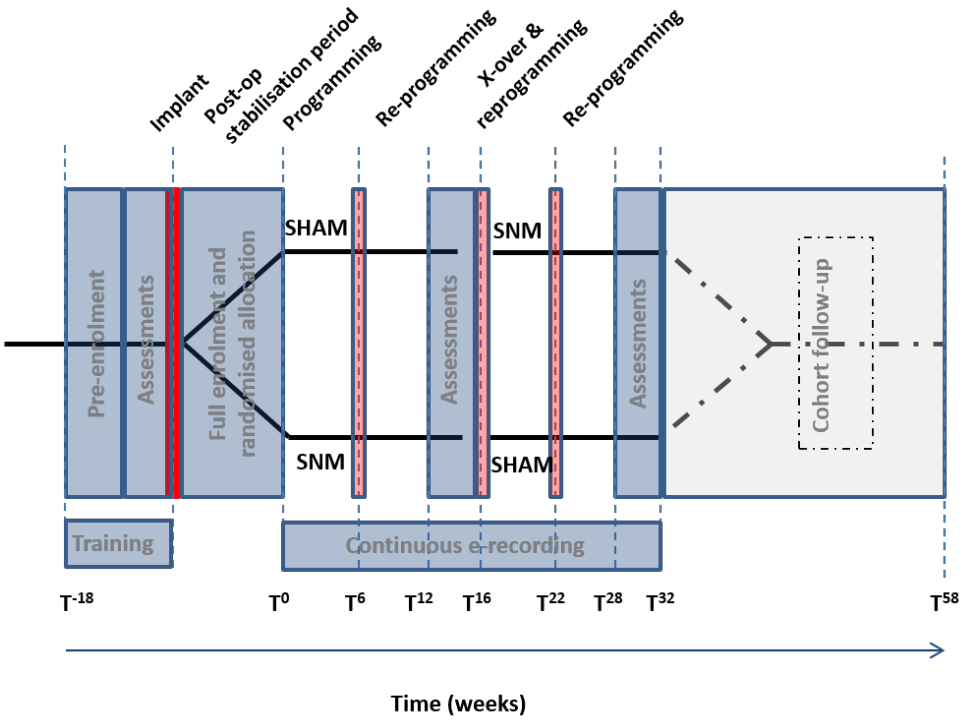
The overall design encompasses a randomised double-blind crossover trial and a follow up cohort study.

6.3.1 Randomised double-blind crossover design overview

Ninety eligible participants will be randomly allocated to two study arms after SNM implantation (see flow diagram below [Figure 1] and study scheme diagram [Figure 2]). Both arms have two intervention periods of 16 weeks duration (T0-T16 & T16-T32). Efficacy outcomes are derived from assessments in the final 4 weeks of each crossover period (T12-16 & T28-32) thus allowing for almost 3 months intervention before outcome assessments. A re-programming session will be conducted by the routine clinical care team at 6 weeks in both periods of both arms (T6, T22). Time-points will have an interval tolerance of +/- 1 week for logistical expedience.

Mechanism studies will be performed in a subgroup of consecutively consenting patients equally from both arms (to avoid risk of performance bias) until saturation (n = minimum 20; aim 25 for both anorectal and anocortical studies) in the final 2 weeks of 4 week assessment periods.

Figure 1: Flow Diagram

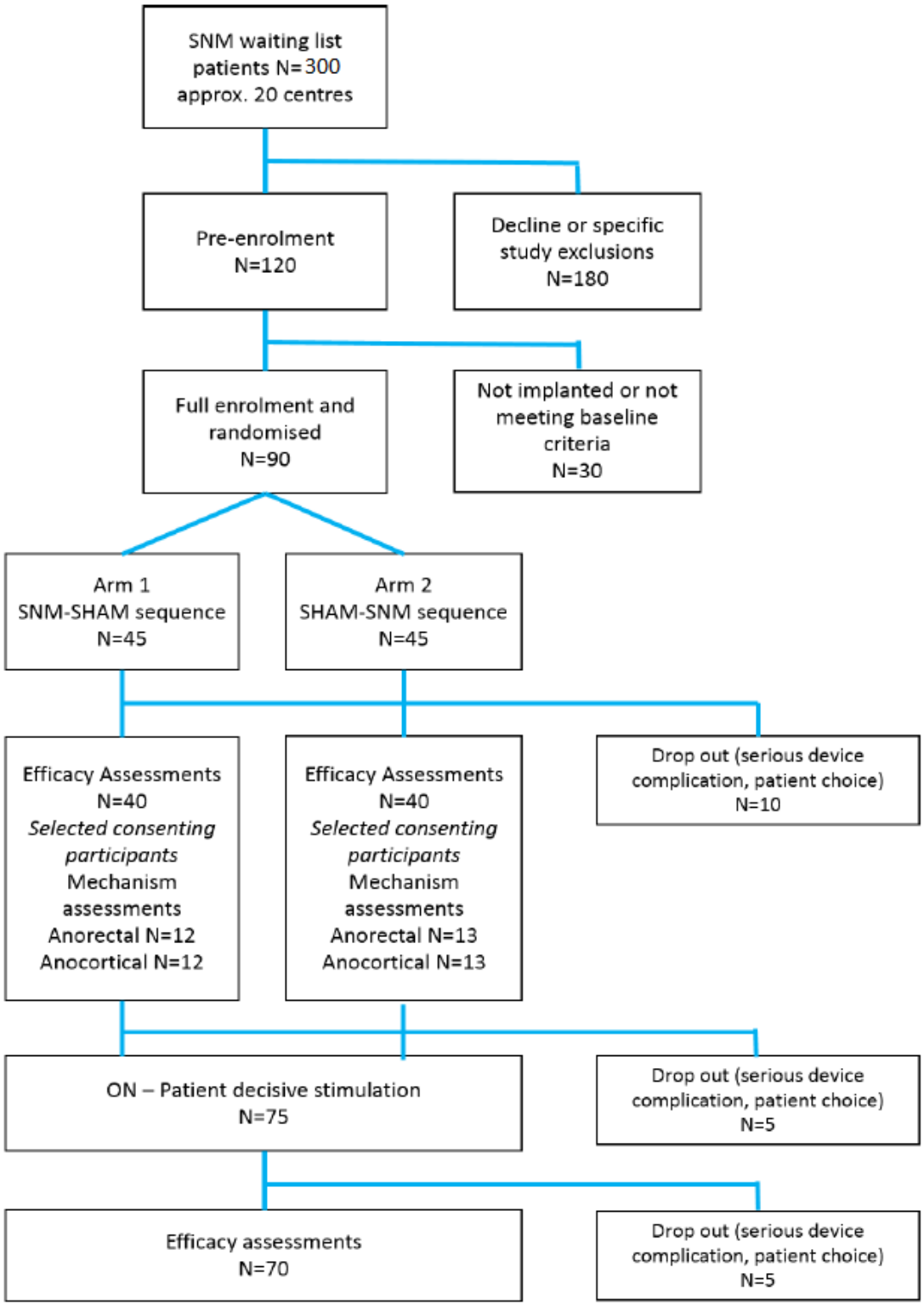


6.3.2 Cohort study: 12 month outcomes

After completing the crossover section of the study patients will continue to be followed up for a further 26 weeks (estimated N=75: allowing for dropouts). During this time, they will have 'open label' patient decisive stimulation (sub- or supra-sensory) as would be normal for routine clinical practice. Further efficacy outcomes will be recorded at T54-58. While it is accepted that these do not represent true 1-year outcomes (16 weeks has been SHAM treatment during the crossover), these will give an indication of the short-term effectiveness of SNM using the optimised lead placement and within the rigor of a CTU-monitored randomised prospective study.

6.3.3 Study Scheme Diagram

Figure 2



7 STUDY PROCEDURES

7.1 Recruitment & consent procedures

Patients will be consecutively assessed for broad eligibility (using the inclusion/exclusion criteria checklist) from the surgery waiting lists of participating centres and counselled in detail about the study prior to any surgery i.e. before test stimulation (pre-enrolment). Patients must have adequate time to consider the patient information sheets and study requirements before consent. Consent for enrolment will be conducted face to face in a private setting with an appropriately trained and delegated member of the clinical or research team. Patients will consent to the study (T-18: see figure 1/Table 1) up to 4 weeks prior to surgery.

7.2 Eligibility for randomization

Participants will not be eligible for full enrolment and randomisation until the baseline (pre-surgery) bowel diary has been assessed for minimum FI severity, and they have completed the temporary evaluation phase (having also met the minimum clinical response required to proceed to permanent implantation; as per NICE guidance). The conduct of the temporary evaluation can be performed in accord with local clinical practice. However, it is recommended that the manufacturer's instructions are followed in terms of evaluation durations: monopolar lead: 7 days and tined lead: 14 days.

7.3 Randomisation procedures

Group 1 (45): SNM/SHAM
Group 2 (45): SHAM/SNM

Randomised allocation (1:1) will be performed at the time of surgery using a computer-based programme developed by the PCTU and stratified by sex and centre with block sizes of 4. The inclusion of sex as a stratification factor is justified by the potential differences in pathophysiology in the small number of male patients with significant FI[45]. Patients will be randomised prior to knife to skin but on the operating table so they enter the study even if it is not possible to implant the stimulator. If there is any problem with the online randomisation system, randomisation can be delayed up until the initial programming giving a window of two weeks, alternatively emergency randomisation may be performed by an unblinded member of the coordinating team.

7.4 Blinding procedures

Research investigators and participants will be blinded to intervention status (SNM or SHAM). Patients will be informed of the allocation ratio of 1:1 and that blinding prevents them from knowing in which group they are participating (and therefore their order of intervention sequence). Patients will be issued with a patient programmer (InterStim iCon Patient Programmer Model 3037) with tamper-proof tape cut so as to obscure the stimulator setting but not obscure the on-off icon (which is in the top left-hand corner of the screen). This enables the patient to switch off the stimulator in an emergency e.g. unwanted neurological adverse events (the only emergency that would require this) and to permit driving (manufacturer's guidance recommends that the stimulator should be turned off for driving).

When the patient has completed their car journey they will simply reactivate the device which will return to the pre-set level (SNM or SHAM). This is a pragmatic consideration that is both necessary to complete the study (recruitment would be impossible if patients could not drive for the whole 32-week crossover period) and 'real-life'. There is published evidence that switching the device off for part of the day (even for long-periods) has no effect on efficacy over a chronic stimulation period [46-48]The settings on the device (to turn stimulation settings up or down) will not be accessible to the participants, having been disabled at the time of programming, in addition to the external buttons being covered with tamper-proof tape. The patient programmer power switch, neurostimulator synchronizaition switch and neurostimulator on/off switch will be accessible to the patient.

We will also compile a Trial Aid Card with their trial ID, emergency contact details and a list of symptoms where this card would be used. This card could then be shown to healthcare professionals looking after the patient if the stimulator settings require any other unplanned intervention.

The Model 8840 Clinician programmer is able to access log data of stimulation usage so there is potential to check all data on ON-OFF cycling during the study intervention periods if this is required to validate fidelity of the intervention (a bit like used blister packs to count unused drugs in a drug trial). During the SHAM period, the neurostimulator will be active but not be providing stimulation (current set to zeroV). Therefore, analysis of neurostimulator activity in the SNM and SHAM phases should be equivocal in percentage of neurostimulator "use" and un-blinding one participant would not compromise blinding for the remainder. The digital programming unit (N'Vision Clinician Programmer Model 8840) will not be supplied to the patient but can be used post-hoc to determine if the patient has changed settings or switched stimulation on or off during the study (the programmed settings will also have been recorded on a CRF by the unblinded clinical team member). The patient will not be removed from the study if the tamper-proof tape has been broken. This will be recorded for statistical analysis.

A nominated member of the research team or normal care clinician will have access to the programmer at the relevant fixed time-points for stimulator adjustment (crossover and 6 week reprogramming). This person who will not be blind to intervention status will not otherwise be involved in the research protocol e.g. outcomes assessments, collection of case report forms, data management.

7.5 Planned interventions

7.5.1 Sacral neuromodulation (SNM) (Medtronic Interstim ®)

The intervention is chronic low voltage stimulation of the third sacral root using surgical implantation of a commercially available CE-marked active implantable (class III) medical device (Medtronic Interstim ®) used in accord with manufacturer's instructions.

Patients meeting the mandated response using the monopolar temporary wire or quadripolar tined lead (lead choice and duration of testing based on local surgical practice) will undergo implantation of the permanent InterStim system under general or local anaesthesia (with sedation) by trained expert colorectal surgeons following the procedural steps developed by Siegel[26] (in brief: fluoroscopic-aided percutaneous insertion of 3889 lead using curved stylet and accepting position only when 3 of 4 electrodes provide low voltage (<3V) contraction of the anal sphincter and pelvic floor +/- big toe). The implantable pulse generator (3058;

Medtronic) will be placed as pre-marked in the ipsilateral buttock only if electrode responses meet the Siegel criteria.

The device will be activated as per local policy. This can be in the post-operative period the same day as surgery or after a surgical stabilisation period of up to 2 weeks (this is routine clinical practice in some centres).

General programming parameters will accord with a written algorithm based on best clinical practice. Prior to programming, an impedance check will be performed and recorded to ensure integrity of the electrical system. The clinical team will set the electrode configuration to achieve sensory threshold defined as the stimulation amplitude where the patient feels the first sensation of stimulation in the anus or perineum at 14Hz frequency, pulse width 210usec (ideally a perception of anal sphincter stimulation). To determine the amplitude necessary to elicit an anal sensation, the amplitude will be increased by 0.1 V from zero until the sensory threshold is reached[22]. The dominant electrode will be defined by initial mono-polar testing of each electrode noting the site of sensation and sensory threshold with each electrode used. The optimal electrode configuration will then be determined based on the programming algorithm. The amplitude required to elicit the sensory threshold with the optimal electrode configuration will be recorded.

The patient will continue with stimulation at sensory threshold for 5 minutes, and the process then repeated to identify the habituated sensory threshold. Sub-sensory chronic stimulation will then be performed at the level of the habituated sensory threshold[15] setting the device at this level. The maximum stimulation setting will be set at the habituated sensory threshold to ensure that an individual patient is unable to increase the amplitude of stimulation to above the sensory threshold and therefore determine whether they are receiving active stimulation or not.

At the 6 week time point after device activation, the patient will be re-assessed by the un-blinded research delegate or clinician. Changes in electrode configuration will be permitted if a patient is having sub-optimal efficacy or significant unwanted effects of stimulation. Any change in electrode configuration or site of sensation will be documented. The habituated sensory threshold will be re-calculated and stimulation thence returned to this level.

7.5.2 Sham stimulation

Device implantation and post-operative optimisation proceeds as above. The habituated sensory threshold is recorded identically however the device is then returned to zero volts and (device remains on but will provide no stimulation). At the 6 week time point after device implantation, the patient is re-assessed for sub-optimal efficacy (anticipated in the majority if the fundamental hypothesis is correct) by the un-blinded research delegate or clinician. To maintain blinding, an identical procedure is followed as above i.e. re-evaluation of sensory threshold and electrode configurations but this is followed by returning the stimulator to zero volts.

7.6 Procedures for mechanistic studies (subgroup of patients)

Because mechanistic studies involve quite burdensome studies and because anocortical (MEG) studies can only be performed at the Wellcome Trust Laboratory for MEG studies, Aston Brain Centre by highly experienced investigators (Furlong, Hamdy), two separate

cohorts of patients will be recruited and separately consented for anorectal and anocortical studies. The numbers of patients for each will be defined by ability to recruit and retain patients in these studies and are in part a function of geographical location of recruitment, however we will aim to recruit 25 patients to the both anorectal and anocortical studies (see sample size).

Consent will be obtained from patients to pass on their contact details to the two sites performing the mechanistic studies at the time of consent for the main study. The Patient information sheets will be given to the patients at this point and a referral will be made. The two sites performing the mechanistic studies will then contact the patients to ascertain if they remain interested. Consent for these studies will take place face to face. Patients that have expressed an interest in the study at Aston Brain Centre will complete a screening form prior to consent if they are interested to make sure they are able to have an MRI.

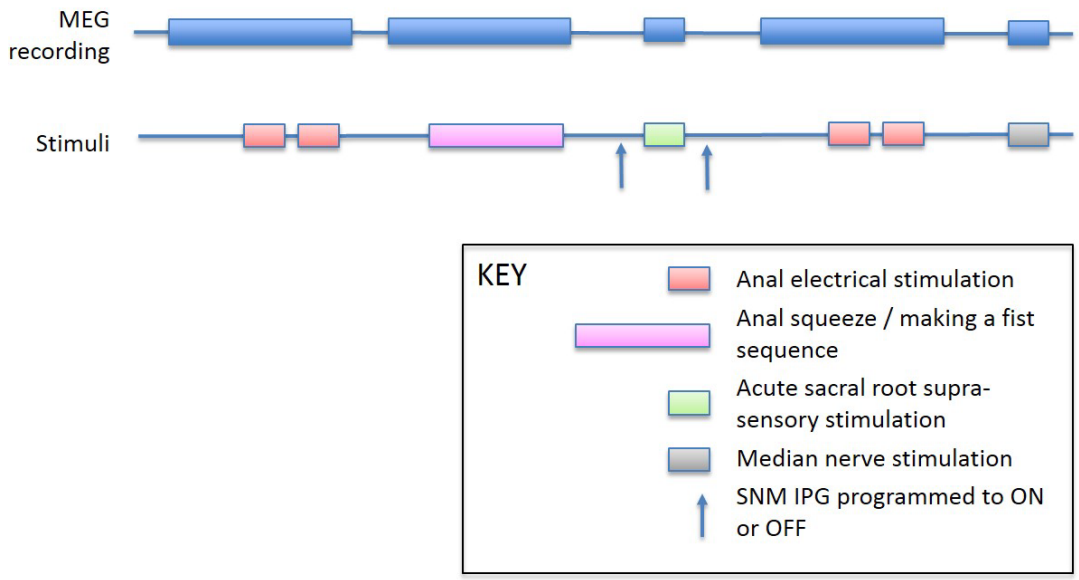
7.6.1: Anorectal studies

Patients in the London area (several centres) will be identified as potential subjects and provided with the specific patient information sheet. Interested patients will need to make two visits to the GI Physiology Unit at Barts Health NHS Trust and transport will be supported (including Taxis). Patients will undergo quick (clinically routine) tests of anal and rectal sensory function. The high resolution manometry catheter [MMS] is then inserted and a standard (clinically routine and internationally agreed) protocol[49] of basic pressure measurements obtained. Thereafter, the patient will undergo a prolonged recording (total 1.5h) of anorectal pressures at rest in a semi-recumbent position in a private room before and after a test meal (45 minutes each phase). During this time, they can watch TV but will be instructed to press an event recorder for any episodes of 'urge' or passage of flatus and complete a sensation record. The catheter is then removed and the study is finished.

7.6.2. Anocortical studies

Patients in the Midlands area (Sandwell & West Birmingham NHS, University Hospital Birmingham, Heart of England NHS, University of Leicester NHS Trusts) Manchester University Foundation NHS Trust and Sheffield Teaching Hospital NHS Trust) will be identified as potential subjects and provided with the specific patient information sheet. Interested patients will need to make a total of 3 visits to the Aston Brain Centre and transport will be supported (including Taxis). Only patients known to be proceeding to implantation will be invited for baseline evaluation and this can only proceed after removal of the test electrode (due to MRI) or in those in whom there is certainty that a tined lead evaluation will progress to implantation. At the first visit, the patient will be shown the facilities at Aston (NB this is a clinical department with excellent facilities for patients) including both scanners and have the tests re-explained. They will also have the opportunity to enter the MRI scanner to exclude claustrophobia and will complete a standard NHS checklist for MR safety. If they are eligible and happy to proceed, informed consent will be taken. A baseline MEG will be acquired according to the specific protocol developed and tested by the applicants (see figure 3). At the same visit (but after the MEG) they will have an MRI head scan using the on-site state-of-the-art 3T scanner [N.B the order of this is important since the MR scanner can induce tiny levels of magnetism in materials such as make-up and hair dye that can effect MEG recordings]. At the second and third visits (SNM or SHAM in random sequence), the patient will have further MEG acquisitions only.

Figure 3: MEG Protocol



The MEG protocol is shown in figure 3. The main steps are (1) the patient changes into a gown in a private changing room (adjacent to the MEG scanner) and then sits for approximately 5 minutes while head coils are applied and anatomical landmarks on the surface of the head and face are digitally mapped (for effective MEG-MRI co-registration) using the 'Polhemus' electromagnetic system; (2) the patient returns to the private changing area and is placed in the left lateral position while a bespoke (clinical physics – Manchester) anal plug electrode is inserted with lubrication (using electro-conductive jelly) by the trained investigator – this takes a few minutes; (3) the patient is wheeled back to the scanning area and helped into the MEG scanner; (4) once positioned comfortably, the patient has the sequence of stimuli and scans re-explained and a digital projection screen is placed in front of them so that they can watch a television programme of their choice during the scans; (5) the anal electrical sensory thresholds are determined (by average of 3 ramped stimulations) and the 75% of discomfort threshold calculated; (6) two runs of 200 stimuli at 2Hz frequency and 200 microsecond duration are delivered using a Digitimer DS7A while MEG (and synchronous anal EMG via the plug electrode) is recorded continuously (the total duration for each is 100 seconds only); (7) the screen is then used to give a series of simple visual stimuli to cue voluntary squeeze of their anal sphincter or to make a fist with their right hand (in random sequence) while further MEG is acquired; (8) [visits 2 and 3 only] an investigator re-enters the scanning room and switches the patient's SNM implanted pulse generator (IPG) to ON and thence increases stimulation amplitude to a comfortable supra-sensory level for 3 minutes (replicating the sequence used in re-programming in the main study) – MEG is acquired during this stimulation period of the sacral root – the IPG is then turned off again and the two runs of anal electrical stimuli repeated at the same threshold as above; (9) a brief run of median nerve stimulation is performed using the patients right wrist and surface electrodes (as per clinically routine neurophysiology testing); (10) the MEG acquisition is complete and the patient is returned to the changing room where the plug electrode is removed and the patient is left to privately wash and dress.

7.7 Schedule of clinical visits (patient timeline) [Table 1]

Visits	0	1	2a	2b	3a	3b	4	5	6	7	8	9	10
TIMEPOINT (weeks +/- 1 week)	Screen	Baseline	Test Stim.	Mech.	SNM Impl.	T^{0}	T^{+6}	T^{+12} to +16	T^{+16}	T^{+22}	T^{+28} to +32	T^{+32}	T^{+54} to +58
SCREENING & ENROLMENT													
Eligibility screen/confirmation	x	x											
Informed Consent		x											
e-diary training		x											
Check MDT decision (UK patients)	x												
Full eligibility & Randomisation					x								
INTERVENTIONS (un-blinded)													
SNM test phase			x										
SNM implantation					x								
Post-operative check					x								
SNM device programming/re-progr.						x	x		x	x		x	x
Crossover									x			x	
ASSESSMENTS (blinded)													
Demographics/Medical & surgical history, physical exam, pregnancy test		x											
e-event recordings (continuous)		x	x	x	x	x	x	x	x	x	x	x	x
Paper bowel diary & Viscerosensory bowel diary		x						x			x		x
Questionnaires (St Marks, Deferment Time, , OAB-QSF, SF-ICIQ-B, FI-QOL, EQ-5D-5L, satisfaction VAS score[2])		x							x			x	x
AEs					x	x	x		x	x		x	x
MECHANISTIC STUDIES (blinded)*													
Information and Consent				x*									
MRI				x*									
MEG studies				x*				x*			x*		
Anorectal studies								x*			x*		

* only in a subgroup of patients either passing test phase or certainty that a tined lead evaluation will progress to implantation

[2]satisfaction VAS score not at baseline visit 1.

NOTE TIMINGS: Allow minimum 4 weeks between baseline and test stimulation for completion of baseline bowel diary. Allow maximum of 18 weeks between baseline and permanent implant. Maximum 2 weeks between SNM implant and programming. Timing for remaining visits starts from initial programming (T0) with tolerance +/- 1 week.

NOTE: All study visits have a window of +/- 1 week for logistical purposes.

For patients with visits affected by Covid-19 please find the updated visit schedule in 7.8

7.7.2 Screening and Baseline Visits

Note: Screening and Baseline visits are currently on hold

Visit 0: Screening
Patients will be initially assessed for eligibility against the inclusion and exclusion criteria checklist. This may be done face to face in clinic or over the phone. The Multidisciplinary pelvic floor MDT discussion needs to be reviewed prior to visit 1. Patients who were initially found to be ineligible but who become eligible prior to any surgery can be rescreened. Eligible patients will be given or sent the REC approved invitation letter and patient information sheet. Patients must be given adequate time to review the PIS prior to consent. All patients screened will be added to the screening log.

Patients will be given a study ID code as follows

Site code – 3 letter code for each site (see appendix V).
Participant code – 3 digit code given consecutively at screening and attributed at each site.
For example the first patient screened at Barts Health NHS Trust would be given the code BLT - 001. This ID is retained throughout the study if they go on to be consented.

Visit 1: Baseline
Eligibility against the inclusion/exclusion criteria will be reviewed, then after discussing the study and PIS patients in agreement complete written informed consent. This visit must take place no more than 18 weeks before permanent implantation.

Once a patient has been consented, they will have the following assessments:

- Demographics, standardised medical/surgical history taken including history of incontinence symptoms, gynecological history and pregnancy test (females of childbearing potential).
- Clinical exam of perineum, anus and rectum (if not documented previously within 6 months)
- Baseline outcome assessments: St Mark's continence score, Deferment time, OAB-Q Short Form, International Consultation on Incontinence Bowel (SF-ICIQ-B) questionnaire, FI QoL score and EQ-5D-5L/VAS

At this visit patients will also be given the 4 week paper bowel diary (which will also record loperamide usage and taught how to use the touch screen electronic device, which will be started from this visit.

A total of 4 weeks is provided to complete the diary. A Viscerosensory bowel diary will also be provided with instructions for completion over 5 days.

7.7.3 Surgical Intervention Visits

Visit 2a: Test Stimulation
A 4 week window must be given between baseline and test stimulation to allow for the completion of the baseline bowel diary. Test stimulation will take place according to routine care, this will require the patient to attend the hospital as an outpatient, and no research data collection is required during this visit if a PNE wire is inserted. Test stimulation is therefore not considered a study intervention and will be performed in accord with local clinical practice. Based on previous data[6, 18]15% patients will fail temporary SNM evaluation and will not proceed to permanent implantation. **However, if the Tined lead is implanted at this visit as part of a two stage implantation, data will need to be collected from this surgical visit to complete the SNM implantation CRF.**

Visit 2b: Mechanistic study enrolment
Before permanent device implantation, those participants passing the test stimulation phase or those patients to have tined lead insertion with a high probability of going through to permanent stimulation, will be selected for and consented to the mechanistic study. All patients must have completed the 4 week bowel diary.

Those selected for anocorticol studies will then receive the following investigations;

- MRI studies and MEG studies
    - MRI head
    - MEG to electrical anal stimulation, anal squeeze, sacral root suprasensory stimulation, median nerve stimulation

Visit 3a: Permanent Device implantation (SNM Implant)
Following test stimulation patients will be admitted as a day case for permanent device implantation. Eligibility for randomisation will be re-confirmed (assessment baseline diary data). This visit must occur no later than 18 weeks after the baseline visit.

Patients are randomised prior to knife to skin to either one of the two groups:
Group 1 will the initially receive sacral neuromodulation and
Group 2 will initially receive sham stimulation.

Sixteen week SNM or SHAM periods will be counted from the initial programming not from the day of surgery.

Intraoperative data will be collected including:

- Lead position – radiological side and foramen level. Number of electrodes in foramina.
- Motor thresholds for each of the 4 electrodes on the quadripolar lead.
- Physiological motor (+/- sensory) response for chosen foramen for lead implantation.

- Other intraoperative data: length of op, type of anaesthesia (including use of any paralyzing agent*), blood loss, any other complications

If the Tined lead is inserted at the start of the test stimulation phase, then these data are collected during this test stimulation visit.

*patients undergoing prone general anaesthesia should do so in the absence of any paralyzing agent. In some cases however this may have been administered and this can affect the response to percutaneous nerve evaluation even in the presence of a reversal agent.

Visit 3b: Initial Programming (T0)

Post-operatively the implant will undergo baseline checks using impedance measurements of the 4 electrodes to ensure integrity of the electrical system.

Patients will have their SNM programmed as per routine care (see section 7.5.1). This can be done in the post-operative recovery period or up to 2 weeks post-surgery.

All further follow up visits will be counted from the initial programming not from the day of surgery.

To reduce selection bias, no consenting patient with an implant *in situ* will be excluded from participation i.e. regardless of the surgeon's views on success or otherwise of implantation. At each follow-up visit impedance measurements will be repeated to ensure maintained integrity of the electrical system. If a closed or open circuit is detected (suggesting possible neurostimulator or lead malfunction) then this will be documented. If satisfactory sensory response can be achieved using an alternative electrode configuration then the patient will be re-programmed and can continue in the study. In the absence of a satisfactory sensory response with an abnormal impedance measurement the patient will still be followed up as per intention to treat and any changes to treatment will be recorded in the deviation log.

At each visit any change in electrode configuration, sensory threshold and location of maximum bodily sensation will be recorded. The percentage of time the implant has been active for will be recorded.

All programming will be performed using the Model 8840 N'Vision clinical programmer. The patient programmer can therefore be covered with tamper proof tape for the entire clinical trial and no access is required to this device apart from to the power on/off button, synchronization button and implant on/off button.

Following initial programming:

Group 1: the subsensory amplitude will be recorded along with the electrode configuration used.

Group 2: The subsensory amplitude will be recorded along with the electrode configuration used before returning the amplitude to zero Volts.

NOTE: Any adverse events will be collected at this visit and all subsequent face to face visits
7.7.4 Crossover phases T0 to +T32

Visit 4: 6 week reprogramming visit (T+6)

The tamper proof tape is left on the patient's programmer, programming is done via the clinician's programmer.

Group 1: Patient assessed for suboptimal efficacy or unwanted effects of stimulation. In the presence of sub-optimal efficacy or adverse effects the electrode configuration can be changed as per re-programming algorithm. The sensory threshold is once again recorded, and device returned to the sub-sensory setting.

Group 2: The Sensory threshold is recorded and the electrode configuration can be changed if the site of stimulation appears to be sub-optimal (aim for anal stimulation) before returning device to zero Volts.

Visit 5: Assessment (T+12 to +16)
All patients will start the 4 week paper bowel diary and 5 day viscerosensory diary. This can be sent by mail or email, a face to face visit is not required.

The selected subgroup will have the first of the mechanistic follow up studies completed, (MEG or Anorectal).

Visit 6: Crossover Visit (T+16)
At crossover, the device is turned off for 20 minutes followed by re-evaluation of the sensory threshold and best electrode configuration in the manner outlined above. The intervention is then reversed for each arm.

Paper diary is completed and returned. Follow up assessment questionnaires (St Mark's continence score, Deferment time, OAB-Q Short Form, International Consultation on Incontinence Bowel (SF-ICIQ-B) questionnaire, FI QoL score and EQ-5D-5L/VAS). Patients will also record their satisfaction on a Likert scale.

Visit 7: 6 week re-programming visit (T+22)
All patients will have a further follow up 6 weeks after crossover at T22.

Leaving the tamper proof tape on the patient's programmer, programming is done via the clinician's programmer.

Group 1: The Sensory threshold is recorded and the electrode configuration can be changed if the site of stimulation appears to be sub-optimal (aim for anal stimulation) before returning device to zero Volts.

Group 2: Patient assessed for suboptimal efficacy or unwanted effects of stimulation. In the presence of sub-optimal efficacy or adverse effects the electrode configuration can be

changed as per re-programming algorithm. The sensory threshold is once again recorded, and device returned to the sub-sensory setting.

Visit 8: Assessments (T+28 to +32)
All patients will start the 4 week paper bowel diary and 5 day viscerosensory diary. This can be sent by mail or email, a face to face visit is not required.

The selected subgroup will have the second of the mechanistic follow up studies completed, (MEG or Anorectal).

7.7.5 Open label cohort follow-up T32-58
Visit 9: End of Crossover (T+32)
At 32 weeks (and after collection of final crossover study data), patients will enter the follow-up phase with patient decisive stimulation (sub- or supra-sensory) as would be normal for routine clinical practice. A member of the clinical team will re-programme the device accordingly. As blinding is now no longer necessary patients can have the option of changing their patient programmer for the new Samsung patient programmer. Further programming and advice can be provided as per routine care during the period 32-58 weeks. All visits or contact with the clinical team during this time will be recorded on the Note to File CRF.

The 4 week paper bowel diary and 5 day viscerosensory diary will be completed and returned at this visit and the set of follow up assessment questionnaires (St Mark's continence score, Deferment time, OAB-Q Short Form, International Consultation on Incontinence Bowel (SF-ICIQ-B) questionnaire, FI QoL score and EQ-5D-5L/VAS) Patients will also record their satisfaction on a Likert scale)

Visit 10: Final Assessment (T+54 to +58)
Patients will be asked to complete a further paper bowel diary and 5 day viscerosensory diary for the last 4 weeks (T54-58). During the final visit both the e-diary and paper diaries will be collected. Patients will undergo final re-programming and complete the outcome questionnaires and Likert scale. Any adverse events will be reviewed and resolved. Patients will then be discharged from the study and continue with normal clinical care.

7.8 Visit schedule for those patients with visits delayed by Covid-19

Due to restrictions and staff redeployment caused by Covid-19, no study activity was performed between March 2020 and September 2020. The study had to be put on hold during this time. Delays in seeing patients for follow-up remain ongoing. The length of delays has meant many patients have missed at least 2 visits and following the original schedule is no longer possible.

A tool to guide the follow-up of these patients can be found in Table 2 below. This tool is to be used to show which visit is first due after the study hold. If possible patients are to fill in a 28day paper diary and viscerosensory diary prior to this visit even if they had filled these out prior to previously arranged visits. Once a patient has been seen all further visits are to be counted from the date of this appointment and NOT the programming visit as before. A note to file will need to be completed identifying their visit was delayed by Covid-19.

If any further face to face visits are to be missed please patients will need to be contacted. All telephone conversations with patients need to be documented in the Note to File.

Table 2. Follow up Tool

Last visit attended	Next visit	Time frame	What to add to the Note to File	How to complete further follow ups
1 Baseline	3a/3b	When possible	Surgery has been delayed due to Covid-19 causing all surgery to be suspended	Once the patient has surgery they are to undergo follow up as per protocol
3b Initial Programming	6 Crossover visit Making sure they have completed their bowel + viscerosensory diaries (visit 5) Do not complete visit 4	ASAP	Visit 4 was missed due to Covid-19 lockdown prolonging the crossover period for much longer than 16 weeks. Visit 6 was performed as soon as services were reopened after suspension due to Covid-19.	Perform visit 7, +6 weeks after visit 6 if able to do so. Otherwise send diaries for visit 8 and perform visit 9, +16 weeks after visit 6.
4 Reprogramming visit	6 Crossover visit Making sure they have completed their bowel + viscerosensory diaries (visit 5)	ASAP	Visit 6 was performed as soon as services were reopened after suspension due to Covid-19.	Perform visit 7, +6 weeks after visit 6 if able to do so. Otherwise send diaries for visit 8 and perform visit 9, +16 weeks after visit 6
5 Diary completion	6 Crossover visit	ASAP	Visit 6 was performed as soon as services were reopened after suspension due to Covid-19.	Perform visit 7, +6 weeks after visit 6 if able to do so. Otherwise send diaries for visit 8 and perform visit 9, 16 weeks after visit 6
Visit 6 Crossover visit	9 End of Crossover visit Making sure they have completed their bowel +	ASAP	Visit 7 was missed due to Covid-19 lockdown prolonging the crossover period for much longer	Perform visit 10 after patient has completed final diaries, +26 weeks after visit 9

	viscerosensory diaries (visit 8) Do Not complete visit 7		than 16 weeks. Visit 9 was performed as soon as services were reopened after suspension due to Covid-19.	
Visit 7 Reprogramming visit	9 End of Crossover visit Making sure they have completed their bowel + viscerosensory diaries (visit 8)	ASAP	Visit 9 was performed as soon as services were reopened after suspension due to Covid-19.	Perform visit 10 after patient has completed final diaries, +26 weeks after visit 9.
Visit 8 Diary completion	9 End of Crossover visit	ASAP	Visit 9 was performed as soon as services were reopened after suspension due to Covid-19.	Perform visit 10 after patient has completed final diaries, +26 weeks after visit 9.
Visit 9 End of Crossover visit	10 Final Visit making sure they have completed their bowel + viscerosensory diaries	When possible	Visit 10 was performed as soon as services were reopened after suspension due to Covid-19. Add the following if appropriate - Visit 10 was performed initially via post/telephone then followed up in clinic when possible - Visit 10 was only performed via post/telephone as face to face appointments have yet to start.	

7.9 Concomitant care and interventions

It is inevitable that participants will seek recourse to loperamide and other medications during the course of the programme. Breakthrough loperamide usage is captured on the patient

diary and St Marks questionnaire. Additional concomitant medication reporting is not required for assessment of eligibility or safety monitoring e.g. contraindication with the intervention. Thus, concomitant medications will not be recorded.

7.10 Discontinuation criteria (participants and study)

Clinical care will take priority. The intervention plan allows the direct care team to remain autonomous in clinical decisions and modify their approach accordingly. It is unlikely that the intervention will need to be formally discontinued. However, if the direct care team or the research team at any point feel that the intervention is affecting the patient's recovery, outcome or prognosis then it will be discontinued immediately. The events and circumstances will be recorded. If any safety concerns have arisen, these will be reported according to research governance framework guidelines.

7.11 Withdrawal Criteria

Patients can withdraw at any point in the study. The data collected from consent to the point of withdrawal will be kept for intent to treat analysis, as outlined in the patient information and consent form.

Patients will be withdrawn from treatment but follow up data will be continued to be collected if

- They electively withdraw from treatment
- Not fit for surgery
- Become pregnant or intend to become pregnant
- They are unable to participate due to an concurrent severe illness
- They develop an acute psychological illness causing concerns

Patients will be withdrawn from both treatment and follow up if

- They chose to withdraw from treatment and follow up data collection
- They become lost to follow up (after at least 3 attempts at contact by research/clinical staff using at least 2 different methods)
- Death or become severely incapacitated so follow up data collection is impossible.

7.12 Criteria for Early Termination

If the DMEC, TSC, REC or sponsor determine it is within the best interests of the participants or trial to terminate the study, written notification will be given to the CI. This may be due to, but not limited to; serious safety concerns, success or failure of the primary outcome, serious breaches, acts of fraud, critical findings or persistent non-compliance that negatively affects patient safety or data integrity. If the study is terminated participants will be returned to the normal follow up and routine care.

7.13 End of Study Definition

The end of study is defined as the last patient last visit (LPLV). The sponsor, REC and local R&D departments will be informed of end of study and site closure and archiving procedures initiated.

8 Outcomes

8.1 Primary clinical outcome

The reduction in FI events in SNM vs. SHAM phase of crossover (16 and 32 weeks).
Frequency of FI episodes per unit time will be patient-recorded using 4-week paper bowel diaries. While the limitations of this method are well-established[50], this remains the gold-standard in FI trials[15, 18, 22, 51] (we will however be recording for 4 weeks rather than only 2 as in many previous studies). The measure of treatment effect is the average number of FI events per 4 week period for patients undergoing SNM as compared with the average number of events for patients undergoing sham simulation. The study is powered to detect a ratio of 0.7. This is not to be confused with the reduction in the actual number of events post-intervention for a given patient, where a 50% reduction has frequently been employed, albeit subjectively, to define "success" for that patient[18, 51]. Rather, we use number of events as a quantitative outcome, achieving greater power than a dichotomous outcome of successful/unsuccessful, and we power to detect a 30% reduction, on average, in this outcome on intention-to-treat principles

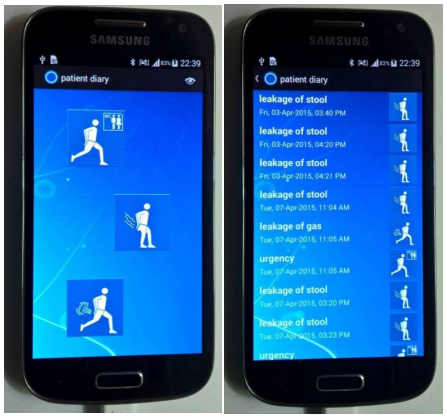
The paper diary will be completed prior to implantation then at the end of each crossover phase and again at the end of the cohort follow up.

8.2 Secondary clinical outcomes

A variety of quality of life questionnaire and bowel diary measures recorded at 16, 32 and 58 weeks:

1. E-event recorder including episodes of faecal material, leakage of flatus, urgency without incontinence, social and physical activity (see figure 4 below);
2. Other bowel diary measures: Urgency, Urge and passive faecal incontinence episodes, use of loperamide and social functioning;
3. Summative questionnaire assessments: St Mark's continence score[52]; OAB-Q SF score, FI QoL score[53]; International Consultation on Incontinence Bowel (SF-ICIQ-B) questionnaire[54].
4. Viscerosensory bowel diary recording quality, site and intensity of defaecatory urge
5. Generic QOL: EQ-5D-5L
6. Likert scale of patient's global impression of treatment success (scale 0-10) and patient perception of group allocation (blinding success).
7. Electrode settings (inc. motor, first and habituated sensory thresholds), programming, & if applicable re-programming data
8. Adverse events and morbidity.

Figure 4. Example (not final) photograph of touchscreen icons on e-recording device



	A	B	C	D
1	leakage of stool	Fri	03. Apr 15	3:40 PM
2	leakage of stool	Fri	03. Apr 15	4:20 PM
3	leakage of stool	Fri	03. Apr 15	4:21 PM
4	leakage of stool	Tue	07. Apr 15	11:04 AM
5	leakage of gas	Tue	07. Apr 15	11:05 AM
6	urgency	Tue	07. Apr 15	11:05 AM
7	leakage of stool	Tue	07. Apr 15	3:20 PM
8	leakage of stool	Tue	07. Apr 15	3:23 PM
9	urgency	Tue	07. Apr 15	3:27 PM
10	urgency	Wed	08. Apr 15	10:16 AM
11	urgency	Wed	08. Apr 15	10:18 AM
12	leakage of gas	Wed	08. Apr 15	10:18 AM
13	urgency	Mon	13. Apr 15	10:27 PM
14	leakage of gas	Mon	13. Apr 15	10:28 PM
15				

A simple touch screen electronic device developed with Medtronic will allow patients to record real-time-indexed episodes of faecal material, leakage of flatus and urgency without incontinence. In addition to comparing fidelity of events recorded by the current gold-standard (paper), this will provide opportunities to analyse novel similarly time-indexed measures e.g. social and physical activity that may thus validate or eventually improve on limitations of current FI outcomes. Finally, the same device will be used as a touchscreen application for digitalisation of established and new (SF-ICIQ-B) summative scoring questionnaires. The touch screen will be used from the baseline visit throughout the crossover and cohort follow up studies.

The information collected in the touch screen electronic device is logged in real calendar time and stored as time-linked data. It will be downloaded by hardwire (USB) connection. The app will not simply be an e-version of a paper bowel diary (which already exists). Rather we are developing a new app that will greatly simplify use whilst also improving the accuracy of data over paper bowel diaries which are acknowledged to have major insufficiencies due to patient compliance[50], the Hawthorne effect, and also by interpretational bias of unblinded investigators. The same android hardware device will also embed established platform technology from the sports and leisure market (GPS, accelerometer).

N.B we will not quantify degree of faecal loss. While this is an acknowledged (and regularly debated) limitation of all existing outcome instruments, we believe that simplicity would be sacrificed if patients were required to judge the semantic differences between ‘staining’, ‘leakage’ and ‘frank incontinence’.

8.3 Mechanistic outcomes

Anorectal sensorimotor function

1. Frequency of perceived and unperceived TASRs per unit time (pre- and post-prandial)
2. Anal sensory electrical threshold
3. Rectal volumetric thresholds (minimum, urge, max tolerated) to balloon distension

Ano-cortical function

Magnetoencephalography (MEG): Recordings will be acquired in response to anal electrical stimulation at 75% pain threshold, voluntary anal squeeze, and to acute supra-sensory sacral root stimulation. Synchronous anal EMG will also be recorded to aid interpretation and a

control area utilised (median nerve). Whole cortical data will be obtained using standard methods on an Elekta Triux 306 channel system utilizing noise cancellation methods to eliminate implant and stimulator artefacts. A beam-former analysis methodology will be employed to evaluate both evoked and induced changes in brain activity associated with SNM and anal stimulation. Brain sources will be constructed using individual co-registered T1 weighted MRI brain volumes. The outcome of this process will be a measure of the changes in brain oscillatory power and/or frequency changes computed from brain structures where maximum changes associated with anal stimulation are observed. These changes will be depicted in statistical brain volumetric images.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size

The sample size is based on the primary outcome i.e. faecal incontinence episodes per unit time as recorded using the 4 week bowel diary at the end of each 16 week crossover phase.

We assume that when the device is inactive the average number of events in 4 weeks for a typical participant is 28. The number of events per month for that individual will have an over-dispersed Poisson distribution, with 95% range 7 to 112. But individuals will also vary, so the average number of events in a month could vary from 14 in an individual at one extreme to 56 in an individual at the other. This means the correlation between log(number of events) for the same individual in two different months will be 0.2, and the standard deviation of log(number of events) for each month will be 0.775 (this is consistent with results from two previous NIHR trials in similar populations[18] and HTA CONFIDeNT[55]), and with our clinical experience). Thus to detect a 30% reduction in FI event rate with 90% power at the 5% significance level with a cross-over design requires 80 participants. Allowing for 10% loss to follow-up a total of 90 participants will be randomized. This sample size would also achieve more than 90% power to detect a 50% reduction in FI event rate using the data from the first period of the cross-over alone. This sample is also sufficient to detect changes in mechanistic outcomes (90% power) based on pilot data. i.e. using a one-sample test comparing logarithm of anal electrical sensitivity post-SNM, the proposed mechanistic sample size n = 25 will be sufficient to detect a 30% reduction in sensory threshold with 95% power at the 5% significance level, assuming the standard deviation of the change in log-sensitivity is 0.47 (consistent with a coefficient of variation of 0.5 for sensitivity, as observed in pilot data, and a correlation of 0.5 between pre- and post-SNM assessments). The anocortical studies are mainly exploratory and sample size will be based on success of recruitment. It is however envisaged that approximately 15 patients will complete all 3 visits for MRI/MEG. Previous MEG studies have drawn important conclusions with sample sizes of this order.

9.2 Method of Analysis

<u>Efficacy: primary analysis from crossover study</u>
This analysis will be completed by the statisticians at PCTU

The analysis of the primary outcome will compare sham and active therapy in both arms of the cross-over trial, at T12-T16 and T28-32, using mixed Poisson regression analysis to adjust for a fixed effect of period and a random effect of individual. To allow observed numbers of events before and after activation in the same individual to have an over-dispersed Poisson distribution we will also include a random effect of time within individual. We will analyse all non-missing data, adjusting for the stratification variables (random effect of centre and fixed effect of sex). This approach is unbiased if missingness is related to observed outcome data or stratification factors from the same participant (a "missing at random" assumption): further sensitivity analyses will explore this assumption if needed.

Secondary outcomes will be analysed in the same way – using Poisson regression for outcomes that are counts, and linear regression for other quantitative outcomes.

Exploratory analyses may also be performed using geospatial data from the touch-screen devices to calculate e.g. number of outings from primary residence, as well as distance travelled and velocity (a surrogate for mode of transport), and to produce numerical and graphical summaries aggregated by trial arm.

Efficacy secondary analysis from cohort study

As in the primary efficacy analysis, mixed Poisson regression will be used to compare the primary outcome at T52-58 with baseline in all randomised participants, adjusting for a random effect of individual, and a random effect of time within individual (over-dispersion).

Mechanism studies:

Anorectal

Data from the subset of patients undergoing advanced anorectal studies (n = 25 approx.) will be collected during each phase of the crossover. These data take the form of counts, e.g. number of events, and continuous measures such as pressure. Data will be analysed as for secondary outcomes in the efficacy analysis.

Anocortical studies will be analysed by the Aston Brain institute using existing bespoke computer analysis packages [Graph (Elekta ™); Matlab ™ and FieldTrip ™ and SPM8 ™].

A beam-former analysis methodology[56] will be employed to evaluate both evoked and induced changes in brain activity associated with SNM and anal stimulation.
Group analysis of this data will allow determination of cortical reorganizational changes associated with chronic SNM. This will be achieved by the spatial normalisation of individual MRI volumes into a grid based on the Montreal Neurologic Institute (MNI) standard template. Statistical analysis will employ a non-parametric cluster-based permutation test[57]. Firstly, an uncorrected dependent-samples t-test will be performed on pre- and post-stimulus brain activity across the entire brain volume. All voxels exceeding a 5% significance threshold will be grouped into clusters. A null distribution will be obtained by randomising the condition label (pre- or post-stimulus data) 1000 times and calculating the largest cluster-level t-value for each permutation. This methodology has been shown to adequately control for issues of multiple comparisons.

Statistical Considerations due to Covid-19

10 The assumption for the primary analysis will be that for participants paused in one of the crossover phases the eventual outcome in that phase is unaffected by the extra time spent in the allocated treatment condition. We had always hypothesised that after the scheduled 6-week interval between re-programming and assessment, a participant's outcomes would have stabilised. We will conduct sensitivity analyses to investigate how conclusions might change if the assumption does not hold. Other than this, the risk of pausing the trial is of attrition of participants paused in different stages. This should not introduce any systematic bias but might result in a small loss of statistical power.ETHICS

The study is a non-CTIMP study, using CE marked devices for SNM. The study will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), ICH Good Clinical Practice Guidelines (1996), and the current applicable local regulatory requirements and any subsequent amendments of the appropriate regulations as well as REC conditions of approval. Excluding a single additional attendance for eligibility, the long-term SNM care pathway is unchanged other than the randomly allocated period of 16 weeks SHAM stimulation required during the crossover. While this period may (depending on the sham response) confer no benefit to the patient in terms of symptom reduction, the duration is in keeping with acceptability based on user involvement data. Activation (up to 2 weeks post-op) and programming of stimulator settings will be identical to routine care (at 6 weeks) as will any reprogramming events (these being recorded with outcomes). Patients may switch the device off as they would in routine care, should they experience any severe unwanted stimulator effects (as per section 11) or for driving purposes. A trial aid card will be provided to patients with clear instructions regarding this.

Outcome data will be collected continuously by the e-recording device and prior to each step for paper forms – this being regardless of stimulation status for the lifetime of the study (58 weeks). This requires some effort on the part of the patient but has no ethical implication noting that for the proposed GPS functions, actual geographical grid reference points will be deleted from the downloaded file for confidentiality i.e. only vectors will be recorded not actual home address or places visited. All questionnaires have been used repeatedly without issues of embarrassment or distress[18].

Mechanistic studies will be performed in two sub-cohorts derived from the main efficacy study. This is because of the burdensome nature of these tests and also the matter of ease of geographical access. Thus, one cohort will undergo the anorectal tests in London region, and one the anocortical tests in Birmingham region. For both cohorts, patients must be prepared to undertake specific detailed studies (see above) and for this reason, each cohort will be given specific patient information sheets and separately consented.

11 SAFETY CONSIDERATIONS:

SNM is an established therapy whose main attraction is non-invasiveness and safety compared to other surgical procedures. The main procedural risks are unwanted stimulation effects: muscle spasms, vaginal pain, scrotal pain, leg pain and paraesthesia (common to some degree but manageable usually by reprogramming), infection (cited at 2%) and leading to device erosion or removal. Other listed adverse events (based on FDA: PMA P080025) include: unwanted changes in bladder function (urgency, retention); pain at neurostimulator and/or

lead site including skin irritation; and allergic or immune system response to the implanted materials that could result in device rejections. Malfunction of the components of the InterStim Therapy System including neurostimulator programming error, lead migration/dislodgement, lead fracture, erosion of the lead into the colon with perforation, neurostimulator battery depletion, extension fracture, neurostimulator migration can also occur.

12 DATA HANDLING AND RECORD KEEPING:

12.1 Data Collection and transfer methods

Data will be handled in accordance with the Data Protection Act 2018, PCTU Information Governance requirement and SOPs. A data management plan for the study will be developed by the PCTU data manager, including detailed information on data capture, transfer, storage and security. In summary; the data collected during the trial will be a combination of data recorded straight on CRFs like Patient Reported Outcome Measures (PROMS) (diaries & questionnaires) and routine data that can be verified with the medical notes. Table 2 shows the data sources, and data transfer.

Table 3 Data Management Summary

Study Assessment	Data Sources	Data Capture	Data Transfer
Screening and eligibility checklist	Patient Interview/medical record	CRF1	eCRF (OpenClinica)
Informed Consent	Consent Form	Copy in site file and patient notes	None
Structured history including eligibility assessment, demographics, surgical and medical history and clinical examination	Patient interview/medical record – routine data	CRF2	eCRF (OpenClinica)
Urine pregnancy test		CRF2	eCRF (OpenClinica)
Randomisation	Online System	CRF 3	Blinded
Intra and Post-operative assessments	Medical Records – routine data	CRF4 and CRF5	eCRF (OpenClinica)
Anorectal studies	PROM- Sensation booklet	Sensation Booklet	None

EQ-5D-5L, SF ICQ B, FI QoL, St Marks Incontinence Score, OAB-Q short form	PROM - Questionnaire	Baseline and Follow up Questionnaire Booklets	eCRF (OpenClinica)
Likert scale & Perceived Group Allocation	PROM - Questionnaire	Follow Up Questionnaire Booklet	eCRF (OpenClinica)
Bowel Diary	PROM - Bowel Diary	Paper diary and electronic diary	eCRF (OpenClinica)
Bowel Viscerosensory Diary	PROM - Bowel Sensory Diary	Bowel Sensory Diary	eCRF (OpenClinica)
Clinical functioning of SNM	Patient Interview/medical records	CRF 6, 7, 8, 9	eCRF (OpenClinica)
AE log	Patient interview/medical record	CRF 10	eCRF (OpenClinica)
Deviation Log	CRF 11	CRF 11	eCRF (OpenClinica)
Note to File	CRF 12	CRF 12	eCRF (OpenClinica)
Early Withdrawal/Study Completion	Medical record	CRF 13	eCRF (OpenClinica)

*Data from the mechanistic studies will be recorded on MEG/MRI for anocortical and HRAM for the anorectal studies. These will be analysed at source and not transferred to the sponsor.

12.2 Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act 2018, The General Data Protection Regulation (EU) 2016/679 (GDPR), NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, ICH Good Clinical Practice Guidelines (1996) and the conditions of Research Ethics Committee Approval and current local regulatory requirements.

Identifiable information to be collected from the participants include, full name, DOB and hospital number and contact details at screening. This information will be used to contact participants but will not leave the study site without prior consent. All case report forms will be pseudonymised. The participant's will consent to their GP and or referring clinician to be informed of their participation in the study.

The trial data will be made available to suitably qualified members of the research team, study monitors and auditors, the REC and regulatory authorities as far as required by law. This includes collaborators from Queen Mary University of London, Aston University, Barts Health Trust and Medtronic USA. The participants will not be identifiable with regards to any future publications relating to this study.

12.3 Record Retention and Archiving

When the research trial is complete, it is a requirement of the Research Governance Framework and Sponsor Policy that the records are kept for a minimum period of 20 years (as per sponsor requirements). For trials involving BH Trust patients, undertaken by Trust staff, or sponsored by BH or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre.

Each site will be required to archive local site files and patient identifiable information such as consent forms and screening logs. At the end of the retention period, the Records Management team will alert R&D that the records are due for disposal. The chief investigator and sponsor will be informed and the full agreement of everyone concerned will be obtained before any records are destroyed.

13 LABORATORIES (if applicable)

Urine Pregnancy testing will be performed for purposes of the trial. We do not require Serum Pregnancy tests.

14 PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

14.1 Devices

The following is a list of all devices used. None are specific to the research itself and are currently used in routine clinical practice. All are CE marked and approved for use in the UK.

1. Disposable proctoscope (supplier as local NHS/hospital practice) used commonly as part of baseline assessment.
2. Surgical Instrumentation including disposable and reusable instruments.
3. Sacral neurostimulator: Medtronic Interstim II Model 3058. This will be inserted under general or local anaesthetic as described in 7.1.1.
4. InterStim iCon Patient Programmer Model 3037
5. N'Vision Clinician Programmer Model 8840
6. InterStim™ smart programmer

14.2 Techniques and interventions

There are no experimental techniques within this study

14.3 Data Collection Tools

Permission has been granted for EQ-5D-5L (registered date 24Feb2016)

No cost is associated with the other outcome instruments:

- St Mark's continence score
- FI QoL score
- OAB-Q Short form
- International Consultation on Incontinence Bowel (SF-ICIQ-B) questionnaire
- Electronic bowel diary developed with Medtronic displayed on a commercially purchased handset

14.4 Medicinal product

None

15 SAFETY REPORTING

15.1 Adverse Events (AE)

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

Notification and reporting Adverse Events
All adverse events will be recorded on the CRF and in the medical notes. Severity, Causality (relationship to study procedures) and assessment of seriousness will be at the discretion of the medically qualified individual (e.g. principal investigator or delegated member of team).

Severity
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL).
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

15.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an AE or untoward occurrence that:
(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

15.3 Expected Events (AE/SAEs)

Expected AEs include

- Bleeding
- Pain
- Wound infection
- Worsening of, or *de novo* urinary incontinence
- Worsening faecal incontinence
- Unwanted/undesirable stimulation effects
- Numbness at neurotransmitter site
- Technical Device issues including lead migration and fracture

Expected SAEs are those related to routine use of SNM. These are:

- Infection of lead or IPG necessitating removal or admission for intravenous antibiotics
- Unwanted stimulation effects necessitating device removal
- Lack / loss of efficacy necessitating device removal
- Revision of IPG placement due to discomfort or displacement
- Revision or removal of IPG due to technical device failure (including fractured lead or failure of impedence check on all 4 leads)
- Unrelated hospitalisation e.g. elective surgical procedures or injury or acute medical problems

15.4 Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to HRA website and JRMO SOPs
• Related – that is, it resulted from administration of any of the research procedures, and
• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Please note in the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of an 'unexpected and related' SAE. Please seek advice on how this can be achieved whilst maintaining the team blind. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

15.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to HRA website and JRMO SOPs.

15.6 Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the HRA template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor. Please see HRA website and JRMO SOP for further information

15.7 Overview of the Safety Reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

Communication organogram for reporting SAE's

AE/SAE recorded on AE log
SAEs will be followed up until resolution.

PI assesses SAE's and reports to CI within **24 hours**, PI reports to local institution as per local protocol

CI reports related and unexpected SAE's to PCTU QA manager and Sponsor within **24 hours of PI learning of the event**

CI reports related and unexpected SAE's to REC within **15 days**

CI reports to DMEC every **6-12 months** CI reports **annually** to REC

16 MONITORING & AUDITING

The PCTU quality assurance manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study monitoring and auditing plan will be produced according to PCTU SOPs. This monitoring plan will be authorised by the sponsor before implementation. Any changes to the monitoring plan must be agreed by the PCTU QA manager and the sponsor.

Definition:
"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

17 TRIAL COMMITTEES

The project will be under the auspices of the Chief Investigator and the PCTU. The project will be overseen by a Trial Steering Committee (TSC).
The role of the TSC is to provide overall supervision of the study on behalf of the sponsor and funder to ensure the study is conducted in accordance with the principles of Good Clinical Practice (GCP) and relevant regulations.
The responsibilities of the TSC will include:

- ensuring that views of users and carers are taken into consideration,
- advising on the trial protocol,
- advising on changes in the protocol based on considerations of feasibility and practicability,
- assist in resolving problems brought to it by the Trial Management Group (TMG),
- monitor the progress of the trial and adherence to protocol and milestones
- consider new information of relevance from other sources,

- consider and act on the recommendations of the data monitoring and ethics committee (DMEC), sponsor and/or REC,
- review trial reports and papers for publication.

The TSC will meet to review the protocol before the start of the trial and then soon after the first participants are recruited and either meet or teleconference every 6 months thereafter throughout the lifetime of the trial.
The composition and responsibilities of the TSC will comply with the NIHR guidance and PCTU SOP on Trial Oversight Committees and include:

- Independent Chairperson & Clinician – Mr Steven Brown, Consultant in Coloproctology, Reader in Surgery, Northern General Hospital, Sheffield
- Independent Statistician - Stephen Gerry, University of Oxford
- PPI/consumer representatives – Bowel and Cancer Research Charity PPI coordinator Lesley Booth plus Patient representatives from the bowel and Cancer Research Charity PPI group.
- Senior Statistician – Richard Hooper (PCTU)

Representatives from the trial sponsor and funder will be invited to attend.

A Trial Management Group (TMG) will meet monthly initially during study set up and then less frequently, every 2 months. The TMG will be responsible for day to day project delivery across participating centres and will report to the TSC. It will include:

- The trial CI
- PI/Co applicant
- Research nurses
- Research fellows
- Trial Coordinator
- Junior trial statistician
- Data manager
- QA manager

A data monitoring & ethics committee (DMEC) will be convened. The DMEC will meet at least four weeks prior to the TSC to enable recommendations to be fed forward. The DMEC will review unblinded comparative data, monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.
The DMEC membership will be in accordance with NIHR/MRC as well as PCTU guidelines and include:

- Independent chairperson– Professor Yan Yiannakou, Professor of Neurogastroenterology, University Hospital of North Durham
- Independent clinician experienced in the clinical area – Mr Thomas Pinkney, Senior Lecturer and Consultant Colorectal Surgeon, Clinical Director of Birmingham Surgical Trials Consortium.
- Independent expert trial statistician - Cassandra Brookes, Principal Statistician, Leicester Clinical Trials Unit

18 PROJECT MANAGEMENT

18.1 Local Co-ordination

Each participating centre will identify a site specific PI who will nominate a local contact for that centre (this may be him/herself). The PI and local contact will:

- Be familiar with the Trial.
- Liaise with the TMG.
- Ensure that all staff involved in the trial are informed about the trial and have received requisite training.
- Ensure that mechanisms for recruitment of eligible participants, including the availability of participant information and data collection tools, are in place.
- Monitor the effectiveness of data collection tools and participant information and discuss the reasons for non-recruitment with relevant staff.
- Ensure site staff collect necessary trial data and perform quality checks.
- Notify the CI of any SAEs and serious breaches within required timelines.
- Make data available for verification, audit and inspection processes as necessary, and respond to requests for documentation and data required for centralised monitoring.
- Ensure that the confidentiality of all information about trial participants is respected by all persons.
- Ensure sufficient local resources available to deliver the study and provide staff cover during times of absence.

18.2 Site initiation and training

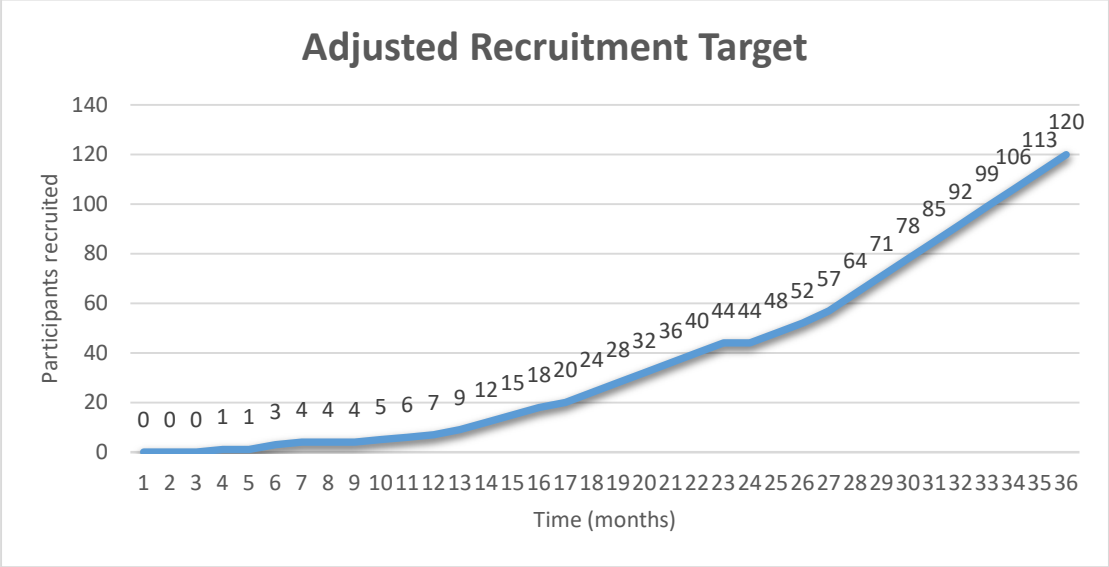
Site initiation and training (SIV) will be conducted with each site face to face or remotely. This will include training in the trial protocol and standard operating procedures, such as data collection, randomisation, taking informed consent and safety reporting. Evidence of appropriate training, local approvals and essential documentation will be required before participants being enrolled at each site. Training will be documented on training logs. SIV will be conducted according to PCTU and sponsor SOPs.

18.3 Project timetable, milestones and projected recruitment

The TMG will be responsible for monitoring adherence to the study timelines and expected recruitment rates. Regular reports will be produced to enable deviations from the project plan to be identified and contingencies planned, discussed and executed in a timely fashion.

A chart with study milestones can be found in Appendix I and the Gantt chart can be found in appendix IV. The projected recruitment rates have been amended to take into account the 18-month extension. The target now is for 120 patients to be consented to enable 90 patients to be randomised and is shown in Figure 5. below:

Figure 5. Adjusted anticipated recruitment rate



The Barts and The London, Pragmatic Clinical Trials Unit (PCTU) will provide quality management of the trial, implementing the PCTU standard operating procedures in regards to trial management, data management, randomisation, statistical analysis, trial monitoring and quality control procedures. The PCTU is a UKCRC registered clinical trials unit, supported by the NIHR and complies with the sponsor and REC conditions of approval. The study will be conducted according to the UK Research Governance Framework for Health and Social Care 2005, The Data Protection Act 2018, NHS Caldicott Principles and Good Clinical Practice Guidelines 1996.

19 FINANCE AND FUNDING

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20 INDEMNITY

Queen Mary University London has agreed to act as study sponsor. Insurance and indemnity will be provided by the sponsor.

21 DISSEMINATION OF RESEARCH FINDINGS:

Scientific findings will be subjected to international reporting and peer review (targeting appropriate clinical journals e.g. BMJ, Lancet or Gastroenterology). We will direct this information to the following groups:

1. Study participants and carers: feedback to individual participants, users and carers who have been involved in, or otherwise contributed to, the trial);

2. Charity links and patient groups: results of the studies will be disseminated using the strong web-based and media infrastructure already developed by the Charity Bowel and Cancer Research (B&CR). This infrastructure includes the B&CR website (www.bowelcancerresearch.org which has 2,500 unique web visitors monthly), social media e.g. Facebook site (12,000 followers and), Twitter, and a public relations officer (a free-lance journalist who is employed by B&CR for one day per week who will help develop and edit press releases: 50 local and national news publications in 2012). B&CR is dedicated to breaking down the taboos concerning discussion of bowel problems such as incontinence. B&CR and several of the applicants have links with other patient organisations and charities e.g. Core, GI Blues, Ileostomy Association and the Bladder and Bowel Foundation;

3. Local health service providers including developing clinical commissioning groups via specially convened local meetings and written reports (led by Janet Sedgewick);

4. NIHR collaboration: the CI is Director of the Bart's NIHR HTC for GI disease. Results will be disseminated by the HTC newsletter / website to all 90 UK industrial and all 25 clinical colorectal centres.

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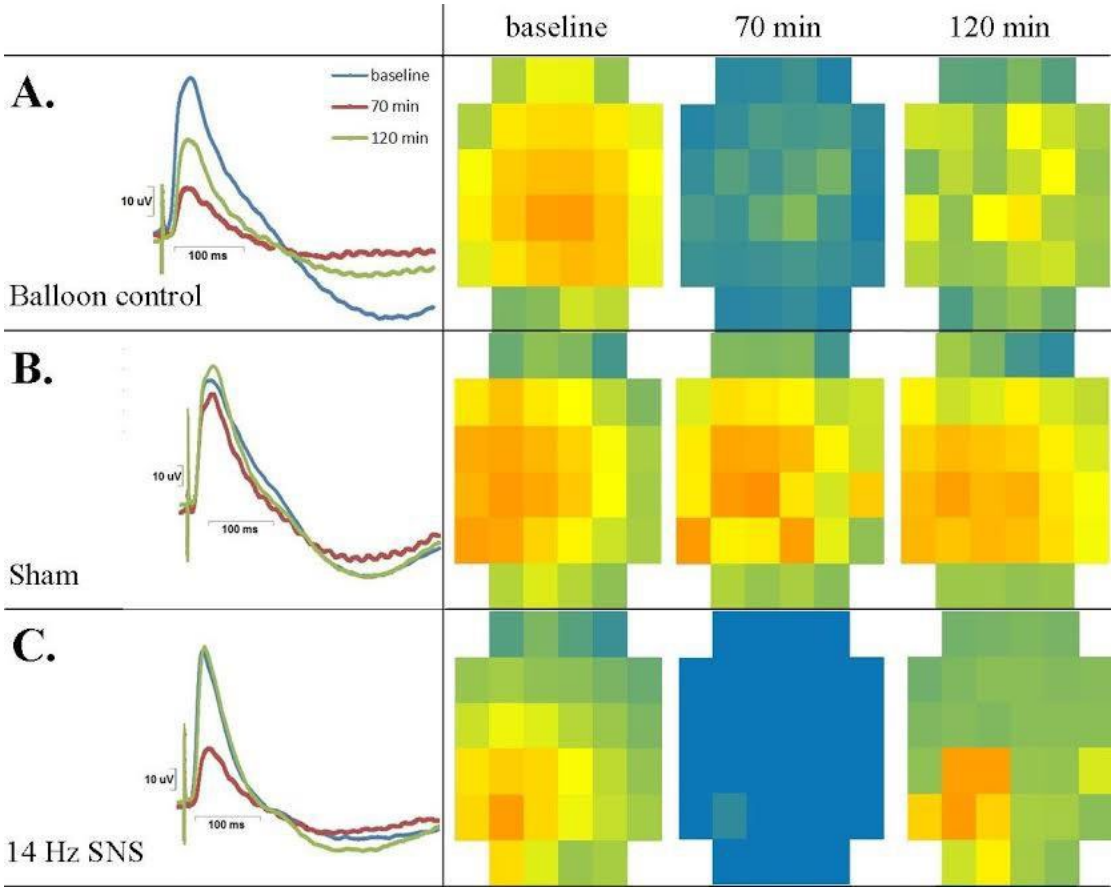
23 APPENDICIES

Appendix I

Project timetable, milestones and Stop/Go Decision points

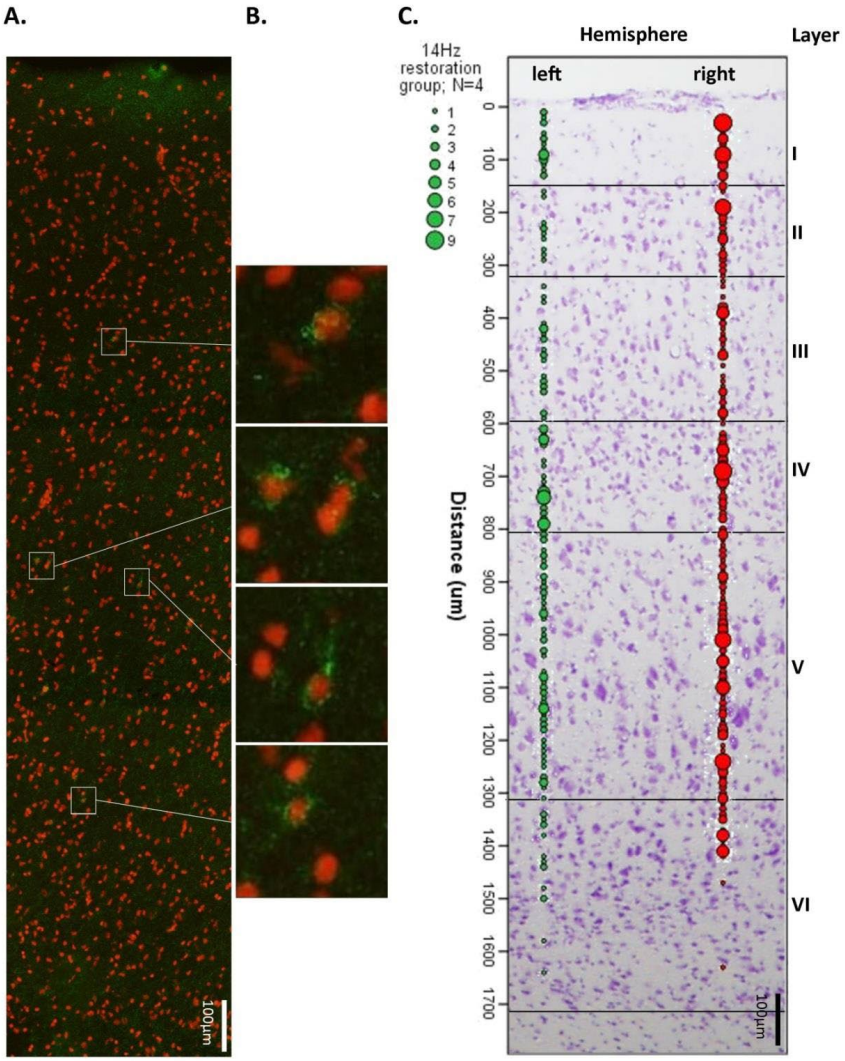
Milestone	Start date	End date	Start date	End date	Measure
Project start	01.04.17	NA	01.04.17	NA	NA
Project set up (part fund)	01.04.17	31.08.17	01.04.17	31.08.17	Staff recruitment, all approvals (5 months)
50% recruitment	01.09.17	31.05.18	01.09.17	31.08.19	45 patients randomised
100% recruitment	01.06.18	28.02.19	01.09.19	31.08.20	90 patients randomised
50% complete crossover study	01.06.18	28.02.19	01.09.19	31.05.20	45 patients complete XO study
100% complete crossover study	01.03.19	30.11.19	01.06.20	31.05.21	90 patients complete XO study
50% complete follow up study	01.06.18	31.08.19	01.09.19	30.11.20	37 patients complete study
100% complete follow up study	01.09.19	31.05.20	01.12.20	30.11.21	75 patients complete study
Data clean and analysis (crossover/mechanistic study)	01.11.19	31.03.20	01.01.21	30.09.21	Draft report tabulated results
Write up report (crossover/mechanistic study)	01.04.20	31.05.20	01.09.21	30.11.21	Submission to NETSCC
Data clean and analysis (cohort study)	01.06.20	31.08.20	01.07.21	28.02.22	Draft report tabulated results
Write up report (cohort study)	01.09.20	31.10.20	01.01.22	30.04.22	Submission report (Medtronic)
Publication consolidated results	01.11.20	30.11.20	01.05.22	31.05.22	

Appendix II figure 1



Anal canal evoked cortical potentials in the anaesthetised rodent.
In panel A, a baseline evoked cortical potential at primary somatosensory cortex is shown with blue line. Pelvic floor distension for one hour reduced the amplitude of the potential (red trace). An hour later there was some recovery (green trace). The fasle colour maps on the right show the peak amplitudes of 32 evoked potentials recorded using a multi-electrode array. In B a sham balloon inflation in the pelvis had no effect. In C acute S1 nerve root stimulation (14Hz) restored the diminished potential to its baseline value (blue and green traces overlap).

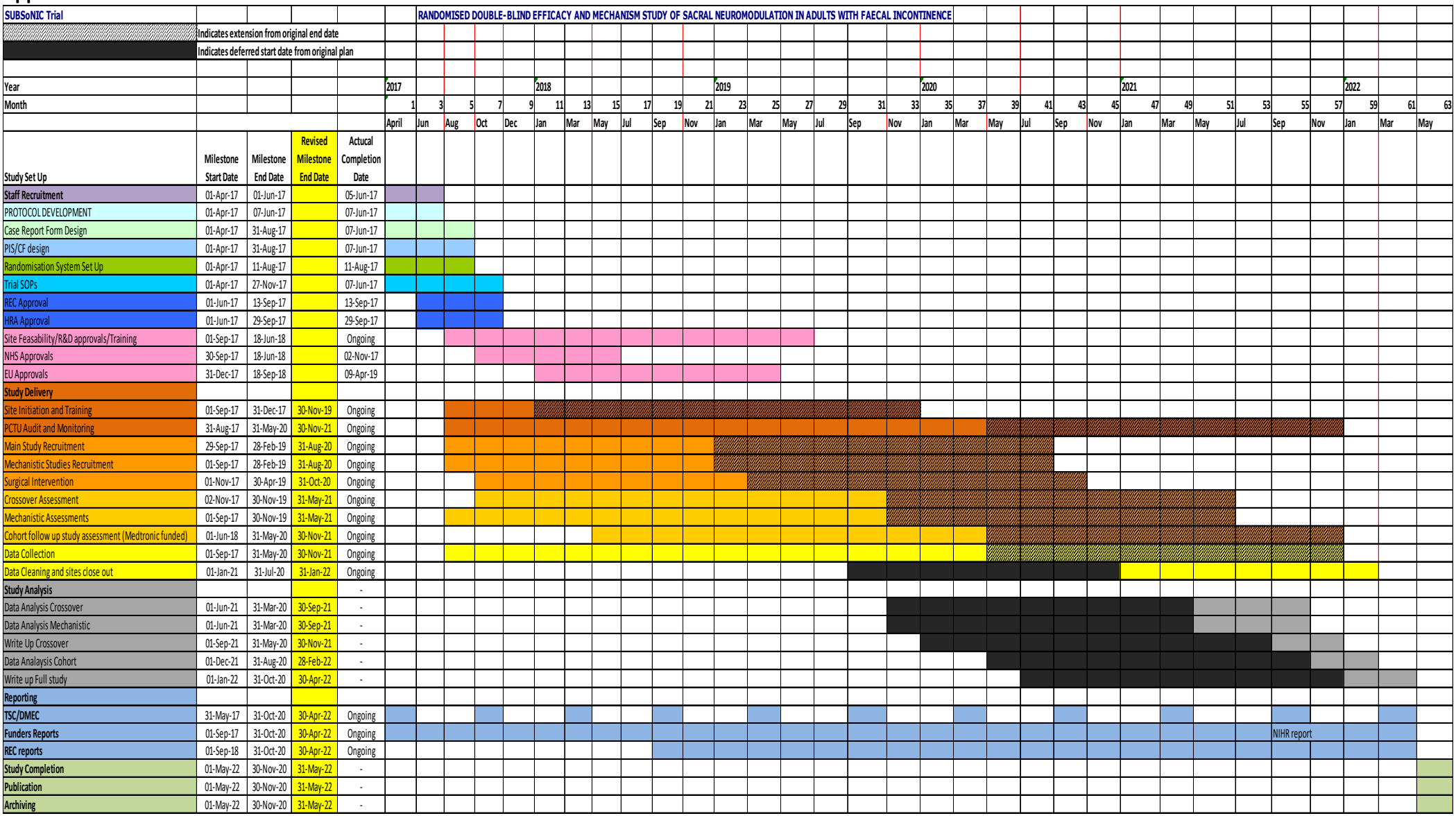
Appendix III figure 2



The distribution of neural cell adhesion molecule (NCAM) in the layers of the rat primary sensory cortex containing the anorectal representation.

In A, a low power micrograph montage shows the full cortical thickness, the red dots represent nuclei and the green stain is NCAM, shown at higher power in B. A spatial density map of NCAM distribution was constructed from all animals (n=4) (C). Following left sided acute S1 nerve stimulation at 14Hz there was a contralateral increase in NCAM expression which was marked in layers 1 and 2.

Appendix IV: Gantt chart



Appendix V: Site Codes

NHS Trust	Site Code
Bart's Health NHS Trust [Knowles]	BLT
Cambridge University Hospitals NHS foundation Trust [Powar]	CUH
NHS Lothian, Western General Hospital, Edinburgh [Collie]	LOT
Plymouth Hospitals NHS Trust [Lai; Oppong]	PLY
Sandwell and West Birmingham NHS Trust [Gill]	SWB
University College Hospital London [Emmanuel]	UCL
University Hospital Birmingham NHS Trust [Bagul]	UHB
University Hospital Leicester NHS Foundation Trust [Miller; Ho]	ULH
University Hospital of South Manchester NHS Foundation Trust [Telford]	USM
Manchester University NHS Foundation Trust, Manchester Royal Infirmary [Curran]	UCM
University Hospital Southampton NHS Foundation Trust [Dudding]	SOT
Ashford and St Peters NHS Trust [Nisar; Thomas]	ASP
University Hospitals of North Midlands NHS Trust [Farmer]	UNM
St Marks Hospital at The North West Hospitals NHS Trust [Vaizey]	SMH
Sheffield Teaching Hospitals NHS Foundation Trust [Kelly]	STH
European Site	**Site Code**
St Vincent's Hospital, Dublin [O'Connell; Hanly]	SVH
University of Erlangen, Germany [Matzel]	ERL