# *Enhanced percutaneous nerve evaluation (ePNE) of sacral nerve stimulation (SNS) using a double-blinded sham-controlled crossover test for idiopathic constipation: Quantitative and Qualitative enquiries. (The TiLTS-cc and Essence studies)*

ETHERSON, KEVIN,JON

# Enhanced percutaneous nerve evaluation (ePNE) of sacral nerve stimulation (SNS) using a double-blinded sham-controlled crossover test for idiopathic constipation: Quantitative and Qualitative enquiries.

(The TiLTS-cc and Essence studies)

1 Volume

Kevin Jon Etherson MB ChB FRCSEd

## Abstract

**Introduction**: Sacral nerve stimulation (SNS) has been increasingly utilised as a clinical treatment for chronic constipation (CC), but only a small subgroup of patients seem to respond to costly long-term treatment and the peripheral nerve evaluation test (PNE) appears less accurate than in other conditions. The lived experience of patients receiving SNS treatment, within a trial or in routine practice for any condition, is also unknown.

**Methods**: Two systematic reviews were conducted to evaluate i) the efficacy of SNS testing, and ii) the patient experience. This was followed by a randomised sham-controlled crossover trial of a newly devised enhanced peripheral nerve evaluation (ePNE) test for SNS (the TiLTS-cc study), and a qualitative study of experiences of receiving SNS treatment for CC (the Essence study).

**Results**: A total of 45 people were randomised, from which 29 (64%) were responders and 27 were implanted with a permanent pulse generator. At 6 month follow up there was no evidence of a difference in response between ePNE discriminate responders (60%) or ePNE indiscriminate responders (57%) (P=0.76, sensitivity 75%, specificity 15%). The study was terminated early (45/75) due to concerns regarding safety, with an infection rate of 22%. Qualitative findings, with a total of 8 people, demonstrate a constant pursuit for control over the disease, a willingness to participate in an invasive trial motivated by desire for a curative treatment, and perceptions of symptom benefit that trial definitions of benefit did not fully capture.

**Conclusion**: The ePNE test of SNS cannot be recommended for any condition due to the high infection risk. The effect of SNS in treating CC may simply be a placebo effect, or sub-sensory SNS may be ineffective for CC. Because of patient willingness to participate in highly invasive and intrusive trials, trial design in this population should carefully monitor ongoing patient burden and patient perceptions of benefit.

# Enhanced percutaneous nerve evaluation (ePNE) of sacral nerve stimulation (SNS) using a double-blinded sham-controlled crossover test for idiopathic constipation: Quantitative and Qualitative enquiries.

(The TiLTS-cc and Essence studies)

1 Volume

Kevin Jon Etherson MB ChB FRCSEd

This thesis is submitted for consideration of the doctoral degree of doctor of philosophy (PhD) in health research

Faculty of Social Sciences and Health

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Supervisors

Dr Helen Close PhD

Professor Yan Yiannakou MD

Professor James Mason D.Phil

Professor Luke Vale PhD

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## LIST OF ABBREVIATIONS

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| **GCP** | Good Clinical Practice | 104 |
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| **ICH** | International Conference of Harmonisation | 104 |
| **IDMC** | Independent Data Monitoring Committee | 147 |
| **IBS-C** | Irritable Bowel Syndrome (Constipation Predominant) | 23 |
| **IBS-D** | Irritable Bowel Syndrome (diarrhoea predominant) | 24 |
| **IPG** | Implanted pulse generator | 2 |
| **MSV** | milliSieverts | 142 |
| **NHS** | National Health Service | 20 |
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| **SAE** | Serious adverse event | 68 |
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## LIST OF ABBREVIATIONS

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| **SV** | Sieverts | 142 |
| **SYM** | Symptoms | 32 |
| **TMG** | Trial Management Group | 143 |
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| **UHND** | University Hospital of North Durham | 94 |
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## Declaration

This thesis is based on joint research involving those listed in the acknowledgements as well as members of the Durham Clinical Trials Unit. The quantitative study (TiLTS-cc) was a National Institute for Health Research-Research for Patient Benefit (NIHR-RfPB) programme grant funded study. I made significant design contributions to this study as discussed in Chapter 5, and I was central to recruitment, patient surgery, follow-up data collection, analysis, evidence synthesis, day-to-day project management, and liaison with team members to ensure the timely, safe completion of the study. Apart from this necessary declaration, I can confirm that this thesis is my original work.

## Statement of Copyright

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I would also like to thank Professor Luke Vale for agreeing to supervise me and help push me over the finish line in the last year. Your generous contribution played a huge part in completing this project.

**Dedication**

Working as a surgeon causes an enormous strain on any family. I frequently regret the amount of time I spend at work and wonder why I chose this profession. In those times I try to remember that without modern medicine and surgery, I would have no family.

*This thesis is dedicated to my children:*

*Abigail, the bravest little girl in the world, and*

*Kate, the most caring little girl in the world.*

*"The art of medicine consists in amusing the patient while nature cures the disease"*

*Voltaire*

The words of French author and enlightenment philosopher Francois-Marie Arouet [Voltaire] (1694-1778) describe what is now referred to as "the placebo effect". Patients can improve their symptoms simply by believing that a doctor's amusing treatments are helping them or because their bodies are naturally healing (regression towards the mean).

Scientific medical research in pursuit of the philosophical truth about the efficacy of a given treatment should always adjust for this, and surgeons in particular should pay heed to this advice.

# Chapter 1- Stimulation for constipation: the pathway from community to tertiary intervention

## 1.1 Introduction to the Thesis

This thesis will present original research on a novel testing technique devised in an attempt to predict long term response to sacral nerve stimulation (SNS) in patients suffering from chronic constipation. I will present a background to the disease and the current treatments used for it in Chapter 1, and then proceed to highlight the knowledge gaps on SNS for constipation through systematic literature reviews in Chapters 2 and 3. Chapter 4 will use the conclusions of the reviews to synthesise the research aims and objectives used to inform quantitative and qualitative study designs presented and discussed in Chapter 5. Chapters 6 and 7 will present and discuss the research findings, and Chapter 8 will then fuse the key knowledge into a formal conclusion for the thesis.

Current evidence shows that only a small proportion of patients who suffer from medically refractory chronic constipation will benefit from SNS, and the current 2-3 week peripheral nerve evaluation test does not adequate identify them before implantation with a permanent SNS device. Identifying the true responders within this group would mean SNS has the potential to prevent these patients from progressing to more expensive and potentially dangerous surgical treatments, and may potentially offer relief from a debilitating disease. As little is known about how to select these patients, and of their perceptions and lived experience of the disease and interventional treatment, a quantitative and qualitative research approach will be used to allow a greater breadth and depth of possible research findings and conclusions within this thesis.

## Introduction to Chapter 1

This chapter will examine the epidemiological, clinical and experiential challenges in treating chronic constipation (CC) in the context of patients suffering from a "functional" disorder (a debilitating condition with no clear pathological explanation), and give a critical appraisal of the standard treatments these patients encounter in routine NHS practice and internationally. The chapter will then outline the background to and rationale for, the positioning of sacral nerve stimulation (SNS) for treatment refractory individuals within current treatment pathways for chronic constipation. The nature and aims of the proposed research will be outlined within this context.

## 1.2 Aetiology

Constipation is a word used by patients and physicians to describe a wide range of symptoms perceived and attributed to infrequent defecation, or inadequate function of defecation. The majority of patients have secondary causes for their constipation which are mostly reversible or easily treated with simple, low cost laxative therapies. Doctors are becoming increasingly aware of a minority who are a severely affected group of patients, and thought to have primary progressive symptoms. Common pathologies are routinely excluded in this group. Their symptoms have been categorised extensively by the Rome foundation which has led to a definition of "functional" or "chronic" constipation (CC), which is a primary idiopathic condition; an unknown aetiology. When doctors do not understand the mechanism of symptoms and have excluded known pathologies, patients are often referred to as having a functional disorder.

The word constipation is used, therefore, to describe both symptom(s) due to diet, medication or secondary to other pathology, and a severe but poorly understood primary functional gastrointestinal disorder (FGID). The prefix "chronic" is

frequently used to indicate the persistent and treatment refractory nature of the condition. Those suffering from chronic constipation (CC) are usually further divided after specialist investigations into separate groups: those who have a slow gut transit speed (termed slow transit constipation-STC), those who have a normal gut transit speed (termed normal transit constipation-NTC), and those who suffer from mechanical obstruction during defecation (termed obstructed defecation-OD) (1, 2).

In practice, patients are not neatly defined by these groups as there is a substantial number of patients who can fulfil inclusion criteria for 2 of these groups. For the purpose of this chapter, I will therefore focus on the whole group of patients classified within CC for this study.

Recent years have seen widespread acceptance that there are likely to be undiscovered pathological mechanisms playing a role in CC, and there is evidence of this emerging in academic journals. This ranges from understanding the role of "normal" neuromuscular bowel physiology in humans (3), to a focus of laboratory-based animal research into the enteric nervous system and its role in the pathophysiology of CC (4). Histological reports of neural abnormalities in bowel sections of humans suffering from CC date back to 1977 when a case series of 4 patients reported a possible developmental abnormality in the myenteric plexus (5). This is the poorly understood motor nerve supply (sympathetic and parasympathetic) of the intestinal circular and longitudinal muscles. Subsequent studies have reported further evidence of both neural abnormalities using standard and specialised tissue staining techniques (6-10), and of neuromuscular abnormalities in the bowel (11). Recently, leading academics in this field have published a classification system for histological findings of neuromuscular bowel pathology (12) and issued guidance on the specialist techniques pathologists should employ to identify them in affected patients (13). This is an attempt to standardise

the methods of tissue acquisition, pathological examination and reporting of these conditions across the world. This uniform scientific protocol and classification system will improve the production rate and quality of evidence of pathology in these “functional” gastrointestinal conditions. In future, researchers hope to be able to diagnose and ultimately treat specific pathological conditions that were once thought to be FGIDs.

### 1.3 Classification of CC

Doctors have struggled to understand and treat the patient with CC for many years now, and it was in 1990 that the term “functional constipation” was coined to describe a particular group of patients with similar symptoms in what was then the Rome I criteria. The latest incarnation of this is the Rome IV criteria; at the time of study design the Rome III criteria for FGIDs was used (14) and defined these patients according to the following criteria:

Two or more of the following symptoms at least 25% of the time:

- Straining at defecation
- Lumpy or hard stools
- Sensation of incomplete defecation
- Sensation of anorectal obstruction/blockage
- Manual manoeuvres to facilitate defecation
- Less than 3 defecations per week

To fulfil the criteria patients must also only rarely have loose stools unless laxative induced, and be consistent during the preceding 3 months with the onset of their symptoms at least 6 months prior to diagnosis.

To clarify an important issue with the Rome criteria, there are also patients who suffer from similar CC but their predominant symptom is abdominal pain. These

patients are described as suffering from an irritable bowel syndrome (constipation predominant or IBS-C) within the Rome III criteria (14) and are defined as follows:

Patients who suffer from recurrent abdominal pain or discomfort for at least 3 days each month in the last 3 months who have 2 or more of the following:

- Improvement of pain with defecation
- Onset of pain associated with change in frequency of stools
- Onset of pain associated with change in form of stool

They must also have lumpy or hard stools at least 25% of the time, and loose stools less than 25% of the time to fulfil the criteria.

This causes confusion amongst clinicians, and is debated in both clinical and academic arenas; it is observed in practice that many patients fulfil both criteria simultaneously, and encounter the same medical investigations and treatments. In 2010 a prospective study reported 1100 adults attending primary care for self-reported constipation, who together with 1700 age and gender matched controls completed a survey on study enrolment and again after 12 months (15). The authors reported that 90% of IBS-C patients also fulfilled FC, and 50% of FC patients also fulfilled IBS-C. The Durham constipation clinic (DCC) is a NHS tertiary centre whose prospective database has 90% of patients fulfilling criteria for FC, 50% fulfilling IBS-C, with 47% fulfilling both, 43% FC only, 3% IBS-C only, and 6% neither. However, these are patients suffering from symptoms severe enough to be referred to a tertiary centre for further investigation and treatment, all of whom would self-report the main cause of their condition as chronic constipation. It is entirely plausible that the Rome III criteria does not adequately distinguish between what is likely to be a spectrum of similar symptoms caused by multiple but subtly different underlying pathologies. Its usefulness should therefore be questioned and its use in clinical studies should be to encompass both FC and IBS-C; consequently

patients in the TiLTS-cc trial (described in Chapter 5) are eligible if they fulfil FC but not excluded if they also fulfil IBS-C, and so termed as suffering from CC.

## 1.4 Epidemiology of CC

The epidemiological factors in chronic constipation have been well documented throughout international literature over the past 20 years. Clinicians and researchers throughout the world have finally grasped the scale of this problem, which is significant, and there are consistent findings which are giving new insights into the condition.

### 1.4.1. Prevalence

The prevalence of CC has been reported throughout the world at between 3.6% to almost 28%. Pre-1992 there was a paucity of data which led Lennard-Jones (St Mark's Hospital, London) to highlight that this severe condition of young women had "remained largely unrecognised since the time of Arbuthnot Lane" (1909), and that "constipation is often regarded as a trivial symptom but for patients it was a major disability" (16). Post-1992 the problem was recognised internationally. There are over 100 papers to date and several systematic reviews and meta-analyses. The 2004 North America review estimates the prevalence in a range of 1.9%-27.2%, with most between 12-19% of the North American population (17). A similar range was estimated in a 2008 review, with a mean value of 17.1% given for European prevalence and 15.3% for Oceania (18). The largest systematic review and meta-analysis to date pooled a prevalence of 14% over 261,040 subjects from 41 populations (19). These studies consistently demonstrate that CC is a common disorder affecting a considerable number of people across the world. The most striking finding, however, is the consistency in reporting a significantly higher proportion of affected females, with the female to male ratio always exceeding 2.2:1, and becoming considerably higher when severity is taken into account.

The ongoing DCC database currently has data on 736 (88%) female and 101(12%) male, a F: M ratio of 7.3:1, a collective mean duration of symptoms of 19.53 years (range 0-76 years) (M=17.5, F=19.8), and a mean age at tertiary presentation of 43.4 years (range 17-86 years) (M=51.7, F=42.2). 253 (30.23%) had onset of symptoms in childhood of which 122 (15%) were in infancy. This seems to suggest that females are more frequently affected by the severest form of the condition, and that most sufferers present or are referred for specialist investigation many years after onset, highlighting the truly chronic nature of the condition.

Prevalence is also consistently reported as increasing with age (17, 20-22), socioeconomic deprivation (19, 23), psychological co-morbidity (24) and with a history of physical or sexual abuse (25).

### 1.4.2. Burden of disease

#### 1.4.2.1. Quality of life

Overall CC is recognised as common in Western societies and patients who suffer from this tend to be more commonly young and female, and report a significant deterioration in their quality of life (26). Their experiences are well documented in the literature and include "*feelings of hopelessness"* in the condition and "*frustration"* at perceived lack of clinician empathy or simply "*not being taken seriously*" (27). Several large studies have reported deterioration in health-related Quality of life (HRQoL) when measured using the short form-36 (SF-36). A Canadian study of 1149 subjects in 2002 demonstrated CC as a common and stable condition with significant impairment of HRQoL (28). A similar conclusion in a larger multinational study was reported in 2007, with the authors also noting that HRQoL impairment was greater in women than men and comparable across all countries involved. The cause of this is unknown but postulated to be either due to variation in underlying aetiology between the sexes or women being more likely to disclose

the severity of the disease and present to a healthcare provider for further investigation and treatment. The authors positioned the overall impairment as comparable in QoL impairment to well-known organic conditions such as chronic obstructive pulmonary disease, hypertension, diabetes, heart disease or depression (29).

**Survival**

There are conflicting data on morbidity and mortality in FGIDs, but the general consensus is that long-term survival is no different to the general population (30). Notable for our study participants is the recent suggestion that the FGID subgroup with chronic constipation may actually have a poorer survival when compared to FGIDs with other predominant symptoms (31). This may be due to the increased likelihood of surgical intervention in patients with chronic constipation, although incidence of surgical intervention was not considered by the authors and this warrants further investigation.

### 1.4.2.2. The economic & health care burden

A medical condition with global evidence of significant prevalence and chronicity on this scale undoubtedly causes strain in any healthcare system. The American Gastroenterological Association reported that almost 8 million primary care consultations in 2004 were attributable to constipation (1). In the NHS (in England) in 2011, 71 million pounds of laxatives were prescribed in the community, which accounted for 16.5% of the 429 million pounds of prescriptions for gastro-intestinal diseases (32). The economic and health care burden of constipation is further emphasised by the statistics for inpatient admissions, where more than 57,000 patients were admitted to hospital in England in 2011 with primary discharge diagnosis of constipation, with over 42,000 presenting as emergencies, and an overall mean length of stay of 3.3 days (33). Sufferers of this disease who have a

significantly impaired HRQoL subsequently increase their health care utilisation (28); the condition therefore poses a challenge to any healthcare system (34) especially as the treatment costs increase with disease severity and bowel symptom exacerbations(35).

## Psychological considerations in CC

Most clinics who treat patients suffering from CC adopt a biopsychosocial model of treatment, recognising that these patients cannot be effectively treated solely with a medical or surgical therapy, and that there is a preponderance of psychological and social influences in their condition (27). Wainwright et al speculate that clinicians will view the social and psychological influences as less relevant and important if future treatments improve sufficiently to be considered as a cure for the condition, which would then be regarded as organic in aetiology (as opposed to functional). Researchers are far from this position and recognise that psychological distress could be involved in the pathogenesis of CC (36), that anxiety and depression are prevalent in this group (36) and it is widely accepted that the associated chronic pain can improve with a variety of psychological and behavioural treatments (37). Psychotherapy, in particular seems to be an effective adjunct to medical treatment in some patients (38), and this may be due to the widely recognised association of physical and sexual abuse amongst sufferers (25, 36, 38). My experience, and that of the Durham Constipation Clinic, suggests patients tend towards being a highly motivated group of individuals who are seeking a resolution to their condition and therefore demonstrate a willingness to participate in clinical trials (evidenced by high recruitment rates at DCC). There is a knowledge gap surrounding their motivations for this alongside anecdotal evidence of a heightened placebo response to therapies which this study will seek to address using both qualitative and quantitative methods.

## 1.5 Summary of treatments

### 1.5.1. Medical

When patients first attend their GP with the symptoms of constipation they will usually receive dietary advice (increase dietary fibre and adequate hydration), and be prescribed simple first line laxatives (sometimes fibre supplements). If other symptoms or signs on examination are suggestive of a secondary cause for their constipation they may be investigated for underlying pathology. Table 1 below outlines the usual first line laxatives GPs will prescribe from using the British National Formulary (2019).

**Table 1- First line laxatives, compiled from BNF 77 (March-September 2019)**

| **Type of laxative** | Generic name (brand name) | Mechanism of action |
|---|---|---|
| **1.Bulk-forming laxatives** | Ispaghula husk (fybogel®)<br>Methylcellulose (celevac®)<br>Sterculia (Normacol®) | Stimulates peristalsis by increasing faecal mass |
| **2.Faecal softeners** | Arachis oil enemas (non-proprietary)<br>Paraffin liquid (BP) | Lubricant and stool softening properties |
| **3.Osmotic laxatives** | Lactulose (lactugal®, Laevolac®)<br>Macrogols (Movicol®, Laxido®, Molaxole®)<br>Magnesium salts (various)<br>Phosphates-rectal (various)<br>Sodium citrate (Micolette®, Micralax®) | Increase water content of colon through either osmosis (from serum) or decreasing absorption. |
| **4.Stimulant laxatives** | Bisacodyl (Dulcolax®)<br>Sodium Picosulphate (Dulcolax®Pico)<br>Anthraquinones (Sennokot®Manevac®)<br>Docusate Sodium (Dioctyl®, Docusol®) | Intestinal motility increased |
| **5.Bowel cleansing preparations** | Macrogols (Klean-prep®, Moviprep®)<br>Magnesium citrate (Citramag®)<br>Phosphates-oral (OsmoPrep®, Fleet Phospho-soda®)<br>Sodium Picosulphate with magnesium citrate (Picolax®, Citrafleet®) | Combinations of 3&4 above with 5 to prepare bowel for surgery or endoscopy.<br>Not licensed for chronic constipation but used by GP's and specialists in practice. |

Patients will usually receive combinations of bulk-forming laxatives and osmotic laxatives initially, progressing onto combinations of osmotic and stimulant laxatives if their symptoms persist. The majority of patients will respond to these simple dietary and laxative treatments; those truly suffering from chronic constipation will be laxative refractory and may even use bowel cleansing preparations on a regular basis (once to twice weekly). These patients are usually referred to specialist secondary/tertiary care after failing 2-3 combinations of treatment with their GPs.

All patients referred to specialist care for diet and laxative refractory constipation are assessed according to the Rome III criteria, and a detailed medical history and examination obtained to rule out pathological causes. Patients are then classified as truly functional in aetiology and appropriate investigations are requested to demonstrate if slow colonic transit, disorders of defecation or both are contributory. Initially patients will be prescribed a course of a selective serotonin 5HT4 receptor agonist (Prucalopride, Resolor®), which is NICE approved (2010) in patients with evidence of chronicity. This has prokinetic properties that decrease colonic transit time, and has recently been studied in phase 3 trials which have concluded that it is safe and effective in CC (39-42). 5 years ago 2 intestinal secretagogues (Linaclotide and Lubiprostone) became FDA approved for CC; these primarily act by increasing intestinal chloride content through mucosal secretion, which results in water being drawn into the lumen (43). These were recently licensed in the UK although most clinicians in primary care will not commence treatment with these and they are primarily prescribed in secondary care. A meta-analysis of placebo controlled studies of osmotic laxatives, stimulant laxatives, Prucalopride, Linaclotide and Lubiprostone for CC has demonstrated superior response in the treatment groups (44), which firmly underlines their position as first and second line treatments in CC.

### 1.5.2. Minimally Invasive Therapies

Patients who fail to respond to these first and second line medical treatments may be treated with biofeedback or trans-anal irrigation.

#### 1.5.2.1. Biofeedback

Patients are selected for treatment with biofeedback by physiological testing which seems to indicate "anismus"—a paradoxical contraction of the anal sphincters on attempted defecation. It is performed by physiotherapists and nurses throughout the NHS, with several techniques employed to help them relax these muscles at the appropriate physiological part of defecation. The methods employed vary from a practitioner using a digit to physically feel when the patient is contracting the muscles incorrectly during a simulated strain, or using a catheter and balloon which measure manometric pressures which are "fed back" to the patient via either auditory or visual stimulus. In the DCC an electromyography (EMG) tracing is used to visually feedback when patients are contracting the muscles during a simulated strain, where they try to expel a rectal balloon. This has been likened, to the sort of muscle training and co-ordination learned when playing a video game, which itself is a form of visual biofeedback, or pelvic floor muscle re-training exercises for urinary incontinence, which are also efficient and effective.

The evidence for this treatment is subject to debate amongst experts, with reviews demonstrating evidence of efficacy in defecation disorders (43, 45), whilst also admitting that the controls used in these studies are very different to the treatment (consequently un-blinded) and variable (either standard laxatives, or muscle relaxants). It is difficult to design a RCT with a suitable control group for biofeedback, and future studies should aim to achieve this in order to provide high quality evidence that can be subject to consistent eligibility criteria in meta-analysis. In the 4 trials that have attempted a control group to date, 2 were positive for biofeedback (46, 47), whilst 2 reported an improvement against baseline

symptoms but not between treatment and control groups (48, 49). Biofeedback currently seems to have a place in the treatment of defecatory disorders in CC, although more conclusive evidence is required in the longer term.

#### 1.5.2.2. Trans-anal Irrigation (TAI)

Colonic or trans-anal irrigation has been performed as a medical treatment for Millennia, TAI is simply the latest incarnation, although arguably the only form with any substantial evidence. Little is known about the extent or exact mechanism of action, but it is thought that irrigation helps to effectively mechanically empty the descending colon and bowel distally, which has been demonstrated scintigraphically (50). The first long term follow-up published in 2004 looked at a consecutive series of 267 patients with either faecal incontinence (FI) or obstructed defecation (OD) who had failed conventional medical treatment and biofeedback, reporting an effective response to treatment of 65% in the OD group at 80 months (51). More recently a systematic review reported successful treatment in the CC group at 117/259 reported cases or 45% of the treatment population (52). The authors proposed that the treatment should be administered after patients had failed medical therapy and before considering irreversible surgery. The Durham experience replicates these results, where a retrospective study demonstrated TAI as an effective second line treatment for a large proportion of patients (48%) who continued treatment for mean duration of therapy of 75 weeks (53). The procedure has been extensively reported as simple to perform and relatively safe (54), with the estimated risk of the most serious complication (TAI induced colonic perforation) being less than 0.002% per irrigation.

### 1.5.3. Surgical

Only the most severely affected and treatment refractory individuals suffering from CC deteriorate further to be considered suitable for attempted treatment through

neuromodulation. Evidence about rates of surgical interventions is currently unavailable but prevalence is thought to be low.

#### 1.5.3.1. Neuro-modulation (SNS)

Sacral nerve stimulation (SNS) is the original form of abdominal neuromodulation that has proven to be a successful treatment for patients suffering from non-obstructive urinary retention, urinary urge incontinence and faecal incontinence, and is currently approved for use in these conditions in the NHS (12, 55, 56). It is not FDA approved for use in the US (1), or NICE approved in the UK for the treatment of CC. Recently European centres have published several case series (57, 58), pilot studies (59, 60) and a clinical trial suggesting SNS may benefit a proportion of CC sufferers (61). The procedure involves a testing phase which attempts to predict if a sufferer will demonstrate a long-term response to the permanently implanted pulse generator (IPG), and this is far less accurate in CC sufferers with a predictive success of just over 50% (62). Patients require a primary procedure to implant a testing lead under anaesthetic which is externalised to a temporary testing stimulator which they can adjust, and typically sensory stimulation is given for 2 weeks. If bowel diaries and validated questionnaire scores (PAC-SYM and PAC-QOL) demonstrate a response to stimulation then patients are offered a permanent IPG in a secondary procedure. The poor performance of the test in CC may be due to many various factors. These may include a potentially enhanced placebo effect in CC sufferers, the short duration of the test (2 weeks) due to limitations in the temporary testing lead, and biases in the clinical interpretation of testing results. The test itself is a cumbersome experience for patients and there is no evidence of patient acceptability, satisfaction or experience in the literature. However, the Durham experience (see below) suggests a strong safety profile and the potential for SNS to avoid high-risk, high-cost, low efficacy surgical interventions outlined below. These issues will be addressed in detail in Chapter 2 and provide a rationale

for a trial to examine a novel testing method for SNS which forms the main part of this thesis (Chapters 5 and 6).

#### 1.5.3.2. Percutaneous tibial nerve stimulation (PTNS)

PTNS is a new form of neuromodulation that is currently being investigated for similar applications as SNS. It involves inserting a small needle like electrode under the skin near the tibial nerve at the ankle, and patients receive weekly exposures of stimulation lasting 30-45 minutes in an outpatient clinic. It is considered to be a serious rival to SNS in the treatment of faecal incontinence (FI), and studies are underway to compare the procedures in this condition. One small pilot study to date has provided empirical evidence of treatment response in CC (63), with 18 patients demonstrating improvement in Wexner score, PAC QOL and stool frequency. The Confident study group reported, however that there was not effect over sham stimulation for FI (64), and therefore PTNS needs a well-designed longer term multicentre trial in order to provide any evidence for use in CC.

#### 1.5.3.3. Stomas/ACE procedure

Patients who fail to respond to neuromodulation, and who also have severely affected quality of life are offered surgical irrigation through formation of an appendicostomy (ACE), or a defunctioning stoma. This is anecdotally reported as between 5-10% of severely affected individuals who progress to more invasive surgical treatments, with a large proportion of patients choosing to live with the burden of disease. There is no formal evidence in the literature of the true proportions and these may therefore be higher.

### Antegrade Continence Enema (ACE)

This procedure was first described by Malone in the 1980's and involves use of the appendix using the Mitrofanoff principle: to create a fistula for the passage of either urine (when the fistula is to bladder) or enema (appendicostomy-the fistula is to

the bowel), with a continent valve fashioned (65). Through this patients with CC can perform antegrade colonic irrigation to relive CC. The literature predominantly reports efficacy in children with those suffering from CC showing an overall improvement in well-being, albeit with significant stomal complications (stenosis, leak and pain) (66). There is little evidence in adults with CC, and these are limited to a few case series reporting a general improvement. These typically report an improvement in defecation time and quality of life (67), but both adults and children require revision surgery in a significant proportion of around 17% (68), usually for stenosis, hernia or infection. This seems to be the most common complication of ACE, and can be either as a self-limiting superficial wound infection, or a deeper abscess, with either occurring in up to 45% of all patients (69). Overall it appears that using an appendicostomy is still relatively safe and does give a proportion of patients' symptomatic relief without major sequelae, and typically the fistula and irrigation can be managed for up to 5 years, after which the fistula tends to fibrose and stricture, and can no longer be used. This justifies consideration of ACE irrigation prior to major surgery or stomas.

### Defunctioning loop Ileostomy

A loop ileostomy, sited on the right of the abdomen, can be either an acceptable treatment for CC (for patients who tolerate a long-term stoma), or a way to trial if a total colectomy and ileorectal anastomosis will actually improve their symptoms. It has the advantage of being completely reversible if symptoms remain unchanged and/or the patient cannot cope with or manage the stoma. Ileostomies have a high rate of complications in general (29%), mostly due to infection, hernia or retraction requiring surgical revision, and to minimise these a loop ileostomy should be performed via a trephine rather than a laparotomy (70). If the stoma seems to considerably improve symptoms and function, then the patient may benefit from

either continuing or proceeding to a subtotal colectomy with ileorectal anastomosis.

### Colostomy

The use of a formal colostomy, which is typically sited on the left of the abdomen and formed from an end of descending colon after sigmoid colectomy (Hartmann's procedure), has only been reported in a small cohort of children with severe CC. This seems to be effective for up to 3 years with high patient satisfaction and low morbidity (71). There is no evidence of this in adults other than a single case report (72), and this is not recognised by experts as an accepted form of treatment. Between 2002-2008 endoscopically assisted percutaneous colostomy (PEC-to create a conduit for distal colonic irrigation) was attempted in adults, but the associated morbidity was unacceptably high (73). Colostomies and PECs are therefore not now considered to be a relevant treatment option.

### 1.5.3.4. Surgery for obstructed defecation

When symptoms of obstructive defecation (OD) are demonstrated through physiological testing and imaging to be primarily due to an anatomical change in the rectum, then procedures to repair these changes may benefit. These changes can be due to a forward pouching of the rectum (rectocele) which is common in women, or to a type of internal prolapse in the rectum (IRP) termed an intussusception. The stapled trans-anal resection of the rectum (STARR procedure) is one option but has failed to gain credence in either America or Europe due to concerns regarding its safety and efficacy (74, 75). Laparoscopic ventral mesh rectopexy (LVMR) is a laparoscopic procedure and a more popular option amongst UK surgeons who report it as a safe and effective procedure for both external rectal prolapse (ERP) and IRP causing OD (76, 77). This evidence is methodologically weak,

however as there are no prospective controlled trials, and surgeons have selected patients before assessing and reporting their own results.

#### 1.5.3.5. Colonic resections

Patients who have failed management of their CC with either SNS or ACE irrigation may be considered for major surgery if their symptoms are severe and impacting on their quality of life. All experts agree that this decision is not to be taken likely as there are considerable risks over benefit. There is evidence that this should only be considered in patients with physiologically demonstrable slow transit constipation (78, 79).

The first surgical treatment of severe constipation by total colectomy and ileo-rectal anastomosis was described more than 100 years ago (80) , and is now considered a last resort in extremely treatment refractory patients who are suffering, due to the associated high morbidity and even mortality of this operation (7, 81). Experience in Australia and the UK during the 1990s was similar, with studies reporting an improvement in patient symptoms, at the cost of unacceptably high morbidity and even mortality (82, 83). Most recently and surprisingly critical of all, was a 2009 study where the authors concluded that the morbidity and mortality rates after colectomy were inadmissibly high, and with such poor functional results that they would no longer recommend colectomy for slow transit constipation (84). Whilst there is evidence that laparoscopic colectomy for CC has an enhanced recovery time, there is no evidence that this reduces the post-operative morbidity and mortality compared to open surgery (85, 86).

Colectomy for severe constipation has been performed and evaluated for over 100 years now with little improvement in the outcomes. Patients appear to benefit from relief of their constipation in a range of between 70-90% depending on how carefully they are selected for surgery, but with high rates of morbidity and an

associated mortality of between 3-5%. Overall most surgical procedures do not appear to be particularly effective in treating CC, and the evidence to date would suggest that more conservative and minimally invasive treatments would be safer.

### 1.6 Algorithms of treatment

International experts in neurogastroenterology have been attempting to construct treatment algorithms in recent years for chronic constipation. There are specific differences in opinion regarding minimally invasive techniques and surgery, and the issue is further complicated by the licensing of secretagogues in the US which have not been licensed in Europe until recently, and the licensing of 5HT4 agonists in Europe earlier than in the US.

#### The American perspective

The American Gastroenterological Association (AGA) issued a technical review in 2013 (1) that separates treatments into primary care and specialist use. In primary care they emphasise investigations to exclude organic pathology and other reversible causes of constipation and the use and safety of dietary changes and osmotic/stimulant laxatives in CC. Patients failing to respond to these simple treatments are recommended for specialist referral and further investigation, ultimately with classification into 3 groups: obstructed defecation disorders (OD), slow transit constipation (STC), and normal transit constipation (NTC), with acceptance that there is overlap between them. Biofeedback is recommended for obstructed defecation initially, and when structural anatomical changes such as internal rectal prolapse are thought to be contributory; but the surgical repair of internal prolapse is not recommended by the AGA. Surgical repair of rectocele is recommended when physiological testing implies it is contributory to the obstructed defecation, but the method of rectopexy is not indicated. Patients with slow and normal transit constipation are recommended to have failed several combinations of stimulant and osmotic laxatives before proceeding to

secretagogue treatment with Linaclotide or Lubiprostone. Prucalopride is recognised as having good evidence of efficacy in slow transit constipation, but FDA approved for CC at the time of this technical guidance. No mention is made of irrigation as a possible short or long term treatment. Psychological support is recommended when patients are refractory to medical treatments and surgery is not indicated. Surgery is recommended principally to treat either obstructive defecation or slow transit constipation, but ACE irrigation, SNS, and STARR procedures are not recommended due to a lack of empirical evidence. A heavy emphasis is placed on carefully selecting patients for Arbuthnot Lane's procedure, with only those who have true colonic inertia and normal upper gastrointestinal motility, without evidence of obstructive defecation, and who respond to a de-functioning ileostomy being considered suitable for this procedure. This heavy emphasis on colectomy is likely driven by the private healthcare system in the US.

**The European perspective**

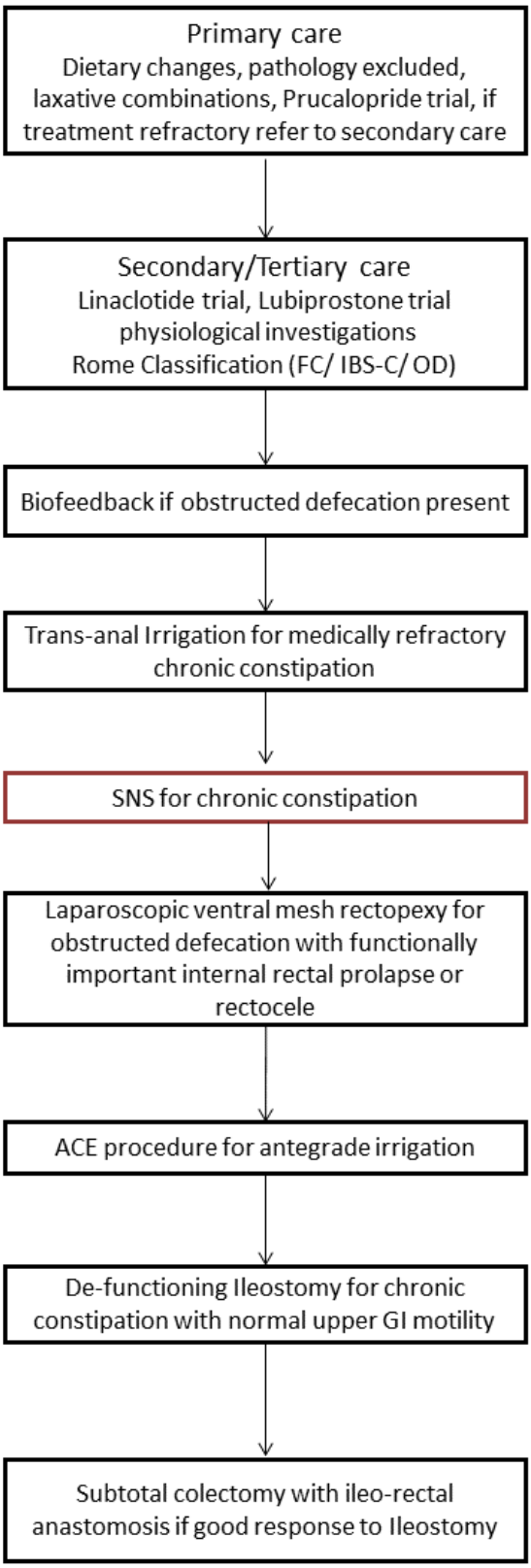
A collaboration of European experts published a treatment algorithm in March 2011 (87), which classified CC into the same 3 groups with recognition of overlap between them. Their primary care recommendations again emphasised the use of dietary changes, osmotic/stimulant laxatives whilst excluding secondary causes or serious organic pathology, but also included the use of the prokinetic drug Prucalopride after combinations of laxatives have failed and prior to specialist referral. Patients are considered refractory only after failing an adequate trial of this drug, and specialists then perform full physiological testing. Biofeedback is again recommended for obstructed defecation, but no mention is made of further surgical therapies for either obstructed defecation or slow transit constipation, other than stating that surgery should be focussed on particular disorders that

require anatomical correction, and only “as a last resort”. SNS does not feature in this guidance primarily due to the lack of high quality trials at this time.

### The Durham perspective

The current practice in Durham encompasses these international opinions with a heavy emphasis on a logical progression of treatments in the refractory patients with CC from minimally invasive procedures to formal surgery. SNS is tentatively placed on the algorithm after failure of irrigation therapies and before intra-abdominal surgery. This is based on the safety profile of SNS in comparison with these procedures, although its efficacy and cost-effectiveness remains to be established. Psychotherapy is indicated wherever treatment refractory individuals seem to report psychological issues that may be contributory or deleterious to their condition. In parallel to this patients are offered holistic therapy in the form of relaxation, mindfulness and neuro-linguistic programming (NLP). An example of the Durham algorithm that patients experience in their pathway to SNS on this study is outlined below. If a patient fails a treatment or has no indication for a treatment they descend in the algorithm. Experience of using this pathway suggests that SNS presents an acceptable, safe alternative to high-risk, high-cost surgery. Current testing regimes, however are inadequate at effectively selecting those patients most likely to benefit from SNS. There is an urgent need to understand more about the place of SNS within the treatment pathway for this challenging condition.

Figure 1 Durham treatment algorithm for chronic constipation



## 1.7 Aims and scope of the thesis studies

Chronic constipation is a common disorder worldwide, mostly severely affecting women, with a significant impact on patient quality of life and on healthcare systems. There is good evidence of a particularly severe form of chronic constipation that is refractory to simple first line primary care treatments and which therefore requires specialist intervention. Patients who are refractory to new medical treatments may benefit from minimally invasive measures such as sacral nerve stimulation, biofeedback and trans-anal irrigation in order to avoid progressing to risky, costly surgical interventions with little effect. Biofeedback and irrigation are currently under investigation internationally but sacral nerve stimulation (SNS) has no firm evidence to substantiate a position on the treatment algorithm between minimally invasive procedures and intra-abdominal surgery, although this is the logical position for SNS when considering complication profiles. The main obstacle for SNS to evolve as an accepted treatment in chronic constipation, and in gaining support from regulatory authorities, lies in the ability of the SNS test to accurately predict long-term response to treatment. It also needs to be confirmed as cost-effective in any healthcare system it is used, and to have a reasonable level of patient tolerance and acceptability in treating their condition. For a small proportion of patients with treatment refractory chronic constipation, SNS has the potential to prevent progression to these expensive, high risk, and low efficacy surgical procedures, but little is known about how to effectively select the patients most likely to benefit. SNS is thus worthy of further investigation, and so this thesis will explore the utility of SNS as a treatment by focussing on a novel idea for a new percutaneous nerve evaluation (PNE) test. This test is termed an enhanced PNE, and may be able to adequately discriminate between long term responders and non-responders to treatment. This thesis will also explore the patient experience of the disease, treatment and perceptions of treatment effect.

I will explain the current research knowledge on SNS for chronic constipation in Chapters 2 and 3 highlighting the knowledge gaps both within quantitative and qualitative studies after performing a systematic review of the literature. This will be used to synthesise the relevant aims and objectives of the thesis (Chapter 4), and inform the design of quantitative and qualitative research studies, the methodology of which will be presented and discussed in Chapter 5. Chapters 6 and 7 will present the findings of these studies and discuss their implications within the chapters independently. Chapter 8 will then summarise the key knowledge gained from each chapter and discuss the key study findings in a fusion of the two research strands to synthesise a formal conclusion to the overall thesis.

# Chapter 2 Sacral Nerve Stimulation (SNS)

## 2. Introduction

This chapter aims to critically analyse the evidence about the effectiveness of SNS and current clinical practice to justify the aims and objectives of the TiLTS-cc study and explain the research questions that provoked the study design. I will explain the background to the interventional treatment under investigation (SNS) and its evolution into a clinical therapy for chronic constipation (CC), the methods used to perform a systematic review of the quantitative literature in search of high quality evidence of the efficacy and safety of SNS for CC. I will present and discuss the results of this search and explain how this was used to synthesise the aims and objectives of the TiLTS-cc study. This chapter will therefore clearly emphasise the relevant knowledge being sought by this research before moving onto the review of the qualitative literature in Chapter 3, a summary of the combined aims and objectives of the thesis studies (TiLTS-cc and Essence) in Chapter 4 and a description of the methodology used to collect the required data in Chapter 5.

### 2.1 Overview

The conditions commonly treated with SNS in a number of countries include faecal incontinence and urinary dysfunction; in the UK, the National Institute for Health and Care Excellence (NICE) has approved SNS for use in these conditions (88-90). Clinicians consider SNS for patients suffering from chronic constipation (CC) who have failed all standard medical treatments (laxatives, pro-kinetics and secretagogues), lifestyle changes (diet and exercise), behavioural treatments (biofeedback, neuro-linguistic reprogramming, cognitive behavioural therapy), and minimally invasive interventions such as retrograde bowel irrigation. SNS is an unproven surgical intervention for CC with potential to benefit a small proportion of patients in the long-term. Clinicians across the UK currently consider it an

acceptable low-risk therapy positioned on the treatment algorithm before more invasive and potentially dangerous treatments such as abdominal surgery.

### 2.1.1. History of SNS for CC

SNS began with the first permanent implant procedure performed in 1981 for bladder dysfunction (91), and since became established as a treatment for urge incontinence and non-obstructive urinary retention. In the subsequent years clinician's observations of this group of patients seemed to suggest a concurrent improvement in bowel functions particularly constipation (92, 93) following which SNS became increasingly investigated and used clinically as a possible alternative therapy to invasive surgery for the treatment of CC (4, 60, 94, 95). Local experience of its use in Durham concurred with the opinion that it had the potential to help a minority of these patients (62). Several small prospective but uncontrolled studies claimed to observe an effect of SNS for constipation, albeit with a lack of data on patient characterization (94-97). In 2007, a Cochrane review concluded that the evidence of effect for CC was very limited, the standard temporary test could not predict long-term response and that high quality RCTs were required (98). In 2010, research interest in SNS for CC was further popularised by a prospective open label cohort study (99) that demonstrated a successful standard temporary SNS trial in 45 (66%) out of 62 patients with severe refractory constipation. Following permanent stimulation in these responders there were improvements in constipation scores, QOL, symptom severity and transit times at a median follow-up of 12 months. Other uncontrolled prospective case series using standard temporary SNS peripheral nerve evaluation (PNE) were less positive (60), but all of these studies seemed to suggest that SNS was effective in a sub-group of patients with CC, but that the standard two week PNE stimulation was a poor predictor of the patients long-term response to treatment.

### 2.1.2. SNS testing technique and implantation procedure.

SNS involves the use of mild electrical pulses to stimulate the sacral nerves located in the lower back. Electrodes are placed next to a sacral nerve, usually S3 as standard, by inserting the electrode leads into the corresponding foramen of the sacrum. This is performed as a day-case procedure with the patient under local anaesthetic or a short general anaesthetic (depending on the surgeon's standard practice). Adequate electrode placement is confirmed using pulsed fluoroscopy and by obtaining the appropriate low voltage anal motor responses. The electrodes are inserted subcutaneously and are subsequently attached, during permanent implantation, to an implantable pulse generator (IPG) sited in the ipsilateral buttock. SNS is minimally invasive, fully reversible, and does not preclude further treatment, but the expense of IPG insertion (NHS tariff is currently £12,745) means that a high long term failure rate would make it economically questionable. A preliminary test stimulation phase (PNE) is therefore conducted to try and predict responders. Patients are currently selected for IPG through a two-week PNE using a unipolar temporary plain electrode with an externally attached pulse generator. Using this method, only about 40% of patients receive long term benefit from SNS (100), threatening the viability of NHS provision. Failure may be due to a short term placebo response or a variation in electrode position at permanent lead implantation.

### 2.1.3. Mechanism of action

The mechanism by which SNS modulates bladder and bowel dysfunction is at best poorly understood. Early research assumed an efferent modulation of the pelvic floor muscles, sphincters and bladder. Recent evidence in physiology research seems to suggest an afferent modulation of somatic and visceral nerves suggesting a more complex mechanism of action that may possibly involve cerebral cortex modulation (101). Further evidence for this afferent mechanism of rectal

neuromodulation has also been observed in a prospective randomised controlled trial of SNS (102). Physiology studies in FI sufferers have demonstrated increased retrograde propagating colonic sequences during active SNS versus sham SNS (103), although another study contradicted this by demonstrating pan-colonic ante-grade propagating pressure waves in response to active SNS compared to basal activity (104). The same group demonstrated that sensory SNS caused more ante-grade colonic propagating pressure waves than sub-sensory SNS (105). As the exact mechanism is unknown, settings of pulse width, frequency and voltage for SNS have been largely guided by trial and error over the years. Increasing frequency settings has reportedly improved outcomes for FI sufferers (106), although this could not be repeated in a RCT for CC sufferers (107), suggesting different mechanisms of neuromodulation or even hinting at no mechanism in the CC group.

## 2.2 Cochrane reviews

To date there have been several Cochrane reviews of SNS in FI and CC. Due to a lack of trials with robust methodology the authors of these reviews have concluded that SNS may help a proportion of FI sufferers(98), but no effect had been demonstrated to date for CC(108). They go on to urge further high quality trials to investigate the value of SNS further. The latest review was in 2015 and requires updating as several higher quality studies have investigating the efficacy of SNS for CC have since been published.

## 2.3 Systematic literature review of SNS trials in CC

### 2.3.1. Aims

The main aim of this systematic literature review was to methodically collect, analyse, critically interpret, summarise and present the published high quality clinical evidence for SNS as a treatment for CC, and the long-term predictive ability of the standard tests used in these studies, along with adverse event (AE) reporting.

The aim was to synthesise high quality evidence of effect, predictive ability of testing, and safety profile within the treated cohort of patients suffering from CC.

### 2.3.2. Methodology used in the systematic review

A review of all available peer-reviewed articles published in indexed scientific journals on SNS was conducted according to the methodology described below. The Oxford centre for evidence based medicine (OCEBM) (109) levels were used to define high quality evidence, of which the target was level 1 and 2 evidence of efficacy and safety for SNS treatment of CC. Evidence of OCEBM levels 3 and 4 were also collected and reported, but not planned to be included in meta-analysis of efficacy due to the inherent low quality methodologies used for data collection within these studies. Risk of bias assessments were made using the appropriate Cochrane risk of bias assessment tools (110, 111).

#### 2.3.2.1. Search strategy

The search strategy of bibliographic databases (example in Appendix 1) was designed to specifically find high quality clinical studies assessing the effectiveness and safety profile of SNS testing and IPG treatment for chronic constipation (CC), where “chronic” can also be described as a functional or idiopathic aetiology. Online systematic searches were carried out on the following electronic databases in March 2014 and repeated in February 2019: AHMED, EMBASE, HMIC, MEDLINE, BNI, CINAHL, COCHRANE, OVID, and Web of science ™ Core Collection (Thomson Reuters™). The search utilised Boolean logic operators using truncated search topics which were standardised and consistent in each database search. The searches were restricted to journal articles and English language publications only. All studies involving animals and children were removed at screening.

#### 2.3.2.2. Inclusion Criteria

The titles and abstracts of all studies revealed through the database searches were vetted and requested as full documents if they appeared to be eligible. These were

then further screened for eligibility and excluded as appropriate. The inclusion criteria for study data extraction and analysis were strictly adhered to and all studies fulfilling the following criteria were selected for further review:

Types of studies- **one of the following**

- Prospective randomised controlled/clinical trials
- Prospective case controlled studies
- Prospective cohort studies
- prospective case series
- Studies written in English
- Patient demographics-**all of the following**
- Subjects > 18 years of age, male or female.
- Subjects suffering from chronic, functional or idiopathic constipation; i.e. an unknown aetiology of CC.
- Subjects receiving SNS as an interventional treatment for CC

#### 2.3.2.3. Exclusion criteria

Studies selected for further review were assessed and excluded from data extraction and analysis if they fulfilled any of the following criteria:

- Studies not fulfilling all of the inclusion criteria
- Retrospective studies
- Studies with an unclear/contradictory study design
- Studies without baseline temporary SNS testing data
- Studies with <10 patients
- Systematic reviews of SNS for CC
- Prospective RCTs of SNS with no reported ethical approval
- Prospective RCTs of SNS with no WHO ICT registration
- Studies focussed on subjects (male or female) who are paediatric or adolescent (<18 years of age)

- Studies where subjects concurrently suffered from other symptoms such as faecal incontinence or urinary dysfunction
- Studies with evidence for aetiology of constipation (i.e. secondary, not idiopathic, including obstructed defecation and neurogenic causes)
- Studies where patients received any other form of nerve stimulation before, or during the study; for example spinal cord stimulation, percutaneous tibial nerve stimulation (PTNS), percutaneous sacral nerve stimulation (pSNS).

Studies shortlisted for further review after fulfilling the inclusion and exclusion criteria were assessed against the inclusion criteria by both KE and HC independently in order to maintain consistency and prevent selection bias. The reference lists of shortlisted studies were used to try and identify further studies that may have been eligible for inclusion. Potentially eligible studies were also assessed against the inclusion criteria.

#### 2.3.2.4. Data extraction and synthesis

Prospective, double-blinded, randomised sham-controlled trials were considered the highest quality evidence of the efficacy of SNS for CC and were planned for meta-analysis if they had similar outcome measures and homogeneity allowed for a pooled analysis with fixed effects methods. Study quality was assessed using the Cochrane handbook to determine the individual study risk of bias in each proscribed domain (112). If the studies demonstrated at least moderate heterogeneity through an $I^2$ test, a random effects meta-analysis of study proportions was performed for testing response, long-term response to treatment, and safety profile. The Cochrane handbook (112) definition of heterogeneity was used for this classification, where moderate heterogeneity is considered when $I^2$=30-60%, substantial when $I^2$= 50-90%, and considerable when $I^2$= 75-100%, where a Chi-squared test has also provided evidence of a significant difference between the groups. The Cochrane handbook specifically states that meta-analysis

of crossover studies is complex and this relates to the mixing of parallel group studies with crossover group studies in the meta-analysis of effect size for the interventional treatment. This is due to crossover studies having a smaller variance than parallel group studies and so they would be over-weighted in a mixed meta-analysis. The solution usually involves using complex statistics utilising multilevel modelling through a Bayesian framework or generalised estimating equation (GEE) regression to manage the design differences. This complex analysis would be beyond the scope of this review, and as such crossover studies and parallel group studies would be reported and pooled separately using fixed or random effects meta-analysis as appropriate. Lower quality evidence in the form of prospective cohort studies, prospective case controlled studies, and prospective case series were assumed to be of an insufficient standard to allow pooled effect analysis and were planned for simple tabulation and description according to the reports within the studies. Study characteristics were extracted including the centre, study design and OCEBM level of evidence. Cochrane risk of bias assessments were made for each study using the appropriate risk of bias tool. Patient characteristics were extracted including demographics, aetiology of CC, use of Rome III criteria, and evidence of slow transit. Testing and implantation procedure specifics were extracted. Efficacy of SNS was considered to be a global improvement in the symptoms of CC; increased frequency of bowel movements, reduced abdominal pain, reduced bloating, reduced straining, reduced toileting time, and a reduced laxative use or dependence on other medications/treatments. Primary outcome measurements were extracted, but where the efficacy of SNS was assessed in studies by a variety of different primary outcome measures, I calculated and assigned studies a long-term response rate as a proportion of the original intention to treat (ITT) or implantation population (IP) that demonstrated efficacy. All adverse event safety data were extracted and reported through tabulation. A

random effects meta-analysis was planned for explantation rate of IPGs for all studies as a surrogate marker for long-term SNS treatment failure. I deemed that the weak methodologies of cohort studies and case series (a cohort study with no robust patient selection) had no effect on eventual explantation of the device, and so could be used to demonstrate a pooled failure rate for the treatment. Mixing the proportion of long term failures in crossover studies with long term failures in cohort studies in this way does not encounter the same methodological problems mentioned earlier as these are not treatment effects within the crossover period.

### 2.3.3. Results and analysis

The search strategy (Table 2) identified 266 records through combining the population and treatment search terms (Figure 2 PRISMA). 3 more records were identified by cross-referencing, giving a total of 269 records identified for screening. Of these 248 were excluded from full paper review during screening for 16 different reasons (Table 3). Twenty-one records were retrieved for a full paper eligibility review against the inclusion and exclusion criteria.

**Table 2 Search results of bibliographic databases for quantitative literature**

| **Search n** | Search term (patient population) | Results |
|---|---|---|
| **1** | ALL=functional constipat* | 4,098 |
| **2** | ALL=idiopathic constipat* | 1,881 |
| **3** | ALL=chronic constipat* | 5,989 |
| **4** | ALL=refractory constipat* | 697 |
| **5** | ALL=slow transit constipat* | 1,540 |
| **6** | 1 OR 2 OR 3 OR 4 OR 5<br>**Target patient population** | 10,344 |
| **Search n** | **Search term (treatment)** | **Results** |
| **7** | ALL= sacral nerve stimulat* | 2,501 |
| **8** | ALL=percutaneous nerve evaluation | 380 |
| **9** | ALL= sacral neuromodulat* | 1,968 |
| **10** | ALL=SNS | 15,254 |
| **11** | 7 OR 8 OR 9 OR 10<br>**Target treatment** | 18,599 |
| **12** | **6 AND 11**<br>**Target research studies for screening** | **266** |
| ALL= All fields | | |

| **Table 3 Records excluded in screening** | 248 |
|---|---|
| Screening exclusions | n |
| Studies of other diseases | 72 |
| Studies of other interventions | 38 |
| Discussion papers | 32 |
| Studies in children | 29 |
| Conference abstract/proceeding | 16 |
| Systematic reviews | 15 |
| Mechanistic physiology study | 13 |
| Consensus statement / paper | 8 |
| Book(s) or book section/chapter | 7 |
| Guidelines | 6 |
| Animal studies | 3 |
| Cochrane systematic reviews | 2 |
| Letters to the journal editor | 2 |
| Individual case reports | 2 |
| New SNS study protocol (ongoing trial) | 1 |
| Postal survey study | 1 |

Fourteen were excluded with reasons as follows:

- One paper of a prospective cohort study was excluded due to participants suffering from a neurogenic cause of constipation (113)
- Three papers were excluded for insufficient study participant numbers
    - 1 RCT had 2 participants (94)
    - 1 prospective case series had 4 participants (114)
    - 1 prospective case series had 8 participants (95)
- Two papers were excluded for including patients suffering from obstructed defecation, one of which was a mechanistic RCT of SNS for evacuatory dysfunction (97, 102).
- One paper of a RCT did not include temporary SNS testing data or patient selection data before IPG implantation, and had no ISRCTN registration, or any national or international registration that I could find (107).
- Seven papers of retrospective cohort studies were excluded (115-120)

Figure 2: PRISMA Flow Diagram

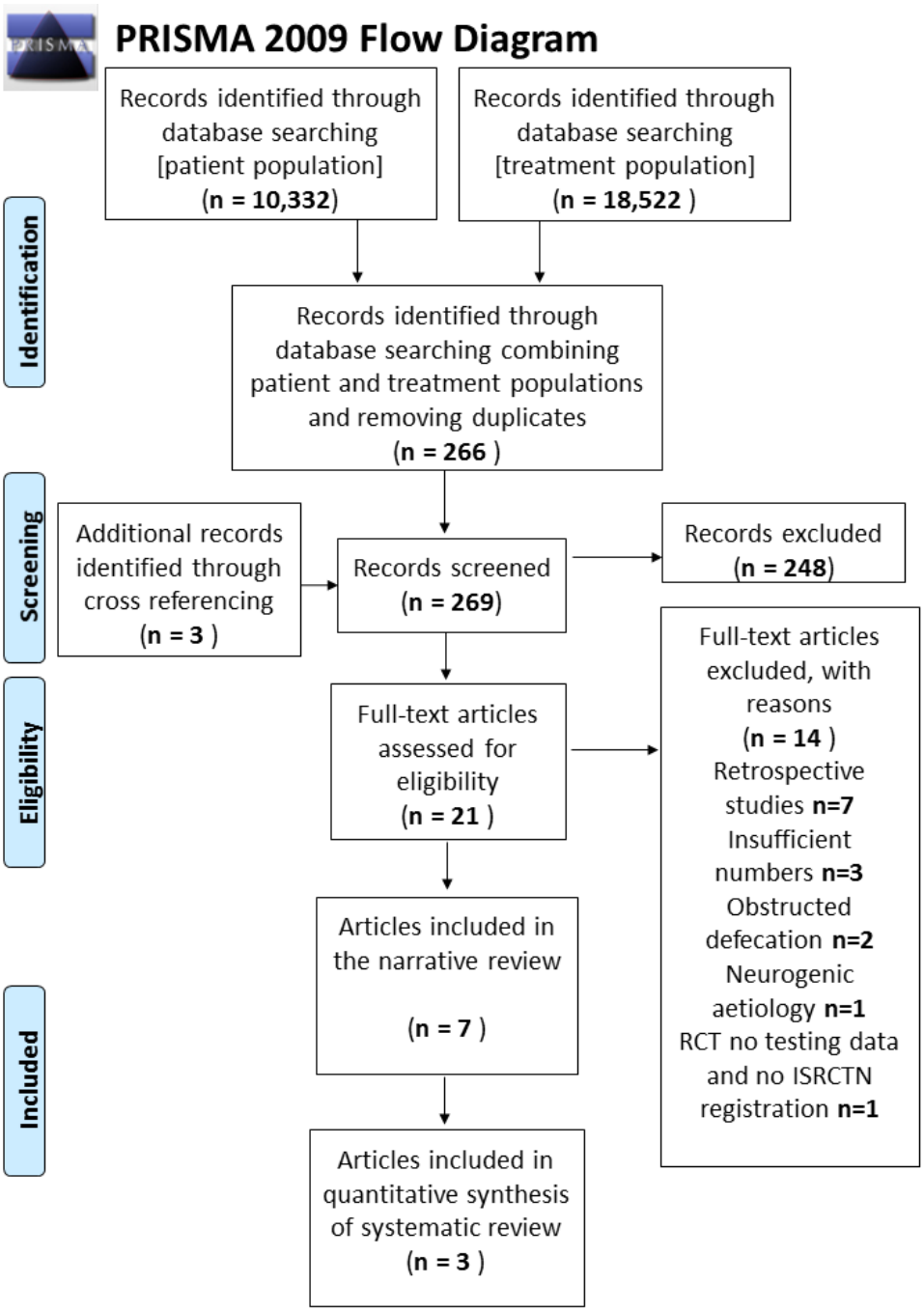



Figure 2 Prisma diagram of included articles

The remaining 7 articles representing 5 individual studies met the eligibility requirements after full paper review, 3 of which were articles relating to 2 RCTs (121-123). Of the remaining 4 articles, 3 described 2 prospective open label cohort studies (99, 124, 125), and one was a prospective case series (126), and they are included in a narrative synthesis.

#### 2.3.3.1. Quality of included study methodologies

Study quality was assessed using the Cochrane collaboration risk of bias tool for randomised controlled trials (111), to determine the individual study risk of bias in each proscribed domain for these studies (Tables 4&5). 3 papers relating to 2 crossover RCTs were identified from the search (121-123). The Zerbib study was a high quality and well designed and conducted RCT that was judged to be of unclear risk of bias due to the primary outcome measure (Table 9). The primary outcome measure was achieved if a patient had an improvement in one of three well defined symptom responses to SNS, and in my opinion it is unclear if this has influenced the findings. Two of the articles were identified as belonging to the same study RCT cohort (Dinning /Patton) but from different phases of follow up; the first study the testing phase (121), and the second the follow up response phase to SNS treatment with an IPG (122). This study was deemed at high risk of bias towards the intervention due to investigators and participants being aware of one of the active intervention periods, although this is completely unavoidable for supra-sensory SNS. In both studies the specific Cochrane questions for crossover trials were satisfactory as the disease was chronic and stable, the interventional treatments were compared to a sham and the crossover order was randomised, and there was an adequate washout between arms with no evidence of a carry-over effect.

**Table 4 Cochrane risk of bias in RCTs, Zerbib et al 2017**

| Bias Domain | Source of bias | Support for judgement | Author's Judgement |
|---|---|---|---|
| **Selection** | Random sequence generation | Centralised remote randomisation in permuted blocks of 4 by study statistician only | **Low risk** |
| | Allocation concealment | Centralised remote randomisation in permuted blocks of 4 by study statistician only | **Low risk** |
| **Performance** | Blinding of participants and personnel | True sub-sensory SNS to participants, setting investigator did not collect outcome measures, all other investigators blinded | **Low risk** |
| **Detection** | Blinding of outcome assessment | Identical outcome assessments at end of each stimulation phase | **Low risk** |
| **Attrition** | Incomplete outcome data | No attrition by end of crossover period for POM, intention to treat for crossover and follow up period. | **Low risk** |
| **Reporting** | Selective reporting | All pre-specified outcomes reported | **Low risk** |
| **Other** | Anything else ideally pre-specified | Cochrane specific questions for crossover trials: design was appropriate, treatments were randomised, no obvious carry over effect (washout period was adequate).<br>The POM was a choice of 1 of 3 separate improvements in symptoms | **Unclear risk** |
| **Overall Summary** | The concerns regarding unclear risk of bias in this study centre around the primary outcome measure, where one of three well defined symptom responses would imply overall treatment response. | | **Unclear risk of Bias** |

POM= Primary outcome measure, SNS= sacral nerve stimulation

**Table 5 Cochrane risk of bias in RCTs, Dinning/Patton et al 2015/2017**

| Bias Domain | Source of bias | Support for judgement | Author's Judgement |
|---|---|---|---|
| **Selection** | Random sequence generation | randomisation performed off site by clinical trials unit, but further description not included | **Unclear risk** |
| | Allocation concealment | randomisation performed off site by clinical trials unit, but further description not included | **Unclear risk** |
| **Performance** | Blinding of participants and personnel | Participants blinded to sham and sub-sensory but not supra sensory SNS. One Investigator set allocation, all others were blinded | **Unclear risk** |
| **Detection** | Blinding of outcome assessment | Participants aware of supra-sensory SNS testing period, but unaware of sham or sub-sensory. Impossible to blind from supra-sensory, main comparator was sham and sub-sensory versus supra-sensory. | **High risk** |
| **Attrition** | Incomplete outcome data | Losses to follow up disclosed and intention to treat analysis performed. Loss to follow up long term presumed to be due to treatment failure | **Low risk** |
| **Reporting** | Selective reporting | All pre-specified outcomes were reported | **Low risk** |
| **Other** | Anything else ideally pre-specified | Cochrane specific questions for crossover trials: design was appropriate, treatments randomised, and no obvious carry over effect (washout period was adequate) | **Low risk** |
| **Overall Summary** | The main concerns of bias centre on participants and investigators being aware of one of the active interventional treatment phases, although this is unavoidable with supra-sensory SNS. | | **High risk of bias.** |

POM= Primary outcome measure, SNS= sacral nerve stimulation

**Table 6 Risk of bias in cohort/case series studies**

| | Type of bias with risk classification per study | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre-intervention | | | Post-Intervention | | | | |
| **Study** | **Confounding** | **Selection Of participants** | **Classification Of interventions** | **Deviations from intervention** | **Missing data** | **Measurement of outcomes** | **Reporting** | **Overall** |
| **Kamm, Maeda 2010/17** | Low | Low | Low | Low | Moderate | Serious | Low | **Serious favours intervention** |
| **Carriero 2010** | Moderate | Moderate | Low | Low | Moderate | Critical | Moderate | **Critical favours intervention** |
| **Graf 2015** | Serious | Low | Low | Critical | Low | Moderate | Moderate | **Critical unpredictable direction** |

Of the 5 studies found 3 articles represented 2 prospective open label cohort studies (99, 124, 125) which were included in the narrative review. One of these cohort studies was described in two papers. The first describing the initial testing and response to IPG (99), then longer term follow up to 60 months (124). These cohort studies were defined as level 4 evidence under the OCEBM classification due to their lack of controls. The search found 1 prospective case series (126) which was included in the narrative review. This was defined as level 4 evidence under the OCEBM classification as a case series study. A risk of bias assessment was undertaken for these studies using the Cochrane risk of bias in non-randomised studies tool (ROBINS-I) (110) (Table 6). This revealed that the overall methodology employed in these 3 studies was of very poor quality, with one judged to be suffering from serious risk of bias, and two from a critical risk of bias. The Kamm/Maeda study was judged overall to be suffering from a serious risk of bias in favour of the intervention; moderate risk of bias for missing data due to the high loss to follow up, and serious risk of bias due to measurement of outcomes due to no intention to treat analysis, the variation in timing of primary outcome assessment from intervention, and the subjective definition of the primary outcome measure as judged by participants and investigators who were aware of the intervention. The Carriero study was judged to be suffering from a critical risk of bias in favour of the intervention due to a moderate risk of bias from confounding and selection factors due to the MMPI-2 questionnaire used for SNS testing selection and including patients with outlet obstruction, and a critical risk of bias in measurement bias due to the subjective nature of test response, and no longer term primary outcome measure with participants and investigators aware of the intervention. The Graf study was judged to be suffering from a critical risk of bias in an unpredictable direction mainly due to deviations from the intervention as

participants received surgery (rectopexy) and biofeedback therapy during the SNS intervention period. There was also a moderate risk of bias due to confounding factors, due to the inclusion of patients with obstructed defecation and past surgery such as rectopexy. This risk of bias analysis further justifies their non-inclusion in a meta-analysis of efficacy data.

**Table 7 Studies included in the systematic review**

| Study Groups | Centre N units | Country | Ethics approval | Trial registration | OCEBM level |
|---|---|---|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | | | | |
| **Zerbib et al 2017 Constimod Study** | Bordeaux 8 units | France | Yes | NCT01629303 www.clinicaltrials.gov | 2 |
| **Patton et al 2016 grant ID 630502 ¥** | Sydney 2 units | Australia | Yes 08/CRGH/59 HREC07198 | ACTRN12611001192976 Australian New Zealand Clinical Trials Registry ICTRP WHO registry | 2 |
| **Dinning et al 2015 grant ID 630502 ¥** | | | | | |
| **Prospective open label cohort studies** | | | | | |
| **Maeda et al 2017 *** | St Marks 7 units | UK | Yes | NCT00200005 | 4 |
| **Kamm et al 2010 *,α** | | | | | |
| **Carriero et al 2010** | Montecchio Emelia 1 Unit | Italy | NR | NR No ISRCTN registration No ICTRP WHO | 4 |
| **Prospective case series** | | | | | |
| **Graf et al 2015** | Uppsala 1 unit | Sweden | NR | NR No ISRCTN registration No ICTRP WHO | 4 |

OCEBM=Oxford centre for evidence based medicine, *Funded by Medtronic, NR=Not Reported
¥ independent funding,α 2 papers relate to one study in separate follow up phases

Table 7 reveals the types of studies, ethics approval, trial registration and levels of evidence from OCEBM classification of the methodology. The study demographics are shown in table 8, of note all studies demonstrated similarly high proportions of female sufferers, a similar age group within the RCTs, demonstrable long chronicity of CC, and a high proportion of patients with slow transit time. The main inclusion criteria within the RCTs were almost identical using 2 or less spontaneous complete bowel movements per week as the main classification of CC similar to recent

pharmaceutical trials for CC. Most other studies inclusion criteria were based around the Rome III classification for CC.

**Table 8 Demographics of review studies**

| Study Groups | SP<br>N | Female<br>N (%SP) | Age<br>years | Main Inclusion Criteria for study recruitment | Chronicity of idiopathic constipation Years (%SP) | Slow Transit constipation<br>N (%SP) |
|---|---|---|---|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | | | | | |
| **Zerbib et al 2017 Constimod Study** | 36 | 34 (94%) | Mean (SD) 45 (14) | -two or fewer complete bowel movements per week -straining to evacuate at more than 25per cent of attempts -sensation of incomplete evacuation after defaecation on more than 25 per cent of occasions | 36 > 1yr (100%) | 28 (78%) |
| **Patton et al 2016**<br>**Dinning et al 2015** | 59 | 55 (93%) | Median (range) 42 (19-74) | -SCBM < 3 days/week for 2/3 weeks - colonic isotope retention ≥20% at 96 h - normal anorectal manometry -No obstructive defecation -Failed medical treatments -Normal colonoscopy within 5 years | >10 y N=43 (73%) 5-10yrs N=7 (12%) 2-5yrs N=9 (15%) | NR (NR%) 68% mean isotope retention (<1% normal) |
| **Prospective open label cohort studies** | | | | | | |
| **Maeda et al 2017**<br>**Kamm et al 2010** | 62 | 55 (89%) | Median (range) 40 (17-79) | < 2 Bowel movements a week, and /or straining/incomplete emptying >25% | Median (range) 10 yrs (1-60) | 50 (81%) |
| **Carriero et al 2010** | 68 | 55 (81%) | 59 (19-78) | -Fulfil Rome II Criteria for FC -failed all medical therapy MMPI-2 score =0 -selection for PNE | NR | 68 (100%) |
| **Prospective case series** | | | | | | |
| **Graf et al 2015** | 44 | 38 (86%) | Mean (range) 55 (20-78) | -CC > 6 months -Failed conservative therapies -Failed TAI and biofeedback -Willing to participate | Mean (range) 16.4 (1.5-50) | 21 (48%) |

SP=Study Population, ITT=intention to treat, NR=Not reported, SCBM= Spontaneous complete bowel movements
TAI=Trans Anal Irrigation
MMPI-2= Minnesota Multiphasic Personality Inventory-2 test

The RCTs had a similar design in that they were randomising to sequences of "ON" or "OFF" after patients had been implanted with an IPG, in other words study

subjects all received the normal PNE and had their response assessed beforehand. The main methodological difference was that the Dinning/Patton study implanted patients regardless of PNE response (patient choice) and the Zerbib study only if there was a positive response to PNE (normal practice). In both studies the primary outcome measure was used to classify a response to testing or long term IPG. The Patton/Dinning study had clearly defined the POM as per table 9 below, whereas it is unclear if the POM in the Zerbib study affected the response classification. The other studies all had clear outcome measures apart from Carriero which was very vague and clearly at critical risk of bias.

**Table 9 Definition of response classifications of included studies**

| Study Groups | Classification of testing response POM PNE and [Sham vs active sub-sensory] | Classification of Long-term response POM |
|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | |
| **Zerbib et al 2017 Constimod Study** | POM any one of three from : -increase from <2 to >3 SCBM/week or ->50% reduction in straining or ->50% reduction in incomplete emptying sensation. Objective assessment of other characteristics (Wexner score, GIQLI score, VAS 0-100) | |
| **Patton et al 2016** | POM= SCBM 2 days/week for 2/3 weeks for supra- and sub-sensory SNS | |
| **Dinning et al 2015** | Pain score, bloating score, laxative free days, stool f and form, SF36-SOM | |
| **Prospective open label cohort studies** | | |
| **Maeda et al 2017** | POM is any one of the following: - bowel frequency from <2 to >3/week ->50% reduction in straining ->50% reduction in incomplete evacuation | POM is any one of the following: - bowel frequency from <2 to>3/week ->50% reduction in straining ->50% reduction in incomplete evacuation |
| **Kamm et al 2010** | | |
| **Carriero et al 2010** | POM= appearance of spontaneous necessity of evacuation and a referred improvement of quality of life | No declared long term POM Bowel diary, Wexner score and SF 36 measured |
| **Prospective case series** | | |
| **Graf et al 2015** | POM= 50% reduction in constipation symptoms | POM= 50% reduction in constipation symptoms |

GIQLI-Gastrointestinal Quality of Life Index, SCBM-Spontaneous complete bowel movement, POM-Primary outcome measure, SOM-Secondary outcome measure

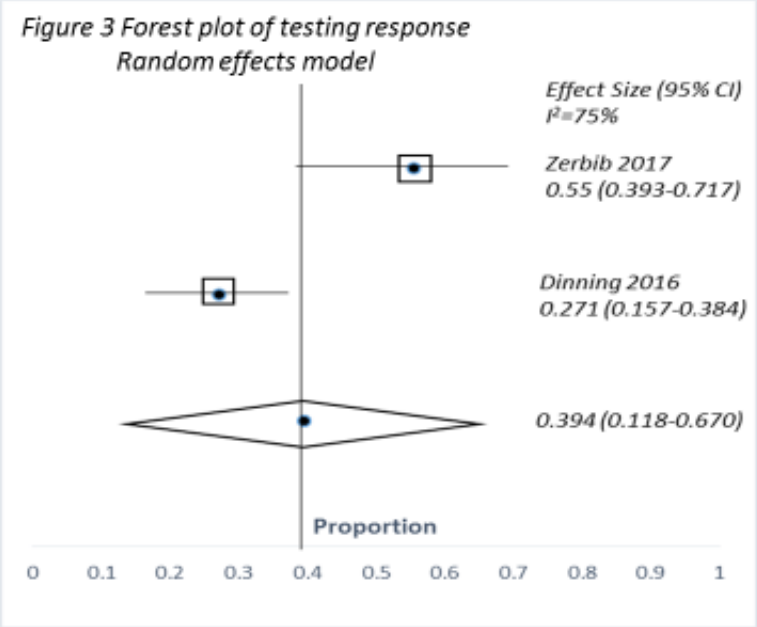
The RCTs had almost identical PNE techniques (Table 10) and equipment apart from the stimulation parameters as Dinning used a slightly higher pulse width of 300µSec. Testing stimulator model 3625 was used by all without evidence of calibration (incidental findings-chapter 4). Of note Dinning had a 27% response to PNE but implanted 93% of participants with an IPG, compared to Zerbib who had a 78% response and implantation rate. Carriero did not comment on the equipment used or on settings, and Kamm did not comment on the technique used to assess adequate lead placement at surgery. There was a high proportion of test responders in the cohort studies (up to 85%) and a lower proportion in the case series (a case series has no robust patient selection). All studies used supra-sensory test settings for PNE which is effectively open label at this stage.

**Table 10 SNS PNE technique and response**

| Study Group | ITT N | Testing PNE type duration (Weeks) | Testing TP N | Test responder N (%TP) | IPG implanted N (%TP) | Testing stimulator model | Sacral formen cannulated Response measured Testing lead model | Stimulation settings Pulse width ( µsec) Frequency (HZ) | IPG model |
|---|---|---|---|---|---|---|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | | | | | | | | |
| **Zerbib et al 2017 Constimod Study** | 36 | Supra-sensory >100% ST (3) | 36 | 20 (78) | 20 (78) | 3625 No calibration | S2,3,4 nerve roots Motor-bellows and great toe Tined Lead model 3093 | 210 µsec 14Hz | Interstim 3023 |
| **Patton et al 2016** **Dinning et al 2015** | 59 | Supra-sensory >100% ST (3) | 59 | 16 (27) | 55 (93) | 3625 No calibration | S3, S4 nerve roots Motor-Bellows and great toe Tined Lead model 3093 | 300 µsec 14Hz | Interstim 3023 |
| **Prospective open label cohort studies** | | | | | | | | | |
| **Maeda et al 2017** **Kamm et al 2010** | 62 | Supra-sensory >100% ST (3) | 62 | 45 (73%) | 45 (73%) | 3625 No calibration | NR | 210 µsec 14Hz | Interstim 3023 |
| **Carriero et al 2010** | 13 | Supra-sensory >100% ST (4) range 3-6 Tined lead test | 13 | 11 (85%) | 11 (85%) | NR | S3 nerve roots Patient Sensation (LA) Tined lead model 3889 | NR | NR |
| **Prospective case series** | | | | | | | | | |
| **Graf et al 2015** | 44 | Supra-sensory >100% ST (3) | 44 | 15 (34%) | 15 (34%) | 3625 No calibration | S2, S3, S4 nerve roots Motor-Bellows response Tined lead model 3093 | 210 µsec 14Hz | Interstim 3023 |

ST=Sensory Threshold, ITT= Intention to treat, PNE=peripheral nerve evaluation, TP=testing population, IPG=Implantable pulse generator, NR=Not Recorded

I calculated the effect size of the test response from the RCTs and demonstrated significant heterogeneity between the groups ($I^2$=75%, P<0.0001). The studies were pooled using a random effects meta-analysis (Figure 3), which found a pooled PNE response of 39% (95 % confidence interval,11.8-67%), which is considerably lower than reporting in most prospective cohort studies (70-85%).




The RCTs were similar in that they randomised patients to sequences of sub sensory active SNS versus Sham SNS with an IPG in situ. In the Zerbib study participants were randomised to sequence and received 8 weeks of each in a crossover design with a central 2 week washout period and an equal allocation ratio. The Dinning study had 4 arms of 3 weeks each comparing randomised crossover sham versus sub-sensory SNS first, and then re-randomisation to crossover sham versus supra-sensory second, again with a 2 week washout period between study arms. In both studies no significant difference was detected between sham and sub-sensory SNS using the primary outcome measure at the end of the testing periods (Table 11). Dinning also detected no difference between sham and supra-sensory SNS.

**Table 11 IPG Randomization for controlled IPG SHAM / Active crossover testing**

| Study Group | IP N | SHAM RES N (%IP) | SS RES N (%IP) | Duration of IPG testing arm | Washout between arms | Randomisation allocation |
|---|---|---|---|---|---|---|
| **Zerbib et al 2017 Constimod Study** | 20 | 11 55% | 12 60% P=0.75 | 2 arms of 8 weeks each | 2 weeks | 10 vs 10 |

| Study Group | IP N | SHAM RES N (%IP) | SBS RES N (%IP) | SHAM RES N (%IP) | SPS RES N (%IP) | Duration of IPG testing arms | Washout between arms | Randomisation allocation |
|---|---|---|---|---|---|---|---|---|
| ***Patton et al 2016 *Dinning et al 2015** | 55 | 14 (25%) | 14 (25%) P=0.95 | 11 (20%) | 16 (29%) P=0.23 | 4 arms of 3 weeks each | 2 weeks | NR |

SHAM versus sub-sensory testing [Zerbib et al],
SHAM Versus Sub-sensory & SHAM versus Supra-sensory testing [Dinning et al]
*Identical study group, IP= implant population, SBS=Sub-Sensory IPG SNS, SPS=SuPra-Sensory IPG SNS, RES=Responder, NR=Not Reported

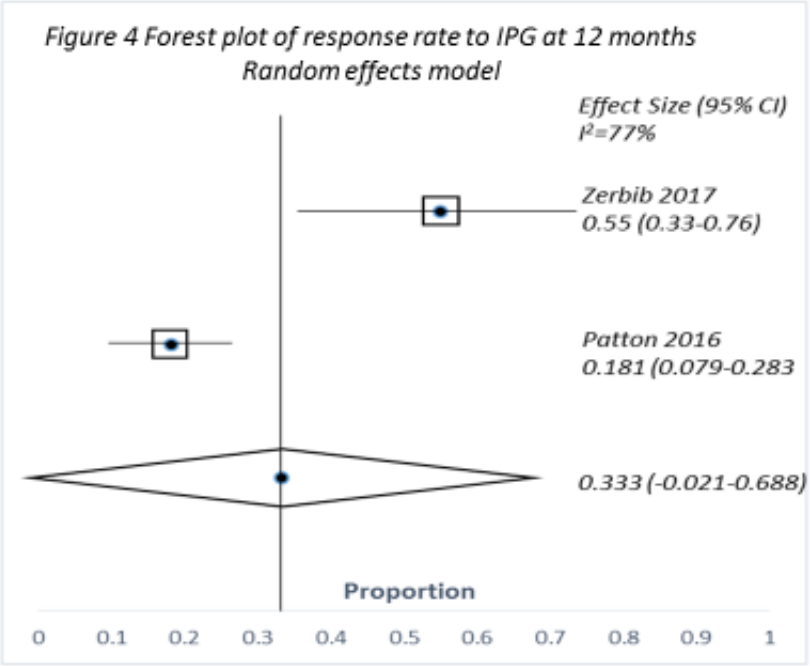
Long term response to IPG SNS occurred at 12 months using the similar POM in both RCTs. Table 12 demonstrates response rates comparing the implant group response to an intention to treat (with PNE) response rate. Patton had a higher loss to follow up than Zerbib, and these patients were all considered treatment failures.

**Table 12 Long term response to IPG SNS**

| Study Groups | ITT<br><br>N | IP Implanted<br><br>N<br>(%ITT) | Quadripolar Tined lead<br><br>N<br>(%ITT) | Number in follow-up<br>N<br>(%IP) | End point FU<br><br>(Months) | End point response<br><br>N<br>(%IP) (%ITT) |
|---|---|---|---|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | | | | | |
| **Zerbib et al 2017 Constimod Study** | 36 | 20<br>(78%) | 20<br>(78%) | 16<br>(80%) | 12 | 11<br>(55%) (31%) |
| **Patton et al 2016** | 59 | 55<br>(93%) | 55<br>(93%) | 31<br>(56%) | 12 | 10<br>(18%) (17%) |
| **Dinning et al 2015** | | | | | | |
| **Prospective open label cohort studies** | | | | | | |
| **Maeda et al 2017** | 62 | 45<br>(73%) | 45<br>(73%) | 45 (100%) | 28 | 39<br>(87%) (63%) |
| **Kamm et al 2010** | | | | 35 | 48 | NR |
| | | | | 18 | 60 | NR |
| **Carriero et al 2010** | 13 | 11<br>(85%) | 13<br>(100%) | 11 | 22 | NR<br>Global improvement in Wexner/ diaries |
| **Prospective case series** | | | | | | |
| **Graf et al 2015** | 44 | 15<br>(34%) | 15<br>(34%) | 11 | 24 | 5<br>(33%) (11%) |

ITT=intention to Treat population, IP=Implant population (per protocol population)

Random effects meta-analysis (Figure 4) demonstrated a pooled 12 months response to IPG SNS of 33%, and again wide 95% confidence intervals. This figure corresponds well with the case series report from Sweden, but is far lower than all previously reported cohort studies, of note Kamm reported 87% response at a mean of 28 months. Carriero did not classify long term response to SNS and analysed mean Wexner scores and diary scores.




In the Zerbib study secondary outcome measures such as bowel diaries, Wexner scores, VAS and Gastrointestinal Quality of Life Index (GIQLI) score, detected no evidence of a difference to short or long term SNS treatment. Similarly physiological measures of colonic transit time and anal manometry pressures had no evidence of significant change either. Patton replicated these results reporting no evidence of a change to colonic transit time either. Adverse events (Table 13) were reported in

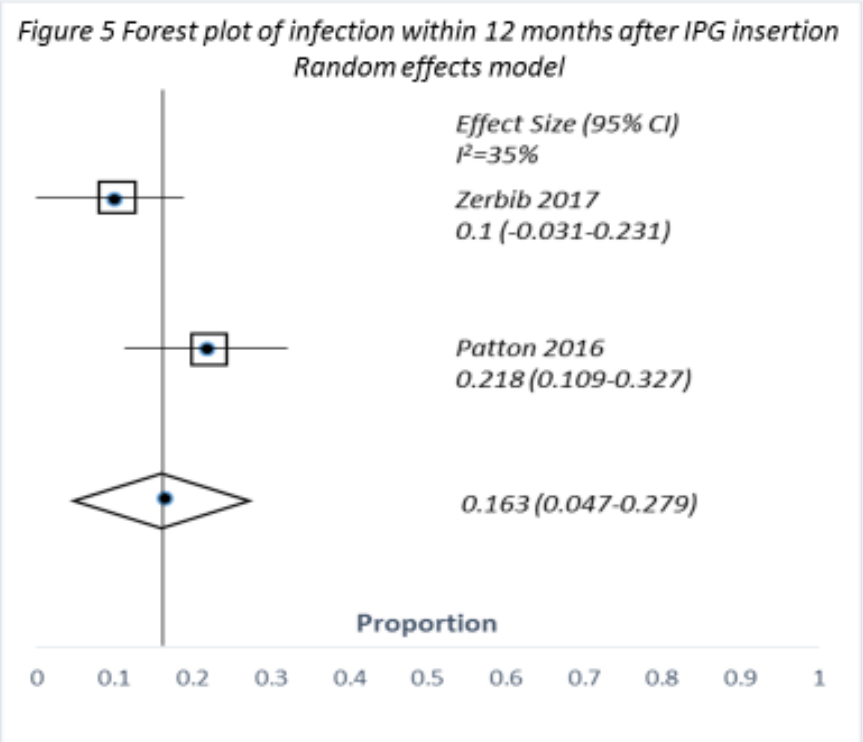
all studies apart from Carriero who did not include any adverse event reporting in the paper other than commenting that there were no complications. Adverse events were common in the RCTs, with 25% of participants suffering a serious adverse event in the Zerbib trial. In the higher quality prospective RCTs, infection rates were considerably higher than the cohort studies, 10% and 22% compared to 0%, 4% and 13%. Of note Dinning calculated wound infection as a proportion of all adverse events, not as a proportion of the study population which artificially lowered the reported infection rate. I adjusted this by recalculating the 12 infections as a proportion of the intention to treat population of 59 patients (22%).

**Table 13 Adverse event reporting**

| **Study Groups** | Testing<br><br>N<br>(TP) | Testing AEs<br><br>N<br>(%TP) | IPG<br><br>N<br>(IP) | IPG AEs<br><br>N<br>(%IP) | SAEs<br><br>N<br>(%TP) | Total AEs<br>N AES<br>N Pts<br>(%TP) | Infections<br><br>N<br>(%IP) | ABX PXP | Lead / IPG removed<br><br>N<br>(%IP) | Other AEs |
|---|---|---|---|---|---|---|---|---|---|---|
| **Prospective Randomised Sham Controlled Crossover Trials** | | | | | | | | | | |
| **Zerbib et al 2017 Constimod Study** | 36 | NR | 20 | NR | 9<br>(25%) | 25<br>11<br>(30%) | 2<br>10% | Y | 2<br>10% | 4 DM |
| **Patton et al 2016**<br>**Dinning et al 2015** | 59 | NR | 55 | NR | 1<br>(2%) | 73<br>NR<br>(124%) | 12<br>(22%)* | NR | 1(2%)<br>12 months<br>47 (85%)<br>60 months | 23/59<br>Lead migration |
| **Prospective open label cohort studies** | | | | | | | | | | |
| **Maeda et al 2017**<br>**Kamm et al 2010** | 62 | NR | 45 | NR | 11<br>(18%) | 101<br>NR<br>(224%) | 2<br>(4%) | Y | 3<br>(7%)<br>20<br>(45%) | Lead migration |
| **Carriero et al 2010** | 13 | 0 | 11 | 0 | 0 | 0 | 0 | NR | 0 | 0 |
| **Prospective case series** | | | | | | | | | | |
| **Graf et al 2015** | 44 | 8<br>(18%) | 15 | 5<br>(33%) | 1<br>(2%) | 13<br>NR<br>(30%) | 2<br>(13%) | NR | 4<br>(27%) | IPG |

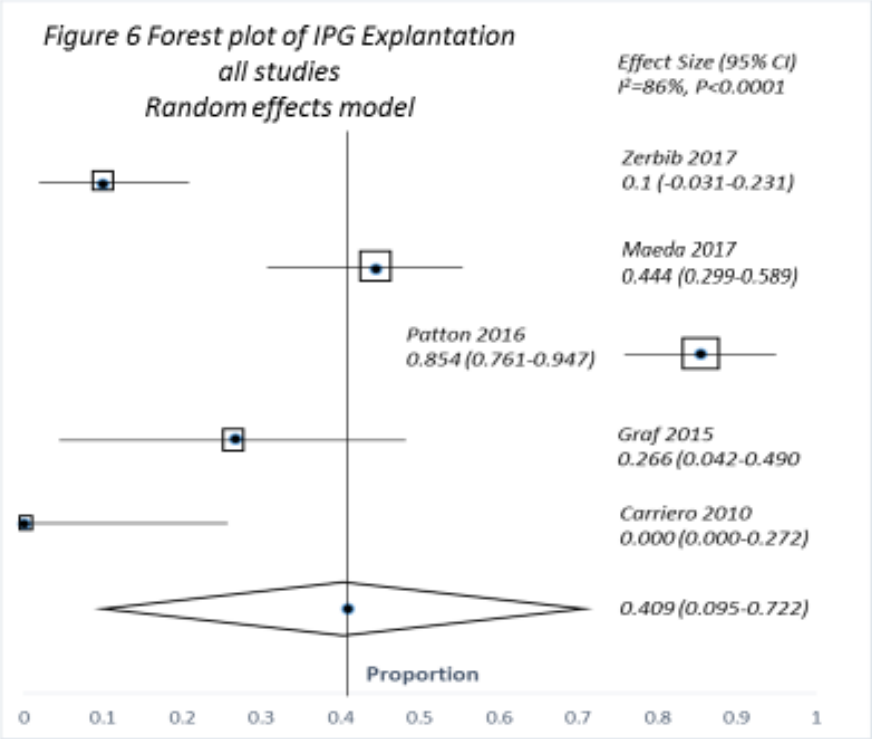
NR =Not Reported, TP= Testing population, IP=Implant population, ABX PXP-antibiotic prophylaxis, DM=device malfunction, *Reported as 16% in study (error by using N=73 of AEs instead of TP=59)

Random effects meta-analysis of the RCTs demonstrated a pooled effect size of 0.163 (16.3%) (95% CI 0.047-0.279) which is considerably higher than all of the previously reported infection rates in cohort studies of CC (Figure 5).




Explantation of the IPG devices was performed either due to infection or lack of efficacy. I considered the methodological differences between the RCTs and cohort studies/case series, and I concluded that these designs could not ultimately prevent or promote device explantation which could be considered a surrogate marker for treatment failure. All studies were therefore included in a random effects meta-analysis of explantation rate (Figure 6). The pooled proportion demonstrated an explantation rate of 41% (ES 0.409, 95% CI 0.095-0.722), with significantly high heterogeneity ($I^2$=86%, P<0.0001) between study groups which is likely due to the methodologies used. The Patton study reported the long term response to SNS of

the Dinning trial subjects (prospectively planned) and had the highest reported explantation rate reported in the literature of 85% at 5 years follow up.




The main design of the Dinning study was to implant a high proportion of PNE test patients in order to calculate the predictive value for PNE based on long-term response to IPG SNS. The Dinning paper reported this analysis based on response at 12 months after implantation which demonstrated a negative predictive value of 78% and a positive predictive value of 50% (Table 14). Patton presented an interesting post-hoc analysis of 5 year response which demonstrated the PNE PPV as 6% and NPV as 94%.

**Table 14 Predictive ability of supra-sensory PNE for IPG SNS response**

| Dinning et al 2015- Positive responses to PNE and permanent IPG SNS | | | |
|---|---|---|---|
| | IPG SNS +ve Response | IPG SNS -ve Response | Total |
| **PNE +ve response** | 8 | 8 | 16 |
| **PNE -ve response** | 8 | 29 | 37 |
| **Total** | 16 | 37 | 53 |

Sensitivity=50%, Specificity=78%, PPV=50%, NPV=78%
PPV=Positive Predictive Value, NPV=Negative Predictive Value

### 2.3.4. Discussion of review findings

The findings of this review using a strict high quality methodology only including OCEBM level 2 evidence studies in efficacy analysis is at odds with the majority of studies in the published literature. The overall quality of the prospective cohort studies and case series was poor (level 4), and the 2 RCTs were the highest quality studies published in the field of SNS for CC to date (level2). The long-term response rate of IPG SNS using a supra-sensory unipolar lead for PNE is nearer 41%, although as the Dinning study deliberately implanted non-responders to calculate the PPV of PNE this will undoubtedly have resulted in a higher proportion of non-responders in this trial at 12 months (17%) and 5 years (5%). The PPV of supra-sensory unipolar PNE is 50% at 12 months and 6% at 60 months, which effectively ends the utility of this form of testing for patients with CC. Both of the RCTs did not detect any physiological change to SNS or any difference between active sub-sensory or supra-sensory SNS when compared to a sham stimulation using the IPG. This seems to imply that there may be a placebo response to treatment, although a significant proportion of these patients (33%) who have proven chronicity and were refractory to all known treatments, still appear to have a response at 12 months. Thus, there may still be a subgroup of patients within the cohort of CC that do respond to treatment, but no studies have demonstrated an ability to discriminately detect them during PNE. The 12 month pooled response rate of 33% is significantly lower than reported by the prospective and retrospective cohort studies who were

typically reporting response rates of up to 87% at 28 months after IPG implantation (99). This is a clear demonstration of the inherent methodological flaws in cohort studies and case series, and an overreliance on these weak methods in fields of surgical research. The overall IPG explantation rate was pooled at 41% within 5 years. This may be artificially higher due to the Dinning study implanting PNE non-responders. Even so this device costs over £12,000 and battery life is typically 5-7 years; this does not appear to be a cost-effective treatment for the NHS. The weak methodology of the cohort studies have also led to biases in under reporting adverse events, particularly infections of devices. The pooled infection rate of 16% within 12 months of IPG implantation is significantly higher than the average 4% reported within the weaker studies. In registered and monitored RCTs all safety data are independently scrutinised by university methodologists, and this is the likely explanation for the higher rates being reported in these studies. In order to understand the current research climate with respect to SNS for CC, I performed a search of the WHO International clinical trials registry on 1st March 2019. This was to identify historical clinical trials of SNS that had been registered and closed, and those that were registered and currently recruiting. The prospective RCTs described in the systematic review were included on the registry, as well as the Tilts-cc study. One further study of SNS for CC is currently underway in Holland and recruiting patients (127). This is an open label RCT of SNS versus personalised conservative treatment. The design of this study would not be considered evidence of effect for SNS in CC, and is as methodologically weak as the cohort studies described in the review.

### 2.3.5. Conclusion of the systematic review of quantitative literature

This review has demonstrated that a subgroup of patients with CC seem to respond to long term IPG SNS treatment, but that the supra-sensory PNE test is unable to

detect them. Consequently a large proportion of implanted patients fail the treatment at 12 months, which is expensive and they have a significant burden of complications (infection). There is also a possibility the testing and long term response may simply be a placebo response to treatment. There is an urgent need to develop an enhanced PNE test that adequately detects the sub group with long term response, in order to make SNS a viable and cost effective treatment for patients in the NHS.

## 2.4 Rationale for the TiLTs-cc study

There were no high quality level 1 evidence RCTs of SNS for CC identified in the literature. The 2 recent OCEBM level 2 RCTs (121-123) have not demonstrated an ability to detect long term response by PNE, or of any treatment effect of SNS over sham therapy. The earlier cohort studies were methodologically weak and overly optimistic, especially one multi-centre open label cohort study (99) which became more pessimistic in longer term follow up (124), and there remains uncertainty regarding the efficacy of SNS for chronic constipation. Whilst there is some evidence of a persistent and significant benefit in a sub-group of patients, it is clear that not all patients benefit from this treatment. The standard method of predicting response using a 2-week PNE technique does not seem as effective in CC as in treating faecal incontinence or bladder dysfunction.

The success rate of PNE in urinary dysfunction and faecal incontinence was reported as between 63%-80% (128-131). In contrast, the Kamm study demonstrated the predictive value for test stimulation in identifying 1 year responders was less than 50% (99), and recently the PPV has been demonstrated to be as low as 6% at 5 years (122). In an audit of patients with chronic constipation treated in clinics at Durham and Hull 60% of patients stopped responding to treatment in the first 6 months after permanent stimulation, despite strongly positive responses to standard 2-week test stimulation. Local experience

anecdotally reported some patients with a strong response to test stimulation having a failure of therapy very soon after insertion of a permanent tined lead.

Failure of the standard test stimulation to accurately predict outcome poses a major barrier to the viability of SNS in this condition, both from a patient perspective and an economic one. The predictive value of PNE in predicting long term response to implanted IPG was inadequate to allow NICE approval for the treatment in CC. The reasons for the poor predictive performance of 2-week PNE stimulation in constipation are unknown. The qualitative literature review described a strong placebo effect in patients with functional bowel disorders (132, 133), and this is a possibility. A placebo effect, if confirmed to be present, would most likely to be strongest following commencement of stimulation, and reduce with time (134). Alternatively, the false positive PNE tests may arise because of the lack of objective testing of disease severity and the natural variation of symptoms over time (135). Finally, there is the possibility that the lead position in the S3 foramen may be more critical in CC. This possibility implies that PNE is only effective at predicting the outcome of a lead in that specific position, and therefore once the testing lead is changed for a permanent tined lead, the small change in position results in a change in efficacy. The use of a tined (barbed) lead during the evaluative phase (enhanced percutaneous nerve evaluation- ePNE) allows the same lead to be used for a permanent implant, precluding electrode re-positioning. It also allows a 6-week evaluative phase which can include periods of active and sham stimulation for placebo control. We hypothesised that 'discriminate' responders (patients responding only to active stimulation) would receive long-term benefit from SNS, while patients responding 'indiscriminately' (during sham or both periods) would be less likely to benefit. Following a positive test with a tined lead, the same lead was used to connect with the permanent implant. This guaranteed that the position of the lead and the electrode did not change. Urological studies have shown the

tined lead testing to be safe and practical over several weeks (136) and therefore a six week period was viable. This also enabled observations of placebo responses, by using intermittent real/sham stimulation. The stimulation was provided using sub-sensory settings so that the patient would not be able to differentiate between real and sham stimulation. The Tilt-cc study was thus designed to test with the permanent tined lead using a methodology that would generate OCEBM level 2 evidence of the predictive ability of this ePNE test.

I will now proceed to Chapter 3 where the results of the systematic review and scoping review of the qualitative literature for SNS in treating CC, are described and presented.

# Chapter 3 Sacral Nerve Stimulation- Qualitative literature

## 3. Introduction

This Chapter aims to examine the current knowledge (at the time of study design) within the qualitative literature on patient experiences of sacral nerve stimulation. This is achieved by both a systematic review of the qualitative literature, and a scoping review of the remaining qualitative literature aiming to identify relevant patient experiences and issues that may have influenced the design of the Essence study.

## 3.1 Systematic review of the qualitative literature

In order to understand the existing knowledge of the lived experience of patients receiving SNS for CC, a systematic review of the qualitative literature was performed. This review aimed to highlight the knowledge gaps in order to inform the design of the Essence study. The review also aimed to provide evidence to assist the choice of the theoretical framework selected to be used in the study, and of the expected experiences of patients either in SNS treatment or related therapies. This section will present the methods used to perform this search, the results and discuss these findings and how they relate to the knowledge being sought through the Essence study.

### 3.1.1. Criteria

This review aimed to demonstrate the lived experience of patients undergoing SNS for chronic constipation. The following inclusion and exclusion criteria were thus applied:

**Inclusion Criteria:**

- Original qualitative research using a recognised qualitative theoretical framework for data collection
- Full papers published in peer reviewed journal
- Patients suffering from Chronic/ functional/ idiopathic constipation

- Patients who have been treated with SNS
- English language articles
- Adults 18 years of age or older

**Exclusion criteria:**

- Letters, abstracts, consensus opinions and review articles
- Patients suffering from secondary constipation
- Patients treated with other forms of neuromodulation
- Children 17 years or younger

### 3.1.2. Search strategy

The following databases were systematically searched for papers written in English from 1900 to January 2014: AHMED, CINAHL, COCHRANE, EMBASE, MEDLINE, OVID, and Web of science ™ Core Collection (Thomson Reuters™). The search used truncated search topics which were standardised and consistent in each database, and refined by utilising the Boolean logic operators “AND” and “OR” to combine the searches accordingly. The patient population search terms were “constipat*”, “function”, “idiopathic” and “chronic” which were combined to identify the target patient group. The treatment search terms were “sacral nerve stimulation”, “SNS”, and “neuromodulat*” which were combined to identify the target treatment administered. The qualitative research search terms were “phenomeno*”, “ethnograph*”, “narrative”, “grounded theory”, and “qualitat*” which were combined to identify the target type of research. The literature for review were thus identified by combining the target patient population, target treatment and target research as demonstrated in Table 15 below.

### 3.1.3. Results

**Table 15 Search of bibliographic databases for qualitative literature**

| **Search n** | Search term (patient population) | Results |
|---|---|---|
| **1** | ALL=constipat* | 15,324 |
| **2** | ALL=function* | 4,446,966 |
| **3** | ALL=idiopathic | 94,894 |
| **4** | ALL=chronic | 802,985 |
| **5** | 2 OR 3 OR 4 | 5,170,514 |
| **6** | 1 AND 5<br>**Target patient population** | 7,273 |
| **Search n** | **Search term (treatment)** | **Results** |
| **7** | ALL= sacral nerve stimulat* | 1,647 |
| **8** | ALL= neuromodulat* | 13,959 |
| **9** | 7 OR 8<br>**Target treatment population** | 14,928 |
| **Search n** | **Search term (research type)** | **Results** |
| **10** | ALL= phenomeno* | 366,253 |
| **11** | ALL=ethnograph* | 30,388 |
| **12** | ALL=narrative | 72,138 |
| **13** | ALL= grounded theory | 60,095 |
| **14** | ALL= qualitat* | 321,988 |
| **15** | 10 OR 11 OR 12 OR 13 OR 14<br>**Target research population** | 819,212 |
| **Search n** | **Combining target populations** | **Results** |
| **16** | 6 AND 15<br>**Qualitative research in constipation** | 118 |
| **17** | 9 AND 15<br>**Qualitative research in SNS** | 248 |
| **18** | 6 AND 10 AND 16<br>**Qualitative research in SNS for constipation** | 1 |
| ALL= all search fields | | |

### 3.1.4. Qualitative research in SNS for constipation

One abstract was identified from the combined search target literature that was potentially of patient experiences of SNS for constipation (137), and the full paper was reviewed. This was a review and commentary of all treatments used in constipation with 3 references to other studies (25, 138, 139) of the condition, and not a formal qualitative study itself. These 3 studies were obtained in full text and none related specifically to experiences of treatment with SNS, but did have qualitative aspects to living with CC. They were included in the narrative of a further scoping review of the literature.

### 3.1.5. Qualitative research in SNS (any disease)

Abstracts from the 248 items identified from the search as potential qualitative research studies of SNS (for any disease), were screened and excluded as follows: 241 were not qualitative research studies, 5 were animal studies, and 2 were qualitative studies in different fields and unrelated to SNS; 1 in psychology relating to perceptions of treatment by neurosurgeons, and 1 in a patient's experience of deep brain stimulation for an unrelated condition. No literature was therefore identified that specifically studied patient experiences of treatment with SNS for any disease process.

### 3.1.6. Qualitative research in constipation

Abstracts from the 118 items identified from the search as potential qualitative research studies of patients suffering from constipation were screened and excluded as follows: 93 were not qualitative studies, and 19 were qualitative studies of children. Of the remaining 6 qualitative studies of adults, 4 were excluded as follows: 1 was a case study of an unrelated condition (Charcot-Marie Tooth syndrome), 1 was of opioid induced constipation in cancer patients, 1 studied neurosurgeons perspectives on specific treatments, and 1 was of the gendered impact bias of IBS in healthcare. The 2 remaining studies were not specific to SNS treatment, but are to CC and were therefore included in the narrative of a further scoping review of the literature.

### 3.1.7. Discussion of the systematic review of the qualitative literature

No qualitative studies were identified during this systematic review of the qualitative literature that explored and reported patient experiences of receiving SNS therapy for chronic constipation. No qualitative studies were identified that explored and reported patient experiences of SNS as a treatment for any condition.

This review has therefore revealed a considerable knowledge gap in the literature; the experience of undergoing SNS treatment has never had the focus of dedicated qualitative research, and the experience of patients receiving treatment in this condition and others is therefore unknown. Following these findings, and in order to inform design of the Essence study appropriately, a further scoping review of the literature was performed in an attempt to anticipate the likely findings and potential problems that could be encountered in this further research.

## 3.2 Scoping review of the qualitative literature

This narrative scoping review was conducted to discuss the literature related to patients' experiences of living with constipation and functional gastro intestinal disorders, of having colorectal surgery (such as SNS or other procedures), and of participation in surgical research trials. The aim of this review is to identify further knowledge gaps that would influence the Essence study design and data collection.

### 3.2.1. Search strategy

This scoping review utilised the search results of the specific searches conducted above in the systematic review for qualitative research in SNS and in constipation. The articles that were considered to be related to either SNS or living with constipation were reviewed and similarly referenced articles obtained in order to try and identify relevant themes that may be related to the treatment or condition. 2 qualitative studies (27, 140) were identified that were specific to living with constipation, and 1 that was interested in gender bias in IBS (141). As such a narrative scoping review was written using these papers, related papers referenced in their bibliographies, and from conducting several searches of the literature for themes related to SNS and constipation that I and supervising researchers felt were

important to the study group. These included themes of “living with a functional gastro intestinal disorder”, the “motivations for patient participation in surgical trials”, the “lived experiences of patients through colorectal surgery”, the “experience of placebo effects in surgical trials” and “psychological considerations in sufferers of a functional gastro intestinal disorder.”

### 3.2.2. Living with a functional gastrointestinal disorder

Diagnosis and treatment of CC represents a significant burden to healthcare providers (34) with costs increasing with disease severity and bowel symptom exacerbations (35). Patients often suffer a significant and chronic deterioration in their quality of life (26), with many attempting a variety of complementary or alternative medicines to try and gain resolution (140). Specifically, the experiences documented in the qualitative literature in CC sufferers include “feelings of hopelessness” in the condition and “frustration” at a perceived lack of clinician empathy, or simply “not being taken seriously” (27). Similarly reported are the experiences of living with constipation predominant IBS (IBS-C), where patient perceptions of symptom unpredictability lead to them “feeling constrained and dependant” (142). One hermeneutic study demonstrated evidence of gender stereotyping by healthcare professionals which the authors concluded may “perpetuate the suffering” of women and men with identical IBS symptoms due to “women being trivialised and men overlooked” (141).

### 3.2.3. Psychological considerations

Studies have demonstrated that psychological distress may be involved in the pathogenesis of FGIDs (36, 138), that anxiety and depression are prevalent within this group (36), and that the associated chronic pain of FGIDs can improve with a variety of psychological and behavioural treatments (37). Psychotherapy, in particular seems to be an effective adjunct to medical treatment in some patients (38). This is possibly due to the increased reporting of physical and sexual abuse

amongst sufferers of FGIDs, especially when constipation is the predominant symptom (25, 36, 38, 139). Anecdotal evidence from clinical practice supports the suggested association between early life trauma and FGIDs. DCC audit data also suggests a significant proportion of patients with concurrent mental health issues such as obsessiveness, anxiety, depression and occasionally suicidal ideation.

### 3.2.4. Motivations for participation in surgical trials

Researchers have scarcely investigated the motivations of patient participation in medical or surgical trials in the last 3 decades. It has recently been recognised that using qualitative methods to understand why patients participate may have the potential to inform future trial design this may increase patient satisfaction, and consequently recruitment and retention which may improve the size and demographic of the study sample (143). Given the burden on participants in trials of SNS, and the potential placebo response, it seemed imperative to understand this issue in more depth.

Altruism is frequently mentioned in the literature as a principle motivating factor for patient participation (in both therapeutic and non-therapeutic trials), by patients and the public. A US questionnaire study in 1982 demonstrated a positive public view of the “importance, ethicality and altruistic rationale” of participation in medical research when applied to “hypothetical others” (144). This was contrasted, however with patient reporting of motivations, where it seemed that “highly personal interests” prevailed. The authors concluded that people use “a different perspective” when viewing the motivating factors of study participation for others, and themselves (144).

In the UK a small study demonstrated up to two thirds of unselected patients may participate in therapeutic trials with purely altruistic motives (145). Another study has contradicted this stating “gaining a personal benefit” is an important primary motivation, and altruism is “largely subsidiary” (146). A detailed mixed methods

study in Brazil has demonstrated that “financial gain and therapeutic alternative” were the most frequent primary motivations for clinical trial participation, with altruism uncommon and secondary to other motivators when present (147). Adherence with research procedures, however may be linked to altruistic motivations at trial recruitment (148). Disease severity is likely to change participant motivations; an important hypothesis given the severity of quality of life changes in CC sufferers. A US questionnaire study in 1996 demonstrated that severely ill phase 1 subjects were primarily motivated by “a new treatment” before altruism, as opposed to phase 3 subjects who were primarily motivated by honorariums before altruism (149). Only one study was identified from the literature that was similar to the Essence study cohort: a qualitative study of women’s views and experiences of the CARPET1 trial. Participants had suffered severely from urinary incontinence and vaginal prolapse, and were randomised into one of two different surgical procedures as a corrective measure. Their primary motivations for study inclusion were “the possibility of additional care”, and a secondary altruistic motive of “the wish to help with research” (150). This literature review has failed to identify evidence of the motivating factors behind CC sufferers participating in medical and surgical trials. The evidence in this group seems to be anecdotally reported by clinicians recruiting them to trials. The general evidence collected above would seem to indicate that patients with severe conditions and undergoing invasive procedures are motivated by the possibility of a new treatment for their condition over altruism, and that altruism is present as a secondary motive.

### 3.2.5. Experiences of placebo effects in surgical trials

Patients with CC are often frustrated with their failed medical and surgical treatments to date, and have unsatisfactory experiences of care (27). The DCC experience anecdotally suggests they tend toward being a highly motivated group seeking a resolution to their condition and therefore demonstrate a willingness to

participate in clinical trials. They also demonstrate an expectation of a "cure" for the condition in the short term, and this may partly explain the heightened placebo response anecdotally observed by clinicians during SNS testing. Doctors treating these patients rarely have a simple cure to their ailments, are therefore eager for SNS to work, and so their perception of the patient's symptom response may be biased. This could possibly be enhancing the placebo effect further. The placebo effect has been shown to be enhanced in patients suffering from functional bowel disorders (132, 133), is greatest at treatment initiation (such as SNS testing) and tends to decrease with time (135). The natural variation of symptoms in severely affected patients may also cause the perception of a "response to treatment or placebo effect" through regression towards the mean (134). Even the ritualistic nature of a testing procedure may change a patient's self-awareness and behaviour such that the self-perceived effects may due to the "ritual" and not the treatment (151).

### 3.2.6. Lived experiences through colorectal surgery

Phenomenology has been used by researchers to interpret and describe the experience of having surgery in most body systems. Sacral nerve stimulation has no published qualitative data of patient experiences. This literature review has identified knowledge on the lived experiences of patients undergoing colorectal surgery, as a comparable group [to CC] with similar symptoms and clinical signs.

Van Manen's existential themes of spatiality, corporeality, temporality and relationality (152) have been used to demonstrate a patient's existential situation pre-operatively in colorectal diseases (153). Patients were uncertain about how the surgery would affect their lived space, body, time and relations despite pre-operative information (153). Hesitation, fear and anxiety about the surgery and its outcome were common findings, and the importance of life-partners for "trust and security" is highlighted. Moene et al demonstrate that patients did not adequately

have these concerns addressed at pre-operative clinics. The life adaptations required to live with an implanted SNS testing lead may potentially leave patients in a similar situation.

A similarly complex surgical programme [to SNS testing] called enhanced recovery after surgery (ERAS) has demonstrated the importance of pre-operative information being supported by consistent post-operative instructions. Patients interviewed in 2010-2011 reported that whilst the preoperative information-giving made them feel “centre stage” and “felt taken care of”, they did not feel acknowledged in the subsequent post-operative ERAS experience (154). Trust in the health care providers was an important theme, with patients citing trust as crucial to them feeling safe and participating with ERAS post-operative care instructions. The authors concluded that more importance should be placed on acknowledging patients post-operatively in order to help them participate and improve self-care. This is likely to be relevant as ePNE is complex and requires close personal care of the exit lead site by patient, family and healthcare provider in order to minimise complications. In the TiLTS-cc study the exit SNS lead is cared for in a similar way to an intravenous central line. The rationale for this was drawn from the lived experiences of vascular nurse specialists who demonstrate lower infection rates when the central line exit site is closely cared for by nurse and patient (155).

There are common themes that occur in other qualitative studies of colorectal surgery. Preoperative experiences commonly include those of fear, isolation, and uncertainty (156). Postoperative experiences are commonly of pain, loss of dignity/functional control, dependence for personal care (from nurses or partners), embarrassment, medical complications and changes to the body (157-159). However, the extent to which these are relevant to the experience of SNS remains unknown.

### 3.3 Discussion of systematic and scoping reviews of Qualitative literature

There is a significant knowledge gap in the literature on the phenomenon of undergoing SNS for CC. Patients may undergo significant disruption to their daily lives; practical, personal and professional. The desperation and suffering of patients with CC is accepted, and may result in an eagerness to participate in trials which are likely to be perceived as a solution to their ailments. Their motivations for surgical trial inclusion are unknown and urgently require exploration to inform future trial design. Experiences and beliefs about the placebo effect have never been qualitatively evaluated in this population. These are important issues which may influence the potential for actual and sustainable patient benefit in current and future surgical trials of CC. The placebo effect may be heightened during SNS testing through a variety of mechanisms. The lived experience of having a testing placebo response followed by a deteriorating treatment response is unknown for treatment with SNS. The patient experience of how the procedure and complex nature of the testing is communicated preoperatively may have a marked influence on their perception of the treatment and attitude towards responsibility for taking care of the exit lead dressing. Patients may experience pain, dependency on others and loss of dignity during this time. Given the invasive nature of SNS, its cost, and its contested effectiveness, I wanted to understand the patient experience and acceptability of this procedure and of trial participation, from SNS testing through to long-term follow up.

### 3.4 Conclusion

The knowledge gained from the literature reviews will now be discussed to inform the rationale for the Essence study design, highlighting the knowledge deficits in the literature and why they are important to this research.

### 3.5 Rationale for the Essence study

The lived experience of patients with CC undergoing SNS testing and treatment, their acceptability of SNS, their motivations to participate in a surgical research trial, and their beliefs of the placebo effect were unknown. A stand-alone quantitative trial would thus have been inadequate to understand all of these complex inter-related issues within a very heterogeneous group of patients, and so the Essence study was designed to capture this information following on from the TiLTS-cc study in a sequential fashion. This thesis will therefore present the methods for data collection in Chapter 5, and report, analyse and discuss the results of both studies in Chapters 6 and 7, and culminate in an informed conclusion at a higher taxonomic level than using a stand-alone quantitative study in Chapter 8.

# Chapter 4 Aims and objectives of the thesis studies

## 4. Introduction

With these quantitative and qualitative knowledge gaps identified in Chapters 2 and 3, the aims and objectives of both the TiLTS-cc and Essence studies were constructed accordingly as follows:

### 4.1 Aims and objectives of the TiLTS-cc study

The primary aim was to improve the predictive performance of test stimulation for CC by using an ePNE test with a tined lead and a double-blinded randomised cross over methodology of active versus sham stimulation testing.

The secondary aims of the Tilts-cc study were hypothesis generating: whether use of this testing technique could improve the proportion of test positive patients with refractory CC who receive long-term benefit from SNS, which would require validation in a hypothesis testing study. Secondary aims also included assessing long-term efficacy of SNS for CC, detecting and quantifying any placebo response during testing, assessing any baseline predictors of response to treatment, assessing the effect of SNS on quality of life, and assessing the cost-effectiveness of the treatment within the NHS including modelling the transition from the standard test to the ePNE test. This knowledge would provide patient, clinical and policy-level data to appropriately inform decision making within the NHS.

### 4.2 Aims and objectives of the Essence study

The primary aim was to explore the lived experience of a patient undergoing SNS testing for CC, and subsequently with the implanted permanent SNS device. Key topics were identified from the literature review as interesting areas for qualitative enquiry namely; participant's experiences of living with CC and the treatments, their motivations to participate in a surgical trial, their experiences of care and support before/during and after a surgical trial, their perceptions of symptom

changes (physical or psychological) in respect to a possible placebo effect, and their experiences of SNS in relation to its effect on other aspects of their life (relationships, socially, professionally, and self-perception).

### 4.3 Conclusion

Chapter 5 will now examine in detail the methodologies used to collect data in these studies and justify the selection of these methods. Chapters 6 and 7 will present the findings of these studies and discuss their implications which will be used for the discussion in Chapter 8 to synthesise an overall conclusion to the thesis.

# Chapter 5-Methodology of the TiLTS-cc and Essence studies used to examine enhanced Peripheral Nerve Evaluation testing of Sacral Nerve Stimulation for Chronic Constipation.

## 5. Introduction

Previous chapters have highlighted a chronic and poorly understood disease which has significant impact on sufferers' health related quality of life (HRQOL), and the paucity of evidence about the place of SNS within treatment algorithms. A substantial knowledge gap is identified in SNS and other surgical research published to date for this condition. In particular, the current SNS test is poor at discriminating who will respond to the treatment in the longer term, the newly devised "enhanced" peripheral nerve evaluation (ePNE) test using a tined lead has not been investigated in this group of patients and consequently the diagnostic accuracy, feasibility, acceptability and transference of this test are unknown. This chapter describes the scientific methods used to achieve the aims and objectives of the thesis described in Chapter 4. The chapter is structured chronologically to represent the real life sequence of events as experienced by trial participants of both studies, following a quantitative-qualitative linear methodology.

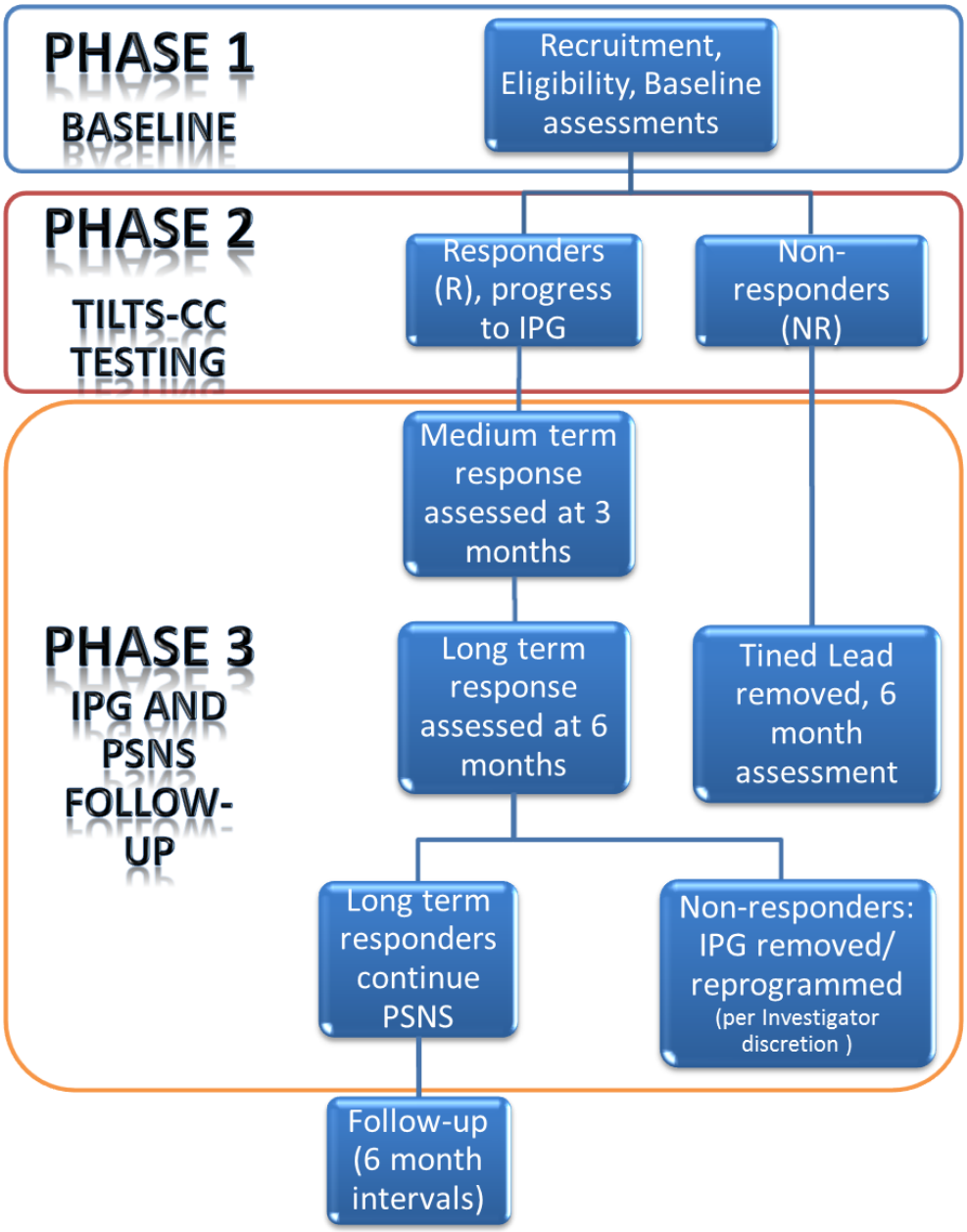
### 5.1 Introduction to the TiLTS-cc trial design

"*Tined-lead test stimulation to predict long term benefit from sacral nerve stimulation in chronic constipation*" (acronym TiLTS-cc) was a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) portfolio study which had significant design and research contribution from myself, and therefore from which this thesis is partly composed. The concept to utilize the enhanced percutaneous nerve evaluation (ePNE) SNS test and apply the novel adaptation of a sub-sensory double-blinded sham controlled cross-over trial design was originally devised by the TiLTS-cc study team (of which I was part); consequently the

diagnostic accuracy, feasibility, generalizability, and transferability of this technique in these patients was unknown. The TiLTS-cc study had Research for Patient Benefit (RfPB) programme funding and NHS Research Ethics Committee (REC) approval to test the null hypothesis that ePNE SNS test discriminate responders are no more likely to have a 6 month response to an implanted SNS IPG stimulator than ePNE SNS test indiscriminate responders, in participants suffering from chronic constipation.

This section will outline and explain the methods used in the REC approved trial design and conduct, in order to demonstrate the integrity and robust nature of methods used in collecting data for this study. The following overall trial schematic demonstrates the main trial activities experienced by participants during each of three phases of the study.

**Figure 7 Overall Trial Schematic**



## The TiLTS-cc research questions

The study is designed to address the following research questions:

- Is **TiLTS-cc** testing in SNS predictive of long-term benefit to permanent SNS (PSNS) in patients with idiopathic chronic constipation?
- Is permanent SNS (PSNS) an effective treatment for discriminate responders as identified by **TiLTS-cc**?
- Is **TiLTS-cc** guided PSNS more cost-effective to the NHS than current TSNS guided assessment?

### Primary Objective of the TiLTS-cc study

- To assess the predictive value of the **TiLTS-cc** method of temporary SNS testing for patients with severe idiopathic constipation.

### Secondary Objectives of the TiLTS-cc study

- To detect and quantify any placebo response present during **TiLTS-cc** testing by a randomised and double-blinded 2 week cross-over of sham versus real stimulation.
- To assess the efficacy of permanent SNS for patients with severe idiopathic constipation at 6 months after implantation.
- To assess the cost effectiveness of **TiLTS-cc** testing to the NHS in order to inform policy decision making.
- To assess any baseline predictors of response to treatment.
- To assess the effect of SNS on quality of life at 6 months after implantation.

## Primary Endpoint

The primary endpoint was the response rate comparing discriminate and indiscriminate responders at 6 months with baseline data. A responder was

characterised by a drop in PAC-SYM score of 0.5 or greater. Since scores for PAC-SYM have good floor and ceiling effects with ranges between 0.5 and 3.5, a drop of 0.5 represents an average of 15-20% reduction in symptoms, which is highly likely to be clinically important (160, 161).

**Secondary Endpoint**

Secondary outcome measures were 6 month assessments comparing discriminate with indiscriminate groups against baseline data of global assessment of symptoms: PAC-SYM; scores from daily diary exercises; PAC-QOL; EQ-5D-3L, EQ-5D-VAS, Cleveland clinic questionnaire and Wexner Score. Those with no response during TiLTS-cc testing provided a 6 month reference group of untreated patients to help explore the absolute value of SNS.

### 5.1.1. Phase 1

#### 5.1.1.1. Recruitment

Potential subjects recruited were patients with severe idiopathic constipation refractory to treatment with dietary changes, laxatives, suppositories, and enemas. Participants were recruited across three sites from specialist clinics, the majority from the University Hospital of North Durham (UHND) with Queen Elizabeth Hospital in Gateshead (QE) and the Royal Victoria Infirmary (RVI) in Newcastle making up the rest. Two sites involved with the original trial design (Castle Hill Hospital in Hull and the Royal London Hospital) could not participate due to changes in Clinical Commissioning Group funding locally for the procedure. Eligible patients represent an unselected group of individuals with symptoms severe enough to justify specialist referral and tertiary intervention. Those who were considered suitable, via record screening by a research nurse, according to standard definitions and who fulfilled the inclusion/exclusion criteria were invited to participate. The study was a prospective randomised double-blinded crossover trial of sub sensory ePNE SNS testing, aiming to recruit 75 participants over an approximate 24-month

period across the three sites. Participants who were withdrawn on clinical or compliance grounds were allowed to be replaced in order to achieve the required sample size as calculated from pre-trial audit data.

#### 5.1.1.2. Inclusion Criteria

Participants had to fulfil all of the following inclusion criteria in table 16 to be recruited into the study.

**Table 16 TiLTS-cc study inclusion criteria**

| | |
|---|---|
| **a** | Males and females aged 18 years or older. |
| **b** | Constipation according to the ROME III criteria⅄ for functional constipation. Participants were not excluded if they also fulfilled criteria for constipation predominant irritable bowel syndrome (IBS-C). |
| **c** | Unknown (idiopathic) aetiology of constipation, as determined by the recruiting clinician. |
| **d** | Symptoms not adequately relieved by the standard treatments of lifestyle modification, laxatives, suppository, and enema. |
| **e** | Symptoms not adequately relieved after a trial of Prucalopride 2mg once daily, given according to licence. |
| **f** | The recruiting clinician had to be confident of participant comprehension and that the consent process was adequate. Translation services were available for non-English speaking participants, if required. |

⅄The Rome III Criteria for functional constipation (Table 17) were accepted and used in the study. (162) The Rome III criteria were assessed using a questionnaire at the baseline interview appointments of participants.

**Table 17 Rome III Criteria of Functional Constipation**

| **Using the Rome III criteria the diagnosis of functional constipation requires <u>at least 2 of the following</u>:** | |
|---|---|
| **1** | Straining during at least 25% of defecations |
| **2** | Lumpy or hard stools in at least 25% of defecations |
| **3** | Sensation of incomplete evacuation for at least 25% of defecations |
| **4** | Sensation of anorectal obstruction/blockage for at least 25% of defecations |
| **5** | Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor). |
| **6** | Fewer than 3 defecations per week. |

#### 5.1.1.3. Exclusion Criteria

Participants who fulfilled any one or more of the following criteria (table 18) were excluded from study recruitment.

**Table 18 TiLTS-cc Study Exclusion criteria**

| | |
|---|---|
| **a** | Age of less than 18 years. |
| **b** | Participants who were not fit enough to undergo the procedure (as per clinical judgement of the site researchers). |
| **c** | Severe psychiatric disease at the time of study recruitment. |
| **d** | Persistent diarrhoea (except when due to laxative over use). |
| **e** | Uncontrolled or decompensated cardiac, respiratory, endocrine, renal, or hepatic disease; as the clinical judgement of the site PI. |
| **f** | The presence of any *progressive* neurological disease, or any neurological disease deemed to be restricting participant mobility and independence. Participants who had a mild non-progressive neurological disease not restricting their ambulation or independence, and not causing or contributing to their constipation were not excluded. |
| **g** | *Secondary causes of constipation (i.e. not idiopathic, e.g. obstructed defecation) |
| **h** | Any participants with an active systemic infection. |
| **i** | ** Participants known or suspected to be pregnant, or any participants intending to conceive within the timeframe of their study involvement. |
| **j** | Any participants who were participating in or within 30 days of participating in any interventional treatment study. |
| **k** | Any participants who had incapacity of higher mental function such that informed consent could not be achieved, as determined by the clinical judgement of the research team. |
| **l** | Any participants with incapacity of higher mental function or physical abilities that prevented accurate completion of study questionnaires. |
| **m** | Any participants using *variable* or *unstable* doses of an anti-cholinergic, iron, antidepressant, or opioid medication. |

*****It was the clinical decision of the investigators as to the cause of secondary constipation, reiterating that this study was to investigate "***idiopathic***" chronic constipation. The assessing clinician decided whether the participant's constipation was ***idiopathic*** and that it was not ***secondary*** to chronic drug (e.g. opioid) use. Secondary causes also included other aetiologies such as obstructed defecation, congenital, metabolic, traumatic, inflammatory, ischaemic, and neoplastic in origin. Obstructed defecation was consistently assessed by the pelvic floor MDT, and participants were excluded if they had evidence of obstructive defecation at proctogram through anismus, intussusception or other mechanical effects causing delayed emptying. Participants using stable doses (3 months of unaltered dose) of known constipating medications were considered suitable if these medications were deemed not causative (i.e. secondary) of their constipation.

**In ladies of child bearing age a pregnancy test was performed before transit studies at baseline, and participants agreed to use adequate contraception for the duration of the study, with signed consent to indicate their agreement.

In forming these study eligibility criteria within the protocol I was consistently trying to keep the recruited population as homogenous as possible from the pool of participants who may be eligible. In particular, our research questions were aimed at adults who have chronic and medically refractory idiopathic constipation with demonstrable chronicity, hence the majority of these criteria. With regards to pregnancy, I could find no evidence of safety data in the literature for SNS during any trimester of pregnancy. The electrical field of the tined lead would be within a participant's pelvis, and most participants would likely be of child bearing age, and so it would be impossible to guarantee that the forming foetus of a pregnant participant would not be harmed by the SNS field. In order to keep recruitment feasible I decided that we could allow participants who had stable doses of medications that may potentially affect constipation, and emphasise to the participants not to adjust the doses during the study.

**Patient and Public involvement**

The participant information sheet (PIS) was reviewed during the design phases by the constipation research advisory group (CRAG), which consisted of Durham clinic patients who had experience of constipation trial participation. They advised and helped with the design of the PIS and overall study, and approved these as acceptable to patients before ethical approval was sought for the study. The information on using appropriate contraception to prevent pregnancy within trial participation, and on stable dosing of constipation inducing medications was included in the participant information leaflet (Appendix 2) which was reviewed by

the constipation research advisory group, although I did not ask the group to specifically consider these issues.

#### 5.1.1.4. Criteria used for early study termination

The study had a trial steering committee (TSC) which reported regularly to the sponsoring hospital trust (CDDFT) and a data monitoring committee (DMC) that comprised independent academics (including a statistician) who both met at routine 6 monthly intervals (and at the urgent request of the sponsor) to advise the sponsor on study safety and futility. These committees considered criteria which were devised to protect trial participants from harm or unnecessary continuation. The TSC approved four conditions for early study termination (Table 19).

**Table 19 Criteria for early study termination.**

| | |
|---|---|
| **1** | Futility: If the trial had no prospect of reaching its recruitment target within the given time frame |
| **2** | If a substantial change in understanding/scientific advancement meant that continuation of the trial was inappropriate/unethical |
| **3** | Safety: If overwhelming evidence for harm through adverse event reporting made continuation non-viable |
| **4** | The sponsor requested trial termination |

#### 5.1.1.5. Participant Withdrawal

Withdrawal was defined as participant termination in the trial through; ***patient wishes***, ***clinical grounds, compliance*** **grounds**, or **data invalidation** as decided by the investigators. Withdrawn participants were allowed to be replaced at each study site. Any phase 3 participant who was withdrawn before the 6 month follow up was offered a PAC-SYM assessment to complete which would be carried forward to the 6 month analysis. It was emphasised to all participants in both the PIS and consent form that if they withdrew of their own accord or were withdrawn for any other reason by the site PI, they would still receive the same provision of care and

follow up as per the standard in the NHS. It was important in the study design to emphasise this to participants in order that this was a continued process of consent, and to protect the data integrity through ensuring compliance with blinding and procedures.

#### 5.1.1.5.1. Patient wishes

***Patient wishes*** were defined as any reasons that the participant deemed continuation in the trial unacceptable to themselves. Participants were provided with contact details for their local investigators allowing them to discuss any issues or concerns if they considered withdrawal. Participants were able to terminate participation immediately or at any time during the study if they so desired. Participants were offered the opportunity to meet an investigator following withdrawal. Data already gathered from participants who had withdrawn were kept and used in the analysis; this fact was included in the participant information sheet and consent form.

#### 5.1.1.5.2. Clinical grounds

Withdrawal of a participant on ***clinical*** grounds was considered by the investigators due to ***any*** illness that either made continued participation a threat to the participants' health or that may invalidate the data collected from the participant. Pregnancy was an absolute indication for immediate withdrawal of active intervention on clinical grounds due to the unknown effects of SNS stimulation fields on embryogenesis. In the event of pregnancy a participant would be treated as per their clinical indication in conjunction with opinions from obstetricians and anaesthetists if surgery was necessary. Pregnancy during the testing phase necessitated a plan to prevent a general anaesthetic during the first trimester: I decided that the exiting extension lead would be removed under a local anaesthetic and the tined lead would remain in-situ for removal or re-testing at later date. I

decided that for pregnancy confirmed in participants during phase 3 the IPG battery would simply be turned off. I considered examples of continued trial participation becoming a threat to a participant's health; one obvious situation would be when a participant required an urgent MRI investigation to assess another unrelated medical condition. In this type of situation, I designed the protocol so that the investigator would make a clinical judgement in conjunction with other treating clinicians before the decision to withdraw the participant and remove the IPG and lead were taken.

#### 5.1.1.5.3. Compliance grounds

Withdrawal of participants on ***compliance*** grounds were considered where participants had non-compliance with assessments and/or any evidence of tampering with the security seals on the test box were demonstrated. This was to protect the integrity of the blinding which was an integral part of the study design. Participants were specifically told about compliance monitoring in the participant information sheet, and advised to contact investigators to arrange an urgent review if they suspected device problems rather than breaking the security seals in an attempt to rectify the problem themselves. In order to preserve their blinding during unlikely emergency situations such as stimulation becoming painful or supra sensory, I requested that participants pull the wire out of the test box rather than switch it off. The participant information sheet clearly stated that device tampering was an absolute indication for immediate withdrawal. I approached a security seal manufacturer and designed a study specific set of tamper proof security seals that could not be taken off from the device without becoming clearly voided. I demonstrated these at trial steering group meetings and as no collaborators could remove the seals without voiding them, they were approved for use in the study. I defined a security seal as "***voided***" when the bold (black) unique identifying number and/or trial lettering had apparent background lettering ("open or void") across the

plain coloured (red) background. This was only possible when the central part of the seal was removed. Background lettering could potentially occur due to fraying of the seal edges from normal wear, but this would not cross over the bold central characters. Please see examples below: A) A normal seal, B) A frayed but valid seal, C+D) Voided seals front or back.

Examples using the “verify” testing stimulator model 3531 Medtronic US


A) A Normal Seal


B) A Frayed but valid Seal


C) Voided seal-front


D) Voided seal back

Examples using the “brown box” testing stimulator model 3625 Medtronic US

A) A Normal Seal.


B) A Voided Seal

C) A Frayed but valid seal


### 5.1.1.5.4. Data Invalidation

Withdrawal of a participant for **data invalidation** was considered where a participant used a new (not previously used, or agreed at baseline) medication during the trial that was known to promote/decrease intestinal motility or influence intestinal bacterial flora. This was placed in the protocol to preserve the data integrity as the final analysis would be of a small sample (up to 75 participants) and consistency of treatments was therefore crucial, the only change should have been the SNS trial therapy. Apart from prophylactic use at surgery, antibiotic courses required during the trial had their indication recorded as an adverse event. Specifically, participants who required antibiotic treatment (not agreed at baseline) were not withdrawn from the study but had these courses of treatment closely recorded and monitored.

### 5.1.1.5.5. Replacement of participants

The protocol design allowed replacement of participants at each site in the event of withdrawal up to the point at which the 75$^{th}$ participant was recruited and completed the testing phase. Replacement of participants was allowed up until 8 months before the anticipated end of all participant's follow-up. Replaced participants were to be recruited and randomised at each site as per protocol and

would be given a new randomisation number and allocation on the permuted block. This was an important design aspect as reaching the sample size was going to be difficult to impossible without replacement of participants.

#### 5.1.1.6. The trial consent process

Participants were required to give written consent in all cases (**Appendix 3**). The site investigators and clinicians explained verbally, in writing (or by using translators), the nature of the study. A copy of the participant information sheet (**Appendix 2**) was provided for consideration by the participant before consent was obtained. Participants were allowed to deliberate for a time appropriate to the participant after the initial discussions, before the consent process was completed. Participants were advised that they were free to withdraw from the study at their own request and at any time during the study. It was explained that the study had been designed following the edicts of the International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) and that they were protected by the 2008 Declaration of Helsinki to ensure their rights, safety and wellbeing. Arrangements were made to ensure adequate consent for any participants who had impairments (e.g. visual or hearing) that could influence the consent process.

Participants were advised that they would be invited to take part in the follow-on qualitative ESSeNCe study after they had completed the 6 month study questionnaires, and if they agreed this would involve structured interview at a later date to reflect on their experiences of the disease and TiLTS-cc trial participation. Funding changes locally in the NHS in the North East for SNS procedures also occurred in 2013. This resulted in SNS only being funded by the CCGs for patients with CC recruited to the TiLTS-cc study. I highlighted this fact in the consent process through the PIS.

#### 5.1.1.7. Participant confidentiality

Participant identification within the study was by a pseudo anonymous coded number which effectively ensured anonymity. A participant's inclusion in the study was visible in their medical notes. Other medical practitioners involved in non-research related care of the patients (for example in a medical emergency unrelated to the study) were able to use the information recorded in the notes about study participation and contact either myself or the local principal investigators if advice was required. Data were recorded on electronic case report forms (e-CRFs) using the DCTU online system with the participant's study number only, and no other personal identifiable information.

#### 5.1.1.8. Information to General Practitioners

General Practitioners were informed of their patient's decision to participate in the study. The GP letter (Appendix 4) provided information about the study, and a copy of the participant information leaflet. The GP was invited to contact me or other site investigators if they had enquires or objections to their patient being recruited into the study.

#### 5.1.1.9. Baseline demographics and assessments

##### 5.1.1.9.1. Baseline assessments

In phase 1 all participants had the severity of their constipation assessed at baseline for two weeks before their trial registration and surgery to implant the tined lead. Participants attended a baseline appointment where the severity was assessed through questionnaires measuring symptoms: PAC-SYM (Appendix 5), a daily diary exercise (Appendix 6), quality of life: PAC-QOL (Appendix 7), and health status: EQ-5D-3L (Appendix 8). Baseline demographic data were collected and a transit study performed as a physiological measurement of colonic transit time (if the participant had not had a transit study within 6 months of baseline). Each participant was

classified as either "***slow***" or "***normal***" transit using the Metcalf protocol. In the original trial design I did not consider repeating the transit study in testing non-responders (not implanted) as this could be considered an unethical use of ionising radiation. Anaesthetic pre-assessment was carried out if required, typically for participants thought to be at higher risk from general anaesthetic. All female participants who could potentially conceive had a pregnancy test performed at baseline, and agreed not to attempt to conceive during the study through the consent process. Participants were informed of theatre dates for both surgical procedures (tined lead implantation and either IPG or removal 6 weeks later) at baseline. I was keen to avoid anxiety caused by uncertainty as this may have affected data, and so each participant was given precise dates and times for surgery. Participants were placed as near to the beginning of the theatre list as possible to ensure the best possible infection control practice, and also to allow for same day randomisation as participants would have recovered sufficiently long enough to understand and remember instructions from the blinded and un-blinded researchers on the study devices. Continuous data collection through daily diaries commenced in the 2 weeks preceding the testing phase to generate baseline pre-intervention scores.

The following demographics were obtained together with specific clinical details:

- Duration and onset of illness
- Demographic profiles
- Symptom profiles using a questionnaire based on the Cleveland clinic constipation score ♦
- Current symptoms and signs
- Medication usage (except anaesthesia and other medication around GA)
- Past medical/surgical history
- Classification of IBS-C

- Eligibility check
- Physiological parameters
    - At baseline in the assessment clinic:
        - Transit study✦and βHcG (for female patients with child bearing potential only)

✦The Transit study was performed at baseline, prior to tined lead insertion, where participants had not had a transit study in the preceding 6 months.

♦Symptom profiles were recorded by clinicians using the Cleveland Clinic Constipation Score questionnaire at baseline and 6 month study visits (163). This uses a Likert scale of severity scoring.

#### 5.1.1.9.2. Transit studies

Transit time was a measured physiological parameter at baseline. This was not repeated if the patient had a transit study within 6 months of baseline. Each participant was classified as either "***slow***" or "***normal***". The original study design was to reassess transit time by the same method at 6 months post IPG implantation, but this did not become feasible due to a sudden and unexpected change to the way the main site conducted the transit study investigations. The radiology department changed the type and number of capsule markers used during the trial without informing the study team, and so there could be no consistency in this analysis. Transit studies were therefore used simply to classify participants into slow or normal transit time. The standardised method used in Durham is a modification of the Metcalf protocol.

The modified Metcalf protocol: This is measured by the patient swallowing 3 standard Sitz marker capsules (total of 72 markers), and a plain abdominal radiograph taken at day 5 post ingestion. The number of remaining markers in-situ are simply counted and classified into 3 locations; right colon, left colon and recto-

sigmoid. Slow transit constipation is diagnosed according to the Metcalf protocol when 45 or more markers remain at day 4 post ingestion (164). Recent expert consensus has established that a single day-5 X-ray is more accurate at discriminating between slow and normal transit and this is the accepted study method at Durham. The full Metcalf protocol demands a second X-ray for further classification when the first X-ray diagnoses slow transit. I felt that this was not useful information to collect, and therefore un-necessary irradiation of the patient. Discussions with our Constipation Research Advisory Group (CRAG) representatives suggested willingness for patients to undergo these extra investigations.

#### 5.1.1.9.3. Daily diary card exercise

Participants were asked to fill in daily diary cards and return them on a weekly basis according to the participant's self-completion schedule (Appendix 6) throughout baseline, the 6 testing weeks, and in phase 3 follow-up. The diaries were initially developed with user involvement, have been used in routine clinical practice, in a previous clinical trial, and their internal consistency was validated in over 50 participants during a physiological and quality of life study/thesis (165). The diaries included assessments of:

- Abdominal Pain Score
- Spontaneous complete bowel movements
- Bloating
- Straining
- Laxative score
- Laxative intake

#### 5.1.1.9.4. PAC-SYM and PAC-QOL

The Patient Assessment of Constipation (PAC) questionnaires consists of two separate scales, PAC-SYM (a 12 item measure of symptom severity across 3 subscales, (example in **Appendix 5**) and PAC-QOL (a 28-item measure of health

related Quality of life across 4 subscales, (example in **Appendix 7**). The PAC-SYM questionnaire has validated and reproducible internal consistency, and is therefore an effective tool to demonstrate a response to medical treatment for constipation symptoms (166). The PAC-QOL questionnaire has demonstrated internal consistency which has been reproduced in multinational studies (167). Both of these questionnaires were administered at determined intervals through the 3 phases of the trial (Participant self-completion assessment schedule-**Appendix 9**). These assessments are widely considered to be the most accurate for measuring the symptoms and quality of life of sufferers, amongst experts in the field. They were chosen due to their proven validity and consistency. PAC-SYM was chosen as the measure of the primary endpoint of the study. This would be defined as a reduction in mean total PAC-SYM score of $\geq$0.5 from baseline.

#### 5.1.1.9.5. TiLTS-cc VAS

The TiLTS-cc visual analogue scale (TiLTS-cc VAS-**Appendix 10**) was constructed by the team to be a simple tool for the participants to demonstrate a subjective symptom response to the SNS testing. I designed this as a 20cm line with a scale from 0-100% which asked the participant to place a cross on the line corresponding to how much they feel the SNS has improved their constipation symptoms compared to baseline, with 100% representing a complete cure and 0% representing no change at all. This was used to identify test responders who were defined as placing a cross on the TiLTS-cc VAS line at or above 25%. The level of 25% was set at an investigators meeting where it was felt that this level would be a significant improvement in medically refractory chronic disease symptoms. The increments were percentage points on the line in order that participants and would not be guided by a scale in 5% increments. We also believed that this would correlate with an improvement in PAC-SYM of 0.5 or greater which is considered a significant response. Participants were obviously not informed of what level

constituted a response to the treatment in order to stop them from self-selecting into the testing response group.

#### 5.1.1.9.6. EQ-5D-3L

EQ-5D-3L is a standardised instrument for measurement and valuation of health status developed by the Euro Qol Foundation (**Appendix 8**). It is used to determine the global and generic status of a person's health and health related quality of life. It is designed for self-completion and is widely applicable to a variety of health conditions and treatments (168). It can be easily completed in a few minutes and has a 3-level design consisting of a five dimensional descriptive profile. The EQ-5D-3L is applicable in clinical, economic and population-based studies. The performance of EQ-5D-3L in irritable bowel syndrome and inflammatory bowel disease has been evaluated in studies (169, 170). The responses to the EQ-5D-3L can be converted to preference based health state utility values using a scoring system developed from a large sample of the UK general population. These health state valuations can be used as an outcome measure in their own right or as the basis for the calculation of quality adjusted life years (QALYs). The tool is very widely used and is the recommended tool by the National Institute of Health and Care Excellence as part of technology assessment reviews. The EQ-5D-3L consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ-5D-VAS). The descriptive system assesses 5 dimensions of a study participants health related quality of life: mobility, self-care, usual activities, pain/discomfort, anxiety/ depression. Each dimension has 3 self-response levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale from 0-100 in 1 % increments, where the endpoints are labelled "Best imaginable health state" and "Worst

imaginable health state." Within this study, the EQ-5D-3L data would form the basis of QALY estimates used in turn to estimate the incremental cost per QALY (off xxx compared with YYY) on an intention to treat basis. The non-response group following the NR pathway (not implanted) was planned to provide a 6 month control group of disease symptom chronicity for these secondary analyses and would be compared with both the test discriminate and indiscriminate responder groups. This was planned to help to adjust for regression towards the mean. The EQ-5D-3L was administered at defined intervals as per the study assessment schedule.

#### 5.1.1.9.7. Laxatives and laxative score

Laxatives were allowed as supplementary or rescue therapy in addition to SNS. During the study design stages I believed that participants would take these irrespective of instructions if they felt no effect from the treatment and were suffering. It was therefore more acceptable to allow this and ask that each participant documented the intake of any laxatives in the daily diary. Newly licensed agents (such as Prucalopride and Linaclotide) were prohibited in order to preserve continuity during the trial. Since all participants were laxative-refractory, and on listening to advice taken from patient research advisory groups on the trial design, I opted to allow each participant to continue with their preferred usual laxative regimen. A simple diary score was devised to assess whether laxative intake on a particular day was: less (-1), more (+1), or the same as (0), their usual daily intake. This was previously validated in a similar clinical trial of SNS in neurogenic constipation (171).

#### 5.1.1.9.8. Medications

All medications were recorded from baseline until the 6 month follow-up visit. The exceptions were medication given as part of routine anaesthesia during study related surgical procedures.

### 5.1.2. Phase 2-TiLTS-cc Testing

This phase of the study commenced on the day of the tined lead implantation procedure and continued until the second procedure when it was either removed or an IPG battery was implanted and connected to it.

#### 5.1.2.1. Measures to avoid Bias

To maximise the study quality, certain measures were taken to reduce bias.

##### 5.1.2.1.1. Randomisation

Participants were randomised into either group A or B to decide the order of active and sham stimulation during the testing phase 2 of the trial (Table 21). The randomisation process was administered by Durham Clinical Trials Unit using a web based permuted block by site to evenly distribute participants to either group A or B, given the low numbers involved in the trial. The randomisation was performed by the un-blinded researchers only, and this was their only task in the whole study in order to preserve data integrity. There were several unique study design features written into the protocol for randomisation. I devised the concept of an un-blinded researcher who only handles randomisation in order to preserve my blinding of the participant's sequence of SNS, in the knowledge that I may influence participants subconsciously during study visits if I were privy to their allocation. Using a crossover design also allowed participants effectively to act as their own controls which would further preserve data integrity in any analysis given the small sample size.

##### 5.1.2.1.2. Double-Blinding

All investigators including myself and participants were blinded to the randomisation grouping of participants (A or B) during phase 2 of the trial. Only the university study monitors (DCTU) and one delegated member of the research team the "un-blinded researcher" were privy to the groupings. The participants were

prospectively informed of the allocation ratio of 1:1, and that the blinding prevented them from knowing their group allocation and thus the order of testing. To robustly conserve blinding, a delegated team member (the "un-blinded researcher") modified the test box accordingly at the appropriate time intervals during phase 2 (Table 21), and the "blinded researchers" were not involved in this process, and the protocol mandated they must not be present in the same room during device randomisation. To further preserve trial integrity and minimise investigator bias, the "un-blinded researcher" was prohibited from any data collection, handling or interpretation. This prevented the un-blinded researcher from giving data feedback to participants which may have influenced their results.

#### 5.1.2.2. Tined lead insertion

In order to ensure consistency of the technique between sites I standardised the surgical procedure and the equipment used (Table 20) in the protocol. Participants were admitted as day case participants on the day of surgery. General anaesthetic was preferred for the procedure, and all participants were administered prophylactic intravenous antibiotics as per the current version of the study antibiotic prophylaxis algorithm, and positioned by the surgeon in the prone position. The usual aseptic skin preparation technique was observed using Povidine skin preparation. Surface skin landmarks were drawn to aid percutaneous insertion of the testing needle to the 3$^{rd}$ sacral foramina (Figure 8).

**Table 20 Technical details of Medtronic kit used for the study**

| **CE Marks all CE0123** | |
|---|---|
| **Lead intro kit model 3550-18** | Test stimulator model 3625 |
| **Tined Lead model 3080** | Test stimulator model 3531 (Verify) |
| **Lead introducer model 042294** | Interstim extension twist lock cable model 3095 |
| **Interstim 2 model 3058** | |

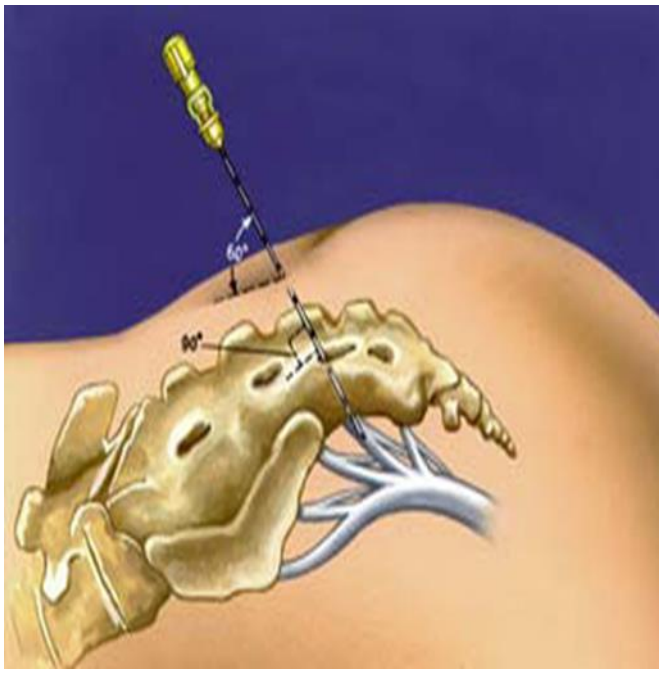


**Figure 8** Insertion of the testing needle to the 3rd sacral foramen

Reproduced with permission from Medtronic

Under image intensified fluoroscopic guidance the position of the testing needle was confirmed, and the side with the strongest low voltage anal motor response (bellows response) was selected. A guidewire was inserted through the testing needle and the needle removed. A small transverse incision (<5mm) was made around the guidewire to allow the trochar to pass through the skin easily, and cannulate the foramen. The trochar position was confirmed by fluoroscopy and aimed to stop within the bone of the foramen to prevent formation of a false passage within the pelvis. With the trochar needle removed an insertion sleeve remained in place to accurately place the tined lead within the foramen and this position was confirmed by lateral fluoroscopic visualisation. The aim was to place at least the two distal electrodes (0 and 1) within the pelvis and the two proximal electrodes (2 and 3) within the foramen (Figure 9).

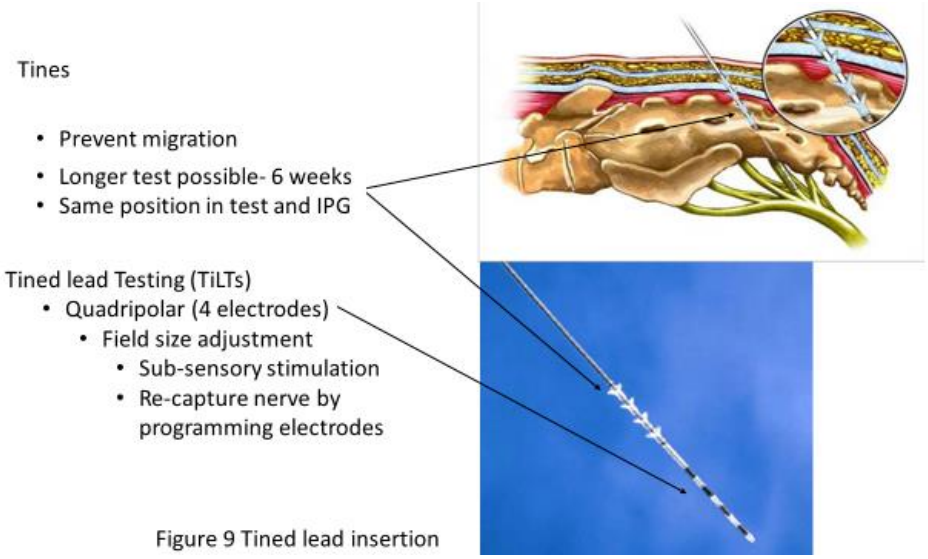



Figure 9 Tined lead insertion

Each individual electrode was pulsed with a testing box in order to observe the corresponding S3 anal motor response. Once the tined lead position was satisfactory, the tines were deployed by removal of the sleeve, and the tined lead was tunnelled to the ipsilateral buttock where a potential IPG cavity was constructed through a 5cm transverse incision. The tined lead was then connected to an extension lead via a boot connector and this was tunnelled and exited laterally on the ***contralateral*** side of the potential IPG pocket. The extra tunnelling was designed minimise the potential for infection spreading down the lead and into the potential IPG cavity or S3 foramen. The smaller wounds were closed with a single absorbable inverted subcuticular suture and sealed with tissue glue over the skin. The 5cm buttock incision was closed in layers, with absorbable interrupted sutures to the fascia over the leads, and a single absorbable continuous subcuticular suture to the skin with sealant tissue glue. A large transparent dressing was applied over all of the wounds. The extension lead electrodes were connected to a twist lock cable and this was anchored to the skin with another dressing to prevent traction on the exit lead site. Participants were instructed to keep the exit lead and all dressings dry, and to apply the further transparent adhesive dressings provided if the edges started to curl.

#### 5.1.2.3. Test stimulator connection

After participants were recovered the external temporary box stimulator (either model 3625 or model 3531) was attached to the external lead on the ward by the site-specific research nurse and the participant randomised into group A or B by the un-blinded researcher. The testing box was switched on a minimum of ***4 hours*** after the procedure (a maximum of 24 hours), with new batteries fitted beforehand. The minimum duration of 4 hours was selected to ensure the participant had a complete washout of all sedating medications and local anaesthetics, to ensure the sub-sensory test calculated the correct habituated sub-sensory threshold. The TiLTS-cc test routine (Figure 10) was followed for test box set up and any subsequent alterations.

#### 5.1.2.4. Test assessments and routine

##### 5.1.2.4.1. Methods

All participants underwent sub-sensory enhanced percutaneous nerve evaluation (ePNE) SNS (also referred to here as tined lead test stimulation [TiLTS-cc testing] the difference being with a sham control), and responders were classified into either discriminate (response to actual test stimulation only) or indiscriminate groups (response to sham or both sham and actual stimulation) after study un-blinding for data analysis. Any responders, however, were offered permanent sacral nerve stimulation (PSNS). Participants with no response in either period of testing were not offered PSNS and simply had the tined lead removed.

Participants underwent the **TiLTS-cc** testing phase for a period of six weeks after being randomly assigned into one of two testing groups (Table 21). The participants and investigators were blinded to the groupings; this enabled a two week crossover for each participant, including two periods of two week tests (either actual stimulation “on”, or sham stimulation “off”) and two weeks of “washout”

(normalisation) between the periods. This washout was essential as a recent trial of temporary SNS in neuro-constipation demonstrated that only at three weeks after cessation of stimulation did positive responses return to normal, and confirmed that 2 weeks of actual stimulation produced a measurable effect (171).

#### 5.1.2.4.2. Assessments

The analysis of test outcomes were performed at the end of week 2 and week 6 using a visual analogue scale (TiLTS-cc VAS). This allowed more than three weeks of washout (**Table 21**) between the end of the second test period (week 6) and the end of the first test period (week 2), whilst allowing us to measure a washout effect (week 4). Maintaining the 2 week daily diary exercise during the washout period also kept the blinded participants and researchers in a constant assessment routine which improved data quality. Please also refer to the full trial assessment schedule (**Appendix 9**).

**Table 21** Randomisation for TiLTS-cc testing phase

| | TiLTS-cc Week 1 | TiLTS-cc Week 2 | TiLTS-cc Week 3 | TiLTS-cc Week 4 | TiLTS-cc Week 5 | TiLTS-cc Week 6 |
|---|---|---|---|---|---|---|
| Group A | On | On | Washout | Washout | Off | Off |
| Group B | Off | Off | Washout | Washout | On | On |

*On = Sub-sensory SNS stimulation received, Off = sham SNS stimulation received*
*(Figure 10 page 122, and test routine page 117)*
*Washout = Device disconnected from the patient*

#### 5.1.2.4.3. Test Routine

The test stimulation was provided using sub-sensory settings to enable blinding of participants during on and off periods of the test. Conventional settings for frequency (14Hz) and pulse width (210µSec) were used so that only the amplitude (voltage or current) of the waveform was adjusted to provide sensory or sub-sensory stimulation. These settings were conventional practice following years of trial and error in other physiological studies of FI and CC, and only in treating FI sufferers have changing frequency or pulse width settings been noted to improve

patient outcomes (102-107). The neuromodulation test box model 3531 behaved in an identical manner during both testing periods giving the impression to the participants and any other observer that it was providing stimulation. Each test box model 3625 was calibrated before and after phase 2 testing, and the digital test box model 3531 was considered calibrated per factory as a brand new box was used for each participant. The calibration of the 3625 “brown box” model was essential and is discussed further in Chapter 6 (Results-incidental findings). I had become suspicious of possible variability in its performance and reported this to my supervisors who suggested devising a calibration experiment to check the output waveform of the device. This found that the old analogue model 3625 was indeed highly variable in performance and did not deliver the same nerve stimulation each time to every participants, likely due to the analogue nature of its dials. These likely suffered damage through wear and tear leading to inaccuracy at setting the dials correctly, resulting in variable output waveforms. Re-calibrating the dials before every testing period was the only feasible solution to this problem and I devised a way for this to be done, as explained in Chapter 6.

A delegated research team member was trained to set the positive and negative electrodes (as per a study specific SOP) prior to the TiLTS-cc testing routine. The research team member adjusting the box settings at the beginning of each testing period was not blinded (and so not involved in completing the case report forms) and performed an adjustment routine (**Figure 10**). This comprised a series of checks: participant identity, assessment compliance, current study week, randomisation grouping, test box number (the same box was retained unless malfunctioned), new battery change and box test. To minimise infection risks and damage to the connecting wire, the wire exit site was viewed through a clear dressing. This dressing was only removed or replaced if there were signs of infection or wear and tear.

**Model 3625 testing routine**

In early protocol versions the analogue “brown box” model 3625 test stimulator was used and the output pulse width, frequency, and voltage was checked on an oscilloscope pre and post participant use to confirm the stimulation parameters were calibrated and consistent. The test was performed by the blinded researcher (usually myself) who set the device to a pulse width of 210µSec, Frequency of 14Hz and I would increase the voltage until sensation was just perceptible, and this was recorded as the participants sensory threshold (ST) = y Volts in the records. The participants then underwent a habituation period of 5 minutes before the habituated sensory threshold (HST) was recorded as HST= x Volts. In order to systematically set all participants to a very similar level of sub-sensory stimulation a value of 75% of HST was chosen for the settings. 75% of the HST value was then calculated (recorded in the notes) and the device was programmed to stimulate at this current; the participants were now receiving active sub-sensory stimulation at 75% of their HST. I and other blinded researchers left the room and the un-blinded researcher set the device as per randomisation for that participant in that period of testing. The active testing period “on” demanded no further adjustments. The sham testing period “off” demanded that the device simply had all internal electrodes switched off by the un-blinded researcher. Two security seals were then placed over the front and battery cover to ensure that it could not be powered on or off, or opened to reveal the internal electrode settings, by either the participant, myself or other colleagues. The device appeared identical to any observer during both “on” and “off” settings with the visible external LED flashing continuously during both settings.

**Model 3531 testing routine**

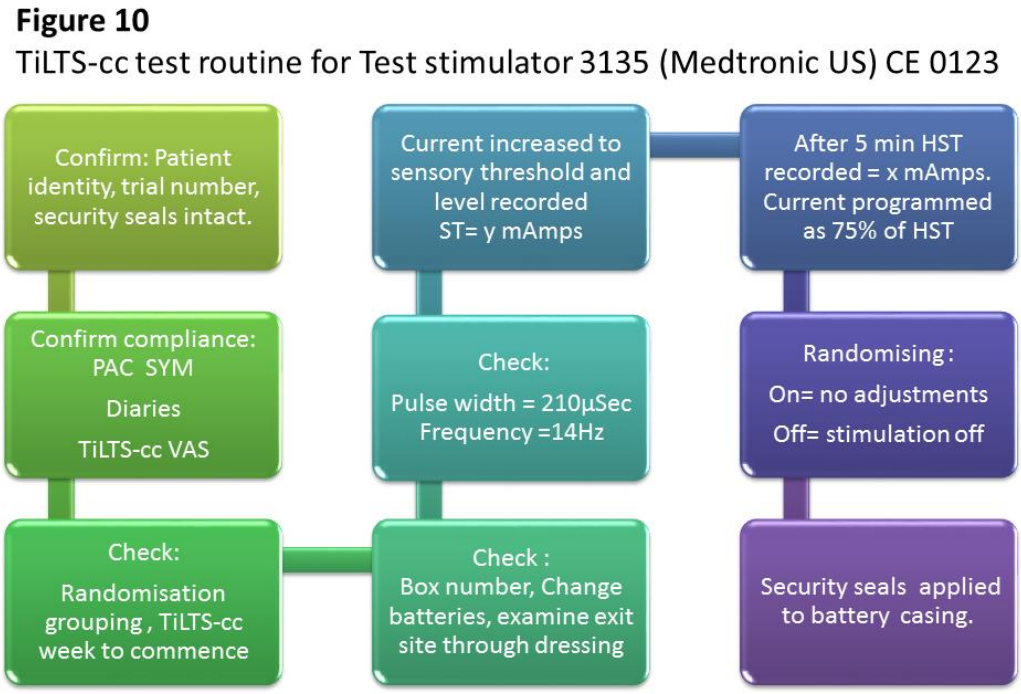
As of protocol version 14 (23/07/2013) only the "Verify" testing stimulator [model 3531] was used in the study. The digital test stimulator model 3531 "Verify" (an automatic constant current, variable voltage device), was considered very accurate after calibration tolerance tests (Chapter 6) and as a new model was used for every recruited participant this calibration process was stopped. The stimulation settings were digitally programmed via a wireless control unit (after Bluetooth pairing) to a pulse width of 210µSec, Frequency of 14Hz, with the stimulation current (mAmps) recorded according to individual participant levels (variable as individual tissue impedance varies). The current was increased from 0 milliAmps (mAmps) until the sensory threshold was reached and this was recorded as Sensory Threshold (ST) = y mAmps. The participant was then left to undergo a habituation period of 5 minutes and then the habituated sensory threshold (HST) was recorded as HST= x mAmps. 75% of the HST value was then calculated (recorded in the notes) and the device was programmed to stimulate at this current; the participants were now receiving active sub-sensory stimulation at 75% of their HST. The active testing period "on" therefore demanded no further adjustments. The sham testing period "off" demanded that the device was simply switched off remotely by the un-blinded researcher using the control unit. Two security seals were then placed over the front and battery cover to ensure that it could not be powered off or paired with another Bluetooth controller. The test stimulator 3531 appeared identical to the participants in both active and sham tests and could only be differentiated by using the programming control unit which was not supplied to the participants or blinded researchers. This model also comprised an internal chip capable of storing stimulation data during the testing period, which was used by un-blinded researchers at the weekly check to ensure the validity of the preceding testing week.

#### 5.1.2.4.4. Resetting in the event of a fault

Participants who reported any problem with their testing box were recalled to the hospital at the earliest opportunity (and within 3 days), for an extra study visit assessment and to have the box settings checked and validated. If no faults with the box or testing leads were found, the test routine as described above was followed and the participant continued unaltered in the trial. If no faults were detected and more than 3 days had elapsed then the participant was returned to the beginning of the current phase of treatment. (I.e. a participant with a fault during weeks 5 or 6 would be returned to the start of week 5 and a participant with a fault detected during weeks 1 or 2 would be returned to the start of week 1). If this was not acceptable to the participant, they were offered the choice to withdraw from the trial. This was to ensure that the peak symptom response was after 2 weeks of continuous sham or active stimulation.

If a fault was detected with the test box or leads this was documented and the box or leads replaced. The test routine as described above was followed and the participant continued unaltered in the trial. If there was a fault detected within the extension exit wire, this was replaced surgically at the earliest opportunity. Following replacement of the extension exit wire, the test routine(s) as described above were followed and the participant returned to their allocated test box routine at the start of their latest two-week testing period (i.e. a participant with a wire fault during weeks 5 or 6 would return to the start of week 5 and a participant with a fault detected during weeks 1 or 2 would return to the start of week 1). If this was not acceptable to the participant, they were offered the choice to withdraw from the trial.

**Figure 10: TiLTS-cc test routine**




### 5.1.2.4.5. Disconnecting in emergencies

Participants were allowed to disconnect the device externally by pulling out the wire from the test box. They were told to do this in emergencies only, and we recommended this over turning off the box by breaking the security seals to remove the batteries. Emergencies were defined as any unexpected symptom or sign that the participants or another doctor attributed to the test box providing stimulation, any situation where the test box was accidentally damaged, submerged in water or thought to be malfunctioning. A detailed list of known complications of, or effects from SNS was provided to the participant (**Table 22**). To protect participants (as distracting stimulation surges are theoretically possible) we recommended that participants abstain from driving during TiLTS-cc testing weeks 1, 2, 5 and 6. Participants were clearly informed in the PIS not to drive whilst the test stimulation was on-going, and if they must drive as a last resort (e.g. emergencies) the box should be disconnected by pulling out the wire. Driving was permitted during weeks 3 and 4 when the stimulator box was not attached to the lead.

#### 5.1.2.4.6. Voided Security Seals

Any participant who had voided the security seals for any reason (including emergencies) was referred to the site principal investigator (without revealing the blinding) and withdrawn from the study on non-compliance grounds. This fact was clearly stated on the participant information sheet (PIS), and was considered vital to protect the scientific integrity of the study. Only 1 participant was withdrawn in this way, and they followed the normal intention to treat pathway used at Durham, and their response to testing classified by these means instead of the TiLTS-cc VAS. Their subsequent treatment and standard of care was not affected by being withdrawn in this way.

#### 5.1.2.4.7. End of TiLTS-cc testing visit

Participants who completed the **TiLTS-cc** testing phase of the trial were assessed by either myself or a delegated investigator, for interpretation of the TiLTS-VAS and decision on intention to treat. Both participants and investigators were blind to the randomised grouping and so to the order of stimulation during the **TiLTS-cc** testing phase. The efficacy of test stimulation was assessed by a visual analogue scale (TiLTS-VAS) of perceived benefit, with 0% as no benefit and 100% as cure. An improvement of equal to 25% or greater in the TiLTS-VAS was deemed a positive test response. In practice we have found that the different scores correlate very closely and that participants responding to test stimulation will show improvement in all, or nearly all, scores. We believed 25% (as a measure of response) correlated well with a reduction of at least 0.5 in PAC-SYM, and although simplistic was a good way of measuring perceived benefit in participant's symptoms and maximising the implantation rate. This would also allow us a secondary analysis to help find the

thresholds of PAC-SYM and PAC-QOL in SNS testing as a hypothesis generating study. If the participant responded to any of the stimulation periods they were offered an implantable pulse generator (IPG) and progressed to the permanent sacral nerve stimulation (PSNS) phase 3 of the trial. They were listed in theatre for connection of the internal component of the same tined lead to a permanent IPG at the next study procedure which was within 1 week maximum of the end of week 6 assessment visit. They were blinded to response classification until the day of surgery in case any questionnaire data queries arose when investigators classified their response between these visits.

### 5.1.3. Phase 3- Responders (R) and Non-Responders (NR)

#### 5.1.3.1. Non-Responders-Tined lead removal

A participant deemed to be a non-responder from the **TiLTS-cc** testing phase had their theatre booking amended on the day of surgery to "removal of tined lead", and the participant was informed of the testing result on the day of surgery. They were also blinded to response classification until the day of surgery in case any questionnaire data queries arose when investigators classified their response between these visits. The participant was admitted to the day-case unit. Pre-procedure checks were performed by the theatre team per routine clinical practice. The participant was given either a general anaesthetic or local anaesthetic/sedation as per centre policy. The surgeon positioned the participant either prone or lateral on the operating table. The usual aseptic technique was observed. The lateral (potential IPG site) buttock incision was re-opened to assist in lead removal by dissecting and disconnecting the boot connector from the tined lead, which would be difficult to do without adequate exposure. The midline scar was also reopened to assist with tined lead removal from the S3 sacral foramen. The tined lead was carefully removed through vertical midline traction over the S3 foramen, and the wounds repaired in the usual manner with sutures and a dressing. The discharge

procedure was as standard for all day case surgery participants in each site. I expected that most participants will be discharged on the same day as surgery, but due to some instances where post-operative pain control was inadequate I allowed for a maximum stay of 48 hours after which time I would report a serious adverse event (SAE) to the data monitoring committee. Participants who had overnight stays were placed on a surgical ward. Our participants classified as NR (non-responders) were followed up in 6 months' time (by a blinded investigator) after discharge to complete the final round of assessments which included PAC-SYM, PAC-QOL, Euro-QOL (EQ-5D-3L), and 2 weeks of daily diary cards (**Appendix 9**). All self-completion assessments were posted out more than 2 weeks prior to a participant's attendance in the research clinic to allow adequate time for completion.

#### 5.1.3.2. Responders--IPG implantation

A participant deemed a test responder would be admitted to the day case surgery unit within a week of the end of week 6 assessment, and the participant informed of the testing results. The theatre list was amended to "IPG implantation and connection of in-situ tined lead." Prophylactic intravenous antibiotics (as per the current antibiotic prophylaxis protocol) were administered by the anaesthetist observing any documented allergies. After being induced to general anaesthesia the surgeon positioned the participant in the prone or lateral position on the operating table. The usual aseptic technique was observed. The lateral (potential IPG site) buttock incision was opened and a suitable cavity dissected to contain the IPG. This was the contralateral side of the externally tunnelled exiting extension lead and ipsilateral to the internally tunnelled tined lead and cannulated S3 foramen. The extension lead was disconnected internally from the boot connector and discarded after being removed entirely via the exit site, with careful attention not to contaminate the IPG pocket by internalising the exit lead. This was an

important design from the first protocol as I was aware infection would be a risk and this was an obvious source of contamination of the IPG. After the extension lead was removed the internal electrodes of the tined lead were connected to the IPG in the usual manner. The IPG was secured underneath fascia, and the wound closed in layers with absorbable sutures as absorbable inverted interrupted sutures to fascia, absorbable subcuticular sutures to skin, and the wound sealed with tissue glue and a dressing. Local anaesthetic was injected around the wound edges and deeper to the IPG cavity to aid with post-operative analgesia. The discharge procedure was as standard for all day case surgery participants in each site. We expected that most participants would be discharged on the same day as surgery, but due to some instances where post-operative pain control was inadequate we allowed for a maximum stay of 48 hours after which time I completed a serious adverse event (SAE) and recorded this with the data monitoring committee. Participants who required overnight stays for pain control were located on a surgical ward.

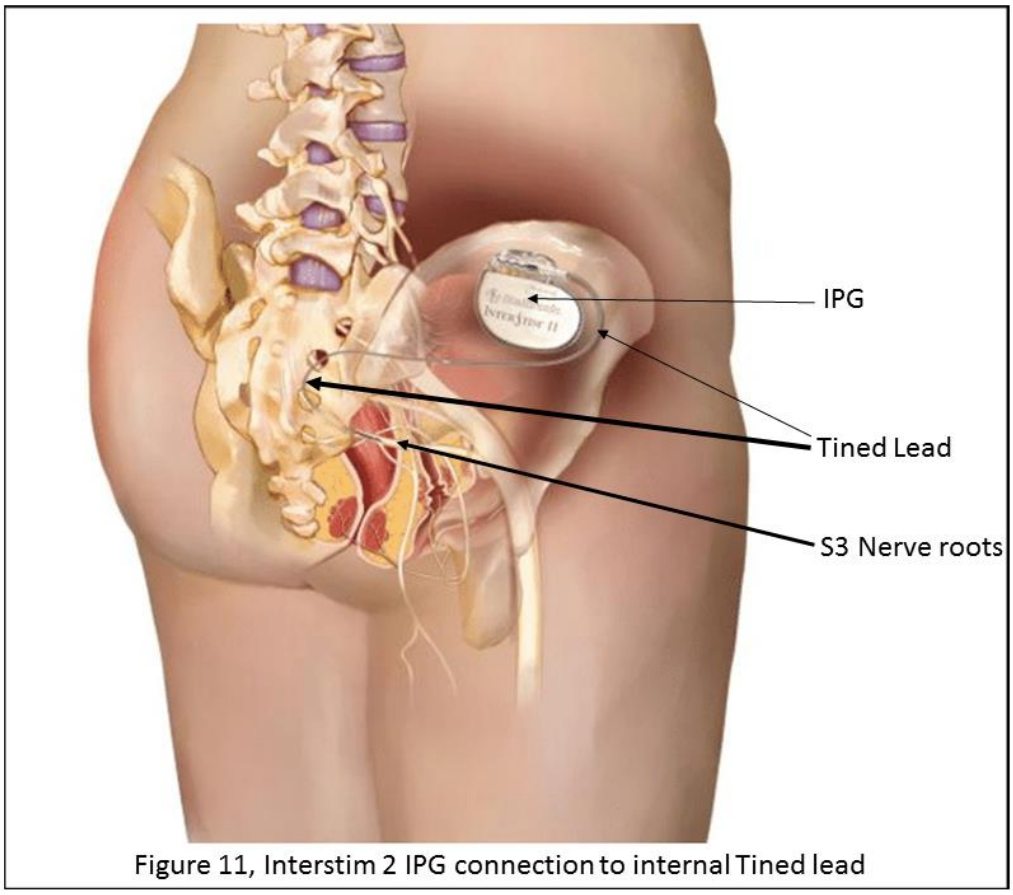


Figure 11, Interstim 2 IPG connection to internal Tined lead

### 5.1.3.3. IPG Activation

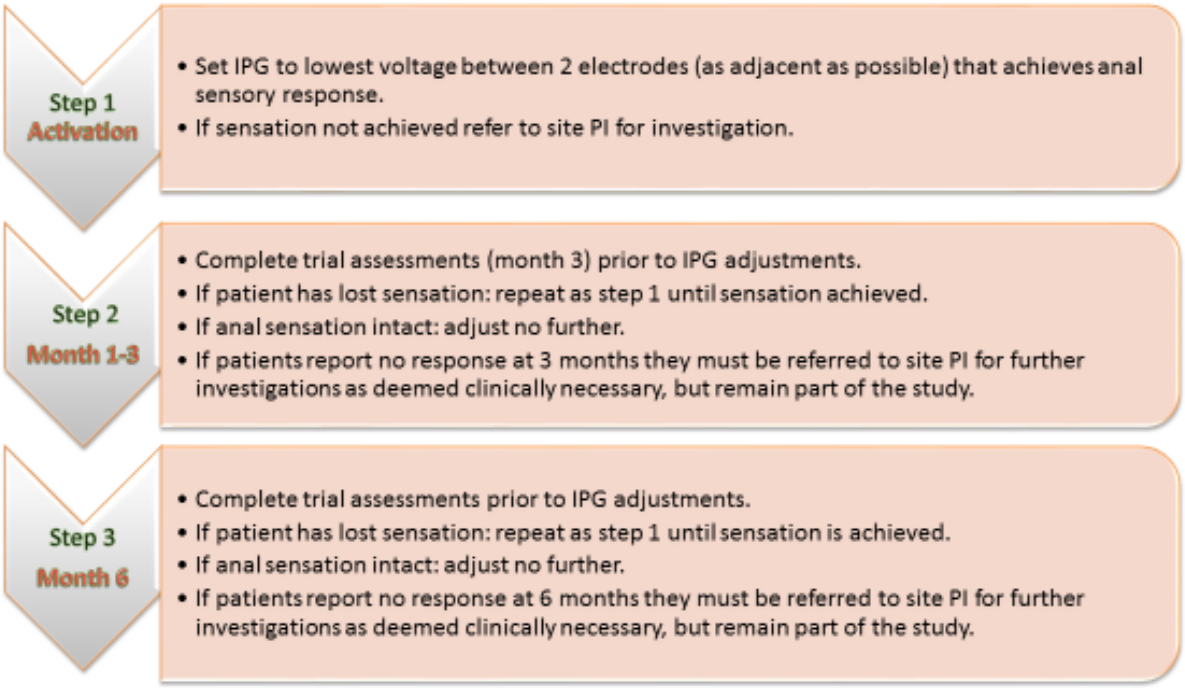
Participants had the IPG activated as per the normal practice of each site within two weeks of implantation, and set accordingly to the usual sensory stimulation settings by the blinded researchers. The standard IPG setup was to obtain the lowest voltage anal sensory response possible between two of the four electrodes. Ideally this was between two adjacent electrodes to help preserve battery life (by focussing the field). The electrode settings (electrode number +ve and –ve) and voltage were recorded at each visit in the notes. Participants were followed up in the research clinic for any necessary IPG setting adjustments at the 3 and 6 month assessment appointments (**Figure 12**). Minute movements of the tined lead could potentially result in the active electrodes becoming less effective (if they had moved slightly away from the nerve), and so the advantage of having four electrodes on a tined lead is the ability to manipulate the size and location of the field between electrodes to “recapture” the nerve. Participants received the same

PSNS follow-up care that is current practice at study sites, which includes urgent appointments for IPG re-adjustments if they were experiencing unusual symptoms or side-effects. Participants were fully educated in turning the IPG on, and off (for emergencies only) using the patient programmer. Participants were also given a temporary IPG TiLTS-cc study information card to carry on their person until the permanent Medtronic IPG information card arrived. This could be used to avoid security scans at airports and to notify clinicians who were considering an MRI (prohibited) for an unrelated clinical indication.

#### 5.1.3.4. PSNS Assessments

Participants who received the IPGs and therefore progressed onto the PSNS phase 3 were followed up at the end of months 3 and 6 from the date of implantation, and given these assessment dates before discharge. We accepted that there would be a degree of variation in timing (due to clinical and service commitments of investigators, and participant holidays) but emphasised that a time limit of +/- 2 weeks be placed on these assessments taking place before a protocol violation occurs. In practice we considered a variation of 2 weeks at the 6 month endpoint as making no significant difference to the outcome measures.

Figure 12 IPG Adjustment routine




#### 5.1.3.4.1. Month 3 assessments

Participants completed 2 weeks of daily diaries, EQ-5D-3L / EQ-5D-VAS, PAC-SYM and PAC-QOL scores at this visit (Appendix **9**). All assessments were posted to participants >2 weeks prior to their 3 month follow up appointment in the research clinic to allow adequate time for completion. Trial assessments were completed prior to any IPG setting changes that were required (Figure 12). It was possible to identify participants at this visit that were classified as early non-responders to PSNS. Participant response to treatment was classified according to their change in total mean PAC-SYM score from baseline, with responders (R) having a greater than or equal to 0.5 decrease from baseline and non-responders (NR) a less than 0.5 decrease from baseline. All participants who were classified at this time as being NR were treated as per standard clinical practice in each centre; the assumption was that this was due to either a technical fault or tined lead migration. Investigations performed to assess non-response included checking the IPG battery and settings, and having an additional lateral pelvic X-ray to look for tined lead migration. If either device failure or lead migration were confirmed then the

participant would have the lead re-sited and/or reconnected to the IPG and /or malfunctioning device replaced, and then continue in phase 3**.** Any of these events would be recorded in the CRFs as an adverse event and reported to the data monitoring committee.

#### 5.1.3.4.2. Month 6 assessments

The 6 month assessment was the primary and secondary endpoint questionnaires. All participants completed 2 weeks of daily diaries, Euro-QOL EQ-5D-3L, EQ-5D-VAS, PAC-SYM, PAC-QOL and Cleveland and Wexner scores at this visit (Appendix 9). All self-completion assessments were posted to participants more than 2 weeks prior to their 6 month follow up appointment in the research clinic to allow adequate time for completion. Clinical assessment data were collected first at the study visit, and then any clinically indicated investigations or IPG adjustments in non-responders could occur. Participants then entered standard clinical follow up from this point.

### 5.1.4. Analysis Plan

The analysis was performed at the end of the study after this analysis plan had been agreed between the study data monitoring committee, trial statistician and chief investigator. I was involved in this process as a member of the study committee and provided input to the whole analysis process.

#### 5.1.4.1. Demographics

Participants' age, sex, and duration of illness are presented in Chapter 6 and data analysed with descriptive statistics in SAS 9.4. The data are analysed and presented as ranges with mean values, standard deviation and outliers highlighted to provide an indication of the characteristics of the cohort. The demographics of the cohort are compared to those of other studies of SNS for patients with CC. The demographics are compared between the randomisation allocations (group A&B) within the cohort to test whether the groups are similar.

#### 5.1.4.2. Medical and surgical history

Participants' history of medical illnesses and past abdominal surgery pre-SNS are tabulated and presented as frequencies across the whole sample.

#### 5.1.4.3. Baseline assessments

All baseline assessments performed during phase 1 of TiLTS-cc are collated and analysed within SAS 9.4 to describe the cohort, and tested for similarity between the randomisation allocations to groups A&B using appropriate statistical tests.

#### 5.1.4.4. Primary outcome measures

The primary outcome measure used in the TiLTs-cc study was the PAC-SYM mean total score, and the baseline measures are described in the feasibility cohort as a range, mean value, standard deviation, outliers, and tested between groups A&B for similarity in the allocation. The testing response classification (TiLTS-VAS) is a patient-centred visual analogue scale measurement tool from 0-100%. The responses indicated during testing using this tool are described as a range with mean values, standard deviation, and the proportion of discriminate (actual stimulation $\geq$ 25%) and indiscriminate (sham stimulation $\geq$25%) response classifications between the group allocations are compared. A correlation analysis between the change in PAC-SYM mean total score from baseline to actual, washout and sham SNS testing, and the corresponding TiLTS-VAS response was performed to test the association between these two outcome measures and whether the threshold of VAS response (using 0.5 reduction in PAC-SYM) changes between testing phases. This investigates the validity and consistency of the testing classification using the TiLTS-VAS.

#### 5.1.4.5. Secondary outcome measures

The secondary outcome measures used in the TiLTS-cc study were PAC-QOL mean total score, Wexner total score, EQ-5D-3L total score, EQ-5D-VAS percentage and

the 6 diary scores. These comprise Likert scale data of daily symptoms including abdominal pain, bloating and straining. Daily spontaneous complete bowel movements are numerical counts, daily laxative use is a simple yes or no, and the laxative score is a simple +1/0/-1 response scale of actual laxative use. These are described within the feasibility cohort as a range, mean value, standard deviation, outliers and tested between groups A&B for similarity in the allocation.

#### 5.1.4.6. Sample Size

Using data gained from clinical audit and from a small pilot study (n=5) it was predicted that In the TiLTS-cc testing phase 40% of participants would have a discriminate response and we estimated that 70% of these would respond to treatment at 6 months based on the reported 6-12 month response rates in current publications at that time (99). We also estimated that for the 60% of participants with an indiscriminate response (based on audit data of follow up after IPG), 20% of these would respond at 6 months. Assuming a power of 90%, alpha of 5%, and an allocation ratio between randomised groups of 1:1.5, we calculated the trial sample size to be 50 participants. As the Durham Constipation Clinic frequently recruited patients to clinical trials we had a good estimate of loss to follow up within the study cohort, and estimated loss to follow-up of 20% which inflated the required sample size to 60 participants. This would make TiLTS-cc the largest reported trial in the field of SNS to date. We received further feedback from peer reviewers (from National Institute for Health Research: Research for Patient Benefit programme) who emphasised that we had likely underestimated loss to follow up and that 50% was more realistic, thus inflating the sample size to **75 participants** to allow for greater loss to follow up.

#### 5.1.4.7. Analysis Populations

The primary analysis was based on the intention-to-treat principle, including all participants that were randomised and classified as indiscriminate or discriminate

responders at the end of tined lead testing. Additional analyses comparing discriminate responder, indiscriminate responder and non-responder were planned depending on the availability of data.

#### 5.1.4.8. Responder Populations

- All participants who were classified as discriminate responders at the end of phase 2
- All participants who were classified as indiscriminate responders at the end of phase 2
- All participants who achieved the primary endpoint at the end of phase 3.
- All participants who were randomised

#### 5.1.4.9. Total Population

- Responder population
- All participants who were classified as non-responders at the end of phase2

#### 5.1.4.10. Safety Population

- All randomised recruited participants.

#### 5.1.4.11. Covariates and Subgroups

The main primary and secondary analyses of the study were based on participants that were classified as discriminate or indiscriminate responders at the end of phase 2. This subgroup of participants are referred to as the "Responder population" in order to differentiate them from the "Total population", which includes non-responders at the end of phase 2.

#### 5.1.4.12. Missing Data

All missing data were described using cross-tabulation tables. No further sensitivity analysis were performed for missing data as these were deemed unproductive due to the small sample size.

#### 5.1.4.13. Multi-centre Studies

No adjustments were made to account for centre effect in the analyses, as there were only a small number of centres (4) and a small sample size (45) rendering any conclusions imprecise and unreliable.

#### 5.1.4.14. Multiple Testing

The main finding of the study was based on the primary endpoint. As such, no multiplicity corrections were performed for the secondary analyses because they were considered supplementary to the primary endpoint.

#### 5.1.4.15. Summary of Study Data

All continuous variables were summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical data. In general, all data were listed with separate tables for the demographic variables, study variables and safety assessment tables. All summary tables were structured with a column for each study group (discriminate, indiscriminate and non-responders) and were annotated with the total population size relevant to that table/treatment, including any missing observations.

#### 5.1.4.16. Protocol Deviations

As the actual sample size (45) was smaller than the target sample size (75) due to early termination of the trial, we expected this would result in lack of statistical power; unless the effect size was considerably larger than anticipated. The early termination of the study also affected the interpretation and validity of formal

hypothesis testing comparing discriminate responders, indiscriminate responders and non-responder.

### 5.1.4.17. Demographic and Baseline Variables

The baselines variables were summarised using n (non-missing sample size), mean, standard deviation, median, maximum and minimum for continuous data, and frequency and percentages (based on the non-missing sample size) for categorical data. Baseline characteristics of the following demographic variables were reported:

- Duration and onset of illness
- Demographic profiles (age and gender)
- Symptom profiles using a questionnaire based on the Cleveland clinic constipation score
- Current symptoms and signs
- Medication usage (except anaesthesia and other medication around GA)
- Past medical/surgical history
- Classification of IBS-C
- Physiological parameters
- At baseline assessment clinic: Transit study

### 5.1.4.18. Prior and Concurrent Medications

These were assessed from the daily diary cards specifically for laxative regimen by reporting the frequencies and percentages of the different laxative used during follow-up.

### 5.1.4.19. Efficacy Analyses

Data were summarised by study group. N (non-missing sample size), Mean, Standard Deviation, Minimum and Maximum were used to summarise continuous

variables, whereas number and percentages were used to summarise categorical variables. All analyses of the continuous efficacy endpoints were based on mixed effects model. Study groups were tested at the 2-sided 5% significance level. All analyses of binary endpoints were based on logistic regression for the primary endpoint and generalised estimating equations for the secondary binary endpoints.

#### 5.1.4.20. Primary Efficacy Analysis

The primary endpoint was summarised using a 2X2 cross-tabulation table with the rows representing “discriminate” and “indiscriminate” responders at the of phase 2, and the columns representing “responder” and “non-responder” at the end of phase 3 (6 months) based on a reduction of 0.5 or more in PAC-SYM score at 6 month. Fisher’s exact test was used to compare the difference in proportions of “responder” at the end of phase 3 between the discriminate and indiscriminate responders at end of phase 2. The risk difference and its associated 95% confidence interval and p-value were also reported.

#### 5.1.4.21. Secondary Efficacy Analyses

The secondary endpoints were summarised by study group (discriminate and indiscriminate responders). Specifically, N (non-missing sample size, Mean, Standard Deviation, Median and IQR, Minimum and Maximum were reported. The endpoint was formally analysed to test the hypothesis of “no-difference” in average scores between discriminate and indiscriminate responders using mixed effect model for continuous endpoint data and generalised estimating equation for binary and ordinal endpoints. The methods were chosen to account for intra-subject correlation between the repeated measures at baseline, 3 months and 6 months.

#### 5.1.4.22. Exploratory Efficacy Analyses

Longitudinal analysis was performed for all the endpoints in order to investigate whether there were significant differences between the longitudinal profiles of discriminate and indiscriminate responders. The Longitudinal analysis also

included interaction between the study group (discriminate and indiscriminate responders) and the time points. The PAC-SYM scores were reanalysed without converting to a binary outcome as done for the primary endpoint and primary analysis.

#### 5.1.4.23. Diagnostic accuracy of TiLTS-VAS

The primary endpoint was re-analysed to estimate sensitivity, specificity, positive and negative predictive values (PPV, NPV) between TiLTS-VAS at the end of phase 2 and the change in mean PAC-SYM score at 6 months. Note that indiscriminate and discriminate responders at the end of phase2 were collapsed as “responder” for this analysis

#### 5.1.4.24. Exploratory Efficacy Analysis for Non-responders

Further analyses as described in 2.3.8.3 above were performed with three groups in order to compare discriminate, indiscriminate and non-responders, but only at baseline and 6 months.

#### 5.1.4.25. Safety Analyses

The safety and adverse events data extracted from the case report forms were summarised using frequency tables. The safety and adverse events by study groups were explored to investigate whether the events are mostly during the TiLTs-CC testing phase or during PSNS phase.

#### 5.1.4.26. Reporting Conventions

The mean, standard deviation, and any other statistics other than quantiles, were reported to two decimal places. Quantiles, such as median, or minimum and maximum used the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) were reported to 3 significant figures.

#### 5.1.4.27. Technical Details

A second reviewing statistician independently reproduced the primary analyses and summary statistics tables. The reviewing statistician had an overview of the entire analyses and explicitly checked the entire code used for the analysis. All statistical analyses were performed in SAS 9.4, and R version 3.2.3 software was used for figures.

### 5.1.5. Provision of on-going care after the study

Participants who had no response to TiLTS-cc guided SNS testing did not have an IPG implanted and simply entered the normal routine clinical NHS care pathway. Participants who had a continuing response to the implanted IPG at the end of 6 months in phase 3 retained the implant with on-going surveillance as part of routine NHS care, as was current practice. Participants who lost response from the implanted IPG at the end of 6 months in phase 3 were offered either removal of the IPG as a day case procedure, or reprogramming of the device in an attempt to regain response prior to removal (both of which were standard practices), and they remained in routine NHS care. All participants were considered to have completed the study per protocol after collection of the 6 month visit assessments.

### 5.1.6. Ethical considerations

All appropriate ethical approvals from the NHS Research Ethics Committee (REC) were received before the start of the TiLTS-cc study through an application to the NHS Research Ethics Service using the integrated research application system (IRAS). The study was approved by the NRES Committee North East-York, REC reference number 12/NE/0228 on 24/08/2012. Local trust approval was also received from host study sites through their respective research and development departments. The study was listed on the comprehensive local regional network (CLRN) portfolio and registration completed on a publicly available international

clinical trials database on 10/10/2012 https://doi.org/10.1186/ISRCTN44563324. There were several ethical dilemmas in this research design that I have outlined below.

#### 5.1.6.1. Alternatives to SNS for CC

SNS for chronic constipation is a relatively novel therapy and experience was still limited. We were recruiting patients who had failed all recognised medical and nurse led therapies, and who would normally be offered temporary SNS testing using the standard 2 week sensory test. Standard 2 week SNS tests in this patient group were funded only on special approval within the NHS until the clinical care commissioning group (CCG) restructuring in July 2013 after which it was no longer funded. Following this time the only access to SNS treatment patients had was through the trial. We ensured that participants were counselled and consented in a rigorous fashion and fully aware of the issues surrounding the procedure. Conversely, short of SNS, the alternatives for patients with severe refractory symptoms were invasive surgical interventions with recognized complications and no guarantee of success. In this circumstance, I believed that not to offer SNS as an alternative would also create an ethical dilemma. By actively studying the predictive ability of our test design in this group I believed we could improve our understanding of how to correctly select the long term responders to SNS from the group.

#### 5.1.6.2. Prolonged SNS testing period

Ethical queries could be raised regarding the design of a prolonged testing procedure with a possibility of higher complication rates, and including a sham stimulation phase. However, I would argue that the existing system of assessing patients for permanent stimulation is poor, often resulting in failure (in 60%) which results in patients having two futile operations (to place, and then remove the IPG)

each with their own complication profile. During study design I discussed the TiLTS-cc research methods with patients who had undergone SNS, and members of the patient and public involvement (PPI) group CRAG, and a clear majority of patient members felt the TiLTS-cc testing method would be necessary, acceptable and justified for the study. A member of the CRAG committee was also appointed onto the trial steering committee in order to facilitate participant perspective feedback into future protocol amendments and overall trial conduct.

#### 5.1.6.3. Placebo /sham responders were implanted with an IPG

The design of the **TiLTS-cc** study also demanded that participants who were true placebo responders (those who responded to stimulation during the sham period only) progressed onto the PSNS phase of the trial, and this is the first study to have implanted sham responders. In reality, I believed this was actually no different to our then current intention to treat practice, as we could not differentiate between true responders and placebo responders with the standard 2 week sensory testing method used in the NHS. It was also possible that a proportion of the placebo responders may have developed a long-term response to sensory PSNS, as we had no evidence to the contrary at the time.

#### 5.1.6.4. Increased risk of complications

It was not anticipated that the study design would lead to additional harm: the trial design caused participants to receive the same care pathway as under routine NHS care, but also deliberately classified the participants into distinct response groups (after un-blinding and analysis) in an attempt to improve the predictive power this testing method. I perceived the theoretical risk of an increase in the risk of localised infection due to the extended testing phase before the study. In the pre-study standard NHS participants these infections were usually routinely managed with antibiotics and self-limiting with no serious sequelae. Table 22 demonstrates the

potential risks as per reporting from trial site audits and in available studies at that time, of which infection was considered the most common and serious.

The study design did increase the risk of infection as the initial tined lead insertion precluded an extended testing phase (ePNE) with an external component to the wire called the extension twist lock cable. The IPG implantation involved the same tined lead which had been connected to the twist lock cable and could potentially be colonised, so I decided with the team to give the participants prophylactic intravenous antibiotics before tined lead insertion (not standard practice), and during the IPG implantation procedure (antibiotic prophylaxis protocol). I also decided to design an exit lead site wound review by weekly inspection through the dressing. I designed the participant study visits to minimised dressing changes to only when clinically necessary in order to avoid unnecessary pathogen exposure by cross contamination or damage to the wire. I was hopeful these measures would reduce the risk of infection due to exit site contamination of the internal tined lead.

**Table 22 Expected complications (adverse events) of SNS testing and PSNS**

| Complication | Incidence at trial sites %[1] | Other trials %[2] | Overall risk % |
|---|---|---|---|
| | ***Commonest*** | | |
| **Infection at testing Lead site** | 4 | 7 | 7 |
| **Transient electric shock/jolt** | 3 | 11 | 11 |
| **Lead or IPG migration** | 3 | 5 | 5 |
| **Pain at IPG or lead insertion site** | 2 | 4 | 4 |
| **Muscle spasm** | 2 | 3 | 3 |
| **Adverse effect on voiding or bowel function** | 3 | 3 | 3 |
| **Secondary seroma/haematoma** | 2 | 2 | 2 |
| | ***Very Rare*** | | |
| **Technical device problem** | <1 | <1 | <1 |
| **Infection at IPG site** | <1 | <1 | <1 |
| **Nerve injury at surgery** | 0 | <1 | <1 |
| **Allergic or autoimmune reaction to IPG or Lead** | 0 | <1 | <1 |
| **Paralysis** | 0 | 0 | <1 |
| ***Overall % risk*** | ***4*** | ***11*** | ***11*** |

***[1]TiLTS-cc Trial site audit data, [2] (99, 122, 125, 126)***

### 5.1.7. Ionising Radiation

### 5.1.8. Radiation Experts

The study protocol was designed in conjunction with 3 experts in ionising radiation, a clinical radiation officer who was a consultant radiologist at the main site, a medical physicist who was a radiation protection officer at the main site, and a regional NHS radiation protection adviser. These experts helped to calculate the potential doses of radiation patients would receive in standard practice versus the study exposure in order to inform on the radiation safety of the TiLTS-cc testing technique.

#### 5.1.8.1. Fluoroscopy and X-Ray

Ionising radiation was used during the study to guide tined lead insertion and positioning, and also to measure transit times at baseline. During design we calculated that the level of radiation participants were exposed to was equivocal to that experienced by patients undergoing the standard treatment pathway on the NHS. In this standard pathway participants would have 2 wires inserted under fluoroscopic guidance at separate intervals, and during the ePNE technique this is slightly reduced by only having one fluoroscopic exposure. Taking into account the plain abdominal X-ray to measure transit time at the beginning of the TiLTS-cc study (note some participants did not require this at baseline) the overall dose of radiation was equivalent.

The expected range was calculated by our radiation protection adviser as 0.60mSv +/- 0.33mSv depending on screening times.

Table 23 below demonstrates these calculations and is followed by the concluding statement from our radiation protection adviser's risk assessment:

**Table 23 Potential radiation exposure during TiLTS-cc trial**

| | C-Arm Intensifier | Abdominal Radiographs | **Total** |
|---|---|---|---|
| **Existing technique** | 0.66mSv | 0mSv | **0.66mSv** |
| **Proposed technique** | 0.33mSv | 0.27mSv | **0.60mSv** |

**mSv= milliSieverts**

**Table 23 Radiation Risk assessment (TiLTS-cc trial)**

*"Given potential variation in both screening time and patient size, I recommend that this proposed change be viewed essentially as dose neutral. For those patients who would need longer screening times, there may be a dose advantage. Where pulsed fluoroscopy may have been used there would be a small dose disadvantage in the proposed technique."* TiLTS-cc study radiation protection adviser Dec 2011.

### 5.1.9. Trial Conduct and Monitoring

The TiLTS-cc study was set up as a multiple center trial adhering to the rigorous principles set out by the International Conference on Harmonisation (ICH) and World Health Organisation (WHO) standards of good clinical practice (ICH-GCP), as these are guidelines founded on the clinical research principles of the World Medical Association's Declaration of Helsinki. On behalf of the TiLTS-cc study sponsor (CDDFT) I set up a trial steering committee to monitor and ensure these standards were adhered to.

#### 5.1.9.1. Trial Steering committee (TSC)

The TSC was comprised of both clinical and academic members of the research team including myself, an independent neuro-gastroenterologist, an independent academic who was a professor in clinical gastroenterology research, and a participant representative from the local participant and research advisory group.

#### 5.1.9.2. Trial Management Group (TMG)

The TMG was comprised of the clinical and academic researchers from Durham University, CDDFT R&D, and myself. The TMG was responsible for the day to day running of the TiLTS-cc study.

#### 5.1.9.3. Independent Data Monitoring Committee (IDMC)

An IDMC comprising an independent statistician, clinician and academic was setup to monitor safety, and futility (recruitment rates). The IDMC were given access to current study data (recruitment, IPG implantation rates including proportions of discriminate versus indiscriminate testing responders (un-blinded data), and all adverse event reporting) before each TSC meeting and advised the TSC accordingly. Of note the TSC and TMG were fully blinded at all times until the study analysis.

#### 5.1.9.4. Monitoring

Monitoring of the TiLTS-cc study was conducted by the Durham Clinical Trials Unit (DCTU), who ensured strict adherence to the current REC approved study protocol. The purpose of these arrangements were to identify any significant developments as the research proceeded that may have necessitated alterations to the protocol, and to protect the safety and wellbeing of participants. Monitoring consisted of site visits to evaluate the site files and verification of source data collected and transmitted onto the online electronic case report form (eCRF) system, and co-ordinating and providing the appropriate data to inform the TMG/IDMC/TSC committee meetings. This monitoring ensured prompt escalation of the infection adverse events to the sponsor, chief investigator and IDMC, and thus proved paramount to participant safety (see Chapter 6 for SAE details).

#### 5.1.9.5. Data handling and participant confidentiality

##### 5.1.9.5.1. Participant trial data

All information collected was securely stored both electronically, on paper and kept confidential. Data were used according to the provision of the 1998 Data Protection Act and individuals were not identifiable when data was transmitted electronically.

All participants were assigned a unique trial number at enrolment. All paper study files and documents, including participants consent forms are retained on-site in locked filing cabinets and are due to be destroyed after the statutory period. Research data were transferred to Durham University for analysis by DCTU staff in collaboration with the clinical study team.

Research data were entered onto an eCRF for each enrolled participant. These data were stored on secure servers that are external to both the NHS Trusts and to Durham University. This data was accessible to the research team, to Durham Clinical Trials Unit staff, to members of the TMG/ TSC/IDMC, and to any auditor or regulatory inspector as required. The data on these servers had access restricted to authorised personnel and was password protected. The data stored electronically contained the age, sex, ethnicity, and assigned trial number for each participant but no other personal identifiable data were transferred outside of the participating sites. Participants who withdraw from the study had all data collected up until the point of withdrawal included in the analysis.

##### 5.1.9.5.2. Electronic Case Report Forms (eCRFs)

This study used electronic Case Report Forms for every participant enrolled and randomised on the study. It was the responsibility of site Principal Investigators (or appropriately delegated to site researchers) to prepare and maintain adequate documentation in the medical notes (source documents) for each participant,

including recording all data and observations relevant to the study. Data that were entered into the eCRF was consistent with the information in the medical notes. Data were only entered into the eCRFs by persons authorised to make entries and corrections, per the delegation of authority log for the site.

#### 5.1.9.5.3. Records retention

The Principal Investigators at each site have archived all study related records and will retain these for a minimum of 15 years following the end of the study, after which they will be confidentially destroyed.

The Principal Investigators are responsible for ensuring that these archived records are accessible, as required by current legislative regulations.

### 5.1.9.6. Adverse Events (AEs)

#### 5.1.9.6.1. Serious adverse events (SAEs)

All serious adverse events (SAEs) were treated as clinically appropriate and reported to Durham Clinical Trials Unit and the sponsoring trust (County Durham and Darlington NHS Foundation Trust) within 24 hours of the research team becoming aware of the event using a study specific SAE Form.

An event was considered serious if it fulfilled any of the criteria in Table 24.

**Table 24 Criteria of serious adverse events**

| **A serious adverse event was considered if it:** |
|---|
| • Resulted in death<br>• Was life-threatening<br>• Resulted in hospitalisation or extended an inpatient admission<br>• Resulted in persistent or significant disability or incapacity<br>• Was a congenital anomaly or birth defect<br>• Was otherwise considered to be medically significant by the Investigator<br>• Was specifically : conception after intervention with SNS |

There were some exceptions to these rules namely: routine planned admissions, including admission for any SNS related procedures as part of this study. SAEs were recorded and reported from the day of the first surgical procedure onwards (day 1 of Phase 2-Tined Lead insertion) until the 6 month follow up visit (phase 3), or until the time of withdrawal. SAEs were assessed for expectedness, severity and relatedness, and followed until the outcome was apparent; resolution, resolution with sequelae or death. SAEs were reported even if the investigator considered them expected or unrelated events.

#### 5.1.9.6.2. Adverse Events (AEs)

Adverse events were recorded in any participant's medical notes when they occurred, and on the electronic case report forms (eCRFs). All study participants were informed about the known complications of SNS in the participant information leaflet (PIS). AEs were recorded from the Day 1 of Phase 2 (first day of Tined Lead insertion) until the 6 month follow-up visit or withdrawal from the study. AEs were defined as any new medical occurrence, or worsening of a pre-existing medical condition in a participant. All AEs were graded as mild, moderate or severe and assessed by the Investigator for relatedness and expectedness to the study procedures.

#### 5.1.9.6.3. Infection

The externalisation of the exiting extension lead from the tined lead resulted in a predicted increased risk of infection, which logically was thought to increase with time, and therefore limited the length of the Tilts-cc testing stimulation phase to 6 weeks. To minimise the risk of exit lead infection, I designed the study to manage

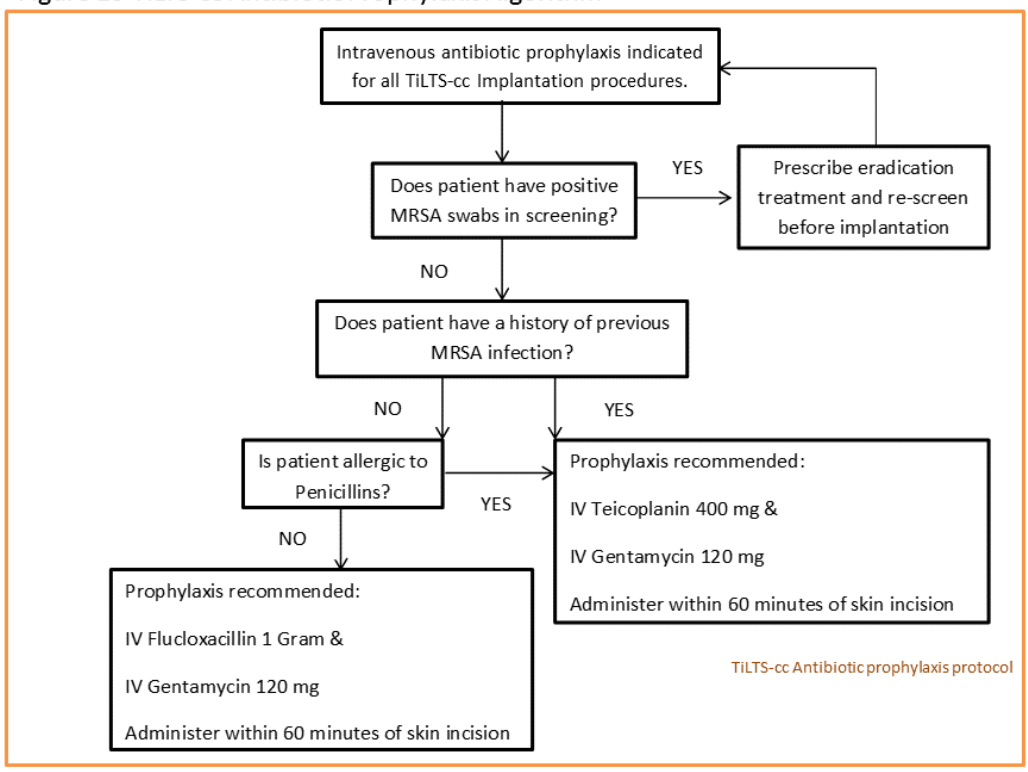
the exit lead as one would clinically manage a central venous catheter or Hickmann line exit site. This design entailed a weekly inspection of the exit site through a transparent dressing, and re-dressing only if clinically indicated. In practice we had found that re-dressing and cleaning the site weekly (i.e. routinely) could increase equipment malfunction due to lead or electrode damage. The lead was also fixed to the skin with another dressing distally to minimise traction on the exit site skin. A strict protocol for managing suspected exit site infections was followed; the PI was informed immediately and the participant examined by a senior clinical team member with appropriate treatment given. This entailed a course of oral antibiotics for relatively minor superficial infections appearing as erythema around the exit site, to inpatient treatment with intravenous antibiotics for superficial spreading erythema (cellulitis) and removal of the tined lead for suspected deep-seated infection. After infection resolution, continuing participants were asked to recommence from the beginning of the 2-week testing period at the time of diagnosis. A diagnosis of deep infection that required tined lead removal necessitated withdrawal from the study. Participants requiring withdrawal from the study due to an infection were followed until full resolution or resolution with sequelae and the details recorded as part of the study. All reports of infection were followed up by the IDMC who advised on subsequent protocol amendments to maximise participant safety.

#### 5.1.9.6.4. Antibiotics

Intravenous prophylaxis was given before each implantation procedure. This was initially a standardised dose of 80mg i.v. Gentamycin for all participants. After several participants had experienced superficial infections in the study and following concerns raised by the independent data monitoring committee and trial steering committee, a review of appropriate antibiotic prophylaxis for the study

implant procedures was conducted. I contacted and assisted the CDDFT antimicrobial management team (AMT) committee with this review of our study procedures for antimicrobial prophylaxis. The AMT chair and I jointly conducted a literature review of the best antimicrobial practice, consulted SIGN and NICE guidance and reported to the independent data monitoring committee and trial steering committee that there was no evidence of best antibiotic prophylaxis relating to this type of procedure, with only the SIGN prophylaxis guidelines stating that prophylaxis should be given "for any implant or device insertion" without stating what that prophylaxis should be. The trust AMT committee formed an expert consensus opinion by considering the bacterial flora on the implant area, the organisms cultured to date from several participants, the duration of the trial procedures and recommended the following prophylaxis protocol for the TiLTS-cc study (**Figure 13).**

Figure 13 TiLTS-cc Antibiotic Prophylaxis Algorithm



All other forms of antibiotic prescribing for participants during phases 2 and 3 were recorded with an associated adverse event also reported. All antibiotics were therefore closely monitored by dose and duration of treatment in the CRFs. Specifically participants were not withdrawn due to antibiotic use as it was accepted that antibiotics were highly unlikely to cause diarrhoea in participants with medically refractory constipation (otherwise this would be an acceptable long-term treatment).

#### 5.1.9.6.5. Pregnancy

Any participant who had a newly diagnosed pregnancy during phase 2 or 3 of the study would be reported as a SAE. The protocol specified that the site PI should discuss the case with the trial chief investigator within 48 hours of SAE reporting, and a clinical plan of management devised to care for both the participant and foetus. This would involve opinions being sought from obstetricians and anaesthetists regarding the safety of surgery or any anaesthetic required. Specifically for pregnancy diagnosed in phase 2, the tined lead would remain in-situ for a later date, and the extension lead removed under local anaesthetic. In phase 3 the IPG would simply be turned off with information given to the participant's obstetrician regarding the use of diathermy in the event of caesarean section (there is no need to remove the IPG during pregnancy). We planned that participants would specifically have any active study intervention stopped if they had a newly diagnosed pregnancy and this fact was very clear in the PIS (Appendix 2). This is simply because I could find no evidence in the published literature for the safety of active SNS during any stage of pregnancy on the developing foetus. The electrical stimulation field around the S3 nerve is only a few centimetres from the uterus and so it may possibly cause an unknown effect on embryogenesis.

## 5.2 ExperienceS of treatment with Sacral Nerve stimulation (SNS) for idiopathic Constipation; a hermeneutic phenomenological study The ESSeNCe study

The Essence study was devised for two main reasons. Primarily I and my supervisors considered the value of undertaking a qualitative study to gain insight into the TiLTS-cc study participant's experiences of and motivations for becoming recruits into what we perceived to be an intensive and demanding surgical trial. This study was designed, therefore to further complement and inform the TiLTS-cc study of participants' acceptability of a new testing technique (ePNE) for SNS in participants suffering from CC. The objectives of the qualitative study are to explore the participants' tolerability of a prolonged test, the interventional treatment in general, and their experiences of trial participation. In addition, the Essence study attempted to assess how generalizable and transferable this technique may be in the NHS. Secondly, this study was for my own education as I had an interest in qualitative research, and as a surgeon I have never actually been formally taught or attempted to undertake a proper qualitative study. I attended a qualitative research methodology course run at Durham University by my supervisors and began reading about the different frameworks that I might utilise to undertake this study. In this section I will discuss my choice of theoretical framework selected for use, my underlying worldview which may have precipitated this selection and the methods I used to perform data collection and analysis from recruited participants.

### 5.2.1. Research Aims

The main aims of the Essence study were to explore the lived experience of participants with CC undergoing SNS testing and subsequently living with the implanted permanent device.

After a thorough review of the literature I identified a knowledge gap which could be addressed by further exploring the following topics in Table 25.

**Table 25 Exploratory topics in the Essence study**

| |
|---|
| • **Participant experiences of CC, background treatments and further interventions.** |
| • **Motivations of participants to participate in the TiLTS-cc trial (or usual care SNS treatment).** |
| • **Experiences of care and support that participants received before/during and after the trial (or usual care SNS testing).** |
| • **Perceptions of symptom changes (physical or psychological), to what extent this was attributed to SNS, and how important were these changes to participants.** |
| • **Experiences of SNS in relation to its effect on other aspects of their life (relationships, socially, professionally, and self-perception).** |
| • **Experiences, perceptions and beliefs about the placebo effect associated with SNS.** |
| • **Perceptions and beliefs about the overall experience of SNS testing.** |

### 5.2.2. Declaration of my worldview

In order for a qualitative researcher to reliably collect, interpret and report their data to peers, I believe that the researcher's biased worldview should be framed for further interpretation by their peers as this will undoubtedly skew their data collection and interpretation. The following is therefore a statement of my political, sociological and religious views that will bias my attitude towards the theoretical framework selected and used for data collection and analysis.

I am a middle aged man with predominantly clinical training in medical sciences, especially general and colorectal surgery in which I am a clinical specialist and a Fellow of the Royal College of Surgeons of Edinburgh. I also have a strong laypersons interest in all other sciences. I view the world we live in and life in general as an absolute consequence of the laws of nature, and to be of no other particular significance; I believe that organised religious belief structures are inconsistent with human observations throughout history and I reject them all as superstition. I believe they persist purely as a psychological comfort to human mortality. I reject atheism as an irrational description of reality, coined by religious

conservatives as an attempt to redefine realism in religious terms. I do not define my worldview as a rejection of a superstition or the supernatural (a-theism), I define it by what can be experienced, observed and measured in our natural daily lives, i.e. Realism. This is an epistemological philosophy championed by Christopher Hitchens that "what can be asserted without evidence can also be dismissed without evidence" (Hitchens's Razor). I view humans as flawed animals (as are all evolved creatures) and of no more significance to other known lifeforms than our slightly higher intelligence. I believe in the socialist principle that all people should be offered an equal opportunity in life by their governing state, and I am particularly opposed to the inherited privilege that is common in the UK; I believe in meritocracy. In summary I would best describe myself as a socialist, republican, and scientific realist. As a doctor I believe these attitudes help me to strive for excellence in treating my patients, whilst also respecting their own unique worldviews.

### 5.2.3. Theoretical frameworks

I designed this study mindful that there was a considerable knowledge gap; the story of the lived experience of participants undergoing SNS as a test or a long-term treatment had not been formally reported in this, or any, population nationally or internationally. A range of theoretical frameworks had potential utility to explore the aims outlined earlier.

#### 5.2.3.1. Narrative Inquiry

I considered Narrative inquiry as a possibility through exploration of biographies of participant experiences during SNS testing in combination with open interviews at home after trial completion. Reporting data of a narrative inquiry, however can sometimes lead to criticisms of the data being too subjective, and without specific objectives. A narrative enquiry in general may have yielded an interesting breadth of data from participants, but it may also not have been highly specific to the

knowledge gap identified. I believed that this study would be best specifically investigating the participant experience of an uncommon surgical procedure, and the treatment it provides to a severe refractory medical condition, and so this required a more focussed approach to answer the research questions. Similarly, I considered an action research approach and also rejected this on the basis that as little was known about the experience of participants, it would have been impossible to integrate the aims of action research into an interventional study whose aims and methods were fixed at the point of funding.

#### 5.2.3.2. Mixed Methods

"Mixed methods' is a research approach where both quantitative and qualitative data are collected synchronously during an interventional study, and this approach to health research has undergone significant growth in recent years due to increasingly complex medical studies. This methodology utilises the strengths of both research methods which enables researchers to investigate, discover and understand more complex relationships, associations and confounding factors that can surround the research questions. As the interventional quantitative study methods were fixed at the point of the NIHR funding application, a genuinely mixed methods approach was also impossible.

#### 5.2.3.3. Phenomenology

My literature review has demonstrated that phenomenological approaches are commonly used by researchers investigating surgical procedures to good effect, offering both depth of experience but also allowing for focussed enquiry about a particular phenomenon. Thus, I selected this theoretical framework for use in the Essence study.

### 5.2.3.4. Descriptive Husserlian Phenomenology

Phenomenology has increased in popularity as a research method since the late 20th century. As a philosophy, phenomenology was originally described by Edmund Husserl (1859-1938), and then further developed by Martin Heidegger (1889-1976), Jean-Paul Sartre (1905-1980), and Maurice Merleau-Ponty (1908-1961), with whom it is most widely associated. In essence phenomenology is a study of human consciousness, with the study focus being on a first person description of *what* and *how* a person experiences a certain phenomenon. It is consequently mostly utilised in psychology research and over the past twenty years has been used increasingly in health research, notably in fields as varied as psychiatry, medical/nursing education and surgery (156, 157, 172-174). It has been used to good effect in a wide range of studies seeking to explore experiential elements of illness and healthcare, giving access to previously under-explored issues such as lived space/relations, insecurities/fear, and changes to the body (153, 158, 175, 176).

### 5.2.3.5. Interpretative Heideggerian Phenomenology

The philosophical differences between using a Husserlian or Heideggerian model of phenomenology centre on a researcher's ability to separate their own past experiences from the research topic they are investigating (177). Researchers using a Husserlian model would aim to describe the experience of the phenomenon encountered by the person, leaving their own biases and pre-conceptions aside in what is now known as transcendental phenomenology. Researchers using a Heideggerian model would aim to declare their presuppositions (and biases) on the research phenomenon and try to interpret the description of the phenomenon encountered by the subject. In doing this they are accepting that it is impossible to be completely neutral in describing and interpreting encountered phenomena. This model of phenomenology is also referred to as Hermeneutic phenomenology. A

further, more modern, model of phenomenology is known as Interpretive Phenomenological Analysis (IPA) in which the researcher moves from a position of naivety (transcendentalism) at the start of the research study towards a shared understanding of the phenomenon (178, 179).

#### 5.2.3.6. Selection of hermeneutic phenomenology

As I was the researcher conducting participant interviews and also the surgeon treating and following the participants through the quantitative trial process, a pure (or an IPA) transcendental approach would be impossible for me. I could not possibly start from a position of naivety: My researcher's experience of treating each and every participant throughout the trial would undoubtedly play a part in my understanding of the data collected. Heidegger's belief that the mind pre-conceives the experience of a phenomenon, and then either validates or revises the pre-conception is highly relevant to this study. I was a central and consistent component of the whole trial experience from the participants' perspective, just as the participants were a central and consistent experience of the trial to me. Consequently I selected a Heideggerian hermeneutic phenomenological framework, and this had previously been used to explore surgical trials in similar populations (Van der Zalm 2000).

### 5.2.4. Potential design limitations

In using a hermeneutic phenomenological approach to data acquisition and analysis, based on the principles of phenomenology outlined by Martin Heidegger, I freely admitted my life experiences that may have biased my collection or interpretation of data from study subjects. I stated these prospectively within the Essence study protocol in order that the ethics committee (both Durham University and NHS REC) would be able to consider them, and to facilitate any readers of this thesis with interpretation of my study findings. The following section was written within the study protocol and begins with my personal experiences of the ePNE SNS

testing technique (from a clinician and researcher's perspective) and my expectations of what participants would experience during the study treatment: These were the beliefs that may have biased my data collection and analysis.

#### 5.2.4.1. My experiences and expectations of the phenomenon (ePNE SNS testing)

I stated within the Essence protocol:

"In treating participants as both an operative surgeon performing SNS procedures, and a doctor assessing symptom response, I have formed opinions of "what" participants will experience during SNS testing, and "how" they will experience this. I expect the postoperative period to be uncomfortable initially with the pain easily controlled with simple analgesia. I expect the greatest problem participants will encounter is due to the dressings. These can cause irritation, pruritus and become malodourous. They require help to be maintained from a close member of the family (usually but not always a partner) due to the position on the back, and I expect will leave the participant feeling dependant on that family member. I expect that it may also leave a normally independent person feeling vulnerable if they have no close family to help. I expect the driving restrictions during the 4 testing weeks to leave most participants feeling a loss of their own independence, and a great inconvenience. I expect that participants with no family or poor family support may consequently struggle with this form of treatment, and that it may be detrimental to their quality of life. However, I am open to the possibility that none of these themes might arise from the data, which may illuminate new, previously unexplored, areas of enquiry."

Appropriate supervision from experienced qualitative researchers was available to me during the data collection and analysis phases, and I ensured, as far as possible, that findings were grounded in participant data rather than my preconceived views

about SNS. An extensive interview schedule was constructed (Appendix 11); I simply used this as a topic guide throughout the interviews in order to keep focus on the key areas. I ensured time was given for participants to express their own views about their experiences, in their own way, and the priorities they assigned to the importance of various factors mentioned in the schedule had primacy in this study.

#### 5.2.4.2. Participant factors

A potential limitation of this study design surrounded the participant's ability to have comfortably reflected and described their experiences to me- a researcher who was central in those experiences. It is potentially feasible that participants felt unable to be as frank and honest to their treating surgeon as they would have been with clinically neutral researchers. They may have potentially described an experience that was more agreeable to me than their lived reality. Conversely this may have been an advantage too, as participants may have felt more relaxed and at ease with a familiar person, and consequently more open, as discussed in similar studies with sensitive issues (180, 181). I considered the option of offering a 'back-up' (non-clinical) researcher as an interviewer but this was rejected by the constipation research advisory group (CRAG) during the development of this study; patients felt that it would be easier and preferable for them to be frank and open with a person known to them who already had a working knowledge of their medical history, and was known to be respectful and compassionate about their difficulties. The participant information sheet (PIS) was reviewed during the design phases by the CRAG, who consisted of Durham clinic patients who had experience of constipation trial participation. They advised and helped with the design of the PIS, overall study including the interview venues and guides, and approved these as acceptable to patients before ethical approval was sought for the study. I was given full training and supervision in conducting the interviews, and I performed a

mock interview with a specialist nurse who treats participants in the biofeedback clinic regularly. This nurse was an expert in managing the complex interpersonal problems displayed by participants, and was able to synthesise their likely responses to particular lines of enquiry. This interview was transcribed and analysed with my supervisor, and I used this to help modify my interview style and understand the process of coding and analysing the transcription data. During every interview I offered the participants an identical 10 minute opportunity to reflect honestly and openly about their experiences, and I assured participants that critical or negative accounts of their care did not influence their subsequent care in any way. This was an important aspect of the design as there was a high prevalence of anxiety within the participant group. I believed the main potential risk of being a clinical interviewer in this study was the way in which my clinical/researcher role was demarcated and perceived by participants. Even if I was clear about the demarcation in my own mind, this may not have been clear to the participants. In realising this I made every attempt to assist participants to understand this demarcation through the study design; the participant information sheet was clearly worded to ensure that participants understood their rights, and the responsibilities of the research team towards them. Any requests from participants for clinical information during the interview, or the disclosure of clinically relevant information during the interview was dealt with [if necessary] during a ring-fenced 5 minute debrief at the end of the interview. I was clear to participants that during the interview I was a researcher not a clinical doctor, and during the ring-fenced time I could stop being a researcher and become their doctor again. I again emphasised that during this ring-fenced time their care was not influenced in any way by the preceding interview discussion, and that if they required clinical information, investigation or treatment this was dealt with in the normal way within the boundaries of their clinic appointments. These methods were written

into the protocol and endorsed by a qualitative peer reviewer who had experience of using similar methods (181) which had built on previous work by other doctors who had undertaken qualitative interviews with their participants (181 182).

### 5.2.5. Methods

The qualitative data were collected sequentially, following on from the quantitative study. This was necessary as the TiLTS-cc study had already commenced recruitment and could not be re-designed to allow qualitative feedback into its own study design without affecting the outcome measures. Participants within the TiLTS-cc study were therefore required to have completed their last quantitative data collection visit before being invited to the Essence study interview. Participants who were recruited from the NHS usual care pathway were invited for interview concurrently with those in the TiLTS-cc study.

#### 5.2.5.1. Sampling

I planned a purposive sample of between 5 to 20 participants who were invited to interview upon their completion of the TiLTS-cc study. The upper limit was higher than might normally be expected in an in-depth phenomenological study (van Manen, 1990); this reflected the fact that little was known about the experience of SNS and allowed for the possibility of multiple perspectives which would have prevented data saturation from being reached in a smaller sample. In terms of phenomenology this was a standard size for this type of study; 5 may have been sufficient but 10-20 was more likely. Previous research shows that it was possible to reach data saturation in a similar population (154, 157, 174, 176) and recruitment could have been extended if data saturation was not accomplished by the 20$^{th}$ participant. In order to avoid selection bias all TiLTS-cc participants were offered participation in the same sequential order, and only participants refusing participation were excluded from the proposed study. Due to the population of participants being heavily skewed towards females it was not possible to interview

any males during this study, although males were invited to participate if possible. Participants who did not speak English were unlikely to be part of this participant population, and their cultural experiences of care and surgery were likely to be so different as to warrant a separate study. I decided, therefore that Non-English speakers were not to be invited to interview. The first interview was performed in June 2014, following which the data were fully transcribed and analysed before I had a debriefing with my supervisor to decide on aspects of my technique, the interview schedule and any relevant participant data that could be used to explore topics further in the next set of interviews. I then conducted the interviews in blocks of three participants with the subsequent data transcribed, analysed and used to modify the interview schedule before the next block of interviews. The rationale behind this was to ensure close supervision between interviews as far as logistically possible, and to allow me reflective space between the interviews. In order to examine the perspectives of participants experiencing SNS in usual care through the DCC, I invited to interview any DCC participants with a historical treatment of SNS in the preceding 5 years who had at least 6 months of clinical follow up after IPG implantation (to ensure similarity to those in TiLTS-cc).

The following criteria were used to select and invite participants to interview:

**Inclusion Criteria:**

All participants with all of the following inclusion criteria were included for study invitation (Table 26)

**Table 26 Essence study Inclusion criteria**

| |
|---|
| Female and male Participants aged 18 years or older. |
| A history of chronic constipation with treatment by SNS (TiLTS-cc or usual NHS care). |
| Competent to give informed consent. |
| Fluent in English. |

**Exclusion Criteria:**

All participants with any one of the following criteria (Table 27) were excluded from invitation:

**Table 27** Essence study exclusion criteria

| |
|---|
| All participants 17 years old or younger. |
| Treatment with SNS for another medical condition that is not CC. |
| Inability to provide competent consent. |
| Non-English speaking or no fluency in English. |

### 5.2.5.2. Data Collection

I invited participants to consider participation in the Essence study via an invitation letter offering a participant information sheet (PIS). All participants were given a reasonable cooling off period of one week after receiving the PIS before a study interview was arranged. Participants were invited to a semi-structured interview at the University Hospital of North Durham in a clinic room with which they were familiar, and were offered a chaperone to be present if they preferred. This was an important design given the known psychological problems participants with CC and FGIDs in general are known to suffer from. I believed that participants required the security of familiar surroundings and of another professional being present to support them and act as an advocate if they desired. Setting this comfortable environment, I believed allowed scope for a greater interview enquiry as participants were relaxed and had low levels of anxiety.

I asked all participants to confirm their willingness to participate in the interviews and to provide written consent, following confirmation that they understood the ethically approved participant information sheet and the nature of the proposed study, including that their views may be used as anonymised quotes in a thesis and journal publications. The interviews were recorded on a digital dicta phone and stored in a secure office within the hospital. Participant identifiable data were only

accessed by the research team through the site master file. The audio data were stored on the team's secure encrypted research database on the trust intranet server, and transcribed into a pseudonymised (alphanumeric code) text document by the team assistants. Pseudonymised audio and text data were transferred to the Wolfson Research Institute through a securely encrypted memory stick approved by the sponsor's IT department. Access to all of these data were restricted to named team members. Printed data was pseudonymised and stored until analysis of the full study had been completed, and then securely destroyed as per the sponsor's confidential waste protocol. All audio data and transcripts within the site file will continue to be kept for 5 years after the full study analysis has been completed and then securely destroyed. An agreement between Durham University and the CDDFT Caldicott guardian was permitted to allow access to the data by named University team members involved in this study.

#### 5.2.5.3. Timing of Interviews

Participants were invited for interview after the 6 month follow up visit of the TiLTS-cc trial or after 6 months following implantation of the device in usual care participants. I planned the interview duration to aim to be within 15 minutes to a maximum of 90 minutes, after which time I felt it would be unlikely to yield further relevant data due to participant fatigue. I ensured all participants were free to terminate the interview at any time if desired and without reason; this was emphasised in the Participant Information Sheet. For the convenience of the participants', if they were due to have a full clinical review of their care in the DCC within one month of the study appointment, I offered to re-arrange this appointment immediately after the study interview. I believed this was justified to prevent extra travel and time off work for participants, and also to help boost recruitment to the study.

#### 5.2.5.4. Location

Based on my previous clinical experience I felt it was highly possible that participants may report themes that could be related to very personal experiences including histories of abuse; therefore it was important to conduct interviews in an environment that was safe, familiar, and comfortable for both participants and myself as researcher. A clinic space in the hospital was preferable as this was familiar territory to the participant, and would constitute a safe environment for both the participant and myself as a researcher. I performed a pre-study participant and public involvement activity discussing these design aspects and the feedback indicated that this location was acceptable to participants. I did consider home interviews and rejected this location due to the possibility of histories of psychosocial trauma arising; I felt my presence in their home would be potentially inappropriate due to these and the very personal nature of care I had given them. The whole supervisory team agreed that professional boundaries were required to be maintained.

#### 5.2.5.5. Transcription and interpretation

Recorded interviews were transcribed by the DCC team personal assistants who were experienced in transcribing clinic letters for this group of participants. The transcribers were paid a reasonable overtime rate for their time helping to do this, funded through a springboard grant from the sponsor.

#### 5.2.5.6. Supervision of researcher and transcriber well-being

I was concerned that given the possible range of topics may have arisen with participants during the data collection, from histories of physical and sexual abuse to deliberate self-harm and affective disorders, formal supervision in the form of psychological support and debriefing should be provided by the DCC team psychologist. Our psychologist was known to all members of the clinical and research team, and she was enthusiastic to help by offering debriefing to me and

any transcriber as required. I requested that the psychologist should be in a position to feedback any concerns they had regarding issues raised (either of the participants or researchers) to the supervising consultant who had clinical responsibility for the participants and professional responsibility for the researchers as the team manager. This process may have appeared to threaten participant confidentiality and anonymity, however the psychologist was a permanent member of the DCC team with clinical input to the participants' treatment and it was therefore an important way to maintain participant safety. Initial participant consultation suggested that as long as this process was made clear in the participant information sheet, it was acceptable to participants.

### 5.2.6. Analysis Plan

Thematic analysis was used to interpret the transcribed data. This involved both myself and my supervisor thoroughly reading the transcribed data, and systematically coding experiences that appeared to be prominent in the text. The transcripts were coded line by line, and these codes were used to form generalised themes that appeared to describe the experiences or phenomena of most of the participants. Transcripts were read and analysed independently by myself and my supervisor using thematic analysis to explore the 'lived experience' of participants. Following independent analysis, each analyst developed a list of preliminary codes, which were added to and refined as coding progressed. This list of codes was captured using Excel spreadsheets with examples of quotes taken from individual transcripts. We met to discuss the code list after the first interview and then after each set of 3 interviews had been conducted and individually analysed. Consensus was thus reached on the code list via in-depth discussion of the transcripts; if consensus was not reached we designed the study to allow a third experienced qualitative analyst to arbitrate. Codes were grouped into categories by myself and from these a set of themes emerged which characterised all of the information

within the categories. Again, consensus was reached on the category list via in-depth discussion of the transcripts; if consensus was not reached we designed the study to allow a third experienced qualitative analyst to arbitrate. Emergent themes were tested using diverse accounts within cases and between cases, in order to challenge the integrity of the boundaries of themes, and to ensure that data saturation was accomplished. Data saturation, (which happened when no new or interesting data were collected), was expected to occur at around 5-20 participants.

### 5.2.7. Ethics

The quantitative protocol for TiLTS-cc could not be amended as the Essence study was considered as a separate follow-on study. Permission was therefore sought and approved from the Durham University ethics committee, before the study was approved by the East of Scotland Research Ethics service (EoSRES) for NHS approval, and County Durham and Darlington NHS Foundation Trust (CDDFT) for local NHS approval.

#### 5.2.7.1. Participant information sheet (PIS)

Participants were contacted by an invitation letter briefly summarising the study (**Appendix 12**). They were invited to contact the research team in order to receive and read the PIS (**Appendix 13**) before study consent (**Appendix 14**) was obtained, and were under no obligation to be interviewed. The Participant's GPs were also informed of their decision to be interviewed in case of any objections for unknown circumstances (**Appendix 15**). The PIS was posted to them for consideration prior to being invited to a study interview, and this included a reasonable cooling off period. Patients were informed of their right to refuse and that their treatment would not be adversely affected by refusing to participate. Participants who were withdrawn from the TiLTS-cc study were also contacted and invited as they may have had unique experiences that were relevant to the study population. Two participants that had experienced a withdrawal from the Tilts-cc study accepted the

invitation. Participants were informed of the confidential nature of these interviews, but also that there was a mechanism for raising clinical concerns. In particular if they appeared to demonstrate deteriorating mental health, then I emphasises that I may refer them to their GP or named psychiatrist for further treatment if I deemed it necessary. Participants were also informed of the requirement for me and the transcription team to debrief following the interview, and that this would not breach their confidentiality as the clinical psychologist was part of the multidisciplinary team. I also emphasised that the interview may have therapeutic potential for Tilts-cc study participants as a means for their debriefing after the study.

#### 5.2.7.2. Consent

Written informed consent (Appendix 14) was obtained from all participants prior to study inclusion. This consent was in triplicate with one copy provided to participants, one copy filed by researchers, and one copy filed in the clinical case files.

#### 5.2.7.3. Researcher bias

During the design phase of the Essence study I accepted and considered the inherent design limitation of using a member of the clinical and research team (myself) who had helped in participant recruitment, surgical implantation of the testing device, follow-up of participants, and blinded assessment of the quantitative data. I considered the fact that I had close contact with the participants and likely formed opinions of them and their response to the treatment. I also realised that the participants would likely hold views of me as the researcher that could have restricted or directly influenced the information they gave to me in the interviews. I also declared that I had a vested interest in the study as it formed part of my PhD thesis, and therefore I may not have been in a position of equipoise when conducting the study. To address these problems, firstly I openly admitted my

expectations of the treatment in the Essence study protocol (quoted in this methods section for the reader's consideration of my subsequent thematic analysis), and I wrote a detailed worldview as part of my PhD thesis (5.2.2 page 152) to lay bare my inherent biases that could influence my interpretation of the subject data. Secondly I involved TiLTS-cc study participants in the study design, and confirmed that most would be willing and able to be open, honest and frank in the interviews with me, and would not feel uncomfortable at doing so. Despite these precautions there was still potential for my bias in the collection, analyses and reporting of data from participants. I sought further advice from a peer reviewer who had proven experience of employing a similar methodology (181), who had provided further evidence of doctors conducting similar research (180, 182) and who endorsed my plan to receive adequate supervision of data collection and interpretation during the hermeneutic circle in order to minimise the potential for bias. I completed directed training before undertaking the interviews; performed supervised and directed reading, attended a Health Research Qualitative Methods course (October 2012), performed mock interviews with specialist nurses who treated this cohort of patients, and received supervisor feedback of my mock interview style. I received full supervisor feedback on my interview style and technique following the first formal study interview, and then subsequently after blocks of three interviews. This directed training took place at both UHND and Durham University Queen's Campus.

### 5.3 Chapter summary

This chapter has demonstrated the complex methods and procedures used to ethically collect data in the TiLTS-cc study, and the reasons for the key methodological features that were written during the design phase to help meet the study objectives; namely sub-sensory testing with a central washout period, device calibration testing to facilitate consistent stimulation and secure blinding,

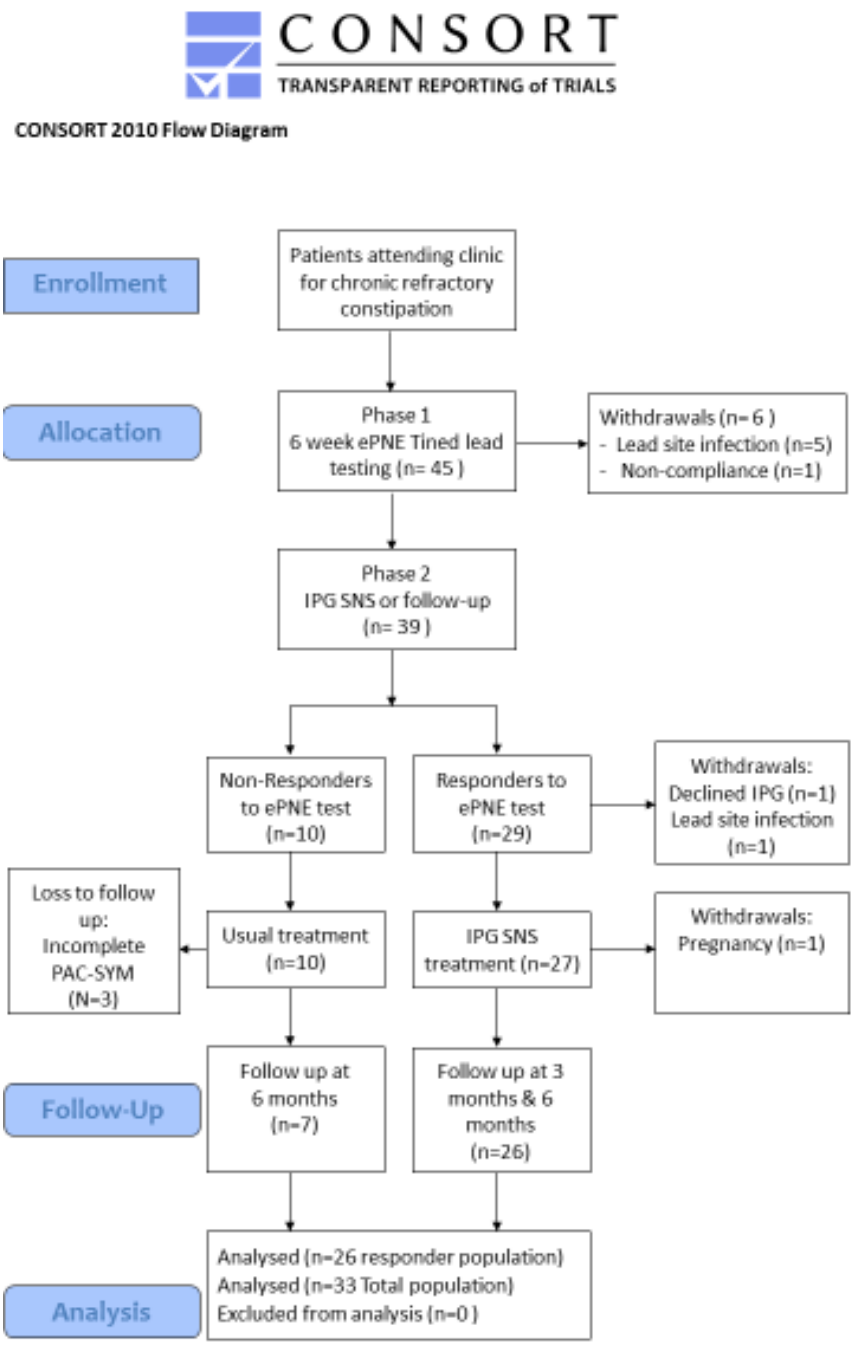
and a randomised crossover trial approach to control the study participants adequately. The methods used to collect data in the follow-on Essence study are described along with the reasons for selecting hermeneutic phenomenology, the inherent potential design limitations to these framework, and how I sought to overcome these with help and advice. The following two chapters will present the relevant study findings and highlight their key findings for consideration in the overall discussion of this thesis in Chapter 8.

# Chapter 6 TiLTS-cc study results, adverse events and incidental findings.

## 6. Introduction

This chapter will present the findings from the TiLTS-CC trial including the baseline demographics, analysis of primary and secondary outcome measures, adverse events and incidental findings. I will interpret these findings in relation to the knowledge gap previously identified and discuss their implications for further research and clinical practice. The key findings from this chapter will be used to inform a critical interpretation alongside the systematic reviews and qualitative study findings (presented in Chapter 7), in Chapter 8.

### 6.1. Figure 14 TiLTS-cc Study Consort Diagram




45 participants were enrolled into the TiLTS-cc study (42 recruited from Durham, 3 from Gateshead) and received a tined lead during phase 1, of which 6 withdrew (Consort diagram). 29 were classified as responders of which 27 received an IPG, and 10 entered phase 2 usual treatment follow up. 1 further withdrawal from the IPG group and 3 from usual care resulted in 26 participants assessed for interventional endpoints at 6 months and 7 from usual treatments.

## 6.2. Stard checklist for the TiLTS-cc Study

The Stard checklist (Appendix 16) for reporting studies with diagnostic accuracy outcomes was completed for reference.

## 6.3. Demographics of study population

Of the calculated sample size (n=75) required for an adequate primary outcome analysis, 45 participants were recruited and randomised to group A or group B. The study was terminated early due to the adverse event profile: The third criterion of the early study termination (Table 19) was initiated by the steering group under advisement of the sponsor and data monitoring committee when it became clear that there was a safety issue with infections that could not be resolved despite repeated attempts at reducing this risk. Recruitment was also slower than originally anticipated due to 2 lead sites being unable to participate as a result of the aforementioned funding changes for SNS by the clinical commissioning groups. Of the remaining 3 sites who recruited to the study the vast majority of participants were recruited via the Durham constipation clinic. Forty-three of the 45 participants were female (96%) with a mean age of 41 years (range 18-68, Table 28). They demonstrate chronicity of the disease with a mean duration of symptoms of 17.6 years, and severity with a mean total PAC-SYM score of 2.19. Their quality of life was also severely affected with a mean total PAC-QOL score of 2.70. As expected almost all of the patients (42, 93%) were currently receiving treatment for their condition (Table 30), and a very high proportion (82%) were suffering from other co-morbidities (Table 29) of which anxiety and depression were the most common mental health illness. Thirty participants (67%) had slow colonic transit identified at baseline by the Sitz marker transit study using the Metcalf protocol.

**Table 28 Baseline characteristics of the study population**

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

**PAC-SYM= Patient Assessment of Constipation-Symptoms questionnaire**
**PAC-QOL=Patient Assessment of Constipation-Quality of Life questionnaire**
**VAS= Visual analogue scale**
**EQ-5D-3L-the 3 level version of the EQ-5D questionnaire**

**Table 29 Study Group Co-morbidities at baseline by body system**

| Co-morbidity | N (%) | Co-morbidity | N (%) |
|---|---|---|---|
| ***Cardiovascular System*** | | | |
| Hypertension | 6 (13) | Ischaemic Heart Disease | 5 (11) |
| ***Respiratory system*** | | | |
| Asthma | 10 (22) | COPD | 2 (4) |
| ***Gastro-intestinal system*** | | | |
| Dyspepsia | 2 (4) | Folic Acid Deficiency | 1 (2) |
| Gastro-Oesophageal Reflux Disease | 3 (7) | Peptic Ulcer disease | 1 (2) |
| ***Nervous system*** | | | |
| Epilepsy | 9 (20) | Insomnia | 1 (2) |
| Nocturnal Enuresis | 1 (2) | Positional vertigo | 1 (2) |
| Stiff Person Syndrome | 1 (2) | Transient Ischemic Attacks | 1 (2) |
| ***Musculo-Skeletal system*** | | | |
| Ankylosing Spondylitis | 1 (2) | Arthritis | 1 (2) |
| Lumbago | 2 (4) | Lumbar disc degeneration | 5 (11) |
| Osteoarthritis | 2 (4) | Sciatica | 3 (7) |
| Spinal pain | 6 (13) | Tendonitis | 1 (2) |
| ***Reproductive system*** | | | |
| Endometriosis | 1 (2) | Menorrhagia | 1 (2) |
| Post-Menopause | 2 (4) | | |
| ***Genito-Urinary system*** | | | |
| Atonic Bladder* | 3 (7) | Erectile Dysfunction | 1 (2) |
| Recurrent Urinary Tract Infections | 2 (4) | | |
| ***Endocrine System*** | | | |
| Diabetes Mellitus | 4 (9) | Hypercholesterolaemia | 1 (2) |
| Hypothyroidism | 4 (9) | | |
| ***Immune system*** | | | |
| Nickel allergy | 1 (2) | | |
| ***Dermatological*** | | | |
| Dermographism | 1 (2) | Psoriasis | 2 (4) |
| ***Mental Health disorders*** | | | |
| Anxiety | 4 (9) | Depression | 14 (31) |
| Bipolar affective disorder | 2 (4) | | |
| ***Vascular*** | | | |
| Raynaud's Phenomenon | 1 (2) | | |

**This table demonstrates the recorded diagnosed Co-morbidities of participants at baseline.**
***These 3 patients may possibly have an undiagnosed neurological disorder which may be contributory to their constipation. (Inclusion / Exclusion criteria 5.1.1.2/ 5.1.1.3 page 95)**

**Table 30 Current treatments for constipation**

| **Treatment** | N (%) |
|---|---|
| *Primary Care Prescriptions* | |
| Bisacodyl | 11 (15%) |
| Sodium Picosulfate | 10 (14%) |
| Movicol | 7 (10%) |
| No treatment | 5 (7%) |
| Phosphate enema | 2 (3%) |
| Glycerol | 1 (1%) |
| Lactulose | 1 (1%) |
| *Secondary Care Prescriptions* | |
| Docusate sodium | 4 (5%) |
| Picolax | 3 (4%) |
| Orlistat | 1 (1%) |
| Prucalopride | 9 (12%) |
| Linaclotide | 3 (4%) |
| *Tertiary Interventional therapies* | |
| Trans-anal irrigation | 9 (12%) |
| Manual evacuation | 1 (1%) |
| ACE irrigation | 1 (1%) |

### 6.4. Analysis

Forty-five participants were recruited and underwent tined lead insertion before being randomised into group A or group B for testing (Figure 14). There were 6 withdrawals during testing due to infection of the tined lead (n=5) and non-compliance with study blinding procedures (n=1) (see section 5.6 on adverse events for further detail). Serious adverse event reports were completed for all of the participants with testing lead infections and this was investigated by the DMC and trial steering committee who made the necessary protocol changes to try and minimise further infections within the study (page 144). The participant who was non-compliant was withdrawn by the research team for device tampering, deemed to be un-blinded, and received usual SNS testing and care within the NHS. Thus 39 participants successfully completed phase 2 of the study, of which 29 were deemed to be responders using the Tilts-VAS, and 10 were deemed to be non-responders.

Of the 29 responders to testing 22 were classified as indiscriminate responders and 7 as discriminate responders (**Table 31**).

**Table 31 Response classification during TiLTS-cc testing**

| Active | Sham | Response | Number (%) |
|---|---|---|---|
| + | - | Discriminate | 7 (18) |
| + | + | Indiscriminate | 18 (46) |
| - | + | Indiscriminate | 4 (10) |
| - | - | No response | 10 (26) |

**Tilts-VAS +ve, response to testing period**
**Tilts-VAS –ve, no response to testing period**
% of the N=39 completing testing

The 10 non-responders were placed in the usual care pathway per protocol and 3 were lost to follow up at 6 months (incomplete PAC-SYM), thus 7 participants were included for analysis from the non-responder pathway in phase 3.

The 29 test responders had planned further surgery per protocol to have an IPG connected to their in-situ tined lead. One patient declined the IPG procedure due to a perceived lack of benefit during testing, and was therefore withdrawn from the study after having had the tined lead removed, and entered the usual care pathway. Twenty-eight participants were implanted with an IPG, of which 1 was subsequently withdrawn due to a tined lead site infection requiring removal of the implant, and another was withdrawn due to pregnancy during follow-up (despite being counselled at recruitment about the need to avoid pregnancy). Twenty-six responders, and 7 non-responders (33 in total) were therefore assessed at 6 months for the primary endpoint of the study.

### 6.4.1. Primary outcome measure

A total of 33 participants were assessed for the primary endpoint of a reduction of ≥ 0.5 mean total PAC-SYM score from baseline. Of these, 15 participants with an IPG (57%) were classified as long term responders to treatment, and 5 (71%) with no IPG also met the primary endpoint.

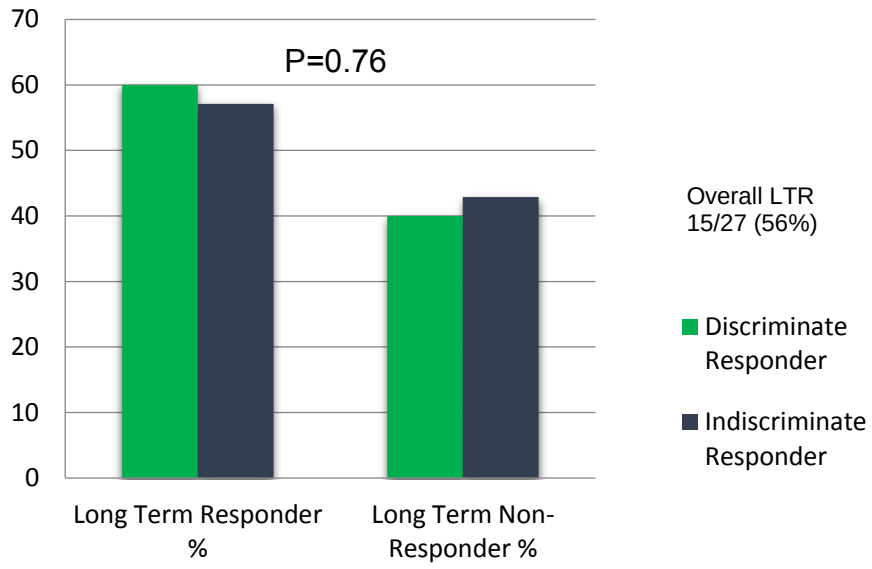
There was no evidence of a difference (P=0.76) in the proportions of long term responders to IPG SNS between ePNE TiLTS-cc testing discriminate and testing indiscriminate responders (**Table 32, Figure 15**).

**Table 32 Primary endpoint analysis**

| **Testing Classification** | **Reduction in PAC SYM ≥ 0.5** | | Total |
|---|---|---|---|
| | Long term Responder (%) | Long term Non-Responder (%) | |
| Discriminate test Responder | 3 (60.0) | 2 (40.0) | 5 |
| Indiscriminate test Responder | 12 (57.1) | 9 (42.9) | 21 |
| RD = 0.03 (-0.45, 0.51), P-value = 0.7586 Fisher's exact test | | | |

RD= Risk Difference, P= Probability value,

**Figure 15 Primary endpoint, Response at 6 months**




LTR =Long term responder to SNS IPG at 6 months follow-up

Discriminate responder = Responded only to active sub-sensory ePNE test stimulation

Indiscriminate responder= Responded to sham ePNE test stimulation

### 6.4.2. Diagnostic accuracy of Tilts-cc VAS during testing

The TiLTS-cc VAS was designed to determine response to testing with a modest threshold of improvement in symptoms of ≥ 25%, in order to maximise implantation rates for an analysis the predictive value of the tined lead test. The Tilts-VAS score at the end of each testing period (weeks 2 and 6) during ePNE was therefore evaluated as a diagnostic accuracy measure for long term response to IPG at 6 months (using ≥0.5 reduction in mean total PAC-SYM score). This demonstrated TiLTS-cc VAS could not identify long term responders from non-responders to IPG SNS, from tined lead testing responders.

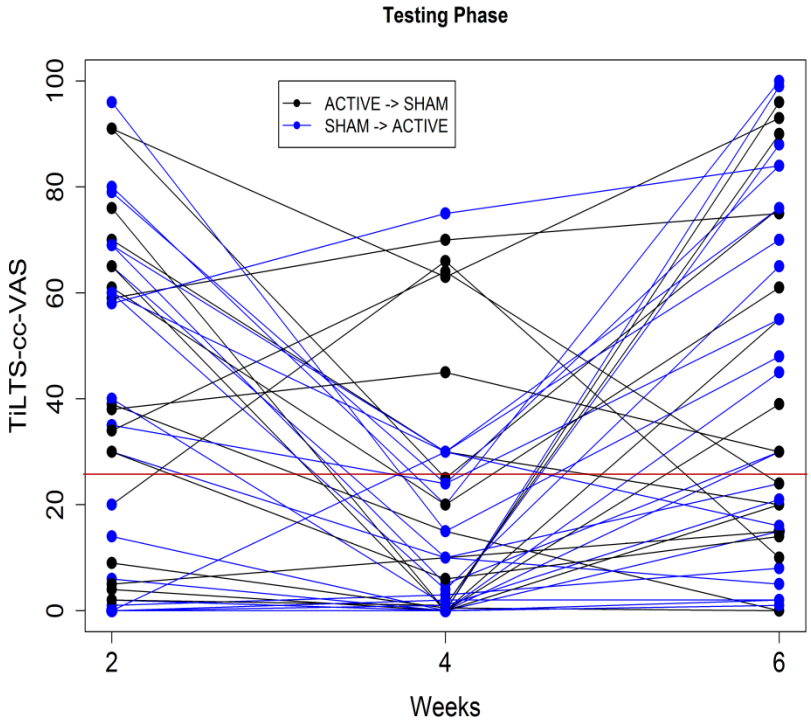
**Table 33 Diagnostic accuracy of Tilts-cc VAS during testing (Total population)**

| **TiLTS-cc_VAS Classification during testing** | **Reduction in PAC SYM ≥= 0.5** | | **Total** |
|---|---|---|---|
| | Long term Responder n (%) | Long term Non-Responder n (%) | |
| ePNE TiLTS-cc Testing Responder | 15 (57.7) | 11(43.3) | 26 |
| ePNE TiLTS-cc Testing Non-Responder | 5 (71.4) | 2(28.6) | 7 |
| % (95% CI)<br>Sensitivity = 75.0 (56.0, 94.0), Specificity = 15.4 (0.0, 35.0 )<br>PPV = 57.7 (38.7, 76.7), NPV = 28.6 (0.0, 62.0) | | | |

PPV=Positive Predictive Value, NPV=Negative Predictive Value

Tilts-VAS was also unable to adequately discriminate between active and sham stimulation during the testing phase using this threshold for response highlighted by the horizontal red line in Figures 16 + 17.

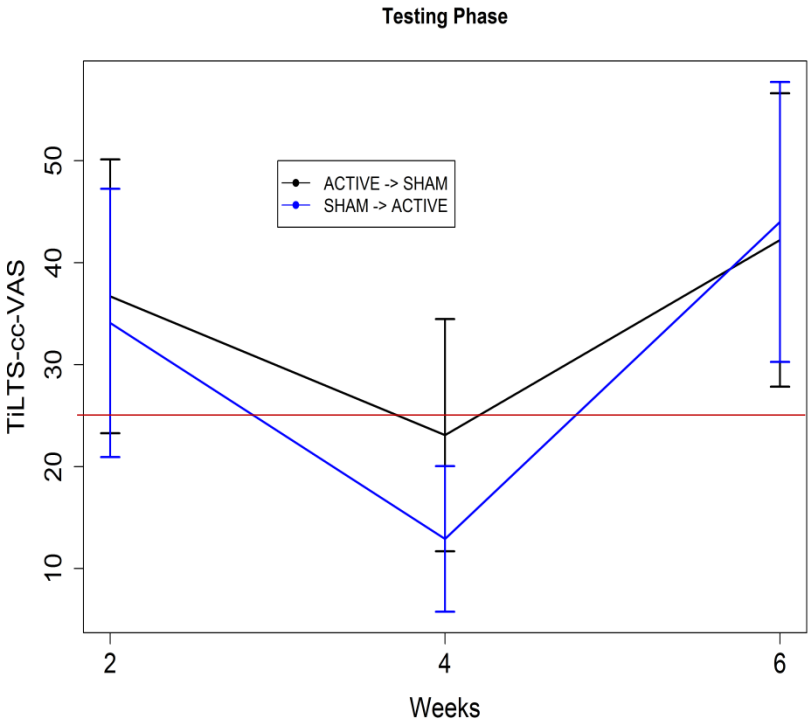
**Figure 16 Tilts-cc VAS longitudinal response profiles (%)**




The red line corresponds to the response classification threshold of TiLTS-cc VAS. Black is group A sequence and blue is group B sequence of ePNE. The majority of responses are above the threshold during testing, and some even during washout at end of week 4.

**Figure 17 Mean Tilts-cc VAS scores during testing**

Active - Sham 3% (95% CI 45-51)




In Figure 17 the mean values and most of the 95% confidence intervals are above the threshold for a defined test response during weeks 2 and 6 in both active and sham testing periods.

### 6.4.3. Secondary outcome analysis

The secondary outcomes for the total population are demonstrated in Table 34. PAC-SYM, PAC-QOL and Wexner scores decrease on improvement, whilst EQVAS increases. The testing non-responders did not have a planned 3 month study visit, and there was some loss to follow up at 6 months, hence N highlighted for each column +/- SD. There is a moderate improvement in mean total PAC-SYM and mean Wexner score over the total population, a slight improvement in EQ-VAS and a slight deterioration in mean total PAC-QOL.

**Table 34 Secondary outcomes for the total study population**

| WEEKS | 0 | 2 | 4 | 6 | 12 | 24 |
|---|---|---|---|---|---|---|
| **PAC SYM** | 45<br>2.19±0.86 | 43<br>1.52±0.81 | 39<br>1.73±0.84 | 38<br>1.24±0.84 | 25<br>0.95±0.74 | 35<br>1.37±0.84 |
| **PAC QOL** | | | | | | |
| **ALL** | 45<br>1.28±0.64 | | | | 26<br>1.28±0.69 | 37<br>1.69±0.83 |
| **Physical** | 45<br>2.70±0.82 | | | | 23<br>1.08±0.80 | 35<br>2.00±1.19 |
| **Psychosocial** | 44<br>2.24±0.96 | | | | 20<br>0.98±1.04 | 35<br>1.44±1.15 |
| **Worries** | 44<br>2.66±0.82 | | | | 23<br>1.15±0.96 | 37<br>1.88±1.09 |
| **Satisfaction** | 44<br>1.17±0.47 | | | | 26<br>2.20±0.84 | 36<br>1.45±0.81 |
| **EQVAS** | 45<br>50.93±18.40 | | | | 26<br>71.85±21.27 | 37<br>55.68±29.19 |
| **Cleveland and Wexner** | 45<br>2.47±0.54 | | | | | 36<br>1.92±0.77 |

**PAC-SYM= Participant Assessment of Constipation-Symptoms**
**PAC-QOL= Participant Assessment of Constipation-Quality of Life**
**N= number**
**Mean ± SD (standard deviation)**

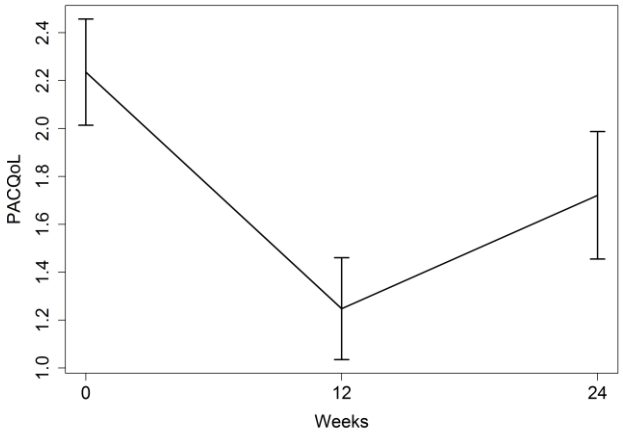
The secondary outcomes for the ePNE testing responder population (all IPG participants) are demonstrated in Table 35. This demonstrates the changes from baseline at 2, 4, 6, 12 and 24 weeks. There appears to be on average a mild improvement across all domains with mean PAC-QOL improving at 12 weeks then deteriorating again at 24 weeks (Fig 18), although this change is not statistically significant compared to the ePNE testing non-responders at 6 months (N=7).

**Table 35 Changes in Secondary outcomes from baseline in ePNE testing responder population (IPG) N=26**

**Mean change**
**(95% CI)**

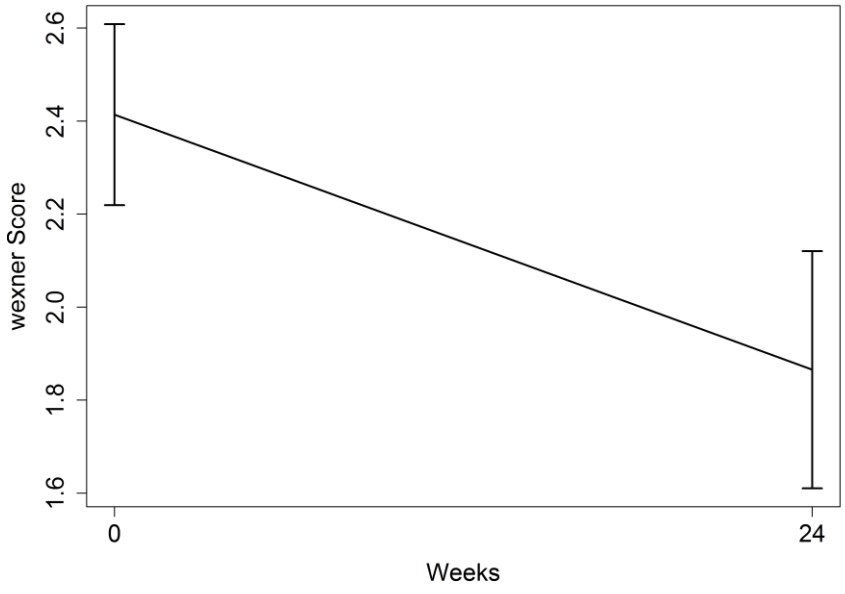
| **Weeks** | 2 | 4 | 6 | 12 | 24 |
|---|---|---|---|---|---|
| **PAC SYM** | -0.57 (-0.86,-0.27) | -0.45 (-0.75, -0.15) | -0.85 (-1.15, -0.54) | -1.03 (-1.39, -0.07) | -0.69 (-1.00, -0.37) |
| **PAC QOL** | | | | | |
| **ALL** | | | | -0.84 (-1.19, -0.48) | -0.50 (-0.82, -0.17) |
| **Physical** | | | | -1.56 (-2.13, -0.98) | -0.62 (-1.14, -0.10) |
| **Psychosocial** | | | | -1.10 (-1.64, -0.56) | -0.68 (-1.18, -0.19) |
| **Worries** | | | | -1.22 (-1.70, -0.75) | -0.66 (-1.10, -0.22) |
| **Satisfaction** | | | | -0.98 (0.61, 1.35) | 0.27 (-0.09, 0.62) |
| **EQ-5D** | | | | 0.21(0.03, 0.38) | 0.10(-0.05, 0.25) |
| **EQ-5D-VAS** | | | | 15.5 (3.13, 27.87) | 3.77 (-8.34, 15.88) |
| **Cleveland and Wexner** | | | | | -0.54 (-0.76, -0.32) |

**Figure 18 PAC-QOL mean total scores baseline- 6 months, responder population**



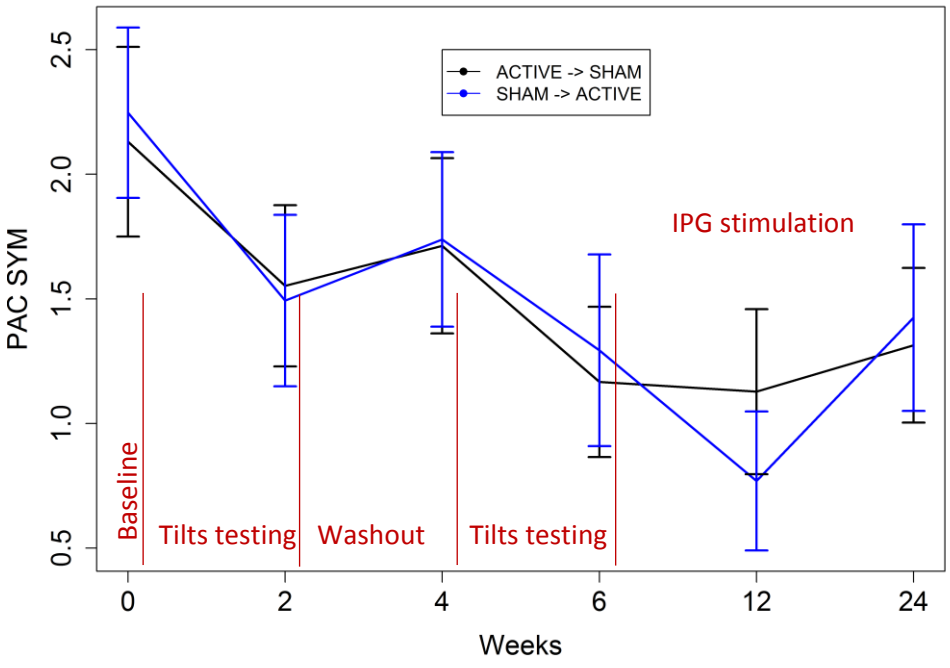

There appeared to be a mild improvement in constipation symptom scores using the Cleveland and Wexner scoring system, from baseline to 6 months in the responder (IPG) population, again this was not statistically significant compared to the ePNE testing non-responders (N=7) at 6 months.

**Figure 19 Wexner score baseline to 6 months, responder (IPG) population**



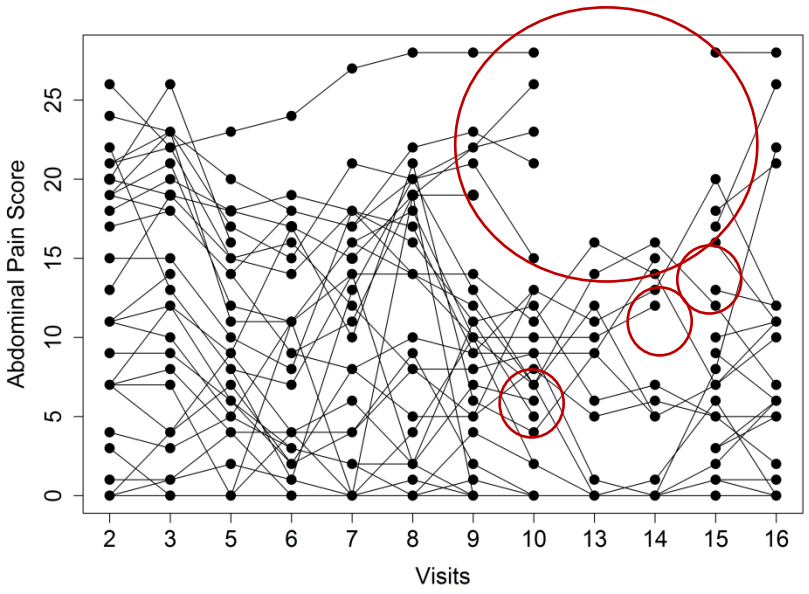
The mean total PAC-SYM scores (with 95% CI) in the responder population were plotted from baseline to 6 months by randomisation order (Figure 20). The most crucial aspect of the study design for the primary endpoint was the randomised sub-sensory blinding of participants. These data imply that participants improved and deteriorated synchronously with no significant difference detected between the groups during testing and washout thereby suggesting the participants were successfully blinded throughout testing.

**Figure 20 Mean PAC-SYM by randomisation order in responder population**



The daily diaries were the only data sheets completed by participants at home and not at study visits. On analysis the source diaries were missing from clinical records for many participants in the responder population at various weeks, and sometimes with omitted data fields within the weeks. Consequently, a full analysis of these would not be meaningful and so it was not performed. Figure 21 demonstrates the omitted data using the abdominal pain score as an example.

**Figure 21 Daily diary abdominal pain score, baseline to 6 months, responder population, illustrating missing data.**




## 6.5. Adverse events

Across the whole of the study population there were 103 adverse events in 40 participants (89%) of which 56 (89%) were directly related to the study intervention (Table 36).

**Table 36 Adverse events classified by severity**

| Category | Number of events | Number of participants (%) |
|---|---|---|
| Adverse events (All) | 103 | 40 (89%)[1] |
| Related to study intervention | 56 | 40 (89%)[1] |
| Severe and related | 11 | 11 (24%)[1] |
| Infections (related) | 10 | 10 (22%)[1] |
| Severe infections leading to tined lead removal during testing phase | 6 | 6 (13%)[1] |
| Severe infections leading to IPG removal during follow-up | 3 | 3 (11%)[2] |

[1]Of total study population (n=45),[2] Of IPG responder population (n=27)

Eleven adverse events were classified as severe and related to the study intervention (24%) of which 10 were directly due to lead infections (22%). One participant (who suffered from epilepsy) developed status epilepticus following general anaesthetic and required HDU monitoring with a Phenytoin infusion. One participant had a superficial lead infection at the exit site which responded to antimicrobial therapy, and 6 (13%) participants had deep seated tined lead infections necessitating urgent removal of the tined lead and withdrawal from the study during testing, one of whom was profoundly unwell with septicaemia and subsequently required inotropic support on the high dependency unit for a short time after lead removal. Three (11%) participants had delayed infections at various points during follow up necessitating removal of the IPG. The full adverse event profile with severity classification is demonstrated in Table 37 below.

**Table 37 Full adverse event profile with severity classification**

| Adverse Event | Mild N (%) | Mod N (%) | Sev N (%) | Adverse Event | Mild N (%) | Mod N (%) | Sev N (%) |
|---|---|---|---|---|---|---|---|
| ***Surgical*** | | | | | | | |
| Infection - superficial exit site | | 2 (4) | 2 (4) | Pain - superficial exit site | 4 (9) | 1 (2) | |
| Infection - Deep lead site | | 1 (2) | 3 (7) | Pain - IPG wound site | 3 (7) | 1 (2) | |
| Infection - Deep IPG site | | | 2 (4) | Pain at stoma site | | | 1 (2) |
| Infection - IPG wound site | | 1 (2) | | Pain – Buttock | 1 (2) | 1 (2) | |
| Erythema - Superficial exit site | | 1 (2) | | Pain - Deep IPG site | | 1 (2) | |
| Exudate - Superficial exit site | 1 (2) | | | Stoma obstruction | | | 1 (2) |
| Burn - left hand | | 1 (2) | | Oedema – Leg | | 1 (2) | |
| Haematoma - wound site | | 1 (2) | | Paralytic Ileus | | | 1 (2) |
| Wound dehiscence | | 1 (2) | | Transient Electric Shock | 1 (2) | | |
| ***Gastrointestinal*** | | | | | | | |
| Nausea | 4 (9) | 2 (4) | | Pain – Abdominal | 2 (4) | 1(2) | |
| Constipation | | 1 (2) | 1 (2) | Heartburn | | 2 (4) | |
| Diarrhoea | | 1 (2) | | Pain on Defaecation | | 1 (2) | |
| Haemorrhoids | | 1 (2) | | Pain – Anus | 1 (2) | | |
| Vomiting | 3 (7) | | | Muscle spasm -Pelvic floor | 1 (2) | | |
| ***Cardiovascular*** | | | | ***Respiratory*** | | | |
| Hypertension | | 1 (2) | | Dyspnoea | | 1 (2) | |
| ***Musculo-skeletal*** | | | | | | | |
| Pain – Leg | 4 (9) | 3 (7) | | Lumbar disc protrusion L5/S1 | 1 (2) | | |
| ***Reproductive*** | | | | | | | |
| Pregnancy | | | 2 (4) | Vaginal Candidiasis | | 2 (4) | |
| Menorrhagia | | 1 (2) | | | | | |
| ***Neurological*** | | | | | | | |
| Paraesthesia | 4 (9) | 2 (4) | | Status Epilepticus | | | 1 (2) |
| Headache | 1 (2) | 1 (2) | | Fatigue | 2 (4) | 1 (2) | |
| Positional Vertigo | | 1 (2) | | Insomnia | | 1 (2) | |
| ***Genito-Urinary*** | | | | | | | |
| Urinary Tract Infection | | 3 (7) | | Urinary frequency | | 1 (2) | |
| Nocturia | | 1 (2) | | | | | |
| ***Miscellaneous*** | | | | ***Dermatological*** | | | |
| Allergic reaction | | 2 (4) | 1 (2) | Pressure sore | | 1 (2) | |
| Hypothyroidism | | 1 (2) | | Skin infection | | 1 (2) | |
| Influenza | | 1 (2) | | Generalised rash | 1 (2) | 1 (2) | |
| Ear infection | | 1 (2) | | General pruritus | | 1 (2) | |
| Ventilation Induced Atelectasis | | | 1 (2) | Pruritus - superficial exit site | 1 (2) | 1 (2) | |
| Oral candidiasis | | 1 (2) | | | | | |

Mod=Moderate, Sev=Severe

## 6.6. Incidental Findings

During the pilot phase I noticed considerable variation in sensations at certain SNS voltage settings being reported by participants undergoing tined lead testing. After discussion with my supervisors, we realised the dials may require frequent calibration, and so I investigated the accuracy of the analogue testing device. I consulted with a medical physicist who then trained me to use an oscilloscope to accurately measure the output waveform of the testing devices. The original analogue model 3625 was thus put through the calibration test laboratory experiment described in 5.7.1, and once the latest digital testing device (Verify model 3531) was available I also checked this with a similar experiment to compare the accuracy of its digital output waveform (5.7.2). Three study participants used solely a cross-calibrated model 3625 device during testing, and this was cross-calibrated at the start of each testing period. As the Verify device was proven to be 4 orders of magnitude more precise it was the sole testing device used in the study from acquisition (at participant 05). Two participants used the analogue device during weeks 1-2 of testing and Verify during weeks 4-6 of testing. All other participants (n=40) thus used Verify alone.

### 6.6.1. Calibration test for SNS testing model 3625 (brown box)

In January 2013 I performed a prospective calibration test of the model 3625 devices by connecting 19 test stimulators to a cross-calibrated oscilloscope (Tektronix model 2230) and a counter-timer (Black Star Apollo 100). These rudimentary analogue testing devices could simply be turned on, dialled to the clinical settings and connected by a circuit to the oscilloscope without the need for a simulated tissue load. The output Frequency (f), Pulse Width (pw) and Voltage (V) of the waveforms generated were measured in 3 runs. The same fully charged 9V Duracell (Pro-cell) square battery was used in each of the devices sequentially. These batteries can typically last for years. In run 1, I attempted to set the dials to

the correct clinical settings for testing sacral nerve stimulation as clinicians do in practice with this device namely a pulse width of 210µSec, and a frequency of14Hz. I noted that there was no dial increment on the dials of this device to indicate these settings. In run 2 I set the dials to the closest dialled increment to the clinical settings which was a pulse width of 200µSec, and a frequency of 10Hz. In run 3, I measured the output Voltage (V) of the waveform at indicated dial increments of 0V, 1V, 2V, 5V, and 10V. A very generous margin of error of 20% difference of expected waveform pulse width and frequency to observed waveform output and a tolerance of +/- 0.5V was considered a pass for each device, and beyond this was considered a test failure.

**Figure 22** Total of 19, left new (8) and right used (11) model 3625 SNS testing stimulators

The first finding was that that an output waveform exists when the device is set to zero volts, and this was confirmed in all 19 devices as Figure 23 demonstrates.

**Figure 23** The oscilloscope demonstrates a waveform when the stimulator amplitude dials are set to zero volts

In run 1 there were marked ranges of frequency values from 10.6 to 29.0Hz (26% failed), and run 2 7.9 to 13.0Hz (11% failed). There were similar findings in run 1with the pulse width observed as variable from 242 to 326µSec (89% failed), and run 2 215 to 274µSec (63% failed) Table 9. In run 3 all devices had a residual positive output voltage at zero (range:0.29 to 1.00V), and the failure rates at dialled settings of 0,1,2,5 and 10V were 53%, 100%, 100%, 68% and 47% respectively (Table 38).

**Table 38 Results of Oscilloscope and counter timer measurements of model 3625**

| Box | Run 1 | | Run 2 | |
|---|---|---|---|---|
| | **Frequency Hz** | **Pulse width µSec** | **Frequency Hz** | **Pulse width µSec** |
| **1** | 12.2 | 259 | 8.7 | 215 |
| **2** | 12.9 | 292 | 10.2 | 241 |
| **3** | 11.2 | 278 | 8.8 | 222 |
| **4** | 12 | 281 | 8.8 | 244 |
| **5** | 12.1 | 259 | 9.3 | 257 |
| **6** | 10.8 | 242 | 8.9 | 221 |
| **7** | 12.3 | 255 | 10.1 | 228 |
| **8** | 18.6 | 283 | 9.6 | 248 |
| **9** | 14.3 | 283 | 10.9 | 247 |
| **10** | 11.7 | 278 | 9 | 243 |
| **11** | 13 | 283 | 9.3 | 237 |
| **12** | 113 | 290 | 9.1 | 251 |
| **13** | 12.5 | 311 | 9.1 | 274 |
| **14** | 29 | 307 | 13 | 261 |
| **15** | 14.4 | 326 | 10.9 | 265 |
| **16** | 13.3 | 296 | 102 | 259 |
| **17** | 13.6 | 272 | 9.9 | 229 |
| **18** | 17.4 | 247 | 11.4 | 215 |
| **19** | 10.6 | 281 | 7.9 | 246 |
| **FC** | 5 (26%) | 17 (89%) | 2 (11%) | 12 (63%) |

**Run 1 expected waveform= 14 Hertz, 210 µSec, Run 2 = 10 Hertz, 200 µSec**
**Failure Count (FC) of calibration test, tolerance of 20%**

**Table 39 Results of model 3625 tolerance test for waveform voltages**

| **Dialled Voltage (V)** | 0 | 1 | 2 | 5 | 10 |
|---|---|---|---|---|---|
| **Observed range** | 0.29-1.0 | 1.6-2.56 | 2.56-3.68 | 5.12-6.36 | 10.08-10.72 |
| **Failure Count n (%)** | 10 (53%) | 19 (100%) | 19 (100%) | 13 (68%) | 9 (47%) |

**Run 3 test stimulator set to dialled increments of 0,1, 2, 5, 10 V**
**Failure count= outside tolerance of +/-** 0.5V

These results demonstrate the abject failure of the model 3625 testing stimulator to stay within very generous tolerances for the measured output waveform. The results show a wide range of variability, with 47-100% of boxes failing Voltage tolerance, 11-26% failing frequency tolerance and 63-89% failing pulse width tolerance levels. An abstract was published within a month of these findings (BIG conference, Belfast March 2013) in order to highlight this issue to clinicians performing SNS testing (183) and research with this model, the results of which could arguably now be considered unreliable. These surprise findings mandated a revision of the Tilts-cc study protocol which emphasised the need to calibrate all of these devices using the counter timer and oscilloscope (which itself was cross-calibrated against another) in order to guarantee that all study participants received identical SNS waveforms during the testing period of the trial. The devices were calibrated by manually rescaling the dials according to the observed output waveforms and clinical settings were marked accordingly (Figure 25)

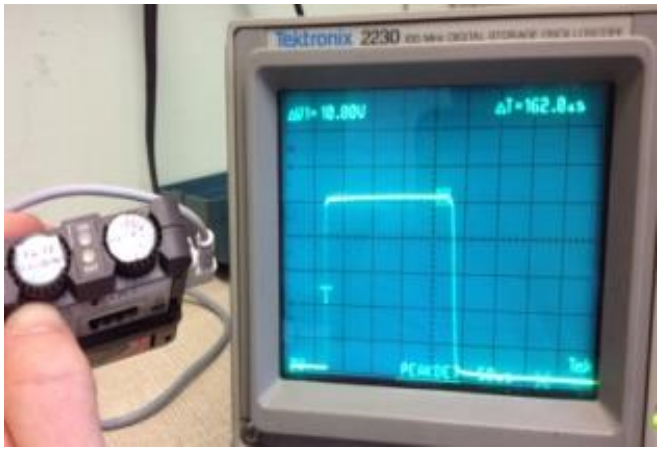



**Figure 24** Re-calibrating the external voltage amplitude dial A


**Figure 25** A model 3625 test stimulator with fully re-calibrated frequency, pulse width and voltage amplitude dials.

### 6.6.2. Calibration test for SNS testing model 3531 (Verify)

Medtronic released the new temporary SNS testing stimulator model 3531, aptly named “Verify”, within 3 months of the calibration test abstract being published. This device is a digital testing device with no analogue components (dials) and entirely controlled by a circuit board and Bluetooth controller unit. The device is power by 2 AAAA batteries and needs to detect a resistance within the testing circuit equivalent to that of human tissue in order to emit an output waveform. I sought to “verify” that the output waveform was indeed as accurate as specified. The calibration test was redesigned for the new device by simulating a tissue load equivalent to human tissue through a parallel circuit 993 Ohm resistor being placed between the stimulator and the cross-calibrated oscilloscope (Tektronix model 2230) and counter-timer (Black Star Apollo 100).

**Figure 26** Verify ENS, controller and circuit with simulated tissue load to oscilloscope

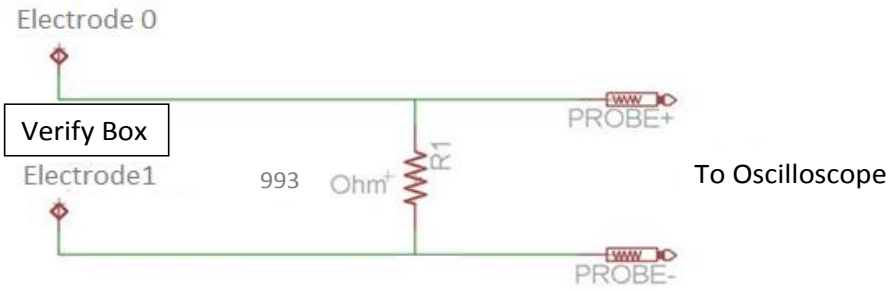



**Figure 27** Circuit diagram to measure Verify output

A prospective output waveform assessment of 15 used Verify SNS test stimulators was conducted. Devices were successively loaded with the same fully charged AAAA batteries and connected to a constant simulated tissue load (993 Ω) circuit with two output electrodes attached to the oscilloscope (Figures 26 & 27). The output waveform amplitude and pulse width were measured at clinically used settings and compared with the expected output values (amplitude by V=IR). Devices passed the calibration test if within tolerances of 10% and 20%.

The new testing stimulators immediately appeared to produce an accurate waveform on the oscilloscope (Fig 28).

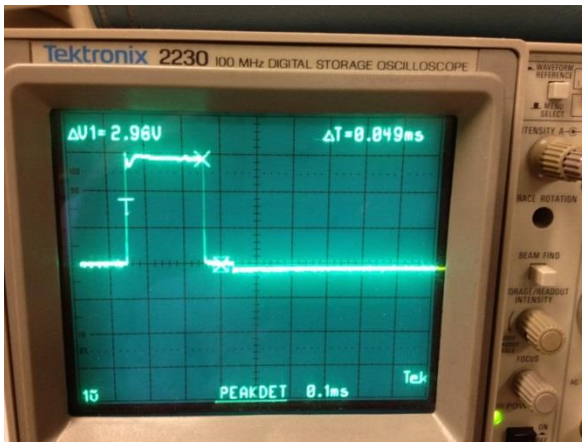



**Figure 28** Accurate square waveform produced by Verify

At clinical SNS settings (14 Hz/210 µSec) the measured amplitude and pulse width did not vary significantly from expected at a programmed current of 0.2, 0.5, 1.0, 2.0 and 3.0 mAmp, and 100% of devices passed the calibration test (Table 40). 6 devices failed at 0.1milliAmps due to more variation at low energy settings.

The variations in device frequency were too small to be measured with the counter-timer and therefore in the order of magnitude of x $10^{-4}$ Hertz. Similarly, the pulse width times were just as accurate at 100, 210 and 400 µSec with the standard deviations 0.48, 0.93 and 0.69 µSec respectively.

**Table 40 Verify calibration test findings.**

| Current programmed (mAmp) | 0.1 | 0.2 | 0.5 | 1.0 | 2.0 | 3.0 |
|---|---|---|---|---|---|---|
| Expected output (V) | 0.099 | 0.199 | 0.497 | 0.993 | 1.986 | 2.979 |
| Mean (V) | 0.107 | 0.205 | 0.492 | 0.96 | 1.911 | 2.87 |
| SD (V) | 0.004 | 0.007 | 0.016 | 0.023 | 0.044 | 0.063 |
| Mean Pulse width (µSec) | 210.5 | 211.43 | 211.567 | 211.267 | 210.133 | 210.933 |
| SD (µSec) | 2.652 | 0.727 | 0.68 | 0.772 | 2.533 | 0.929 |
| **N Passed (% of total)** | 9 (60%) | 15 (100%) | 15 (100%) | 15 (100%) | 15 (100%) | 15 (100%) |

At all clinically relevant settings 100% of the devices passed the calibration test. The failures at 0.1mAmps were irrelevant as these settings are below therapeutic

thresholds. Given these results, the lack of manufacturer support for the 3625 model, and its reported variability, I concluded that only the Verify testing device was fit for purpose in clinical practice and research. I presented these data at the BSG conference in London in 2015 and published an abstract to highlight these findings (184) and the Tilts-cc protocol was amended, and ethically approved to only allow testing with the new Verify device. This device had another advantage that it was easier to conceal the settings to ensure blinding concealment as the digital controller was not issued to participants.

### 6.6.3. Analysis of lead fractures

During the study a participant reported that there was no sensory perception during the sensory habituated test performed immediately before I set the sub-sensory stimulation, and the un-blinded researcher then randomised and concealed the actual stimulation (by simply continuing stimulation or turning it off). This occurred at week 5 of testing, therefore 1 week into the second testing period. All participants had used the same testing twist lock extension cable for the 6 weeks of the test. The participant was provided with a new twist lock extension cable and the sensory perception immediately returned on habituation testing. The returned lead was examined and although the external twist lock cable (28cm) appeared normal, an X-ray (Figure 29) revealed that the number 2 and 3 conductor wires were fractured in the distal end of the cable. Electrical testing did not reveal any short circuits. The manufacturers confirmed that these were due to repeated stressing by flexing of the cables which were designed for 2 weeks of continuous use only. The protocol was amended to ensure that all trial participants had full sensory perception confirmed during habituation and a new twist lock cable was issued at the start of each new 2 week testing period.

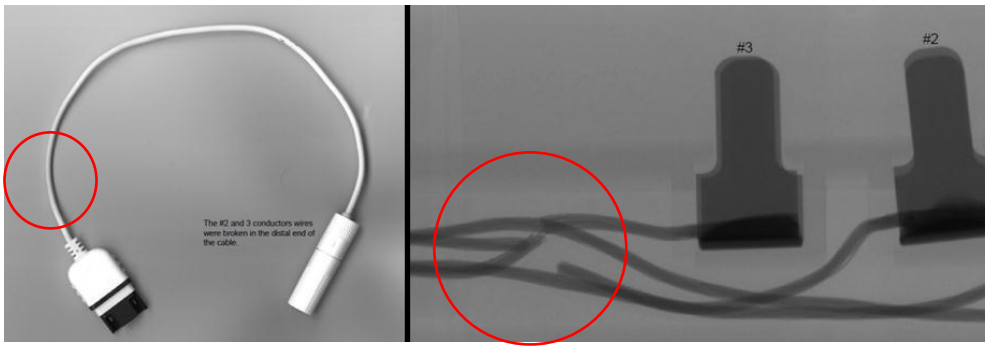



**Figure 29** X-ray confirming extension lead fractures through flexing

## 6.7. Discussion

### 6.7.1. Key study findings

The study was terminated early by the DMC and CI before full recruitment was obtained (45/75) due to the persistently high rate of infection of participants during ePNE testing (22%). 29 participants responded to ePNE (7 discriminate and 22 indiscriminate), and 27 were implanted with an IPG (2 withdrew). There was no significant difference in long-term response (at 6 months) to SNS treatment between the sub-sensory test discriminate (60%) and indiscriminate (57%) responders P=0.76. There was no significant difference in secondary outcome measures through testing or long term follow up between discriminant and in-discriminant responders. The original study design included a secondary objective to assess the cost effectiveness of TiLTS-cc testing to the NHS in order to inform policy decision making. The under-recruitment of participants due to early cessation of the study prevented this analysis, but it is clear that this form of SNS testing for CC cannot be cost-effective; no evidence of an effect on the disease has been demonstrated and the trial was halted early with clear evidence of safety concerns.

The design of the ePNE testing phase (randomised sub-sensory active or sham SNS with devices security sealed) protected the blinding of participants as confirmed by the synchronous responses between active and sham testing groups. The SNS testing devices were subject to scrutiny of their output stimulation waveform, with a small pre-trial lab experiment confirming unacceptably high variability in the 3625 analogue model, and a far more expected and measured precision to stimulation waveform parameters in the 3531 model. This model was also far more difficult to tamper with as its digital controller was only used by the un-blinded researcher to adjust settings, and was not issued to participants.

### 6.7.2. How study findings relate to existing knowledge gaps

Early studies of SNS for constipation were very positive and seemed to imply that response rates may improve to the levels seen in other conditions (up to 80% response) such as faecal incontinence and non-obstructive urinary dysfunction. More recently SNS studies in two randomised controlled trials testing efficacy for constipation have not reported any evidence of a difference between sham and active SNS (121-123). In the Dinning et al study, only 16/59 participants (28%) responded to a 3 week supra-sensory PNE (non-randomised). All participants were implanted however, and in a double-blinded randomised crossover study of the IPG, the proportions of participants responding to treatment and meeting the primary outcome measure demonstrated no evidence of a difference; supra-sensory (30%) vs sham (21%) and sub-sensory (25%) vs sham (25%). In the Zerbib et al study 20 of 36 (56%) participants responded to a 3 week supra-sensory PNE, and only responders were implanted. These participants received an IPG and were randomised to periods of active and sham sub-sensory SNS over an 8 week period, and then had active SNS until 1 year of follow up. Twelve of 20 (60%) responded to sub-sensory SNS during the randomisation period compared to 11 of 20 (55%) responding to sham SNS (P=0.75). These studies have slightly different

methodology, but have remarkably similar results; Both seem to demonstrate a strong and persistent placebo effect during blinded, randomised, sub-sensory SNS testing (albeit with IPG), with no ability to predict a long lasting effect to active supra-sensory stimulation. The Tilts-cc study findings appear to fit well with these other high quality studies in failing to detect any evidence of a response signal in the testing or follow up data. The TiLTS-cc study was designed differently by primarily attempting to assess whether an extended tined lead test may predict longer term responders to SNS, and demonstrated that this test was unsafe for these extended durations and had no diagnostic accuracy for predicting long term response to SNS. In light of the inability of the TiLTS-cc VAS to discriminate long term response using a threshold of ≥25% during testing, the study team completed a post hoc analysis of the TiLTS-cc VAS by altering the diagnostic response threshold from ≥25% to ≥50% which could be considered a more realistic response level. Table 41 below demonstrates the results of this post-hoc analysis, and that there was still no improved accuracy at predicting long term response to treatment with an IPG, the sensitivity being 60% and specificity 46%.

**Table 41 Post-Hoc analysis of Tilts-cc VAS response threshold**

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

The PAC-SYM data were synchronous during testing between the sham and active stimulation groups (no significant differences statistically); this confirms the blinding as intact and I believe points towards a very strong placebo effect which seems to persist for months after an IPG device has been fitted. This reinforces the

findings from Zerbib, Dinning and Patton that SNS may be no more than a placebo effect as a treatment for constipation.

The main finding which should be highlighted throughout the literature are the safety concerns during ePNE tined lead testing. An infection rate of 22% is unacceptable for standard clinical practice, especially as this technique has been widely adopted in other surgical specialties such as urology without any robust prospective trials of safety. This rate was despite repeated attempts by the study team to minimise the risk of infection, and with the expert help of microbiologists and infectious diseases consultants who advised on antimicrobial prophylaxis regime changes around surgery, and with close observation (weekly) of participants' dressings and wounds. Clinicians and researchers should also be aware of the variable waveform of the old 3625 testing stimulator and consider the implications this has for prior research evidence in SNS and for clinical use. It may be true that the analogue device has delivered variable pulse stimulation to participants of the other clinical trials and that the results of these trials are therefore not reliable. Certainly a variable device should not be used in clinical practice and all clinicians should be using the new accurate digital device as a way of delivering a consistent and reliable testing therapy. Clinicians and researchers should also consider testing and / or replacing the twist lock cables frequently at study visits as these can be fractured leading to ineffective therapy. Of concern, 2 participants became pregnant during our study despite the participant information sheet and consent process, one of whom delivered a baby with a congenital heart malformation (atrial and ventricular septal defects). There is a possibility that the proximity of the SNS field may have affected embryogenesis, postulating that it may affect the spin of Hydrogen atoms within water molecules causing alignment to the electrical field as is demonstrated in MRI signals. This may or may not affect embryogenesis. It could be argued that the informed consent process was not

robust enough, as this lady felt that she became pregnant due to her symptoms resolving during the trial, and this potentially emphasises that the informed consent process should be continually revalidated during the follow up period of these interventional studies.

### 6.8. Summary of chapter

In this chapter I have presented the findings of the Tilts-cc study through the intended analysis plan as was prospectively agreed within the study team. I have demonstrated the primary and secondary outcome measures, and safety data with subsequent analysis and interpretation. My main conclusions are that these data demonstrate that tined lead testing using an ePNE technique is potentially dangerous to participants due to an increased infection risk, and that there is no evidence that it is effective in predicting long term response to IPG SNS in participants with chronic constipation. This adds weight to the literature that observed effects of SNS in treating constipation may simply be placebo effects. Safety concerns of ePNE testing will be highlighted to clinicians and researchers alongside the key message that the data does not support the future use of SNS in routine clinical practice for chronic constipation.

# Chapter 7 Essence Results and Discussion

## 7. Introduction

This chapter describes findings from a series of semi-structured phenomenological one-to-one interviews with eight participants, seven of whom participated in the TiLTS-cc trial, one of whom also experienced usual care, and one of whom experienced both a pilot version of the TiLTS-cc trial and usual SNS care. The aim of this qualitative work was to explore the lived experience of CC and of participation in a blinded trial in order to inform future trial design. Although the study is described as mixed-methods, the qualitative study was scheduled following completion of the testing period and 6 month endpoint of follow up in order to avoid contaminating the results of testing (see Methods Chapter 5).

## 7.1 Recruitment

A total of 36 Invitations were made to all 13 (female only) eligible participants of the TiLTS-cc study (who had either completed the study per protocol or withdrawn), and 23 (22 female, 1 male) participants of the Durham constipation clinic who had been historically treated with standard SNS and had previously indicated that they were amenable to research invitations. Of these invites 8 people (all female) requested further information in the form of the specific PIS, and all consented for study enrolment. The recruitment rate was thus 22% in total, and for TiLTS-cc study participants and standard SNS participants, 54% and 4% respectively.

## 7.2 Participants and Interviews

The first participant (EE01) was interviewed in June 2014 and data saturation was identified by both myself and the senior supervising research team member (HC) after re-analysis of all interviews in December 2014. All participants were female (only one male was eligible and did not wish to enrol), with an average age of 38 years (range of 25-57) and participants had a mean duration of symptoms of 13 years (range 5->30, Table 41). 6 participants were employed at the time of

interview, one was unemployed and another retired. 7 participants were living with a partner of which 5 were married, and only 3 participants had children: 07EE was retired with adult children and also had grandchildren, and 2 had young children (03EE and 04EE). Only one participant was single and living alone (08EE). All participants attended interviews as invited and no interviews were terminated early. Interview durations ranged from 21 minutes to 76 minutes, with an average of 46 minutes and a total time across all interviews of 364 minutes. Transcripts were over 50,000 words and 114 pages in total with an average of 6,300 words over 14 pages per participant interview.

Table 42- Essence study participant demographics

| Participant Study number | Sex | Age (years) | Duration of Symptoms (years) | Family life | Employment status |
|---|---|---|---|---|---|
| 01EE | F | 37 | 5 | Married no children | Employed |
| 02EE | F | 30 | >10 | Partner no children | Employed |
| 03EE | F | 41 | 8-10 | Married young children | Employed |
| 04EE | F | 38 | >20 | Married young children | Employed |
| 05EE | F | 47 | 7 | Married no children | Employed |
| 06EE | F | 27 | 5 | Lives with partner no children | Unemployed |
| 07EE | F | 57 | >30 | Married adult children | Retired |
| 08EE | F | 25 | 17 | Single no children | Employed |

One of the eight participants returned immediately after the interview for a further debriefing and was counselled by both the researcher (as a clinician) and a specialist nurse. This participant was interviewed for 76 minutes, and returned to the clinic a short time after crying and feeling tremendously upset. An opportunity to talk

further and debrief with the researcher and a specialist nurse was taken during which she stated that she had relived her experiences of suffering from the condition and most importantly the effect it had had both on her and her family. She had finally realised just how much she had suffered and felt that she had put a lot onto her family over the years. This event could be construed as an adverse event within the Essence study as the interview had clearly precipitated this recall of traumatic life events. It could also be construed as a talking therapy, (like cognitive behavioural therapy) as she ultimately felt the benefit of discussing these events and then debriefing, as the Essence protocol was designed to facilitate. She had been withdrawn from the Tilts study due to life-threatening sepsis and returned to usual care during which she had routine SNS as a second attempt, from which she thankfully perceived a long term and lasting benefit.

### 7.3 Emergent Themes

Overall, three main themes emerged concerning the lived experience of participants;

- **Self-managing** the physical, social, and emotional effects of a life-dominating, progressive and prolonged disease;
- An experience of **angst** characterised by anger at the failure of healthcare to provide a cure;
- A proactive approach to taking personal **control** by seeking a cure, and participating in a clinical trial.

The main overarching theme linking these is of <u>participants' regaining and maintaining **control** of their body and lives.</u> The coding and thematic analysis is visually demonstrated in Appendices 17-20. Findings describe the shared experience among participants of a life-dominating condition and a transition from seeking standard medical therapies, through desperation, to a process of self-management when standard therapies failed. A shared distrust of medical

professionals reflects the participants' sense of personal failure, of being let down by medicine, and every participant sought to try and take back control through any means possible. This may partly explain their motivation to participate in trials of new interventional medical products and their subsequent high recruitment rate, and high retention rate. Coding and thematic analysis is demonstrated through Appendices 17-20.

## 7.4 Self-managing a life-dominating, progressive and prolonged disease

### 7.4.1. Onset and progression of the disease

Several participants described symptom onset from childhood to early adulthood, some with a defined point of onset, which they each associated with a traumatic incident involving physical and/or psychological harm, even though medical attribution was not clear. These participants have been treated by multiple clinicians and form interesting and unique case studies – as such further detail would render them identifiable so relevant quotes specific to the incidents themselves are not included . What follows are general comments about disease onset.

*"Probably in childhood when it originally began, it was awful. Can't really remember but according to my Mam it was just awful as a Mam to a child. I went on all the normal Lactulose, all the stuff and got by. Got to teenage years and didn't tell a single soul about it cos that's what I did as a teenager. Hit pregnancy and it was just absolutely horrific."* Participant 4

*"It's a vicious circle, once you start it's like being on a wheel and the wheel goes round and round and round and how do you get off? You can't really because even now I still think, well I know I'm still on that wheel, for all the treatment that I've had has helped, it certainly doesn't cure."* Participant 5

*"No, I've always known it. I mean I've had bouts where it's been not too bad and I could live with it and then it just hit the stage where it went beyond I couldn't live with it. They did everything that they could. I felt like they gave me everything that they could, but it just wasn't working."* Participant 8

"*Em …. It's been a constant sort of …….(pause) I would say it's got so much worse since about, think it was 2009 and it just seems to keep slipping downhill all the time*." Participant 1

The condition was described as progressive by all interviewees. Participants reported fluctuating symptoms which would improve for short periods of time, but in all cases these would recur and gradually appear to deteriorate with time, and with increasing age.

*"I think I'm used to it now [medicating] cos it's 10 years on, so obviously I'm used to doing it for 10 years. It's getting more difficult now as I get older because I find I'm more tired"* Participant 2

*"Probably about 8-10 years of constipation……. But as the years progressed, initially it [Picolax]would take 3 hours to work, then the longer I was using it, it was taking longer – 7-8 hours to work . So in the end it was pretty much a full day out"* Participant 3

### 7.4.2. Physical impact of the disease

All participants reported experiencing a range of physical symptoms that were resistant to treatment, long-standing, and debilitating. Most of these symptoms were commonly experienced by every participant, whilst others were unique to an individual. The main shared symptom experience was of prolonged constipation over many years (from childhood in some), with constipation for months at a time, and which all participants believed was causation for their other shared symptoms.

The majority believed that their constipation sapped their energy for daily living, leaving them feeling ill and fatigued and constantly deteriorating over time.

*"Basically I think I was going to the toilet like every 12 to 14 weeks. I just couldn't go at all. I tried laxatives, I tried everything. Just nothing worked at all."* Participant 8

*"they're just wasted days, completely wasted days, and sometimes even the day after that I don't function properly because obviously I haven't got the energy, I'm tired and sometimes in a lot of pain as well, so it's … it's not fun"* Participant 1

*"Probably in childhood when it originally began, it was awful. Can't really remember but according to my Mam it was just awful as a Mam to a child. I couldn't eat, couldn't exercise, couldn't get out of bed some days, I couldn't live properly."* Participant 4

Another common factor shared by all participants was abdominal pain and bloating which was experienced daily, spasmodic in nature, and resistant to strong analgesia. The experience of pain and bloating and their effects on daily life formed a sense of a constant, ever-present backdrop to the lives of participants, informing (and limiting) their day-to-day decisions about social and physical activities, as well as being the driving force for a constant pursuit of curative treatments. The majority of participants had tried prescribed opiate analgesia and a range of anti-spasmodic treatments which had all failed to ameliorate pain (and conversely can aggravate constipation), as well as over-the-counter, and non-regulated treatments purchased via the internet. This left them with debilitating chronic pain and bloating.

*"I got used to it, but it was just so uncomfortable. Like the discomfort after 7-10 days and I knew I must have needed to go but my body and my brain didn't tell each other that I needed to go. So I was bloated, uncomfortable, headaches. Even though I went to work, I was just uncomfortable all the time."* Participant 3

*"And each time you try these laxatives, you're getting – well I personally was getting pains in my stomach, pains in my back. It makes normal everyday life not possible, and of course when they do work, they work with side effects, i.e. excruciating pain. I sometimes just had to go to bed with it cos it was that bad. Painkillers didn't touch it."* Participant 5

*"Horse riding's really difficult. I was getting a lot of bloating in my stomach and it's quite painful to do."* Participant 6

A commonly described experience linked with the experience of pain and bloating was one of constant fatigue and lethargy. This was perceived to affect the capacity to function and carry out one's responsibilities effectively.

*"constant fatigue ....I would be in bed for two or three days."* Participant 7

*"it makes you ache, dehydrate, but just very very tired. And you can write at least one day off then, if not two, dependent on how bad it is."* Participant 5

*"I couldn't do anything, basically ended up just living in the house, not going out cos I was just so tired all the time, so run down and bloated and…"* Participant 8

There were other commonly shared symptoms which were sporadic, fluctuating and not constant features but considered by most as indicators of worsening constipation. These included; loss of appetite, hair and skin changes, headaches, and nausea/vomiting.

"*I couldn't eat, couldn't exercise, couldn't get out of bed some days, I couldn't live properly."* Participant 4

*"there's the spots, there's the way it affects your skin, the way it affects your hair . There's nothing it doesn't impact on, absolutely nothing"* Participant 1

*"I think the maximum I like to go is 2 – 3 nights, because if I go longer than that I'm very, very sick. It seems to act quite violently, cos obviously there's a lot of food, and I'm quite sick, so it's worse."* Participant 2

Most participants also suffered from at least one additional symptom that they attributed to their condition. The type and severity of these symptoms varied across individuals. These included pallor, recurrent urinary infections, cognitive impairment, faeculent vomiting, loss of urge to defecate and requiring manual disempaction procedures.

*"I mean I was getting kidney infections as side effects of it, I was getting extreme sickness as a side effect…"* Participant 08

This participant believed that her recurrent urinary and kidney infections were directly related to her bowel frequency, and she visualised her symptoms in relation to a 'bowel obstruction' which she felt caused nausea and vomiting, even though a mechanical bowel obstruction had been ruled out. Participant 07 went as far as describing an experience when she was admitted to hospital as an emergency with a perception of a 'bowel obstruction' and faeculent vomiting, which was again ruled out following extensive investigations.

*"At one time when I was in they said that my bowel had fused together and I was actually throwing up the contents of my bowel. Because it couldn't go anywhere, it had to get out…."* Participant 07

The three most commonly shared symptoms of all participants, namely abdominal pain, bloating and fatigue had the greatest perceived impact on each individual's personal, psychological, social and professional life, described below.

### 7.4.3. Impact on working life

All participants reported that their disease affected their working life, with sick leave taken by all participants on a regular basis, ranging from an occasional sick day to months in duration, leading in some cases to a decision to resign, or being asked to leave employment. For these participants, not being in employment was perceived as easier to manage than working with their condition.

*"I was on the sick for quite some time as well"* Participant 06

"*many a time I would have at least a couple of days off a fortnight because I felt so bad, but other times I wouldn't feel quite as bad you know, so I'd go for a few months where it just didn't seem to bother me quite as much but in the end I had to leave work because of it. Because I was having that much time off and when you're the manager it's not really any good. You can't get the others for being off when you're doing the same. So I just left in the end. It was easier. Because as I say as I got older it got worse.*" Participant 07

Others felt that their unemployment was directly attributable to being unwell.

*"…it rules your life socially, completely socially as well as doing my job – I mean, it stopped me working. The pain and the fact that I couldn't go to the toilet and drink when I needed to because of the job I did..."* Participant 01

*"Yes, I couldn't work, I couldn't do exercise. Everything I did, I mean I had to quit my job…." Participant 08*

In the 18 months since completing the TiLTS-cc study this participant's symptoms had improved so much that she was managing to hold down a permanent job at the time of the interview which was a huge relief and personal gain for her.

Some participants reported employers who were more sympathetic about their medical problems, but these tended to be participants in a higher status, highly paid professions. Those who were more likely to report difficulties from employers tended to work in lower paid jobs outside of a formal profession.

*"My work and my boss are aware of it. They were aware of my accident but I qualified through the same xxx and trained through the same xxx, so they have always been very supportive but I don't get consideration really anyway, but I don't ask for it either."* Participant 02

*"…because I could get rushed into hospital. The truth's got to come tumbling out so I sort of got a real bollocking off them because I should have really been under Occupational Health. I should have had more powers to take time off so it sort of backfired…"* Participant 04

For most participants, medication routines seemed to be a daily struggle. The difficulties centred on juggling an onerous self-medication regime at night-time with a busy demanding professional life.

"*It's very difficult to manage it but obviously you can't take laxatives during the day if you've got to be at a particular meeting or … It has to be managed through the night, so it's a bit difficult to manage*." Participant 02

### 7.4.4. Social Impact

The social impact of the condition was perceived to be as severe and long lasting as the physical effects of the disease, with all participants reporting a sense of restriction of their freedoms, with most feeling a sense of isolation and abandonment at home. The symptoms restricted their ability to socialise on many levels with friends and family; exercise was painful or embarrassing, fashion choices were restricted by their pain and bloating with many feeling uncomfortable in feminine clothes, and the proximity and availability of a toilet in any social or travel situation was of paramount importance. These led to such a severe loss of confidence that when symptoms were severe most felt unable and unwilling to leave the house never mind attempting to travel abroad for holidays. Most felt that their activities of daily living were completely and totally organised around treatments, and some were prepared to overdose on laxative medications in order to participate in certain social situations or prevent admission to hospital when their symptoms were becoming severe. Repeated unplanned hospital admissions

would still occur for many and this in itself would have a significant impact on their ability to socialise and to plan for the future.

*"I was in and out of hospital about 6 times in less than 6 months probably…."* Participant 07

*"I've always known like being in and out of hospital, I remember being in xxxxx Hospital 3 weeks during like the summer holidays"* Participant 08

The experience of fluctuating abdominal bloating was challenging for most participants who required several different sizes of clothes to accommodate this. Participants often discussed how their condition forced their appearance as they were uncomfortable wearing feminine clothing. The issue of bloating and its effect on clothing was discussed by all participants and was extremely important to them both socially and professionally. The participants who had no children frequently commented that they felt that they looked pregnant when the bloating was severe.

*"I've got clothes in different sizes. Some days I look normal, some days I don't, to the point where I look like I'm pregnant – but what can you do about it. It's extremely frustrating."* Participant 05

*"On certain days you're that bloated depending on how long it's been since you've had any laxatives, that you don't feel comfortable wearing nice girly clothes, you have to wear big baggy clothes because you're that embarrassed about your belly because everybody thinks you're pregnant"* Participant 01

All participants spoke at length about how their life revolves around medication routines and sometimes more invasive procedures, which left them feeling their independence and freedom was restricted with some feeling isolated at home. There was a sense of organising daily life according to treatments.

*"…so I've always had to take medication for the last 10 years. It's debilitating insofar as I have to plan my life around it…"* Participant 2

*"I was getting extreme sickness as a side effect. I couldn't do anything, basically ended up just living in the house, not going out cos I was just so tired all the time, so run down and bloated and…"* Participant 8

For most this social isolation or limitation was longstanding as the condition had affected most participants for years, and some for their whole life.

*"So the constipation over the years, we're talking about 30 years –it just seems to have got worse…….and now I feel my whole life looks at 'when can I go to the toilet', you know, so there's things I haven't done when I was younger, you know, holidays…. It's not quite the same when you're on holiday, sitting on the toilet for an hour…… But you just kind of learn to live with it even though it's a pain. You do kind of learn to live with it, it just seems to have got worse…"* Participant 7

*"Since it began? Probably in childhood when it originally began, it was awful.....Got to teenage years and didn't tell a single soul about it cos that's what I did as a teenager…….Hit pregnancy and it was just absolutely horrific. ….Saw the GP after that……I couldn't eat, couldn't exercise, couldn't get out of bed some days, I couldn't live properly."* Participant 4

### 7.4.5. Family issues

The majority of participants felt they had very caring, supportive relationships with family and friends but some expressed a perception that their illness had led to the end of significant relationships with past partners, and all acknowledged the burden the disease posed to their loved ones who have had to support them in times of crisis.

"*Yeah, so it can cause quite a few arguments on a personal level, probably family and relations, but they do allow for this*" Participant 02

*"Drove my husband and my Mam to the ground with despair but I felt I just brushed them off"* Participant 04

*"My mother, when I first started with this, was very surprised – 'I don't know where you get this from' and to her it was absolutely horrendous…… that so on my mother's side there was no trace at all of bowel problems and she found it quite unacceptable"* Participant 05

*"That I was annoying them, maybe. Feeling a burden to people, but I would do it for them so…"* Participant 06

## 7.5 Angst about experiences of primary / secondary care

The disease was experienced with such a chronicity and debilitating effect on a person's quality of life, that across the cohort it seemed to be constantly deteriorating despite the best medical treatments they received, including novel experimental treatments. This led to an experience of chronic and extreme psychological angst. This sense of 'angst' was directed towards the perceived failure of healthcare to treat symptoms, and was expressed in terms of chronic anger, disappointment, low mood, and frustration. There was a sense of being willing to try anything in order to regain control over their bodily functions and symptoms. It was no surprise that all participants described negative healthcare experiences over their years of attending hospital for a refractory condition. The eligibility requirements for the TiLTS-cc study guaranteed a highly selected group of people who had consulted numerous physicians and failed multiple medical therapies, and as such may be expected to share negative perceptions about healthcare. Even though this was an anticipated finding, the strength of feeling and bitterness about perceived negative experiences was much higher than previously thought. In particular it was a shared experience of the group to have a lack of faith in their GP

for their initial management, investigation and referral for the condition. There was a sense that primary care providers failed to understand or acknowledge the severity of the condition and its impact on the participant's life.

"*The fact is going to the GP wasn't any help whatsoever. Em, I don't think that the GPs understand the problem, in all fairness. And that's no disrespect to the GPs because the general practitioner is not taught about things like this…… I just don't think they get it. And in my GP practice there's, crikey, several different GPs and I think at one point I've seen most of them and they do not understand the impact that it has on you."* Participant 01

*"He kind of just didn't really understand everything that was going on and how much it impacted, and seemed to fob me off with different tablets to try, and didn't really take an interest"* Participant 06

*"You know, he said we can't just send you to a specialist…"* Participant 7

Once participants attended secondary care the shared experience was also initially disappointing, and most felt they should have been referred to a tertiary centre earlier.

*"I think people accept what their GP and possibly their local hospital will say to them. And I'm not criticising every consultant but obviously I don't have faith in ******* or the ******. So yes, I think people don't push and I think there will be many people in the UK who have not been referred."* Participant 02

Specific negative comments had been made by specialists to individual participants, sometimes many years ago, which had clearly stuck in their minds and caused further healthcare angst. These comments were of a disbelieving nature, indicating that it was a psychological problem, or belittling their complaints.

*"it was 'typical of my age and I would grow out of it'. So I hadn't had a good experience."* Participant 02

*"So, those few words … I did put a complaint in about it but he just said he didn't mean it the way it came over. But he still shouldn't have said something like that."* Participant 07

GPs deferring responsibility to secondary care and vice versa was another common complaint and cause of healthcare angst. All participants felt that no single doctor had complete ownership of their management and there was a distinct sense of a belief about lack of continuity of care between primary and secondary care.

*"Oh, nothing to do with us, go back to the Professor. So, I'm really banging my head against a wall now if I do have any problems when I go to the GP….Because I think they're frightened to overstep anything that the Professor wants to do but again it's like – oh well you're under them, and he's the big guy for it, so…"* Participant 01

"*Cos I mean I ring them up now and it's like we can't deal with you, you've got to ring Durham. And it's like – you're my own GP, I should be able to go for help*." Participant 08

Frustration at normal investigation results and a sense of no-one believing in their symptoms were frequent. Most participants now understand that normal investigations do not exclude ailments, but felt a sense of disbelieving from their care providers on receipt of the initial results.

*"He actually told me it would be so much easier if I had bowel cancer. He would cut it out, throw it away and get on with life."* Participant 07

### 7.5.1. Psychological response to angst

Most participants expressed the view that they were overly irritable with loved ones and they admitted that despair and anger was a prominent feature of their

daily lives, and that this in turn could lead to despair affecting their relationships within the family. The perceived failure of healthcare to address their symptoms in turn led to stress, frustration and eventually to low mood or depression at the thought of no release from the chronic suffering that they perceived to be their lot in life. Personal and sexual relationships also suffered as a result of both disease symptoms and psychological angst.

*"Yeah, so it can cause quite a few arguments on a personal level, probably family and relations, but they do allow for this."* Participant 2

*"Honestly, I just can't understand how with medicines being so clever now, nobody can help me go to the toilet. It seems so bizarre. You can do nearly everything now, and then I can't go to the toilet. I get so frustrated*." Participant 3

*"it makes me very self-conscious. I mean, I hate getting undressed because I feel I look an absolute disgrace and a mess and for all he tries to convince me otherwise, in my mind I'm a mess……It affected me badly, very very badly. Frustrated my husband to death."* Participant 5

*"It used to make me really annoyed, cos it's like well what else can you give me?"* Participant 8

### 7.5.2. Effects on mood and self-perception

All participants expressed low mood, irritability, stress, frustration, and anxiety about their symptoms and treatments.

"*I'm quite low with everything that's going on at the minute and I just think that if I can help move things on, if we can get something sorted out for people with our condition, then that would be brilliant.* Participant 1

*"Probably just teary, as I am today. I suppose in social situations I'm conscious of….obviously I don't want to take the tablets if I'm out at night"* Participant 2

"*…..but it also affects all of your life. It stresses you, it gives you anxiety…."* Participant 5

The disease was universally presented as being life-dominating and affected all aspects of participant's physical, psychological, and emotional lives. Many participants felt self-conscious or embarrassed at their appearance due to their bloating, and this in turn led to further social anxiety on the occasions when they had the confidence to venture into social circles. This was apparent across the whole cohort with a consistent experience of feeling suddenly bloated and larger which resulted in an immediate loss of confidence.

*"Yes, I wasn't horrible in other people's eyes, I was horrible in mine, my eyes. I was, I used to call it the invisible wife cos xxxxx would go to places on his own cos* ***I'd be all up to go, then I'd put something on and it wouldn't fit*** *because I was that bloated or I'd break out in spots or … that was it, I wouldn't go. So we used to have a joke that he just used to have this invisible wife, had a wedding ring but no wife to go with him…."* Participant 4

*"If you want to go out, it's finding something that'll fit. It has greatly affected my confidence very much so because I always feel I look a mess.."* Participant 5

### 7.5.3. Personal beliefs about the disease

Some participants had strongly held (and medically unverified) views about the perceived 'toxifying' dangers of constipation (the old myth of auto-intoxication, see Chapter 1), leading to perceptions of prolonged harm to every system in the body.

*"No you can't fix it because it's got to be fixed internally and you can't move the toxins through your body, so we can't …then you're told, oh you've got acne because of all the toxins you're carrying around in your bowel"* Participant1

## 7.6 Taking control

Overall, participants were very committed to taking control of their own symptom management in a variety of ways, some of which were mediated via their relationships with clinicians and some of which were self-directed and in some cases experimental and potentially dangerous. All participants had followed treatment pathways which were unsuccessful and as a result, left them to try to maintain a sense of control over the symptoms in ways including strict dietary regimes involving low residue diets, individualised laxative regimes, and alternative therapies including herbal remedies, Chinese medicine, and coffee enemas. Trying these remedies represented the pursuit of hope that a curative treatment could be found for their symptoms.

*"Just think it's my body just not wanting to play any-more. I don't know. I'm trying every supplement that I possibly can to make things better, even taking something called Triphala which is ….it's the worst thing you've ever tried –ha ha it tastes grim but ..."* Participant 1

*"I just bought every combination of everything over the counter and tried to do it my way. I spent 8, 9 weeks on the cabbage soup diet. I have done everything I could do to the ridiculous to the sublime …. Literally everything I could do, I've done. … But it wasn't until I got pregnant and realised I had another life to look after, that I couldn't just randomly buy stuff off the internet."* Participant 4

This represented a shift in the locus of control in relation to finding a successful treatment away from clinicians, who had failed to do so, to the participants themselves who via a process of trial and error, took it upon themselves to pursue a miracle cure. One participant recognised the limited effectiveness of these treatments and their effect of limiting their loves and social activities even further, but elected to continue taking them regardless again underlining the need to control one's self-management.

*"**Because there will be that miracle**"* Participant 1

## 7.7 Taking personal control by participating in a stable and routine clinical trial of a surgical procedure

As previously described, participants were highly motivated individuals attending a tertiary referral centre which specialised in treating participants with refractory bowel disorders and frequently invited these participants to consider novel treatments for their condition within clinical trials. Consequently, participants were experienced trial participants who had experienced treatment in other novel interventions prior to participating in the TiLTs-cc study.

"*Whilst I know that there isn't a cure, I'm never going to have a cure, I'm able to try what's available as it becomes available."* Participant 2

*"I had had a few studies, tried a few trial medications which didn't work for me"* Participant 3

*"Frustrated, annoyed , at the stage of where **I wanted my life back** because at the time that I had the operation I was only 24 and it was just like …"* Participant 8

### 7.7.1. Motivations for trial participation

The main motivating factor for participants was the opportunity of trying a new treatment for their condition, and a belief or wish that this may actually be the cure they have been seeking.

*"…so I wanted the pacemaker putting in to see if it would do marvellous miracle things!"* Participant 1

*"I thought about it quite in depth and discussed it with family members, and thought it was better to try it than regret not giving it a go. "* Participant 2

*"Picolax was taking longer and longer to work and if that stopped working there wasn't really anything left to try. So I thought I would just give that a try"* Participant 3

*"Just to see if it would help. To see if it would make my symptoms either disappear or help in trying to get me back to a normal life."* Participant 6

*"So I thought if I do something like this and it works, it would just take all that stress away and I would feel normal……. So I thought nothing ventured nothing gained."* Participant 7

*"Well it was the next thing for me to try and I was getting to the point where I was getting so annoyed and frustrated. I was willing to try anything if it was going to help me."* Participant 8

One participant had viewed the trial participant information sheet, and was motivated primarily due to a perception that the treatment offered a very high chance of success.

*"You know you could say it's clutching at straws but having done the background research and having been given the information that I had, we considered it to be a very very acceptable success rate. If it didn't work it didn't work, but at least it was tried."* Participant 5

Secondary motivating factors were largely due to altruism [as research participants] as participants were aware the blinding test being applied during therapy may help identify other participants in future who would benefit from treatment.

*"Because I want to help other people. I would like to say that I'm quite low with everything that's going on at the minute and I just think that if I can help move things on, if we can get something sorted out for people with our condition then that would be brilliant."* Participant 1

*"You know if it helps them and helps others. You know even if it doesn't really help them, I mean it didn't really help me but there might be something in it for somebody else who's in my position that it would help."* Participant 7

Other secondary motivating factors emphasised the recurring theme of participants wanting to taking back control of their lives from their disease. Participant 4 emphasised this point on describing her inclusion into the trial:

*"I felt like everybody just said,* ***whoa this is it, this is it, and I went out feeling like on top of the world.*** *I really did."* Participant 4

### 7.8 Demands of trial participation

The burden of testing (and overall trial participation) impacted on participants social, personal and professional lives in a number of different ways. Testing involved invasive surgery, weekly hospital visits (sometimes from well outside of the region), weekly diaries, wound care requirements, against a background of being unable to drive for 6 weeks. Dressings were itchy and uncomfortable, had to be kept dry, and participants were not allowed to bathe for the duration of testing.

"*The worst thing about it was not being able to have a proper shower. I was pleased it wasn't the summer time, it was more winter so it was a bit easier I suppose, but that was one of the worst things, not being able to have a shower properly*." Participant 7

"*I just really sat on the side of the bath to be able to wash my hair, to bend my head forward to wash my hair cos that was one of the main parts I didn't really know how I was going to wash my hair*" Participant 6

All participants appeared to adapt to this burden very well, and were motivated by a desire for benefit, with only one participant reporting that the daily diaries were onerous, although they were still completed with very little missing data.

*"They were good, yes. I found them quite easy after doing a few"* Participant 6

*"Erm, yes I suppose it is onerous because if you've got to remember to do it"* Participant 2

An unexpected consequence of the burden of testing was becoming dependent on others, particularly close family members and partners, to help with transport and personal care. One busy professional participant reported organising the management requirements by relying on a secretary to transport the participant to appointments. Others without those professional resources were willing to rely on partners and family members. Most participants felt that this was acceptable within the time limits of the testing period.

*"I travel the country so I couldn't drive for that period of time, so running up to it we had to make sure that we didn't book me into any meetings where I needed to drive to, or drive to the train station. I did travel and I did do meetings ……..my secretary would have to drive me, and then we would get the train. So it took quite a lot of planning to do it."* Participant 2

*"That was hard cos obviously I'd been passed for some time and my fiancé doesn't drive. It was a stumbling block but, people kind of rallied round."* Participant 6

Participants were very willing to manage these burdens because of the sense of agency, control, and potential for benefit that trial participation afforded them.

For the majority (n=5) of ESSENCE participants, for the duration of testing (and the duration of the trial) there was a very marked perception that the TiLTs-cc treatment was beneficial in itself, independent of symptom change (and in the full knowledge of a sham period of treatment). This lead to a strong sense of regaining control in their lives, returning to work and in some instances new relationships and peer support opportunities with other trial participants. This perceived benefit meant that participants were willing to adapt to the day to day demands of testing. It is notable that this sense of control continued during up to 8 months of follow-up. One participant experienced similar perceptions of benefit during testing as those described above but this did not last for the duration of follow-up. A minority (n=2) did not experience any perceived benefit during testing, the TiLTs-cc treatment was perceived as yet another failure after a series of treatment failures, and the hope of a 'miracle' cure and control of their body [and life] had again slipped away. However, all participants valued the opportunity to participate and did not regret taking part, and again valued the sense of agency and control afforded to them during the testing period.

*"But strangely I still have been able to go to the toilet. So while it was working in that period that it was working, it's stimulated my bowel sufficiently that I now know I need to go."* Participant 3

***"****It was a relief to maybe be given the opportunity to have the stimulator fitted because at that time I didn't know whether I was going to get it or not. So it was purely and simply a trial. And it was something I was very keen to do because anything to help alleviate the problems that I had have is more than welcome and I believe I'm very lucky to have been given this opportunity"* Participant 5

One of the questions during interview focused on perceptions of the blinded sham/treatment testing process. Participants felt that this attempt to understand

the placebo effect had the potential to reduce the legitimacy of their physical symptoms. Two participants felt it suggested to them that their symptoms might be perceived as 'made up' or psychological.

*"I don't know, because it makes you think have you made it all up, but I couldn't make 10 years of constipation up. So I knew it must have been doing something …."* Participant 3

All participants felt that they were unable to differentiate between active and sham treatment, supporting the physiological legitimacy of blinding, but they often admitted trying to subvert the blinding by monitoring symptoms very closely. At the time of interview all participants were still blinded to their randomisation. They were unable to tamper with the device undetected, so blinding was protected, but participants often wished they could break blinding in order to understand whether their perceived benefit was a result of active treatment during testing.

*"I think it's just you're wanting to hope that it's working so you are, whether you consciously doing it …"* Participant 3

*"So that might have been the implant or it might not. So I didn't know whether it was switched on at that time or whether it wasn't. So that was hard to tell like the second period, so I don't know"* Participant 3

*"…you're waiting to see if during that first two weeks whether it was switched on or whether it was switched off and it was constantly on your mind…. So obviously however many years you've suffered from the condition you obviously want it to work, so you are trying to guess it."* Participant 2

All participants felt that this process of blinded testing was acceptable and understood the reason for this.

*Interviewer: "Do you think having a pretend test is actually ethical as part of a trial?*

*"If they think it's worked and then you tell them that actually you had an Aspirin instead of what they thought they were getting, or whatever. But you can convince yourself if you want to I think. So yeah, I think it's right"* Participant 3

*"I think some people would think it's not but if they don't have these kind of symptoms then they wouldn't understand the feeling of it, so you've got to go on your body's instincts and I think it was better that way."* Participant 6

Although participants were concerned that evidence of a placebo response might reduce the legitimacy of physical symptoms, they all acknowledged the possibility of a placebo response.

"..*because some people could say that oh great, it's worked, it's helped, but a lot of it could be in their minds as well. Wondering you know, if you're the one that's getting the placebo or not. But no, I can understand why they did it."* Participant 7

### 7.8.1. Testing stimulators

During the trial, some participants were required to move from using an unreliable analogue device, to a new more reliable, digital device (Page 181). Participants experienced problems in using the analogue device in that they kept shutting down, requiring more visits and re-randomisation, and they were six times the size of the digital device, with associated implications for managing hygiene and sleep. Additionally, the analogue device triggered supermarket alarm systems where-as the digital model did not. Despite these additional burdens, no-one in the Essence study cohort dropped out of the Tilts testing period, again demonstrating a commitment to the trial and individual pursuit of benefit.

*"then I had another old one* [model 3625] *but that was the constant worry that it was going to stop again. But once I got the new one on, that was absolutely*

*brilliant. It was much easier to cope with as well because it was smaller."* Participant 1

*"my sister did used to laugh because the barriers would go off if we'd gone to the Metro after here, and she'd go " it's your butt isn't it" and I'm like "no, no, no, no it's not my butt!"* Participant 8

### 7.8.2. Living with Permanent Sacral Nerve Stimulation (PSNS) with an implantable pulse generator (IPG)

The majority of ESSENCE participants (n=6) were given permanent SNS, of the remaining 2, one did not meet the criteria for implantation and had no further trial participation, and the other was a pilot study participant receiving usual care who had no testing response to treatment. One of the 6 participants who went on to have an implant was excluded from the trial during testing due to a severe adverse reaction. The decision was taken to withdraw this participant from the trial clinically, but the participant was deemed eligible for SNS implantation outside of the trial envelope and ethical approval was granted to include this participant in the interviews in order to fully explore the dimensions of the experience. What follows is a description of the experience of those having a permanent implant as part of the trial or as part of routine NHS care.

A number of participants felt that they experienced profound global symptom improvement, for example in bloating, pain and bowel function which seemed to extend over the period of long-term follow-up.

"*Then obviously I got into doing every trial. I grabbed everything I can and tried it and none of it worked. Same symptoms, maybe a bit of relief for a month here and there, but nothing until I had the SNS and then it was much life-changing….I feel like I'm living my life now."* Participant 4

However, for this participant, the perceived benefit was complex and difficult to disentangle from the apparently modest improvements (or stasis) in quality of life measures. Even when participants spoke about life changing effects, the measurable effects on pain and bowel function were modest. The positive psychological effects, combined with an experience of a large perceived reduction in bloating, seemed to be the driver in the perception of benefit for this participant.

"*I've still got fat club, still got fat clothes and normal clothes but some days aren't as bad. Some days are pretty horrific but now there's an end, every bad day there's an end of maybe 4 days maximum, 5 days. Before it could be weeks, so everything's just toned down"* Participant 4

She was further questioned on whether she felt she had regained control of her life after having the permanent device fitted.

Interviewer: "You've got control back? Is that a fair point?"

"*Yes, completely. I can go to the park in my fat clothes because now it's alright you know"* Participant 4

The youngest participant in the study was urging others to have the device fitted; her perception was of complete success, and yet her symptoms were still classified as severe and chronic under the Rome definitions of CC, but ultimately the marginal symptom improvement she experienced, whether placebo or effect, has given her a sense of taking back control.

*"I've been telling everyone about it and I've said* ***I've literally got my life back... Cos from my experience it's like changed my life.*** *I started to be able to go like swimming, walking, managed to get a job, managed to get out the house, managed to start seeing my friends again. I've been able to start going to the toilet, everything like that. I wouldn't hesitate to have it done again. I've been able to go back to*

*work, I've been able to start doing exercise again. If they're offered it I've said take it.*" Participant 8

For this participant, her symptoms had been experienced for her whole life since early childhood and the outcomes of importance were fatigue, bowel function, and bloating. Her bowel function had improved to opening her bowels just once per week which is still defined as severe constipation, but from her perspective the impact of the implant was profound, prolonged, and positively affected every aspect of her life.

Another participant who was a test responder and received the IPG implant expressed her surprise during the test when she seemed to regain sensation from her bowel

*"When you just don't move your bowel at all then all of a sudden* ***you can feel this sensation then it's like Wow!*** *You know, it's totally different."* Participant 5

She also noticed a profound prolonged benefit regarding pain, bloating, and frequency of defecation, and described the experience it in a familiar way.

*"I first started to feel my bowel move, it was so totally unexpected and it was like somebody had given me a miracle."* Participant 5

For the remainder, perceived benefit during up to a year of follow-up was more modest, particularly for hard outcomes such as frequency of bowel movements, but still conferred a sense of benefit in the symptoms most valued by them, particularly bloating. They would be identified in the trial as a non-responder due to the lack of significant improvement in symptoms, but they still regarded benefit as being significant enough to them to warrant keeping the implant, even if it did not result in the much hoped for cure.

*"It has helped to an extent …. I am not vomiting as much, I am not bloating as much … So I'm still happy, regardless that it hasn't worked how I wanted it to for the moment, I'm still happy that things are doing something….For all that it hasn't made me have my bowels opened yet there has been significant difference that I'm not vomiting as much and I'm not getting as much bloating."* Participant 1

For two participants, they welcomed the sensory effect of being able to turn up the voltage of the permanent implant which seemed to reinforce a feeling that it was 'working'. Prior to the trial, one of these participants had experienced lack of urge and felt that this was returning as a result of the implant, suggesting future avenues of enquiry.

"I think when you haven't had any movement at all, you haven't had any sensation, then it makes a big difference. Because as I'm sitting here talking to you now, I have no bowel sensation at all without this stimulator." Participant 5

*"So while it was working in that period that it was working, it's stimulated my bowel sufficiently that I now know I need to go."* Participant 3

For one participant, she perceived the long-term benefit to be modest but if measured in terms of hard outcomes, benefit was captured by the fact that she was able to discontinue all laxatives. She initially had bowel movements once a month and was able to move her bowels every 4-5 days as a result of implantation (so would be deemed as a non-responder in the trial). Because her baseline symptoms were so severe, her perception was of benefit.

*"I was going to toilet a lot more easily and not getting the bloating and stabbing pains that I normally got, during some of it and then obviously on some of it I still got it."* Participant 6

Of those interviewees who did not receive the permanent implant, both felt no significant response to the testing period what-so-ever and their experience during follow-up followed the same pattern of relapsing remitting chronic severe symptoms. For them, they reverted back to a self-management process based around control, and a pursuit of a miracle cure.

*"I was hoping that personally I would get a result from it and my condition. I don't regret doing it … so I'll keep managing it until something … a study, or a procedure or a tablet that comes out that is effective for me personally."* Participant 2

The disappointment of SNS failing in these two participants also had a negative feedback into, and perception of their healthcare angst.

"*but I've been coming over here now for over 2 years and* ***I don't feel like I've got much further forward****….. Well when I first saw the doctor again to come and see a specialist, he said Professor Yiannakou, he'll get you sorted, he's very good at his job and he will get you sorted. So I thought 2 years down the line, something might have happened before now. But …"* Participant 7

This participant, however was also keen to express her gratitude at trying new trial therapies in an attempt to regain control of her life, and of the hope that she may have helped others in doing so. She had also underwent a normal sensory SNS test as part of routine NHS care following on from the Tilts pilot study trial and was still deemed to be a non-responder so did not undergo permanent implantation.

"*There's always that chance it could have helped me, and if I didn't do it, I would think well what if? What if it did work? So it was worth a go……I mean it didn't really help me, but there might be something in it for somebody else who's in my position that it would help."* Participant 7

### 7.8.3. Managing the permanent implant

The permanent implant (with internal components and a control device) posed a reduced burden to day-to-day life compared to the testing device with external components and blinded stimulation. As expected, the more costly device had no reported malfunctions compared to the testing device. Driving was permitted with the permanent device and wound care was only required for 1 week post-op. The main drawbacks identified by participants concerned the device triggering theft detection at barriers in shops and airport security but this was seen as a minor problem, dealt with using humour.

*"The only time it alters anyone's perceptions is when I have to be strip searched in airports. …. But once they saw the scars they were alright. … I made a joke of it and had a laugh …. I would have worn different underwear …"* Participant 1

*"... my sister did used to laugh because the barriers would go off if we'd gone to the Metro after here, and she'd go "it's your butt isn't it" and I'm like "no, no, no, it's not my butt!"* Participant 8

### 7.8.4. Psychological response to testing

The concept of a placebo effect was introduced to participants as a necessary part of the consent process in order that participants would understand the need for a cross-over trial design. The process of testing seemed to contribute to anxiety among several participants about whether or not any effects were down to a placebo effect, and contributed to concerns about not having symptoms taken seriously. One participant felt it made her question her sanity and worry that she might be judged to be mentally ill and admitted to a psychiatric unit if her response proved to be due to a placebo effect. In addition, participants expressed anxiety about the surgery and the experience of being tested and implanted.

*"…because every time you were starting to go to the toilet it was like, I am actually going to the toilet because of the test or am I going because I'm a nut job…… cos you kept thinking well am I just ending up as like a nutcase and going to end up in the nut house or have I actually got something wrong, cos there is actually no name for what I've got wrong.."* Participant 8

In contrast, the permanent device was perceived to be under the control of the individual and did not seem to be associated with any psychological detrimental effects.

### 7.8.5. Adverse effects and reflection on trial participation

Rates and types of adverse events are reported in Chapter 6. This section describes the perceived experience of two Essence study participants who experienced severe adverse events, one of which led to trial withdrawal, and the perceived negative experiences of participating in the trial, which were not systematically recorded but never-the-less have implications for future trial design.

Of those with severe adverse events, participant 4 experienced life threatening sepsis during testing, requiring urgent admission to the high dependency unit and emergency surgery overnight. This participant was gravely ill, and as such required urgent advice from microbiologists and intensive care specialists. She required removal of the implant as the source of the sepsis and made a rapid recovery. In line with trial protocol, she was withdrawn from the TiLTS-cc study but elected to receive permanent SNS via routine NHS care, and continued to respond positively (and continues to at the time of writing), according to long-term NHS measures. Despite the severity of her septicaemia, she was very reluctant to allow removal of her implant because of perceived benefit, and immediately after the surgery, was requesting re-implantation to the surprise of the clinical team.

*"I was very poorly, and I was just like, I remember saying* ***- you're not touching my pacemaker! you're just not touching it!****…. I was just devastated and at the time I*

*thought I wouldn't get another chance at anything…. I was questioning people to ask when I could have it done again."* Participant 4

This underlines the sense of desperation in pursuit of a cure described earlier; a participant would rather risk their life than lose the implant, and also a sense that even tiny gains in symptom control were seen as significant to this patient group.

When asked if she would do anything different in regard to trial participation she responded:

*"It's still an opportunity to try and get over your bad days. If you tried and you had one bad day out of 10 or 10 bad days out of 10 and it spoiled it by one, to me that's positive."* Participant 4

Essentially she is stating that a life threatening event caused by the trial was considered to her as nothing more than a normal bad day for her.

A second participant describes her experience of being assessed for a potential exit lead infection (it was erythema cause by the dressing) and her immediate reaction to the possibility that the SNS lead may need to be removed.

*"Quite emotional, thinking that it might not work at all, and it might have got infected and I'd have to start again…"* Participant 6

A second participant experienced a device malfunction, requiring significant additional travel to have the (analogue) device repaired, and personal anxiety about legitimacy of the active/sham periods of the testing period. Again, in this case, the participant did not choose to be withdrawn, despite the additional burden on her time, and felt she did not regret taking part in the trial.

*"That (the device malfunction) was quite devastating …. I got all the way back to where I live in XXXX (100+ mile round trip) and it just stopped flashing."*

Participant 2

When asked if she would do anything different, she commented:

*"I was hoping that personally I would get a result from it and my condition. I don't regret doing it. … I'm glad I tried it."* Participant 2

This lady did not meet the criteria for progression to a permanent implant, but as per protocol, she was offered routine NHS testing, which she also failed.

Aside from the per protocol adverse events, all participants in the Essence study described negative experiences during the trial, the majority during testing, relating mostly to the physical and social effects of having an implant. Most of these are captured above, but these do not fully capture the level of burden required by participants and families, and the sense of desperation and disappointment (and thus burden on the research team) if there was no perceived response.

Participants who seemed to be losing long term response to the implant wanted the opportunity to find out whether the permanent implant settings could be manipulated to regain control.

*"There's different settings that we can use isn't there, so we can keep trying."* Participant 1

Overall, participants perceived the trial experience as overwhelmingly positive. They enjoyed the experience of additional interaction and care from specialist clinicians and welcomed the invasive, demanding nature of surgical interventions, testing periods, and treatment, all of which placed high demands on their time, energy and resources. This was surprising given that participants were already perceived to be, and perceived themselves to be, depleted and fatigued and again indicates the willingness of participants to try anything that might relieve symptoms.

Participants were given the opportunity to reflect on their trial experience, and this resulted in several key suggestions for trial design, namely:

- Telephone follow-up in place of face-to-face
- Personal experience sheets to qualitatively feedback the level of burden during the trial - to capture individual perceptions of benefit rather than global scores
- Remote data capture to replace paper diaries
- Improved reliability of devices
- Ability to change batteries by participants
- Improved dressings to reduce skin itch

For a minority, the effects of the permanent implant were experienced as life-changing, for others the trial did not result in any meaningful improvement in symptoms. Despite the high burden on participants, and the negative experiences (life threatening for one), all participants stated they had no regrets about participating and would do so again.

*"…and like I've said now that I've had that acceptance of it, it didn't work anyway. I'm glad I tried it. I would never have known if I hadn't"* Participant 2

*"Things didn't go right but I'd still do it again. If they asked me tomorrow to go back to day 1 I would still do it all again"* Participant 4

*"Because like I say I believe that it's improved my situation physically. I do believe it's helped me. And for that I have no regrets, in fact I'm very grateful that I was given the opportunity."* Participant 5

*"If you'd asked me in the last week of it, I'd have probably said no. But now when I look back it wasn't as bad as I thought it was going to be so no, I probably would do something like that again."* Participant 7

Although there is likely to be selection bias at play, and a potential reluctance to be overly critical to members of the research team, this does reinforce the finding that participants were so desperate for control and to find a cure that they would be willing to undertake almost anything asked of them. This has important implications for trial design and is discussed further in the discussion chapter.

## 7.9 Discussion

Three main themes emerged concerning the lived experience of participants which describe the process of **self-managing** the physical, social, and emotional effects of severe chronic constipation; An experience of **angst** (despair and anxiety) accompanied by anger at the perceived failure of healthcare to provide a cure; A proactive approach to taking personal **control** by seeking a cure through participating in a clinical trial. The main overarching theme linking these is of participants' regaining and maintaining **control** of their body and lives. As such, this qualitative study is the first study to describe not only the experience of participating in a trial of sacral nerve stimulation, but also extends knowledge about the experience of a functional disorder that has the potential to inform future trial design and delivery. Participants describe a chronic condition whose symptoms are resistant to treatment and either had an onset coinciding with a traumatic event, or traced back to childhood. The effects of symptoms were experienced in participants' social, emotional, professional, psychological and family lives, and participants placed individual values on resolution of particular symptoms that were not adequately assessed in the quantitative study. In particular, bloating and its effect on clothing and subsequently on social self-perception, self-confidence and professional life was of particular importance to participants.

Participants described a long process of negative healthcare experiences precipitating their deep dread or anxiety or despair (angst) at being repeatedly told everything is normal , ending in a more positive experience of referral to tertiary

care, with many investigations and (both licenced and un-licenced) treatments along the way. The physical effects of severe chronic constipation are well-described elsewhere in the literature (27) what is less well understood is the way that sufferers turned their angst and secondary anger against the medical model into a constant pursuit for control and cure. This meant that patients felt they would do anything in pursuit of a miracle cure, including participating in a trial which posed significant burden on their personal and professional lives. The implications of this are discussed in more detail in the discussion (Chapter 8) but in summary, patients were willing to undertake significant burden during testing and follow-up.

The study has several key strengths. It is the first study to explore perceptions of the placebo effect, and the first study to explore motivating factors for trial participation in this population. Findings suggest that the key motivating factor for trial participation was pursuit of a cure at all costs, with altruism as a secondary factor. This is at odds with studies in other populations suggesting altruism as a major motivation (145) and is the first to describe the lengths some patients will go to in order to participate. In regard to the placebo effect, the qualitative findings demonstrated that although blinding was protected via good study procedures, the participants felt they would have subverted the blinding if they had the opportunity. Findings also suggest that awareness of the possibility of a placebo effect had a detrimental effect on a minority of participants who suffered increased anxiety about the legitimacy of physical symptoms.

The study design has several key strengths and weaknesses. The fact that I was also the operating surgeon, recruiting clinician, and blinded assessor poses some interesting strengths and potential weaknesses. It can be argued that knowing the participants so well led to a sense of comfort and familiarity for participants that improved the honesty and quality of data. It can also be argued that this leads to

an inherent bias in how I interpreted their descriptions of their experiences as I will have had pre-conceived thoughts on their experiences during treatment as I was a central and consistent component of that phenomenon. If these were quantitative data then they would be judged as having a high risk of bias (111). The design of the study was deliberately sequential with the qualitative interviews only allowed after either withdrawal from or completion of the TiLTS-cc study per protocol in order to prevent contamination or influence of the primary outcome measure in the TiLTS-cc study. This was primarily because the studies were designed sequentially with the quantitative study first and its methods were fixed at the point of funding approval before the qualitative study was designed, and this sequential approach protected the integrity of the data.

The fact that I was a recruiting clinician may have meant that participants felt obliged to participate in the qualitative study but we deliberately designed the recruitment process so that patients were not approached individually by me. The study is inherently biased because patients self-selected from a sub-group of eligible trial participants. It is possible that selection bias restricts generalisability but the range of views and the depth of findings about trial participation makes this a worthwhile exercise. Participants were in effect serial "trialists" from a tertiary centre with repeated exposure to research studies; thus findings may be unique to this sub-group. However, it is likely that the motivations for trial participation, and the response to the placebo effect are more universal. The fact that members of this self-selecting sub-group felt that they benefited from trial participation even without a measurable quantitative response to treatment is worthy of further investigation. It is a weakness of this study that no men were included but this reflects the largely female population who have the severest, most chronic form of the disease. In addition, recruitment processes meant that we were unable to explore reasons for non-participation. It is possible that TiLTS-cc study non-

participants had a more negative experience of prior trial participation and this would require further investigation.

# Chapter 8 Discussion of the key study findings and conclusion for the thesis

This is the first study to evaluate a novel ePNE testing technique attempting to discriminate those patients most likely to benefit from SNS. It is also the first study to adequately assess the safety profile of ePNE SNS testing in this population which points to an unacceptably high and severe infection risk. This chapter summarises the key findings presented in each of the previous chapters and discusses their implications for policy, practice, and future research, both for SNS, and more broadly for any study involving people with functional disorders. I will outline the epidemiology and current treatment for chronic constipation, and will highlight the key findings from both the trial of SNS and the qualitative exploration of the participant experience. This chapter will include a critical interpretation of these findings in the context of the gaps in the prior research, consideration of the strengths and limitations of the research, and reflection on learning points from each phase of the research.

## 8.1 Summary of findings chapter by chapter

### Chapter 1

The critical analysis of epidemiological data on chronic constipation and its treatment (Chapter 1) demonstrated a significant prevalence of chronic constipation of 14% in western populations (based on pooled data from a systematic review of prevalence studies). It emphasises that this condition disproportionately affects women and is a chronic debilitating disease with a significant impact on quality of life and activities of daily living. Consequently, there is an economic burden on health care providers and a physical, economic and psychological burden on sufferers and their families. Medical treatments are improving with novel drugs such as Prucalopride, Linaclotide and Lubiprostone, but those at the severest end of the disease spectrum usually progress onto more

invasive treatments. These include biofeedback therapy and irrigation, and ultimately formal surgery. Sacral nerve stimulation with limited evidence of efficacy has been considered a possible intermediate intervention to attempt before adopting invasive abdominal surgery such as an ACE procedure, stoma formation or total colectomy. SNS treatment is costly and cost-effectiveness may be improved if a test predictive of long-term response to therapy were available. There is currently no evidence for any test which can adequately discriminate long term responders to SNS therapy from non-responders for chronic constipation.

**Chapter 2**

In order to understand the evidence for the use of SNS in functional disorders, a background to SNS treatment evolution was written and systematic review of the published literature on SNS trials for chronic constipation was performed. Currently SNS is approved for other conditions affecting organs with the same S2/3/4 nerve supply, namely urinary dysfunction and faecal incontinence, but is not approved by NICE for chronic constipation. The early research studies of SNS for chronic constipation are based on mostly single centre, single surgeon prospective and retrospective cohort studies/ case series. These studies have numerous methodological design flaws meaning that the resulting data are of very low quality. These very low quality studies implied that treatment was highly effective when measured using an un-blinded sensory test. The later higher quality RCTs began to detect a placebo effect and hint at much lower response rates, although participants were randomised during the implant phase of treatment and not during temporary testing, which implies placebo responders (to testing) received permanent implants. Based upon data from the included trials there is no evidence of a difference in efficacy of SNS for chronic constipation compared with placebo therapy. This finding may be due to the cohort being selected for implantation as

all had supra-sensory stimulation and a short duration of temporary SNS testing before implantation.

The knowledge gap identified for a potential trial of a new testing technique was based on an extended peripheral nerve evaluation (ePNE) using the permanently implanted tined lead during testing, which allows for a novel sub-sensory and therefore a double-blinded temporary testing phase and the basis for the quantitative study (TiLTS-cc).

**Chapter 3**

In order to understand the evidence of patients lived experiences of SNS as a treatment for this disease, a systematic review of the qualitative literature was performed yielding no results, and so a scoping review on patient experiences of the disease burden and treatments was performed. The qualitative literature review identified no evidence of: the lived experience of patients having sacral nerve stimulation testing and subsequently living with the device, the motivations of participants with chronic constipation for participating in these trials, and experiences / beliefs of the placebo effect in treatments for these patients. Hence, these became the core topics to be explored further in the qualitative interview study (Essence) which was designed to follow on after the TiLTS-cc study was completed in order to prevent data contamination between studies.

**Chapter 4**

Chapter 4 presented the aims and objectives of the quantitative and qualitative studies after the knowledge gaps had been identified in Chapters 2 and 3. These included the urgent need to develop a test that could adequately identify long-term responders to SNS treatment who suffered from chronic constipation, and their experiences of the treatment and motivations for participating in these studies.

**Chapter 5**

Chapter 5 demonstrated the methods adopted for the quantitative (TiLTS-cc) and qualitative studies (Essence). These studies sought to treat participants and collect data on their response to treatment and experiences of the disease and trial participation. The TiLTs-cc study was designed jointly within a research group but included significant design contributions by myself. Notably these included the design contribution required to adequately blind the participants at a habituated threshold (sub-sensory stimulation) and maintain the integrity of blinding, the calibration of devices to ensure identical test stimulation was received by each participant, the antimicrobial prophylaxis algorithm before surgery, the consistency of the surgical technique (and equipment) and application of dressings, and the design of the study schedule and follow up of participants. The crossover design of the testing phase and primary endpoint of comparing long-term response to SNS between discriminate and indiscriminate testing responders were jointly devised by the senior researchers within the team. I was present during the meeting where these were decided but my contribution to this aspect of the trial design was minimal. As the study research fellow I undertook the majority of the recruitment, surgical procedures and follow-up of the participants, and I interviewed all of the participants in the qualitative study. The design amendments to the final TiLTS-cc protocol was informed by a pilot study undertaken by the research team during which I was the lead surgeon. In this pilot study the potential to blind participants through security seals was tested and improvements identified. Inherent problems were also detected with the analogue testing device in common use. In response to these problems I developed a laboratory experiment (in conjunction with help I sought from a physicist) that demonstrated the variability in the analogue testing device, indicating the requirement for precise calibration of each device before being used on a study participant. The same experiment was repeated on the new

digital testing device which demonstrated an exponential improvement in accuracy (4 orders of magnitude) and performance which validated the expected improved accuracy of this device over the analogue version. Other design changes that became necessary during the TiLTS-cc trial through ethically approved amendments to the study surrounded an attempt to minimise infection rates through changing the dressings used and modifying the antibiotic prophylaxis after a further literature review (designed and conducted by myself) and careful consideration and advice from experts in microbiology. I recruited the majority of participants to the study through the Durham constipation clinic and was the lead surgeon performing the study procedures in over 90% of participants.

The Essence study was designed jointly by myself and a senior supervising qualitative researcher (Dr Helen Close) 6 months after the ethics approval for the TiLTS-cc study was given. I attended a qualitative research methodology course run by Durham University, and considered various frameworks as possible methods for this study. I elected to proceed with hermeneutic phenomenology as this clearly had an evidence base in the literature for surgical trials, and would allow my detailed interpretation of the participants' experiences given the central role I played to them during the trial. I collected all of the data in the form of semi-structured interviews with suitable safety mechanisms in place for the participants in an environment with which they were all familiar. The data was recorded and transcribed verbatim, and data saturation was confirmed by both myself and my supervisor before recruitment was halted.

## Chapter 6 findings from the Tilts study.

### Summary of key TiLTS study findings

The study was terminated by the DMC and CI before full recruitment was obtained (45/75) due to the persistently high rate of infection of participants during ePNE

testing (22%). 29 participants responded to ePNE (7 discriminate and 22 indiscriminate), and 27 were implanted with an IPG (2 withdrew). There was no evidence of a significant difference in long-term response (at 6 months) to SNS treatment between the sub-sensory test discriminate (60%) and indiscriminate (57%) responders P=0.76. There was no evidence of a statistically significant difference in secondary outcome measures through testing or long term follow up between discriminant and in-discriminant responders. The design of the ePNE testing phase (randomised sub-sensory active or sham SNS with devices security sealed) protected the blinding of participants as confirmed by the synchronous responses between active and sham testing groups. The SNS testing devices underwent a pre-trial laboratory test of their output waveform to assess their variability. This confirmed unacceptably high variability in the analogue device (model 3625), and a far higher precision to stimulation waveform parameters in the digital device (model 3531). This model was also far more difficult to tamper with as the digital control device was only used by the un-blinded researcher.

## Chapter 7 -findings from the Essence study

### Summary of key Essence study findings

Three main themes emerged concerning the lived experience of participants which describe the process of **self-managing** the physical, social, and emotional effects of severe chronic constipation; An experience of **angst** (anxiety, dread and despair) characterised by a secondary anger at the perceived failure of healthcare to provide a cure; A proactive approach to taking personal **control** by seeking a cure through participating in a clinical trial. The main overarching theme linking these is of participants' regaining and maintaining **control** of their body and lives. This understandable need for control over healthcare angst led to a move from passive aggressive anger towards constant pursuit for a cure, implying that future trial designs should be viewed within this specific context for these participants.

Participants placed individual values on resolution of particular symptoms that were not adequately assessed in the quantitative study, and as such the participant's perception of benefit didn't conform to the TiLTS-cc trial definition of benefit. Bloating and its effect on clothing and subsequently on social self-perception, self-confidence and professional life was of particular importance to participants. Very small gains in these symptoms were very significant to individual participants, regardless of how little quantitative improvement was measured. This has implications for trial design and the need for more person centred outcomes including the need for more person centred assessments of cost benefits during a trial (monitored by a data monitoring committee). The cohort were regular participants in trials and thus it could be argued, prevents the generalisability of findings; I would argue this should be exploited by methodologists not ignored in trial design with this and other similar populations, although I agree that this would still limit external validity. This study has also explored perceptions of the placebo effect, demonstrating an awareness and acceptance of it through the cohort, but also an anxiety that it may demonstrate a psychological cause for their symptoms. Participants also admitted to attempting to subvert the blinding either consciously or unconsciously due to a desire to gain control of symptoms, and that this was futile and the blinding was protected throughout. This study has also found that the key motivating factors for trial participation was pursuit of a treatment, cure and control of their lives over altruism.

## 8.2 Key findings – what does this research add to current knowledge?

### 8.2.1. Safety

The main finding which I believe should have an immediate impact on clinical practice is the safety concern surrounding enhanced percutaneous nerve evaluation with an extended 6 week test using a tined lead. This form of SNS testing has been clearly demonstrated to have a persistently high incidence of infection in

our study participants 10/45 (22%) despite numerous attempts to prevent these. Of particular note 9 (20%) were categorised as severe infections with one participant requiring HDU for treatment of severe sepsis. It is likely that the tined lead, although internally connected to an exiting extension lead during testing, can easily become colonised causing either immediate or delayed infection to the participant. One study has demonstrated that tined leads tips do become colonised after ePNE (185), this in combination with our findings of high infection rates despite fastidious antimicrobial prophylaxis and dressing management, should be a warning to other researchers and clinicians. We have demonstrated that ePNE over a 6 week testing duration is not viable in its current design, and should not be attempted in clinical practice. As the study was halted with clear evidence of safety concerns and with no evidence of a treatment effect, then it cannot be a cost-effective testing technique for chronic constipation.

### 8.2.2. Efficacy of SNS for Chronic Constipation and the placebo effect

The Tilts study was designed as an attempt to refine the predictive ability of SNS testing at identifying long-term "discriminate" testing responders to this treatment. The overall efficacy of SNS for CC is questionable as we have measured within this thesis. Even considering the possibility of a type 2 error (limitations) there was still no evidence of any apparent signal within the data collected during testing in either the primary or secondary outcome measures when compared to the sham control group. Both the sham control group and the active treatment group improved and deteriorated synchronously throughout the testing phase across all measured outcome domains. Interestingly the proportion of long term responders at six months was almost identical between the test discriminant and test in-discriminant groups. Limitations aside, I believe this could be argued as direct evidence of a persistent placebo effect, which has rarely been reported in the surgical literature. This may explain why SNS appears to benefit some participants in the longer term.

The qualitative data also provides further insights into this placebo effect, as it clearly highlights that participants had different perceptions of benefit from the treatment, and so it may also be true that a signal may have been detectable in the quantitative data if the outcome measures were more participant centred and specific. The placebo effect detected during the study can be explained very succinctly by the participant interviews; this effect was more than just about the treatment, it was about the entire experience of trial participation which was viewed as therapeutic in its own right by the participants, they were pro-actively taking control of their condition through participating.

### 8.2.3. Perceptions of benefit and perceptions of burden

The Tilts trial design attempted to take into account chronicity and severity but the Essence study identified cases in which the disease was so severe at baseline that any improvement was deemed a success by the participant, but would not be captured as such in quantitative terms. It is possible that the implant gave a sense of medical legitimacy to the disease that was previously missing, thus reducing the sense of angst and distrust of clinicians. Key methodological findings from the qualitative study include the use of personal experience sheets which capture qualitative symptom benefit and also a recommendation to review these in data monitoring committees to address participant burden within the context of desperate participants willing to do anything who are open to exploitation. The interviews all took place prior to un-blinding of the Tilts results so it was impossible to disentangle at the time whether this perception of benefit was associated with a placebo effect. Un-blinded findings suggest that participants in the Tilts trial did experience a placebo effect while the SNS was switched off, and that this also affected ESSENCE participants. Qualitative data however, suggests that perception of benefit was not just associated with a psychological placebo boost but more than that, participants experienced a renewed sense of agency and control by taking an

active part in the TiLTs-cc treatment, which may have in itself have had a therapeutic value. Bloating was the most important outcome for some participants and was a significant factor in their perception of benefit, for others, abdominal pain, vomiting or bowel function were the most important outcomes. Every participant differed in their priorities for outcomes, with important implications for trial design; we could argue for a more nuanced outcome framework in constipation trials. This could be achieved using alternative frameworks to measure outcomes such as a Participant Generated Index.

## 8.3. Reflection on the research conduct

### 8.3.1. Strengths

The Tilts study was a prospective methodology powered appropriately to detect effect size, utilising a novel double-blinded, sub-sensory sacral nerve stimulation crossover testing design. This is the most robust scientific design to date in sacral nerve stimulation trials by finally attempting to adjust for and explore the placebo effect which has been suspected to play an important part of SNS testing being unreliable. The Tilts study is the first study to evaluate SNS testing using this design, and the Essence study is first qualitative study to evaluate the testing process and trial participation more generally in this population of participants. The Tilts study design was informed by piloting of the study methods in a small cohort which identified refinements required to guarantee adequate blinding of the participants and myself. The security of blinding of TiLTS-cc study participants was then validated during the Essence study.

A separate experiment measured the output waveform of the testing stimulator and identified variability in the analogue device, which was addressed by re-calibration of all devices before the Tilts study commenced, and between each single use of the device on the study. This has not been previously reported in any

preceding trial of SNS in any field, and given the variability detected in these testing devices, prior research may be inaccurate. I participated throughout this research as a clinician recruiting patients from an NHS clinic (with senior supervision from my consultant), a researcher explaining the study processes and consenting patients, a surgeon who operated on the participants, and an interviewer who was able to put participants at ease and facilitate their reflection and debrief of the whole experience. As a result I was able to form a detailed interpretation of the participants' descriptions of their experiences, which brings the qualitative data collected very close to true Hermeneutic phenomenology (152).

### 8.3.2. Limitations

There were several limitations to both the Tilts and Essence studies which may influence the interpretation of these findings.

#### 8.3.2.1. Data Adequacy-Possible Type 2 Error

A type 2 error is possible from 3 separate factors; sample size calculation error, heterogeneity of the population and early trial cessation.

#### 8.3.2.2. Sample size

The endpoint for response was a reduction in the mean total PAC-SYM score of 0.5 which differs from recent evaluations of utilising this outcome measure in clinical trials where a defined higher reduction (-0.75) was suggested as a meaningful clinical response over placebo (186). Consequently the TiLTS-cc study design may have over classified responders to testing (false positives in the endpoint analysis) and thus a far larger sample size would have been required to detect any signal within the data using a higher response classification (-0.75). Finally, due to the persistent infections that participants seemed to suffer from, the DMC ended the Tilts study 30 participants short of the sample size target originally calculated as required.

#### 8.3.2.3. Endpoint variability

The determination of test responders and long-term responders was deliberately different; this may have contributed to the results and can be argued as an error as a validated tool was not used to classify the initial testing response. The visual analogue scale was invented and used to define a test responder simply to increase conversion rates to implantation in order to improve the PPV and NVP analysis of the test. The best scientific design would be to implant all participants eligible and measure PAC-SYM throughout testing and implant follow up, but this was declined by the ethics committee as non-responders would proceed to unnecessary surgery. This would have given a very accurate analysis of PPV and NPV. In order to increase the implant rate sufficiently enough to make the required sample size and study feasible, the TiLTS-cc VAS scale was devised with a relatively low threshold of response decided at $\geq$25% improvement in symptoms. This allowed a secondary analysis of PAC-SYM which did not demonstrate any difference between active and sham groups during testing.

#### 8.3.2.4. Heterogeneity

The study was adequately powered but also did not take into account the heterogeneity of the participant population; many experts in this field theorise that many multiple aetiologies are at work causing chronic constipation(12, 13), including but not limited to abdominal surgery and adhesions, myenteric nerve plexus neuropathies, smooth circular muscle myopathy, collagen disorders and even post exposure to an unknown environmental antigen. Clearly a group with this level of heterogeneity will be far more likely to have a false negative result. Indeed this may even be part of the explanation as to why some participants feel no effect whatsoever from SNS whilst others are reporting a life-changing event.

#### 8.3.2.5. Sub-sensory stimulation

The Sub-sensory design might actually have been both a strength and a weakness to the study, as it may not actually work as well as supra-sensory SNS in this disease. Outside of clinical trials of participants receiving SNS for faecal incontinence and urinary dysfunction this method for SNS has not been utilised. A small physiological study attempted to measure colonic propagating pressure waves during sub sensory SNS and found that it did not potentiate these compared to supra sensory SNS (105). This study assumed that the mechanism of action of SNS for CC would be to increase these waves of muscular contraction, but the mechanism for SNS in all clinical applications is very poorly understood, with some even hinting at an afferent mechanism on the cerebral cortex (102). Overall it may be that sub-sensory SNS has no effect for participants with chronic constipation, this simplest of explanations for the results may be true.

#### 8.3.2.6. Human error- Complex study with complex patients

It is possible that the TiLTS-cc study, in trying to perform a randomised and completely double-blinded SNS tined lead testing for the first time, became far too complex a study. Running the study was incredibly demanding on myself and the study team. Typically 2-3 researchers were required per participant visit in order to protect blinding and perform the correct assessments.

#### 8.3.2.7. Not a mixed Methodology

The overall thesis research utilised two methodologies but was not a mixed-methods study. The Tilts study design prohibited interviewing participants before the endpoint to avoid any contamination of the primary trial outcome. This occurred as the study design was fixed at the point of funding approval, which preceded the qualitative study design. Thus the results of the qualitative study could not be used to inform the design of the trial itself. The overall study was therefore sequential and not “mixed-methods”, but these qualitative findings still

have important implications for the design of future trials in participants with chronic constipation, and methodologists should take this learning into account for mixed-methods design.

#### 8.3.2.8. Equipoise

It can be argued that I was not in true equipoise during the Essence study as I was the interviewing researcher who was also the participants' surgeon during the TiLTS-cc trial. This raises the possibility that participants may have been too optimistic, positive or polite towards me in their descriptions of their experiences within the trial, and that the truth was that their experience was more negative. Conversely it could be argued that the professional relationship that I had developed with all participants actually meant they trusted me more than most clinicians and as such would be frank, open and honest.

#### 8.3.2.9. Possible biases

##### 8.3.2.9.1. Recruitment Bias

There was potentially recruitment bias in both the Tilts and Essence studies as these participants were serial trialists in a tertiary centre. They therefore represent a highly selected group of patients who are at the severe end of the disease spectrum and are therefore not generalizable to the population at large. The question of whether the informed consent process was truly valid is also linked to bias – consent was taken from clinicians who weren't impartial (I was a researcher in both studies) and participants were desperate and vulnerable and "willing to try anything" for their condition "in pursuit of a miracle cure". This is a specific weakness within the research performed in these studies and that we may have recruited severely refractory patients who were desperate and as such unable to give properly informed consent to us as clinicians. I would argue that our participant information sheets were informative and that patients had an appropriate cooling off period to consider the information prior to agreeing and consenting to become

study participants. Future studies in this patient group may want to consider using neutral non-clinical researchers to take informed consent in order to address the concerns highlighted above.

#### 8.3.2.9.2. Selection Bias

During the Essence study participants self-selected for recruitment after receiving an invitation letter. The results demonstrate that we interviewed only 2 participants who did not have a response to the testing phase, so it can be argued that these data represent a self-selecting sub-group who gained a lot from trial participation and felt they derived benefit from this.

#### 8.3.2.9.3. Interpretation bias

As the primary researcher performing both the surgery and interviews I was in the unique position of having pre-conceived ideas (declared within the methodology) about their experiences. It can be argued that I have been biased towards my own perceptions rather than interpretative of the participant's individual phenomena during the trial. I would argue against this as I explained in detail in the methodology of the Essence protocol (Chapter 4) about my preconceptions of the trial experience, and these have been proven to be inaccurate. I did not predict or expect that participants would on the whole have a positive or beneficial experience, or presume that the overarching theme would be about regaining control of their lives. I remained blinded to the participants' quantitative results throughout the qualitative interviews; my naivety prevented bias at the time of data collection. I accept that despite all of these measures, however that a subconscious bias on my part may still have influenced the interview conduct and my interpretation of the data. I also felt that there was a cost to myself as the researcher doing both the surgical intervention and qualitative interviews; it was mentally exhausting and I became very involved in the participants' follow up and subsequent care, far closer than in the usual clinical doctor-patient relationship. In

future similar surgical studies I believe it would be more beneficial for participants, clinicians and researchers to have dedicated qualitative researchers embedded in the trial design from the beginning in a true mixed methodology; this would allow appropriate amendments to the quantitative strand as qualitative issues are reported.

#### 8.3.2.10. Participant Demographics

Only two men were recruited to the Tilts study, and no men were recruited in the Essence cohort, but this demographic is representative of the wider population of participants with this condition. It is possible that men would have given differing qualitative findings to the study, and this will remain a knowledge gap.

## 8.4. Personal lessons learned during the research

### 8.4.1. Adopting mixed methods in pilot phase

As previously stated, this thesis has demonstrated to me the importance of feedback into study design within the context of designing complex surgical trials. There is a deficit of such research methods being employed within the surgical literature and I believe this learning opportunity will help me to promote it in future.

### 8.4.2. Quantitative trial design

I have gained considerable insight into research design within surgical trials, in particular how difficult it can be to adequately control these trials, and I would advise colleagues accordingly. Techniques such as crossover trials where subjects can become their own control group are very useful in patients with stable and chronic diseases. I would advise colleagues of the importance of utilising an experienced university research team to help with these designs, pilot them and feedback into the research design for either a hypothesis generating or definitive hypothesis testing study. I would also advise on the importance of utilising help in the statistical aspects of study design, data collection and analysis, especially where

preserving data integrity through monitoring and cleaning are concerned in order to produce the highest quality of research output from a prospective study.

### 8.4.3. Qualitative study design

The importance of using hermeneutic phenomenology in surgical trials, especially in heterogeneous patient groups such as those suffering from chronic constipation is clearly evidenced by this thesis. This is the first time I have undertaken qualitative research in any form, and although this was a new technique and philosophy I had to think very carefully about, I have embraced this framework and will promote this within my specialty as a design necessity in future clinical trials.

### 8.4.4. Calibrating equipment.

I learned a valuable lesson from this experience; clinicians should not always assume that medical devices behave as they are intended or designed. All fields of clinical practice have their instrumentation that requires re-calibration to provide verifiable readings and consistent results. Failure to calibrate during temporary SNS may result in participants receiving variable stimulation, potentially reducing the clarity of research findings, and may have been a factor in the poor predictive power of testing in chronic constipation reported in all prior studies of SNS. To date this is the only reported study to calibrate these devices before a trial.

## 8.5. Implications to further research

### 8.5.1. SNS for faecal incontinence and urinary dysfunction

The main clinical indications for SNS are faecal incontinence and urinary dysfunction, studies of which demonstrate far greater efficacy and test response (80%). It is clear that clinicians and researchers in these fields have been utilising ePNE instead of the standard 2 week test with a plain temporary electrode. This thesis demonstrates that the 6 week ePNE testing would also be unsafe in these participant populations due to the increased infection risk of up to 22%. Using the ePNE technique this thesis has demonstrated the potential ability to conduct a

double-blinded sub-sensory sham controlled crossover test in other groups, but we would not recommend 6 week testing given the adverse events, and this should be considered by clinicians and researchers alike.

### 8.5.2. SNS testing for chronic constipation

This thesis in combination with other studies (121, 123) has failed to detect any signal within any testing data that would suggest we can go onto discriminate long-term response effectively between testing responders and testing placebo responders. This is more than likely due to the heterogeneity of their undiscovered aetiologies, where some participants report no symptom change whatsoever in the qualitative data and others report a life-changing event. I agree that it is still possible a small subgroup with a very particular aetiology may respond well to SNS therapy and report a life changing event; however trials to date of sensory 2-3 week unipolar lead testing, and now blinded 6 week quadripolar lead testing have failed to discriminately identify these patients. Given the current expense of this treatment (now over £12,000 in the NHS) if overall testing responders do not translate into long term responders then it is unethical both clinically and financially (for the NHS) to offer this as a treatment. Further research may potentially concentrate on blinded physiological response to SNS testing, as this is an underexplored area within SNS testing for chronic constipation.

### 8.5.3. For other SNS work/research

Future researchers in SNS studies may want to pay attention to the specific details we have learned from our participants during the qualitative interviews. Participants wanted the ability to change the SNS testing box batteries to prevent an unnecessary extra trial visit, but this would obviously not be possible in a blinded control trial. They also specifically commented on the occlusive dressing being too itchy, and tissue glue may be worth an attempt as an alternative temporary

dressing instead. Paper diaries were easily completed, but could be forgotten and so some suggested an online data collection system for participants to complete in real time at home. A telephone preference for routine follow up appointments was also expressed and this could be feasible for many study designs that do not require physical examination. A simple but important point emphasised repeatedly in this thesis is the unreliable variable nature of the old analogue testing stimulator (model 3625) and we would clearly not recommend using this during clinical practice or future research (183, 184). More consideration should be given by clinicians and methodologists in estimating the efficiency of trial participation for patients so desperate for benefit, where any improvement is a success to some patients and this should be taken into account in trial design. This may be achieved through more consideration of experience sheets, patient-centred outcomes and "patient-meaningful differences in outcomes", alongside definitions of "clinically meaningful differences in outcomes." One of the most interesting findings [from my perspective] was that participants were not predominantly motivated by altruism but by a desperate pursuit of a cure for their condition which helped them to feel they were regaining control of their bodies and life. This potentially leaves them vulnerable to exploitation, and this is an important addition to the literature and for methodologists to consider during trial design. I would suggest that researchers who are clinicians treating patients with severe functional gastrointestinal disorders should not be taking informed consent for their inclusion in clinical trials. These patients clearly depend greatly on these clinicians as their last hope of finding a treatment or cure, and they are "*willing to do anything*" to achieve that control. This is therefore not informed consent, and I would suggest a neutral research team member (who is not a treating clinician) should do this instead.

## 8.6. Concluding comments

The efficacy data presented in this thesis is consistent with other recent quality studies of SNS for chronic constipation and in combination with these findings on the placebo effect, I would suggest that SNS is unlikely to be an effective treatment and that it is clinically and financially unethical to offer this as such to patients with chronic constipation. Given the findings recorded within this thesis any future clinical trials on SNS for chronic constipation would be too expensive to justify with the current level of evidence. This relatively low cost study has therefore offered value for money to the NHS by evaluating feasibility. We can now avoid any definitive hypothesis testing study in this population, thus saving on further NHS clinical and research resources. The prolonged placebo response that has been demonstrated is very likely due to the higher therapeutic contact with participants during the trial; this is directly measured in the quantitative data, and substantiated through participant experiences in the qualitative data. Two participants qualitatively reported a life changing event after SNS therapy, although their quantitative data did not demonstrate an effect over placebo therapy in the efficacy measurements taken. It is still possible a small subgroup (from the overall heterogeneous group) with an unknown aetiology may benefit from SNS, although I believe these data are more likely to represent a pronounced and prolonged placebo response.

In future trials within this population a mixed-methods approach should be considered as every patient seems to differ in their priorities for outcomes. This could be achieved using approaches that allow patients to value what they think is important using methods such as a Patient Generated Index (187).

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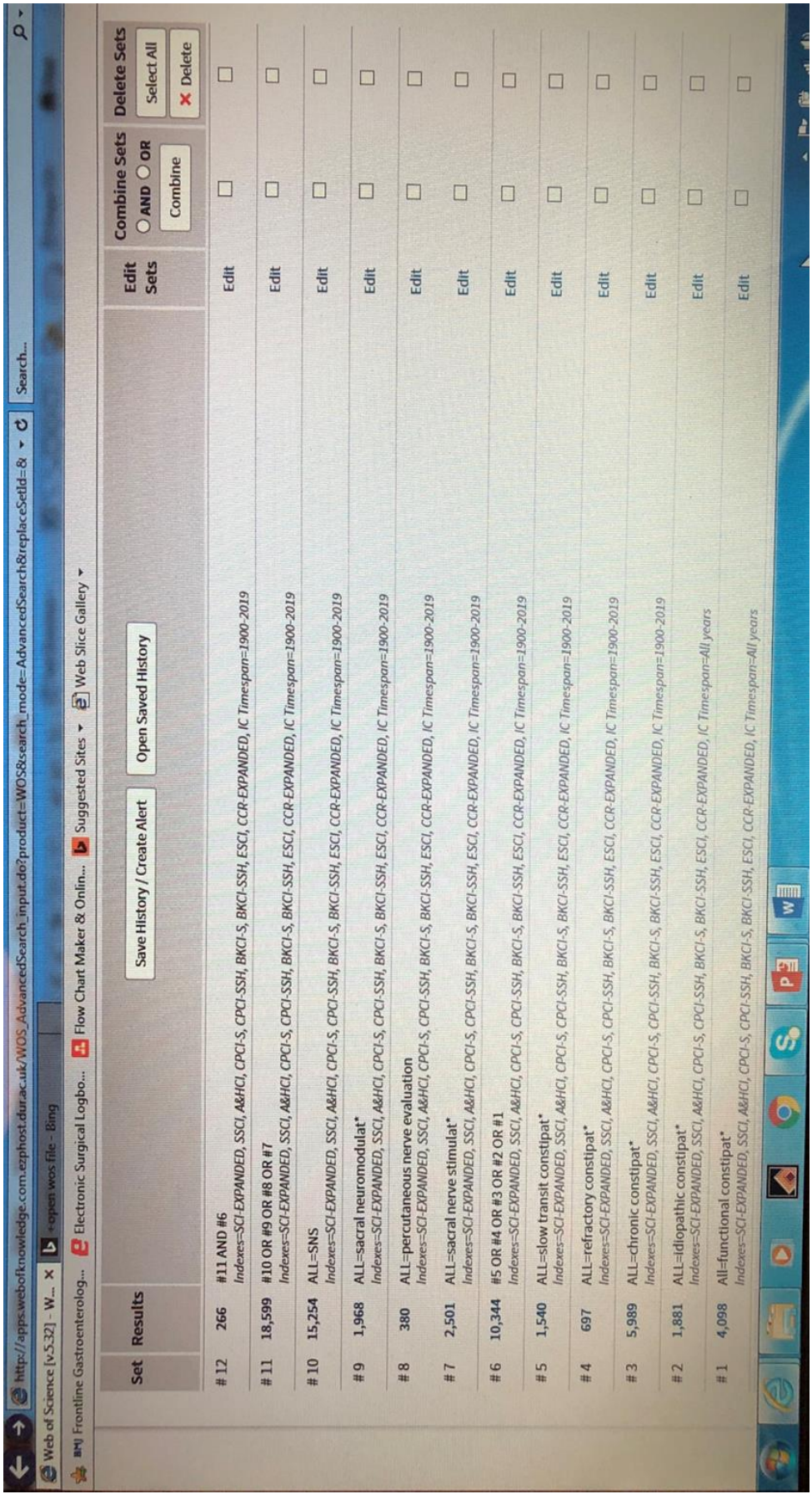
# Appendices

**Appendix 1**- Search strategy of bibliographic databases, example Web of science



## **Appendix 2-**TiLTS- study Participant information Leaflet

**Tined lead testing in patients with chronic constipation: Patient Information Sheet**

We would like to invite you to take part in a research study. It is important for you to understand why the research is being done and what it involves before you decide if you want to take part or not. Please read the following information carefully. Ask us if anything is unclear or if you want more information. Taking part is entirely up to you and does not involve any financial cost. The study involves several steps so it will take us a few pages to explain everything properly to you. Please don't worry if you do not understand it all – we can explain it all face to face if you would like to talk it over with us. If you decide you would like to take part but then change your mind, that is okay. You can withdraw at any time.

**What is the purpose of the study?**

We are studying a condition called severe refractory constipation. This means that the symptoms of constipation have not responded to other treatments and are causing many problems in daily life. We want to understand more about a treatment called sacral nerve stimulation (SNS) which may be able to help the bowel to work better. A fine wire is placed through the skin near to the spine sending mild, painless, electrical pulses to the nerve which controls the bowel. We already know that this treatment is safe and effective if you suffer from certain bowel and bladder problems. Permanently implanted SNS can help peoplelive a more normal life, but it only provides lasting benefit for about 4 in 10 people. We want to find out the best way to decide who will benefit from SNS.

Currently, doctors use a temporary wire near the spine for 2 weeks (as a testing period) to see who might benefit, before giving those who do benefit a permanent wire. This has some problems. Firstly, it may not be possible to place the temporary and permanent wires in exactly the same place changing the benefit you receive. Secondly, you may improve simply because you are being cared for: this is known as a placebo effect. It means you may feel better and be given permanent SNS but your symptoms may quickly become severe again.

We will use a different type of wire and a different kind of assessment to address these problems. Firstly, we will use the wire that is normally used for permanent SNS which is designed to prevent movement and has a greater number of electrodes causing a more focussed "electrical field" area. This is more likely to contain and therefore activate the nerve which controls the bowel. Secondly, we will use the testing period to assess you using both real ('active') and pretend ('sham') stimulation time periods. You will not be able to tell which stimulation you are receiving. This assessment has the potential to tell us if you will benefit long-term from SNS. Patients that have a good level of response to either of the testing periods will be given a permanent implantation of a pulse stimulator. We will assess you at 3 months and 6 months (after permanent implantation of a pulse stimulator-IPG) to measure quality of life, symptom benefit and costs to the NHS. Better targeting of this treatment will prevent disappointment for other patients suffering from this condition.

**Why am I being invited to take part?**

You are being asked if you would like to participate because your doctor has found that you have severe constipation that is not responding to other treatments. Your doctor will be giving this information sheet to all patients who are in the same position as you.

**Do I have to take part?**

No, you don't have to take part. If you want to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the care you receive. If you don't take part in the study all other care will continue as normal.

**Can I have the standard SNS testing?**

Recent changes to funding SNS treatments for severe constipation mean that SNS is now only funded by the GP care commissioning groups (CCGs) through this trial. Standard SNS is therefore not available.

**What will happen to me if I take part?**

***Before the study:***

We will ask you to sign a consent form. We will ask your permission to look at information about you that is held by the NHS in your medical records. This information will be used to make sure you are suitable for the SNS treatment, and to follow up your care and health during and after the study. Then we will arrange for you to visit the out-patient clinic for a health check. You will be asked to have an X-ray of your tummy taken after swallowing X-ray markers in an examination called a transit study. **Ladies will also be asked to have a pregnancy test at the beginning and be asked to use appropriate contraception during the study. It is very important that you do not get pregnant during the study as the study procedures may harm you and your baby.** (There are no known risks to men who go on to father children). We will also ask you about your general and past health, your current medications, and ask you to complete a short questionnaire to understand your quality of life at this time. Some of the measures done at this stage will be repeated at different stages of the study. We will give you some diary cards to take home to record your symptoms and medications over the next 2 weeks.

***At day one of the study:***

After this, we will ask you to come to the out-patient clinic for a day. You will be given a short anaesthetic (and some antibiotics to prevent infection) to have the wire fitted to your back (more information about this is included on page 7). The wire will be connected to a small electronic box (which connects to the wire outside of the body and you wear on a belt) for 4 of the next 6 weeks. We will show you how to keep the wire and the box safe. The electronic box will be switched on to create an electric current to help your bowel to work.

***During the 6 week testing stage:***

For the next 6 weeks, we will test whether SNS works for you by switching the current on and off at certain times. One group of patients will have the current switched on for the first two weeks and off for the last two weeks, and the other group will have the current switched off for the first two weeks and on for the last two weeks; your group will be decided by a process called *randomisation* so all patients will get at least one 'active' period. Each group will have half of the study participants randomised to it. You will not be told which group you are in because patients can improve simply because they are being cared for: this is known as a placebo effect. You will feel no difference when the device is switched on or off, and this means that you cannot tell when you are receiving active or sham stimulation. Not telling patients which group they are in will help us to find out who gets true benefit from the SNS and who would benefit from having it over a long period of time.

We will ask you to visit the out-patient clinic **once a week** for these 6 weeks so we can check how you are, check your wound, and will check that the wire and the box are working properly. At some of these weekly visits, we will ask you to complete more of the questionnaires and will ask you to take home some more diary cards to tell us how you feel, what medications you are taking, how your bowels are doing, and how this affects your daily life. During the central 2 weeks the device will be removed to allow the bowels to normalise between testing (we call this a *washout period).* You will simply have the wire under a dressing at this time. It is important that you understand that you will be unable to bathe or swim for the entire 6 week period, and that driving is not permitted during testing (the first and last 2 week periods connected to the box). Driving is permitted during the central washout period of 2 weeks.

***If you respond to treatment after the 6 weeks testing stage:***

After 6 weeks, we will ask you to tell us if you have seen any improvements in your symptoms and we will then decide if you are suitable for a permanent SNS implant. If you agree to this, this will involve a short procedure to place a small implant in your buttock. This does the same job as the previous treatment but the wire and electronics will all be placed under your skin which will heal over. We will ask you to visit the out-patient clinic again after 3 and 6 months for another health check, including another transit study (X-ray of your tummy). At this point, your participation in the study will be over but you can choose to keep the implant in after this time if it is helpful for you. If you choose to do this, you would be cared for in the usual way by your consultant.

***If you do not respond to treatment after the 6 weeks testing stage:***

If the SNS is not working well we will discuss further options to treat your symptoms and will discuss the option of removing the wire with you. This will involve another short procedure and recovery time. We will ask you to visit out-patient clinic again after 6 months for another health check, including another transit study (X-ray of your tummy). At the end of the 6 months your participation in the study will be over. Everyone should be aware that no matter what happens during the study, every patient will receive the same standard of care as you would normally expect from the NHS, and continue to receive this after the study.

**What are the benefits of taking part?**

We understand that you might be wondering whether or not to take part in this study which asks you to take part in a lot of clinic visits, asks you not to bathe or swim for 6 weeks, and not drive for 4 weeks. We invite you to take part because we believe that there is a reasonable chance that you may benefit from the treatment. Currently, around four in ten people have long-term benefit from the treatment, but the standard testing is inaccurate. By participating you may be more likely to receive the permanent implant, as we expect the trial design will increase the implant rate from about 50% to an estimated 80%.This is what some patients who have tried SNS have told us:

***"It has given me a new lease of life and a real sense of freedom from the condition for the first time in my life"***

***"SNS was an extremely cumbersome experience that unfortunately did not work for me"***

Our study might increase the number of patients who get long-term benefit from SNS but there are no guarantees. These two quotes demonstrate why the testing needs to be changed to identify the patients who will benefit from SNS. They also show that we cannot guarantee success or failure of SNS either on the study or through our normal testing procedure.

**Expenses and payments.**

You will not be given any payments or expenses for taking part in this study. If you find travelling to appointments is causing financial hardship the research team may be able to help with some or all of the travel costs.

**What are the possible disadvantages and risks of taking part?**

All of our surgeons are very experienced in performing sacral nerve stimulation procedures and the risks are very small. The most common risk is of infection or bleeding from the small wound in your back (where the wire is inserted). Infection is almost always successfully treated with antibiotics but very occasionally this does not work and we have to remove the wire or implant. Bleeding is usually only of a very small amount, but can sometimes occur around the testing wire after the surgery. Severe reactions to the device or permanent injuries to the nerves are also possible but this has never happened in any of the institutions participating in the study. Some patients experience electric “shocks “or “jolts” from time to time, and this is due to small currents being generated in the wire either from nearby magnetic fields or sudden movements. This is not harmful and does not cause any problems. However, we ask you not to drive during the 4 weeks of testing (connected to the box) because the jolts may distract you and cause an accident. It is safe to drive during the middle 2 weeks of “washout”(not connected to the box). Strong electromagnetic fields such as in MRI scanners or power generators must be completely avoided as they can cause permanent injury to you by heating the wire. Weak electromagnetic fields such as theft detectors or security gates in shops and airports should be avoided if possible but are not dangerous. You may experience a “jolt or shock” on passing through them, so we would recommend asking a member of staff to bypass the gates. We will provide a study card to explain the reason to security staff discreetly. Please make sure you contact the team if you have any concerns or if you experience any signs that concern you such as redness around the wound, oozing, pain around the wound, high temperature, odour from the wound. The study requires 2 X-rays to be taken which are above normal practice. Our medical physics expert has calculated that the radiation risk is considered to be the same as if you were receiving the standard care for SNS.

**What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. The hospital you are being treated at will have a complaints procedure (page 6).

**Loss of capacity**

In the very unlikely event that you lose capacity to make decisions about your health during the study, you will be withdrawn from the study and continue to be looked after by the clinical team. Any data already collected will be used as part of the study.

**Will my taking part in this study be kept confidential?**

All information which is collected about you during the study will be kept confidential. Any information and data about you which leaves the hospital will have data which identifies you (such as your name and address) removed so that you cannot be recognised from it. However, the following data about you will be leaving the NHS Trust: your unique study identification number, your age, gender and your ethnicity. Your medical records may be inspected by the regulatory authorities or monitors from Durham University who are helping to manage the running of the trial to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

**What will happen to the data collected?**

Your data will be analysed by the team organising the trial to determine which of the treatment options is better. You will be assigned a unique number which will be used instead of your name when the team discuss your data. This team includes the Clinical Trials Unit at Durham University (who will analyse the data), and a small committee of independent doctors, academics and a lay person who have responsibility for overseeing the quality of data and conduct of the study. The results of the study will be used in reports and scientific presentations or publications. Your data will not be transferred outside of the UK and it will be stored securely for a period of time as required by the authorities in the UK before being destroyed. Your data will be stored both electronically and in paper form; this will be held in a database, operated by a third party, but only accessible to the research team. Your data will be stored for a period of 15 years after the end of the study by both Durham University, on the database and at the Trusts following the end of the Study. It will be confidentially destroyed after this point. If you decide to withdraw from the study at any time, the information collected on you up to that point will be kept and used in the analysis of the study.

**Who is organising and paying for the research?**

The study has been started and planned by doctors in various hospitals across England, together with researchers at Durham University. The Study is funded by the National Institute of Health Research (NIHR) through their Research for Patient Benefit (RfPB) scheme. The sponsor for the research is County Durham and Darlington Foundation Trust.

**Who has reviewed the study?**

The study protocol has been reviewed and approved by the National Institute of Health Research. The study has also been given a favourable opinion by "*The Northern and Yorkshire"* NHS Research Ethics Committee who are part of the central body for ethical approval of research studies in the NHS in the UK.

**What will happen to the results of the research?**

The results will be published in scientific medical journals and presented at national and international medical meetings. You will not be able to be identified from any of the results or reports that are produced and published from this study. We hope that the results of this study will enable us to manage patients with severe constipation better in the future. A

summary of the results will be available to all participants. Please let us know if you would like these to be sent to you so that we can record your address at your Trust.

**Further information needed?**

**If you would like to discuss this information in more detail or want further information please contact:**

**Your Consultant in your NHS hospital.**

**Details will be inserted for individual Principal Investigators and the study nurse**

**Details of the local site complaints process to be inserted here:**

If you decide to take part in this study you will be given a copy of this information sheet and a signed consent form to keep. We will also write to your GP to let them know you have agreed to take part.

**Thank you for reading this information sheet**

**Further Information on the procedures**

The insertion and removal of the testing wire, and the insertion of the permanent implant are procedures that are performed under a general or a local anaesthetic. It is important that you have fasted for 6 hours before anaesthetic, that you have arranged an escort to accompany you home and there is somebody to be with you for 24 hours following discharge. Once you have returned from theatre you will be able to eat and drink as you would previously. There are no restrictions on eating and drinking within the SNS testing periods.

***Insertion of the SNS wire ("tined lead")***

This is a simple procedure under an anaesthetic where the surgeon will position the lead near the sacral nerve by threading it through a needle under X-ray guidance. It is then "tunnelled" (a tiny passage is created through the fat) from the spine to the buttock where it might be later connected to an implanted stimulator (IPG). After being attached to a connecting wire it is then tunnelled again where the wire exits the skin. The reason for this is that we want to reduce the chance of an infection in the lead that goes to the nerve. You will have 2 very small (<1cm) scars which will be closed with glue, and through the outermost scar the wire will exit and be covered by a dressing. You will have a slightly larger scar (3-5cm) over the buttock where the lead is connected to the external wire, and this same scar will be used to implant the device if you respond well to testing. This scar will be closed with stitches internally and dressed with tissue glue.

***Implantable Pulse Generator (IPG)***

This is a simple procedure under an anaesthetic where the surgeon will disconnect the external wire from the internal tined lead (which goes to the nerve). A permanent IPG is then connected to the tined lead at the scar on the buttock made during the previous operation, and positioned in a pocket of fat where it will be more protected from damage. The wounds will be closed again with stitches and glue, and within 7 days you will return to the clinic and will be shown how to programme and use the IPG through a remote programmer.

***Removal of tined lead***

This is a simple procedure under a general anaesthetic where the surgeon will disconnect the external wire from the internal tined lead, and then remove the tined lead from the spine. The wounds will be closed with stitches and glue.

**Some Do's and Don'ts for participants**

We have some rules that need to be followed by everyone involved to ensure that you are safe and that the study produces valid scientific results.

You should be aware ***that you may cease participation at any time you like during the study***, immediately if you so wish, and that ***doing this will not affect your care***. Any data that we have collected from you so far in the study, however, will still be used in our analyses.

We ask that you ***do not try to remove or adjust the security labels*** that are placed on the testing stimulator box. If these labels are voided through tampering then we have to invalidate the test and withdraw you from the whole study. These security labels are also to protect you as they stop the batteries being removed and the Bluetooth "bonding" button from being depressed and altering the stimulation.

We ask that you ***please attend all weekly review appointments*** during testing. We will routinely change the battery after each week of testing to prevent it from running out, and monitor the dressing and wound. It is essential that ***the dressing is not removed or changed*** by anyone other than a researcher.

Please ***do not drive*** during the 4 weeks that you are connected to the testing box (the first and last two weeks of the testing phase). Your car insurance will be invalid if you do so.

Please ***tell medical staff of your SNS testing, or permanent SNS implant*** if you have any other treatment during the study.

Please ***contact us if you think the wound site is sore or inflamed***, or if you are concerned about the wire or the box, or any other symptoms or problems that develop during the study.

Please, for ladies, **do not get pregnant** during the study as the study procedures may harm you and your baby.

- **Frequently Asked Questions (FAQs)**

- ***Can I have a shower instead of a bath during the 6 week testing?***
  No, unfortunately not. We recommend using a flannel cloth only to prevent damage to the wire and testing box, and minimise the infection risk around the wire exit site. We understand that most people who suffer from this condition have extremely high personal hygiene standards, but our patient testimonials inform us that this short term inconvenience is worth doing to find out if SNS works for you in the longer term.

- ***Will I still be able to have a normal sex life during the study?***
  This is a question that many people find difficult to ask and wish to be informed of before starting SNS testing or treatment. There is no known reason why your sex life should change by participating in the study. We would ask that care is taken not to dislodge the wire or dressings. The stimulation being provided to the sacral nerves,

may cause changes to occur to the normal sensations experienced during sex – these may be higher or lower than nomal. If you have the permanent device (IPG) this can obviously be turned off at this time.

- ***How will the testing device affect me physically***?
  The testing can very occasionally result in electric shocks or jolts in your bottom, pelvic muscles or legs which can occur at random and be uncomfortable. These usually stop very quickly and do not return. If they happen more than once or you are concerned you should contact us to check the device and settings.

- ***How will the testing device affect me socially?***
  -The testing box will need to be carried on your person at all times day and night for the testing period of 2 weeks at a time. It can be attached to clothing via a belt clip and is the size of a matchbox. It can easily be concealed under clothes but in practice might be noticed by close family and friends. You might want to decide what to tell people who ask if they notice the device.

  -You will not be able to drive during the two separate testing periods of 2 weeks at a time, and should consider how this would affect you and whether you would be able to obtain help with travel during this time. You will be able to drive at all other times on the study.

- ***Can I be seen if there are any emergency problems?***
  We will provide you with the details of your local study investigators who will be able to advise you in the event of unexpected complications or problems. Your medical notes will also contain details of the study for other doctors' information if you need treatment for another unrelated problem.

- ***What will happen to me if it does not work?***
  You will need to have either the testing lead or the implanted device (IPG) removed. You will then need to consider other more invasive forms of treatment through your specialist in the constipation clinic.

- ***Has anyone died during these operations?***
  There have been no known fatalities to date either from the SNS testing, implanted device (IPG) or during anaesthetic for these. In any surgical procedure there are always risks of unforeseen serious complications, however, but we would emphasise that these are incredibly small.

**Contact details of study team**

| | | | |
|---|---|---|---|
| Prof Yan Yiannakou | Chief Investigator | Durham | 0191- [redacted] |
| Mr Kevin Etherson | Research Fellow | Durham | 0191- [redacted] |
| Mr Charles Knowles | Principal Investigator | London | 020- [redacted] |
| Mr Mark Mercer-Jones | Principal Investigator | Gateshead | 0191- [redacted] |
| Mr Stefan Plusa | Principal Investigator | Newcastle | 0191 [redacted] |

**Appendix 3** –TiLTS-cc trial Consent form

Headed paper of Trust

## Patient Consent Form: The TiLTS-cc study

**Title of Study:** Tined Lead Test Stimulation to predict long-term benefit of Sacral Nerve Stimulation in patients with Chronic Constipation (TiLTS-cc).

**Clinical Researchers:** Dr Y Yiannakou, Mr C Knowles, Mr M Mercer-Jones, Mr S Plusa

**Hospitals:** County Durham & Darlington NHS Foundation Trust
Barts and the London NHS Trust
Gateshead Health NHS Foundation Trust
Newcastle Upon Tyne Hospitals NHS Foundation trust

**Patient name:** _____

**Patient study number:** _____

Please initial the following statements in the box opposite:

1. I confirm that I have read and understand the participant information sheet version no. ..... dated..... for the above study and have had the opportunity to ask questions. Q1
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without reason, and without my medical care or legal rights being affected. Q2
3. I understand that any data collected from me before this time will be used for analysis and I consent to this. Q3
4. I understand that sections of my medical notes may be examined by responsible individuals from Durham Clinical Trials Unit or regulatory authorities where it is relevant to my participation in this research study. I grant permission for these individuals to have access to my records. Q4
5. I understand that the investigators would like to inform my GP of my participation in this study, and I grant permission for my GP to be informed. Q5
6. I agree to participate in this study and to comply with the assessments and guidance laid out in the participant information sheet. Q6

| Name of Patient | Date | Signature |
|---|---|---|
| | | |

| Name of Person taking consent | Date | Signature |
|---|---|---|
| | | |

**Appendix 4** TiLTS-cc trial GP letter

**To be printed on hospital headed paper**

**TiLTS-cc GP Letter**

Re Your Patient:

Fix patient label here

TiLTS-cc research team. Contact:

Enter details of site PI.

Dr X,

Another practice,

Town and postcode

Dear Doctor,

We write to inform you that your patient (named above) has consented to participate in a NIHR funded research trial entitled "**T**ined **L**ead **T**est **S**timulation to predict long term benefit of sacral nerve stimulation in **c**hronic **c**onstipation (**TiLTS-cc**)".

This national, multi-site study is recruiting patients with severe refractory constipation to offer them sacral nerve stimulation (SNS) in order to predict long-term responders and assess long term efficacy of SNS. The main differences in our trial from standard SNS testing are (i) we plan to use the permanent "tined" lead for testing, and (ii) will test for a prolonged period of 6 weeks (instead of the usual 2 weeks) which will include randomised and blinded "active" and "sham" periods of testing. We suspect that placebo response plays a large part in unreliable testing results in constipation patients, hence the new testing design. Patients who respond to the testing will be implanted as normal with a permanent stimulator (called an IPG) and followed up in the usual manner in our clinics.

We do not have evidence to suspect that the prolonged period of testing is more likely to result in infection of the testing wire as this has been performed successfully in urological studies of SNS. As a precaution, we will administer prophylactic antibioticsimmediately prior to tined lead insertion, and will treat the exit lead like a central line catheter; **therefore, your patient will be invited to the out-patient clinic for weekly wound checks for the 6 week duration of the tined lead testing.** If you would like further information about the study, please contact me. If you have any queries, then please do not hesitate to contact us as above,

Many thanks,

Yours Sincerely,

Prof Y Yiannakou (or PI details).

**Appendix 5** PAC-SYM questionnaire

PAC-SYM ©

PATIENT ASSESSMENT OF CONSTIPATION

This questionnaire asks you about your constipation symptoms in the **past week**. Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate **how severe** your symptoms have been during the **past week**. If you have not had the symptom during the past week, tick 0. If the symptom seemed mild, tick 1. If the symptom seemed moderate, tick 2. If the symptom seemed severe, tick 3. If the symptom seemed very severe, tick 4. Please be sure to answer every question.

| **How severe** have each of these symptoms been in the past week? | **Absent 0** | **Mild 1** | **Moderate 2** | **Severe 3** | **Very severe 4** |
|---|---|---|---|---|---|
| 1. discomfort in your stomach | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. pain in your stomach | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. bloating in your stomach | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. stomach cramps | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. painful bowel movements | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. rectal burning during or after a bowel movement | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. rectal bleeding or tearing during or after a bowel movement | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. incomplete bowel movement, as though you didn't "finish" | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. stools that were too hard | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. stools that were too small | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. straining or squeezing to try to pass stools | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. feeling like you had to pass a stool but you couldn't (false alarm) | ☐ | ☐ | ☐ | ☐ | ☐ |

**Appendix 6** –Daily Diary exercise cards



Baseline Week 1

**WEEK 01** TILTS–cc SYMPTOM DIARY CARDS.

NAME.....SUBJECT NO._____

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Date (DD/MM/YY) | | | | | | | |
| A PAIN | | | | | | | |
| B SPONTANEOUS COMPLETE BOWEL MOVEMENTS | | | | | | | |
| C BLOATING | | | | | | | |
| D STRAIN | | | | | | | |
| E LAXATIVE SCORE | | | | | | | |
| F LAXATIVES | | | | | | | |

My agreed daily laxatives are: 1.....2.....3.....4.....5.....

End of week Question: (**please circle** the most appropriate answer)

Have you had satisfactory relief of your symptoms this week? **YES / NO**

**Appendix 7**-PAC-QOL questionnaire

PAC-QOL ©

PATIENT ASSESSMENT OF CONSTIPATION

The following questions are designed to measure the impact constipation has had on your daily life **during the past week**. For each question, please tick one box.

| **The following questions ask you about the intensity of your symptoms. To what extent, during the past week...** | **Not at all 0** | **A little bit 1** | **Moderately 2** | **Quite a bit 3** | **Extremely 4** |
|---|---|---|---|---|---|
| 1. have you felt bloated to the point of bursting? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. have you felt heavy because of your constipation? | ☐ | ☐ | ☐ | ☐ | ☐ |

| **The next few questions ask you about the effects of constipation on your daily life. How much of the time, during the past week...** | **None of the time 0** | **A little of the time 1** | **Some of the time 2** | **Most of the time 3** | **All of the time 4** |
|---|---|---|---|---|---|
| 3. have you felt any physical discomfort? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. have you felt the need to open your bowel but not been able to? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. have you been embarrassed to be with other people? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. have you been eating less and less because of not being able to have bowel movements? | ☐ | ☐ | ☐ | ☐ | ☐ |

| **The next few questions ask you about the effects of constipation on your daily life. To what extent, during the past week...** | **Not at all 0** | **A little bit 1** | **Moderately 2** | **Quite a bit 3** | **Extremely 4** |
|---|---|---|---|---|---|
| 7. have you had to be careful about what you eat? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. have you had a decreased appetite? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. have you been worried about not being able to choose what you eat (for example, at friend's)? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. have you been embarrassed about staying in the toilet for so long when you were away from home? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. have you been embarrassed about having to go to the toilet so often when you were away from home? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. have you been worried about having to change your daily routine (for example, travelling, being away from home)? | ☐ | ☐ | ☐ | ☐ | ☐ |

| **The next few questions ask you about your feelings. How much of the time, during the past week...** | **None of the time 0** | **A little of the time 1** | **Some of the time 2** | **Most of the time 3** | **All of the time 4** |
|---|---|---|---|---|---|
| 13. have you felt irritable because of your condition? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. have you been upset by your condition? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. have you felt obsessed by your condition? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. have you felt stressed by your condition? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 17. have you been less self-confident because of your condition? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18. have you felt in control of your situation? | ☐ | ☐ | ☐ | ☐ | ☐ |

| The next questions ask you about your feelings. To what extent, during the past week.. | Not at all 0 | A little bit 1 | Moderately 2 | Quite a bit 3 | Extremely 4 |
|---|---|---|---|---|---|
| 19. have you been worried about not knowing when you are going to be able to open your bowels? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 20. have you been worried about not being able to open your bowels when you needed to? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 21. have you been more and more bothered by not being able to open your bowels? | ☐ | ☐ | ☐ | ☐ | ☐ |

| The next questions ask about your life with constipation. How much of the time, during the past week... | None of the time 0 | A little of the time 1 | Some of the time 2 | Most of the time 3 | All of the time 4 |
|---|---|---|---|---|---|
| 22. have you been afraid that your condition will get worse? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 23. have you felt that your body was not working properly? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 24. have you had fewer bowel movements than you would like? | ☐ | ☐ | ☐ | ☐ | ☐ |

| The next questions ask you about how satisfied you are. To what extent, during the past week... | Not at all 0 | A little bit 1 | Moderately 2 | Quite a bit 3 | Extremely 4 |
|---|---|---|---|---|---|
| 25. have you been satisfied with how often you open your bowels? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 26. have you been satisfied with the regularity with which you open your bowels? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 27. have you been satisfied with your bowel function? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 28. have you been satisfied with your treatment? | ☐ | ☐ | ☐ | ☐ | ☐ |

**Appendix 8** –EQ-5D-3L and EQ-VAS

EuroQOL Health Questionnaire

(English version for the UK)

***(Validated for use in Eire)***

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

**Mobility**

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

**Self-Care**

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

**Pain/Discomfort**

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

**Anxiety/Depression**

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

**EQ-VAS**

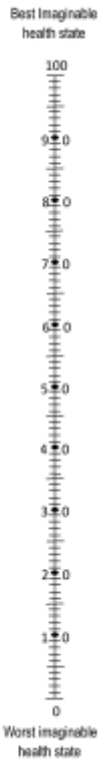
6. **SCORE how good or bad the patient considers his / her own health today.**

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Overall, how would you score your own health today between 0 and 100?

**SCORE =** | | | | Or N/A

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.




Your own health state today

**Appendix 9-** Participant self-completion assessment schedule

*Self-completion assessment schedule for all study participants*.

R=responder, NR=non-responder.

| Assessment Phase | Baseline Assessment | Tilts-cc end of week 2 | Tilts-cc end of week 4 | Tilts-cc end of week 6 | R-PSNS 3 months | R-PSNS 6 months | NR 6 months |
|---|---|---|---|---|---|---|---|
| PAC SYM | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PAC QOL | ✓ | | | | ✓ | ✓ | ✓ |
| 2 week daily diary | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Euro-QOL EQ-5D | ✓ | | | | ✓ | ✓ | ✓ |
| EQ-VAS | ✓ | | | | ✓ | ✓ | ✓ |
| TiLTS-cc VAS | | ✓ | ✓ | ✓ | | | |
| | Phase 1 | | Phase 2 | | | Phase 3 | |

**Appendix 10** TiLTS-cc-VAS

TiLTS-cc SNS testing for Idiopathic constipation

**TiLTS-cc testing Visual Analogue Scale (VAS)**

**Place a cross on the line corresponding to how much you feel your symptoms have improved during the last 2 weeks, compared with before the study. The line ranges from 0%= not at all, to 100%=complete cure. Thank you.**

## **Appendix 11** Essence Study Participant interview guide

The interviews will last between 15-90 minutes and follow a semi-structured format.

The interview will start by confirming that the patient understands the interview process and agrees to take part. Written consent will be taken before the interview starts. Participants will be reminded of their right to withdraw at any time and to stop the tape if they so wish.

The open and specific questions for each of the topics will be as follows:

- **Experiences of CC and its treatment**

*"Can you tell me a bit about how your condition has affected you since it started?"*

*"Can you tell me what has been done to try to help your condition?"*

- **Motivations of patients to participate in the trial (or usual care SNS testing).**

*"What made you want to take part in this study?"*

*"Why do you think other people with your condition take part in these trials of surgical procedures?"*

*"Should people take part in this type of research?"*

- **Experiences of care and support that patients received before/during and after the trial (or usual care SNS testing).**

*"Tell me about the process of being recruited into the trial…."*

*"How much information were you given?"*

*"How did you feel about having SNS?"*

*"What was it like to have the surgery (the first and second procedures)?"*

*"What were the 6 (2) weeks of testing like?"*

*"What was it like filling out diaries and questionnaires?"*

*"How has your life been since receiving the implant or having the SNS lead removed?"*

*"Tell me about the care and support you received from the study team…"*

- **Perceptions of symptom changes (physical or psychological), to what extent was this attributed to SNS, and how important were these changes to patients.**

*"Can you tell me a little about how SNS affected your condition?"*

*"How important were these changes to you?" or " How do you feel about having no effects from the treatment"*

*"Did SNS affect you mentally or psychologically ?"*

- **Experiences of SNS in relation to its affect other aspects of their life (relationships, socially, professionally, and self-perception).**

  *"Can you tell me a little on how/if SNS affected your private or social life?"*

  *"Can you tell me a little on how/if SNS affected you professional life?"*

  *"How did you view yourself during the treatment?"*

  *"How did you perceive others viewed you during the treatment?"*

  *"Are there other ways SNS affected you that we have not discussed?"*

- **Experiences, perceptions and beliefs about the placebo effect associated with SNS.**

  *"As you know one of the two testing periods was a placebo……what was your experience of having a placebo test?"*

  *"Could you work out the real stimulation from the placebo stimulation, and if so how?"*

  *"What do you think about doctors using a pretend test as part of the trial?"*

  *"Do you think it is an acceptable way to give a treatment?"*

  *(For all participants who lost a treatment response at 6 months)*

  *"Why do you think you lost response to the treatment?"*

- **Perceptions and beliefs about the overall experience of SNS testing.**

  *"Overall are you happy with the experience?"*

  *"Can you suggest anything that would improve SNS for others?"*

  *"What do you think about the length of the test?"*

  *"What do you think about living with the dressings?"*

  *"How could the staff help you more than they did?"*

  *"If you could turn back the clock would you participate in the trial (have SNS) again?"*

  *"Why or why not?"*

- ***"Are there any other issues or points you would like to mention or discuss?"***

**Appendix 12** Essence Study Participant interview letter

**ExperienceS of treatment with Sacral Nerve stimulation (SNS) for idiopathic Constipation; a hermeneutic phenomenological study (ESSeNCe)**

Patient's name, DOB, NHS number

Dear Mrs/Ms/Miss/Mr

I am writing to you because you have chronic constipation and you have been treated with sacral nerve stimulation (SNS) under the care of Professor Yiannakou at the University Hospital of North Durham. We would like to invite you to consider participating in the research study named above. This research study will explore experiences of chronic constipation and SNS treatment. If you choose to take part, the interview will take place at the hospital at a time to suit you and will last between 15 to 90 minutes. We will reimburse your travel expenses.

If you are interested in knowing more about the study, we will give you an information booklet which has been ethically approved by Durham University and the NHS ethics service. If you are interested in participating in the study, please contact me through the details below.

Please note that your treatment will not be affected in any way whether or not you choose to take part. Thank you for reading this.

Yours Sincerely,

Kevin Etherson,

PhD student Durham University,

Research Fellow to Professor Yan Yiannakou,

University Hospital of North Durham,

DH1 5TW.

Phone: 0191-33[redacted]

Email: kevin.etherson@cddft.nhs.uk or k.j.etherson@dur.ac.uk

## **Appendix 13** Essence Study Participant Information Sheet

**ExperienceS of treatment with Sacral Nerve stimulation (SNS) for idiopathic Constipation; a hermeneutic phenomenological study (ESSeNCe)**

We would like to invite you to participate in a study of patients' experiences of sacral nerve stimulation (SNS) during the TiLTS-cc study. Before you decide whether to participate you need to understand why the study is being undertaken and what it would involve for you. Please take time to read the following information carefully. This information leaflet will provide you with details of the purpose of the study and what will happen if you decide to participate. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do wish to take part then there is a consent form for you to complete and return. **You do not have to take part if you do not want to and declining involvement will not affect your future treatment.**

**What is the purpose of the ESSeNCe study?**

The research team who treated you during the TiLTs-cc study would like to explore the experience of having the SNS test and follow up, from your point of view. Very little is known about what patients actually experience during this kind of treatment or how it feels to take part in a study of this kind: This is an opportunity for you to help us understand the acceptability of SNS and to decide on the future use of the test and treatment.

**Why have I been invited?**

You have been invited to take part because you have been identified as a patient who has been treated with SNS for chronic constipation on the TiLTS-cc trial.

**What will happen to me if I take part?**

This study will comprise an interview typically lasting for about 15 to 90 minutes, during which the researcher will ask you questions about your experiences of receiving sacral nerve stimulation as part of the TiLTS-cc trial and give you the opportunity to say whatever you want to about your experience of SNS. At the start of the interview I will ask you to sign a consent form to confirm that you are happy and willing to take part in this study. The interview will take place in the Durham Constipation Clinic in a private room at a time that is convenient for you. The interview will be carried out by myself, Kevin Etherson. At any time during this process you will be free to end the interview and leave, and the recording of the interview up until this point would not be retained.

**What are the possible benefits of taking part?**

There are no direct benefits to participation other than you may enjoy sharing your experiences of SNS in the interview, and find this a helpful experience as a way of reflecting on your involvement in the TiLTS-cc trial. You may also feel satisfied that you have contributed towards further research into the condition and treatment, and this may indirectly benefit other patients.

**Do I have to take part?**

Participation is entirely voluntary and it is up to you to decide if you take part. After you have read this information sheet, if you would like to participate, please complete the consent form and sign it to show that you have agreed to take part. There is a copy of the consent form for you to keep with this information sheet.

**What will happen if I start the interview but don't want to continue?**

You are free to withdraw from the study at any time without giving a reason, either before, or during the interview. At any time during this process you will be free to leave, and the recording of the interview up until this point would not be retained.

**Will my interview be kept confidential?**

Yes. The only people who will know that you have taken part will be the research team and your GP. The interview will be recorded on a digital Dictaphone, and then written (transcribed) into text by Anne [redacted] or [redacted] the team assistants. Your name and any identifiable details will not be attached to the text; instead we will give you a unique ID code so that it is anonymous. The interview and anonymous text document will be kept securely until all patients involved have had their interview data completely analysed, and then it will be destroyed after storage for 5 years. The interview and transcription files will be encrypted and stored on a secure part of the team research database on the trust intranet server. Access requires 3 levels of password protected identity verification, and then the encryption password. Your confidentiality will be respected at all times as in the same manner as a clinical consultation. In order to analyse the interview properly we will ask for your permission to allow specialist researchers at Durham University (Dr H Close and Dr H Hancock) to supervise the analysis of the interview recording and transcription. They will not be provided your personal details and will simply refer to you by the unique ID. The interviewing researcher (Kevin Etherson) is a trained clinical doctor who also has a clinical responsibility for your care (under the supervision of Professor Yiannakou), and so has an obligation of care to you if there is a suspicion of deteriorating clinical or mental health as a result of the treatment or interview. In this unlikely situation it may be deemed necessary to discuss concerns raised in the interview with either your GP and/or named psychiatrist to give you the appropriate help. We would discuss this with you immediately after the interview and would let you know if we were doing this in advance.

The researcher and the team assistant will be offered debriefing sessions with the team psychologist in order to protect your and their wellbeing, but this will not compromise your confidentiality as the psychologist is part of the Durham multidisciplinary team who care for you. At all times we will comply with the Data Protection Act 1998 as per the trust information governance policy.

**What will happen to the results of the ESSeNCe study?**

The results of the ESSeNCe study will be presented at national and international conferences, and published as a peer reviewed paper in a medical journal. Direct quotes from interviews may be published, but no information will be published that would allow anyone else to identify you as a participant.

**Will it cost me anything to take part?**

No, but we are asking you to give up some of your time, which might be unpaid time from work.
As you will incur costs for travel and parking we will reimburse these.

**Who has reviewed the ESSeNCe study?**

This qualitative study has been approved by the Research Ethics Committee at the School of Medicine and Health at Durham University. It has also been approved by both the NHS Health Research Ethics Service (HRES) committee of North East and York, and the research and development department of County Durham and Darlington NHS Foundation Trust.

**Harm**

A potential psychological impact on your mental health may occur due to the process of reliving and describing life experiences related to either your condition or the SNS treatment. It is possible that you might find it upsetting to talk about your illness and its treatment, in which case you can stop the interview at any time and support will be offered to you following the interview by Sister [redacted] (nurse specialist) or Mrs [redacted] (team assistant) who you know from the clinic.

**Further information and contact details**

If you would like any more information or if you would like to discuss anything verbally or in person please contact the lead researcher, Mr Kevin Etherson, on 0191 33[redacted], or e-mail kevin.etherson@cddft.nhs.uk or k.j.etherson@dur.ac.uk

If you have concerns about the research and wish to speak to someone confidentially at any point before or after the interview then you can contact:

**Professor Yan Yiannakou on 0191 33[redacted].**

**If you have a complaint you can contact your local PALS office:**

Patient Experience Team

Darlington Memorial Hospital

Hollyhurst Road

Darlington

DL3 6HX

Telephone: 01325 74[redacted]

**List of Researchers in the ESSeNCe study**:

| | | |
|---|---|---|
| Mr K Etherson | Lead researcher | UHND & Durham University |
| Dr H Close | Supervising Researcher | Durham University |
| Dr H Hancock | Supervising Researcher | Durham University |
| Mrs R Maier | Supervising Researcher | Durham University |
| Prof Y Yiannakou | Supervising Researcher | UHND & Durham University |
| Prof J Mason | Supervising Researcher | Durham University |

If you decide to take part in this study you will be given a copy of this information sheet and a signed consent form to keep. We will also write to your GP to let them know you have agreed to take part.

***We would like to take this opportunity to thank you for reading this information sheet and considering the interview.***

**Please keep this information sheet and the consent form for your records**

**Appendix 14** Essence Study Consent form

| **ExperienceS of treatment with Sacral Nerve stimulation (SNS) for idiopathic Constipation; a hermeneutic phenomenological study** | | |
|---|---|---|
| Lead researcher: Mr Kevin Etherson,<br>PhD student, School of Medicine, Pharmacy & Health, Durham University.<br>Research Fellow / Specialist Registrar, University Hospital of North Durham<br>Contact email: k.j.etherson@dur.ac.uk or kevin.etherson@cddft.nhs.uk<br>Phone: 0191-3332889 | | |
| **Participant name:** _____<br><br>**Patient study number:** _____<br>**Please initial the following statements in the box opposite:** | | |
| I confirm that I have read and understand the information sheet dated 12/12/2013 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | | |
| I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care or legal rights being affected. | | |
| I understand that all relevant regulations regarding data protection will be adhered to, and that confidentiality will be protected and anonymity assured by the research team. I understand that relevant sections of my medical notes or data collected during the study may be looked at by staff from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that individuals from Durham University (Dr H Close or Dr H Hancock) will have access to interview recordings and transcripts. | | |
| I understand that if concerns are raised during the interview the researcher may contact Professor Yiannakou, my GP or named psychiatrist in order to provide help. I would be advised of this in advance. | | |
| I agree to take part in the above study interview and I confirm that I am aged 18 years or older. | | |
| _____<br>Name of participant | _____<br>Date | _____<br>Signature |
| _____<br>Name of person taking consent | _____<br>Date | _____<br>Signature |

## **Appendix 15** Essence Study Participant's GP letter

**ExperienceS of treatment with Sacral Nerve stimulation (SNS) for idiopathic Constipation; a hermeneutic phenomenological study (ESSeNCe)**

Patient's name, DOB, NHS number

Dear Dr

Your patient named above has agreed to participate in a qualitative study exploring sacral nerve stimulation (SNS) for patients who suffer from chronic constipation. The aims of this study are to explore the experiences of the disease, the SNS testing and implantation procedures, and the motivations patients may have for participating in surgical research. The ESSeNCe study has been approved by both the ethics committee of Durham University School of Medicine, Pharmacy and Health, and the North East-York research ethics committee (REC) of the NHS national health research ethics service (NRES).

The study involves a qualitative interview lasting between 15-90 minutes, during which I will conduct a semi-structured phenomenological interview. This will be recorded and transcribed, and analysis will be performed in conjunction with and under the expert supervision of qualitative researchers who are fellows of the Wolfson Research Institute of Durham University. No significant risks have been identified or are expected from this study. As you are no doubt aware, asking patients to describe life experiences that may potentially be traumatic can very occasionally lead to deterioration in mental health. We have designed this study with this in mind and mechanisms are in place to report concerns to yourself or the relevant mental health team if this is deemed necessary.

If you have any questions or would like to discuss the study I would be delighted to provide further information,

Yours Sincerely,

Kevin Etherson,

PhD student Durham University,

Research Fellow to Professor Yan Yiannakou,

University Hospital of North Durham,

DH1 5TW.

Phone:0191-33[redacted]

Email: kevin.etherson@cddft.nhs.uk or k.j.etherson@dur.ac.uk

**Appendix 16** Stard checklist (188) for the TiLTS-cc Study

| Section & Topic | No | Item | Reported on page # |
|---|---|---|---|
| **TITLE OR ABSTRACT** | | | |
| | **1** | Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) | 2 |
| **ABSTRACT** | | | |
| | **2** | Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) | 2 |
| **INTRODUCTION** | | | |
| | **3** | Scientific and clinical background, including the intended use and clinical role of the index test | 81 |
| | **4** | Study objectives and hypotheses | 83 |
| **METHODS** | | | |
| *Study design* | **5** | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 85-142 |
| *Participants* | **6** | Eligibility criteria | 89 |
| | **7** | On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) | 89 |
| | **8** | Where and when potentially eligible participants were identified (setting, location and dates) | 89 |
| | **9** | Whether participants formed a consecutive, random or convenience series | 85-142 |
| *Test methods* | **10a** | Index test, in sufficient detail to allow replication | 107-116 |
| | **10b** | Reference standard, in sufficient detail to allow replication | N/A |
| | **11** | Rationale for choosing the reference standard (if alternatives exist) | N/A |
| | **12a** | Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory | 102 |
| | **12b** | Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory | N/A |
| | **13a** | Whether clinical information and reference standard results were available to the performers/readers of the index test | N/A |
| | **13b** | Whether clinical information and index test results were available to the assessors of the reference standard | N/A |
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| | **16** | How missing data on the index test and reference standard were handled | N/A |
| | **17** | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory | 171, 189 |
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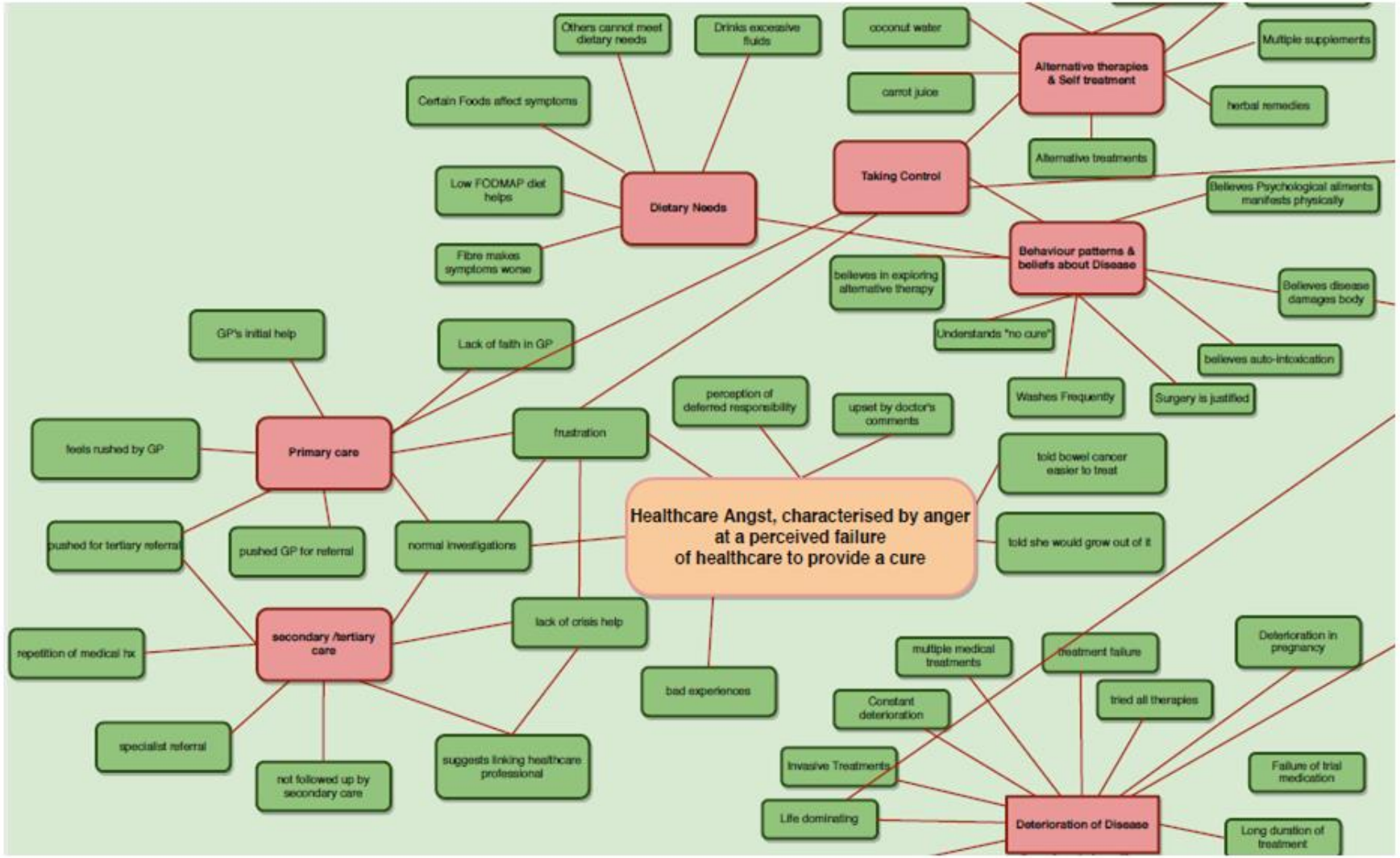
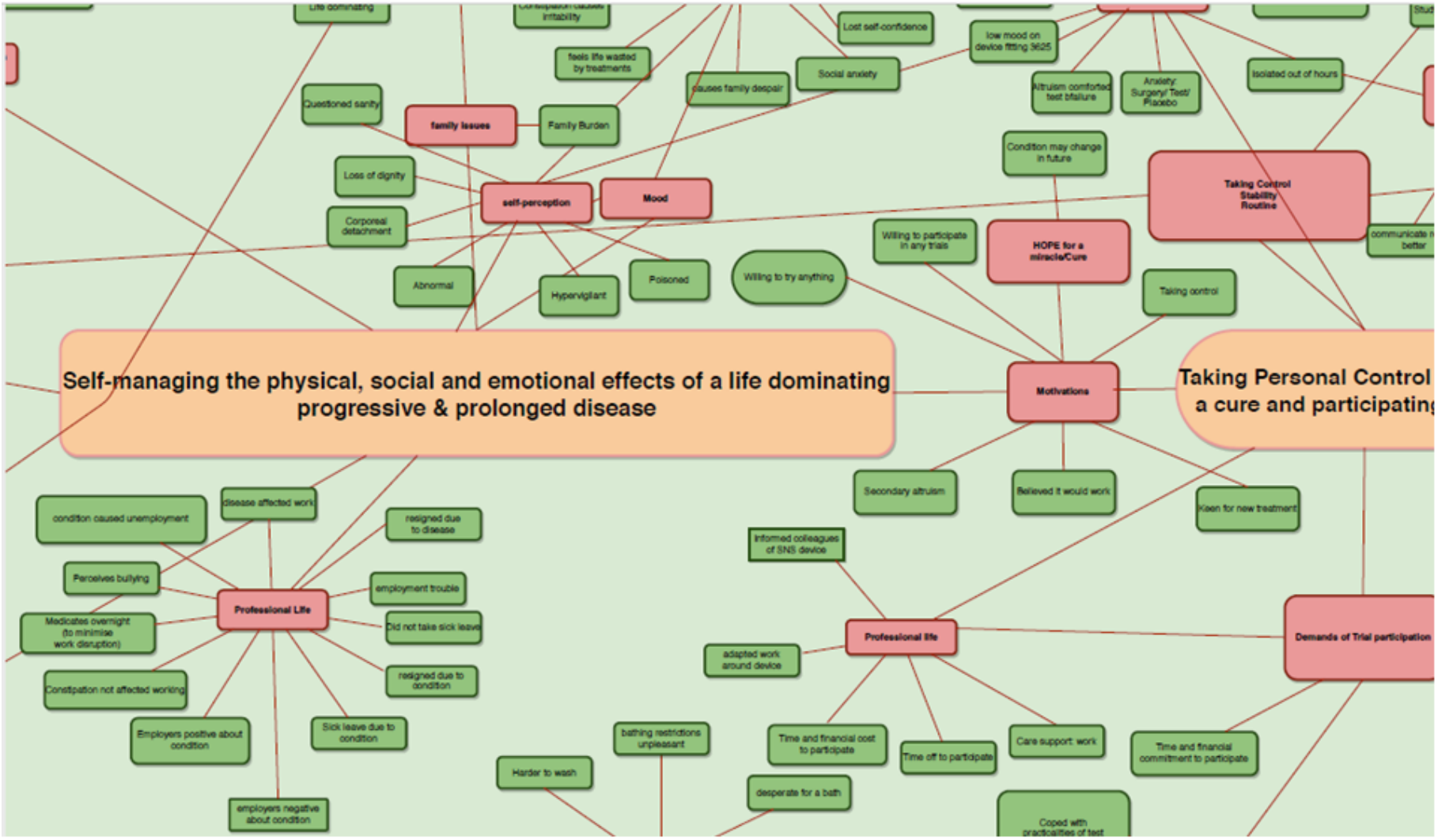
| | **29** | Where the full study protocol can be accessed<br><br>**http://www.isrctn.com/ISRCTN44563324** | |
| | **30** | Sources of funding and other support; role of funders<br><br>**NIHR-RfPB grant approval number: PB-PG-1010-23212** | |

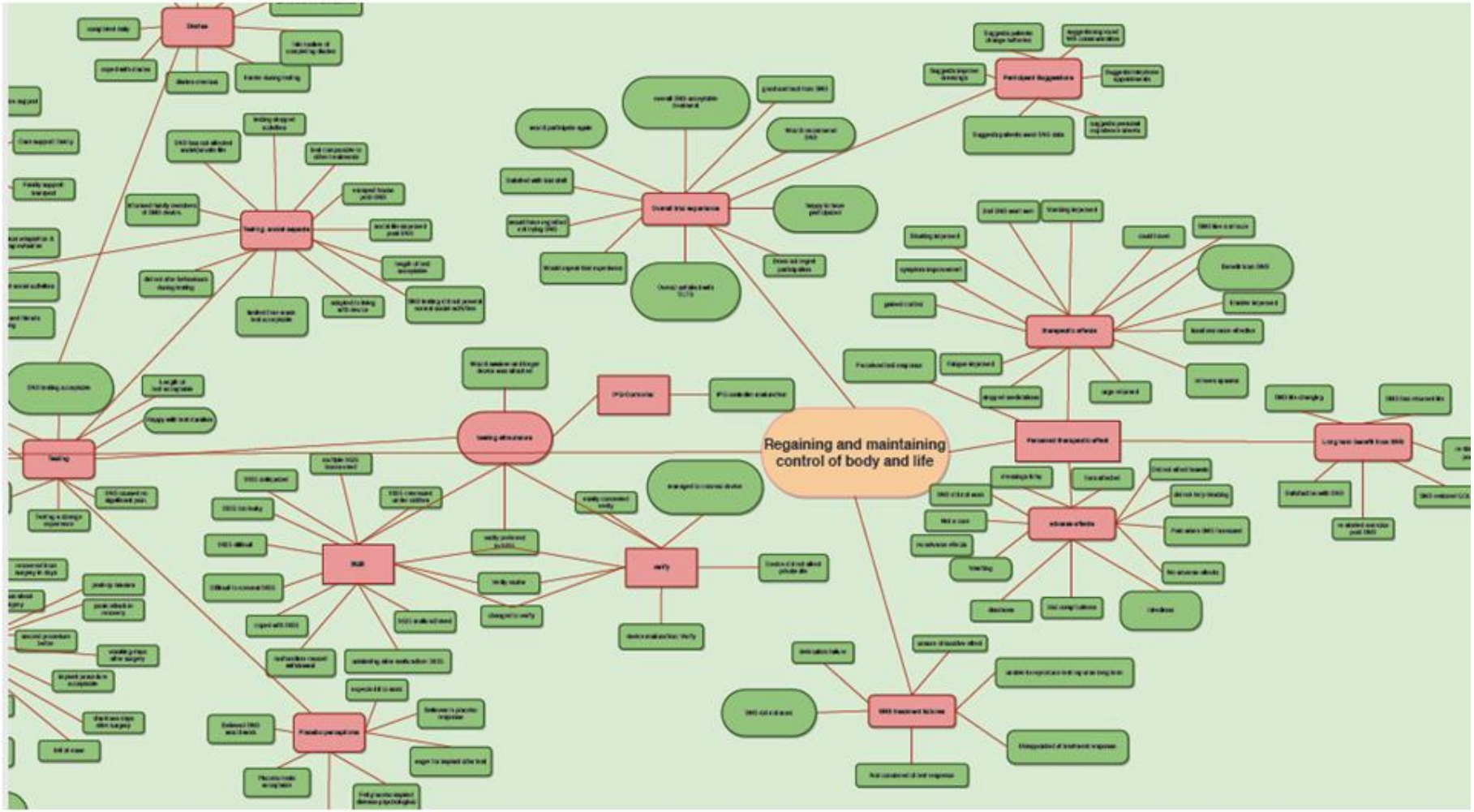
# Appendix 17 Mind Map of Healthcare Angst thematic development



# Appendix 18 Mind Map of Life-dominating disease, thematic development



# Appendix 19 Mind Map of taking control, thematic development



# Appendix 20 Mind Map of overall Coding and thematic analysis