THE EFFICACY OF SACRAL NERVE STIMULATION IN PATIENTS WITH NEUROPATHIC CONSTIPATION

USMAN KHAN

THE EFFICACY OF SACRAL NERVE STIMULATION IN PATIENTS WITH NEUROPATHIC CONSTIPATION

Usman Asad Khan

PhD Thesis
School of Medicine and Health
Durham University
2012

Supervisors:
Dr. Y. Yiannakou
Prof. J.M.Mason

THE EFFICACY OF SACRAL NERVE STIMULATION IN PATIENTS WITH NEUROPATHIC CONSTIPATION

Usman Khan

Rationale:

Constipation is a common complaint in people with neurological diseases causing significant physical and psychological distress. Poor response to therapy is due to a number of factors: severe disruption to normal physiology (gut denervation); use of constipating drugs in the presence of immobility; and co-existence of faecal incontinence and constipation precluding treatment with standard oral laxatives.

Sacral nerve stimulation (SNS) has been shown to have a beneficial effect in patients with functional constipation. It is a treatment with established efficacy for faecal incontinence, including that due to neurological disease. However, there are no studies on the efficacy of SNS in neuropathic constipation. Pilot work in this patient group was positive, thus a formal trial was indicated.

This thesis reports a proof-of-concept trial examining the effectiveness of temporary SNS in neurological constipation. The study assessed efficacy over a three-week period of temporary SNS using an off-on-off design.

Methods and principal evaluation criteria:

The trial aimed to recruit 30 patients with constipation of neurological origin from the specialist clinic at the University Hospital North Durham, over a two-year period. For each patient, the trial lasted twelve weeks, including: a pre-SNS period of six weeks of baseline assessment, a three week period of stimulation and a three week period of post-treatment assessment. The measurement schedule of symptoms and quality-of-life during the trial assessed symptom stability and the temporal effects of treatment. Physiological data was collected before and during treatment, in the form of transit studies and laser Doppler flow cytometry of rectal mucosal blood supply.

The primary outcome measure was a global assessment of severity of constipation. Self-administered questionnaires including patient assessment of symptoms (PAC-SYM) and patient assessment of quality of life (PAC-QOL), transit study, and laser Doppler flowcytometry (LDFC) constituted the secondary outcome measures.

Patients responding to temporary SNS were offered implanted permanent SNS and long term response was evaluated.

Results and possible implications:

Twenty-two patients were recruited, including 8 men and 14 women with an average age of 51.5 years (Range 38-69 yrs.). Four patients dropped out and were lost to follow-up; 18 patients completed the trial. Twelve patients (67%) had a successful response after three weeks of bilateral temporary stimulation and underwent permanent implant. The Global Assessment Score for constipation, PAC-SYM and PAC-QOL scores for these patients improved during treatment with temporary SNS ($p<0.05$). There was also an improvement in toileting time ($p=0.04$) and decrease in overall laxative use ($p=0.03$). Physiological parameters did not change. The overall response rate during long-term follow-up (mean 20 mths) was 6/12 (50%, 95%CI: 21% to 79%).

Interpretation:

Short term treatment with SNS helped two thirds of patients with neuropathic constipation in the short term. There was good symptom stability before treatment and rapid return to baseline after treatment. However, there were no improvements in the physiological measures used, so that a placebo response may have brought about the improvement in some patients. Temporary SNS only identified 50% of long-term responders.

TABLE OF CONTENTS

List of Figures

STATEMENT OF COPYRIGHT

ACKNOWLEDGMENTS

I am indebted to Yan Yiannakou and James Mason for their support and guidance over the last four years. I would also like to thank Jag Varma for supervising me and for being extremely accommodating in scheduling these research patients for SNS on his theatre lists. Without their invaluable help and encouragement it would have been impossible to conduct and finish this research.

Many thanks to Debbie Rowlie-Conwy, Anne Kelly and Liz for providing immense help with the recruitment and scheduling of participants during the study. Thanks to Mr. M Mecci for providing support and advice in the recruitment of spinal cord injury patients. Many thanks to Inspire Foundation for funding the last year of this study.

Thanks to my brother Ali Khan for helping with the illustrations, editing and proof reading the thesis.

Finally, thanks to all the patients who agreed to take part in this research trial.

DEDICATION

To my parents Asad and Nahid

1. Introduction

In this introduction constipation is described broadly as well as in terms of the more severe spectrum of patients referred to specialist clinics. The range of current treatment modalities are reviewed with their strengths and weaknesses. Particularly, attention is paid to the management of patient with neuropathic constipation, who are the subject of this thesis. Finally sacral nerve stimulation is introduced as a novel intervention requiring further evaluation in patients with severe neuroconstipation.

Constipation is caused by a range of heterogeneous conditions many of which are poorly understood. Chronic constipation can be refractory to treatment and significantly affects quality of life. Constipation has a prevalence of 5% to 20 % in the general population. In one population survey of 10,000 people in United States its overall prevalence was found to be 14.7 % (Stewart, Liberman et al. 1999). In the UK, constipation is prevalent in less than 10% of the non-clinical population but this increases to up to 25% in those above 70 years of age (Campbell, Busby et al. 1993). A recent multinational survey of 13,000 participants showed that 12 % of women and 5% of men in the United Kingdom have constipation (Wald, Scarpignato et al. 2008). The association with age is documented in the literature with constipation being more common in the very young and the very old. Similarly, women are affected more by constipation with an estimated female to male ratio of 2.2:1(Higgins and Johanson 2004) .

Constipation usually takes a chronic course with nearly half of the subjects having constipation for five or more years (Stewart, Liberman et al. 1999). Laxatives are used more often by those over 65 years of age but the overall use of laxatives has reduced in recent years (Heaton and Cripps 1993). A recent review has shown that laxatives fail to treat up to 40% of patients (Wald, Scarpignato et al. 2008). Although there is a shortage of studies directly looking at the reasons for poor quality of life with constipation, it seems to be a direct effect (O'Keefe, Talley et al. 1995).

There are nearly half a million GP consultations each year arising from constipation. As a result constipation has a substantial economic impact on the health service with an expenditure of £65 million in prescription costs for laxatives in 2009 alone (The Prescription Cost Analysis, England - 2009). A proportion of patients with constipation will not respond to standard treatment and have refractory constipation. This can be due to anatomical defects, mechanical obstruction in the bowel wall, neurological

disease or side effects of medications. These patients are difficult to manage in the primary care setting and will often require referrals to secondary or tertiary care for further treatment.

The Durham Constipation Clinic is a regional referral centre for patients with refractory disease. The clinic was established in 2001 at the University Hospital of North Durham. The clinic receives referrals from all over the Northeast of England for difficult constipation cases, receiving around 150 new patient referrals per year and with 400 currently being followed-up. In an audit of new referrals to the specialist constipation clinic at University Hospital North Durham, constipation was found to be idiopathic in 69% (Cowlam 2008). Around 10% of patients had neurogenic constipation (see section 1.5), and the rest had drug induced or other secondary constipation. These referrals represent a distinct group compared to those whose symptoms can be self-controlled or managed within primary care. The ability of the clinic to find solutions where others have failed is partly dependent on pursuing detailed assessment of patient symptoms, lifestyle and physiology, together with a multi-disciplinary approach to treatment.

1.1 Definition

Constipation is a condition caused by a variety of heterogeneous conditions. The American College of Gastroenterology described constipation as "a symptom based disorder defined as unsatisfactory defaecation and is characterised by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard /lumpy stools, prolonged time to stool or need for manual manoeuvres to pass stool" (Ramkumar and Rao 2005).

Due to the heterogeneity of the symptoms in constipation and disparity between patient and physician perceptions of constipation, it is important to classify constipation into subgroups. Constipation can be classified as either primary or secondary (Gattuso and Kamm 1993). Table 1-1 shows the classification of constipation and enlists some examples of causes of secondary constipation.

Table 1-1: Classification of Constipation

Primary Constipation	Secondary Constipation
Functional constipation	Intrinsic *(neoplasms, diverticular disease)*
Irritable bowel syndrome *(constipation predominant)*	Anorectal *(anal fissures, anal strictures, proctitis)*
Pelvic floor disorders	Neuropathic *(spinal cord injury, multiple sclerosis, Parkinson's, stroke)*
Chronic pseudo-obstruction	Metabolic *(electrolyte imbalance, thyroid disease, coeliac disease)*
Hirschsprung's disease	Pharmacological *(antidepressants, opiates, antipsychotics, iron supplements)*
Idiopathic megacolon or megarectum	Psychological
	Lifestyle or Diet

1.2 Normal Defaecation

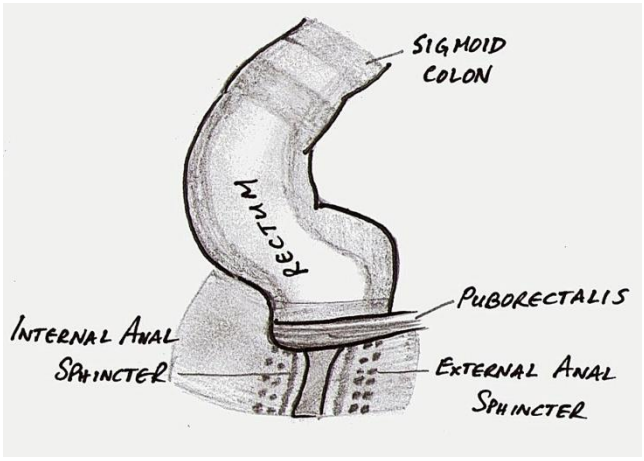
To understand the pathogenesis of constipation there is a need to understand the physiology of defaecation. Defaecation involves a complex sequence of events requiring coordination between smooth and striated muscles, central, enteric and autonomic nervous systems. The rectum acts as a reservoir for faeces, which is propagated from the colon into the rectum with help of colonic contractions. Distally, the rectum continues as the anal canal. The anorectal junction is controlled by puborectalis part of levator ani muscle. The tone of the internal anal sphincter, puborectalis and external anal sphincter help maintain continence (Figure 1-1). The external anal sphincter is the distal continuation of the levator ani and can be voluntarily controlled. Colonic mass contractions propel the stool forwards past the recto-sigmoid junction into the rectum (Sarna 1991). This leads to distension of the rectum with faeces and eventually leads to an urge to defaecate (Wester and Brubaker 1998). The intensity of this urge increases as more faeces is pushed into the rectum and causes further distension (Sun, Read et al. 1990). This distension causes rectal contractions and involuntary relaxation of the internal sphincter which pushes the rectal contents into the distal anal canal. Also,

there is contraction of the external sphincter to prevent soiling. This reflex is known as the rectoanal inhibitory reflex (RAIR) and helps in the sampling of the rectal contents to establish the need for defaecation (Read, Timms, et al. 1986).

The anal canal opens up during the defaecation reflex by straightening of the anorectal angle and blunting of the anal cushions. This is achieved by a rise in the rectal pressure and a drop in the anal canal pressure. Contraction of the abdominal muscles and a decrease in the tone of the pelvic floor musculature causes the expulsion of the rectal contents (Womack, Williams et al. 1985). As the anorectal angle opens, the stool can be pushed out by performing the Valsalva manoeuvre. If the time or place is inappropriate, the defaecation process can be voluntarily deferred.

To maintain continence the anal canal must return to its closing position. This is achieved by restoration of the anorectal angle, internal sphincter tone and the anal cushions.

Figure 1-1 Anorectal Angle



1.3 Assessment of Constipation

1.3.1 Clinical Assessment

At the Durham constipation clinic patients are assessed during a 45-minute long consultation, which includes quality of life and symptom assessment using validated questionnaires. Patients classified as having primary or secondary constipation are further subclassified predominantly into either functional constipation or irritable bowel syndrome (primary) or neuropathic or drug-induced (secondary). All patients undergo an abdominal and pelvic exam in addition to detailed history taking. At the end of the clinical assessment appropriate investigations are requested.

1.3.2 Laboratory Blood Test

These may include a full blood count, routine biochemistry profiles, liver function tests and thyroid function tests. There are no studies directly observing the utilization of laboratory blood tests for screening and managing constipation. Although there is lack of evidence in this regard, certain metabolic and biochemical disorders predisposing to constipation can be ruled out by employing specific blood tests.

1.3.3 Endoscopic Assessment

Constipation presenting in older patients may require endoscopic investigation. In a study looking at the yield of lower GI endoscopy in cases of constipation, the investigators found that the rates of colonic cancers and adenomas were similar to those seen in studies of screening in an asymptomatic general population (Pepin and Ladabaum 2002). Chronic constipation on its own may not be an appropriate indication for lower GI endoscopy. Age-appropriate screening should be pursued when patients present with constipation.

1.3.4 Imaging

Nearly all patients referred for constipation will at some point have some form of imaging to assess their large bowel. There are three types.

1.3.4.1 Colonic Transit and Plain Abdominal Films

Plain abdominal films may be helpful in diagnosing constipation but are of limited value in assessing the severity of symptoms (Cowlam, Khan et al. 2008). Scintigraphic transit studies have been validated and are reproducible, but are not routinely used due to their cost. Radio-opaque marker transit studies are routinely used and have been validated. The estimation of transit time can be achieved by using a simple bolus technique and then performing plain abdominal films. Alternatively, segmental transit can be determined with a single plain abdominal X-ray taken after ingestion of radio-opaque markers for three consecutive days (Metcalf, Phillips et al. 1987). This latter method allows a reduction in the number of x-ray exposures compared to previously described techniques.

1.3.4.2 Proctography

A defaecating barium proctogram can be utilized to rule out organic defects like rectoceles, intussusceptions, and enteroceles and to map out the function of the rectum. Measuring the anorectal angle, pelvic floor descent, rectal evacuation and time taken to initiate defaecation achieves these aims. There have been no recent reviews on the value of proctography for the initial assessment of constipation. Proctography has been shown to have no correlation with the severity of symptoms or transit times (Infantino, Masin et al. 1990)

At the Durham constipation clinic we utilize a radioisotope defaecating proctogram to determine anorectal function and identify rectoceles or prolapse. This is done by measuring parameters that have already been validated and described (Papachrysostomou, Smith et al. 1994).

1.4 Treatment options for constipation

Constipation can be an intractable condition and the aim of the therapy is to achieve normal stool frequency and consistency without unnecessary complexity. The management of constipation follows a stepped therapeutic pathway starting from lifestyle modification.

1.4.1 Lifestyle Modification

This includes increasing dietary fibre and fluid intake as well as exercise. However there is not much evidence for the use and efficacy of non-pharmacological measures and conflicting evidence concerning the role of fibre in chronic constipation. Some studies have shown a beneficial effect on constipation with improvements in symptoms where as others have shown little or no effect. (Bingham and Cummings 1989; Muller-Lissner, Kamm et al. 2005; Johanson 2007; Pare', Bridges et al. 2007).

1.4.2 Laxative Therapy

Laxatives can be prescribed if lifestyle modification proves inadequate to control symptoms. Laxatives are one of the most commonly prescribed medications and the prescription costs of laxatives in 2009 in the NHS was £65 million (The Prescription Cost Analysis, England - 2009). Generally, there are four types of laxatives: bulk-forming, stimulant, osmotic laxatives and stool softeners.

Bulking agents like psyllium retain water inside stool and facilitate peristalsis. These have been shown to increase transit time and stool frequency in adults (Cheskin, Kamal et al. 1995). Osmotic laxatives like lactulose or polyethylene glycol work by retaining water inside the colonic lumen by osmosis to prevent the formation of hard stools. These have been shown to be beneficial in chronic constipation but can produce bloating due to fermentation in the colon. Sodium docusate and other stool softeners have an unknown efficacy and there is limited data available. Similarly, due to inadequate data, the efficacy of stimulant laxatives for treating chronic constipation is not known. However, prescribing stool softeners and a stimulant laxative has been shown to be appropriate and feasible (Larkin, Sykes et al. 2008).

Newer agents like prucalopride (5-HT_4 receptor agonist) have been approved for use in chronic constipation after failure of laxative treatment (NICE guidance 2010). (See Table 1-2)

Constipation is managed in a stepwise fashion reflecting the invasiveness, complexity and in some cases cost of the available treatment. When all conservative options have been tried and exhausted, invasive treatment options may be offered to patients.

Table 1-2: Pharmacological agents for treating constipation

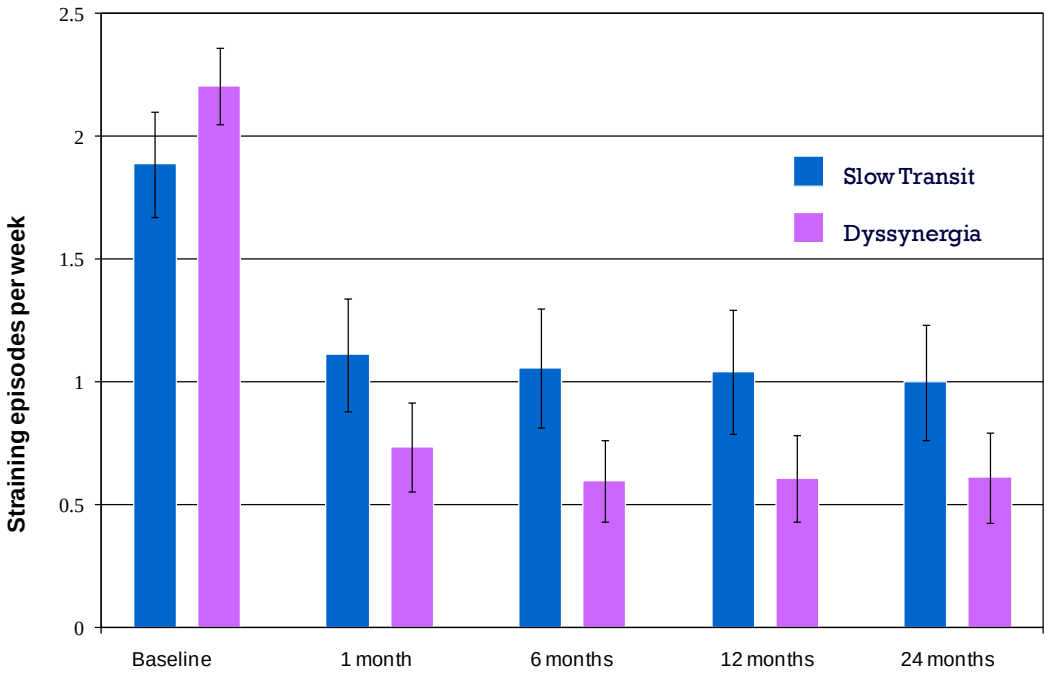
Type	Examples	Recommendation *
Bulking agents	Methylcellulose, sterculia. Psyllium (Ispaghula husk)	Unknown effectiveness Likely to be beneficial
Stool softeners	Arachis Oil, docusate, Liquid paraffin	Unknown effectiveness
Osmotic agents	Lactulose Polyethylene glycol Magnesium salts Phosphate/Citrate Enemas	Likely to be beneficial Beneficial with no side effects Unknown effectiveness Unknown effectiveness
Stimulants	Senna, Bisacodyl, glycerine suppositories	Unknown effectiveness
Newer Agents	Lubiprostone Prucalopride	Superior to placebo** Superior to placebo**

*(Frank Frizelle and Barclay 2007), **(Ford and Suares 2011)

1.4.3 Biofeedback

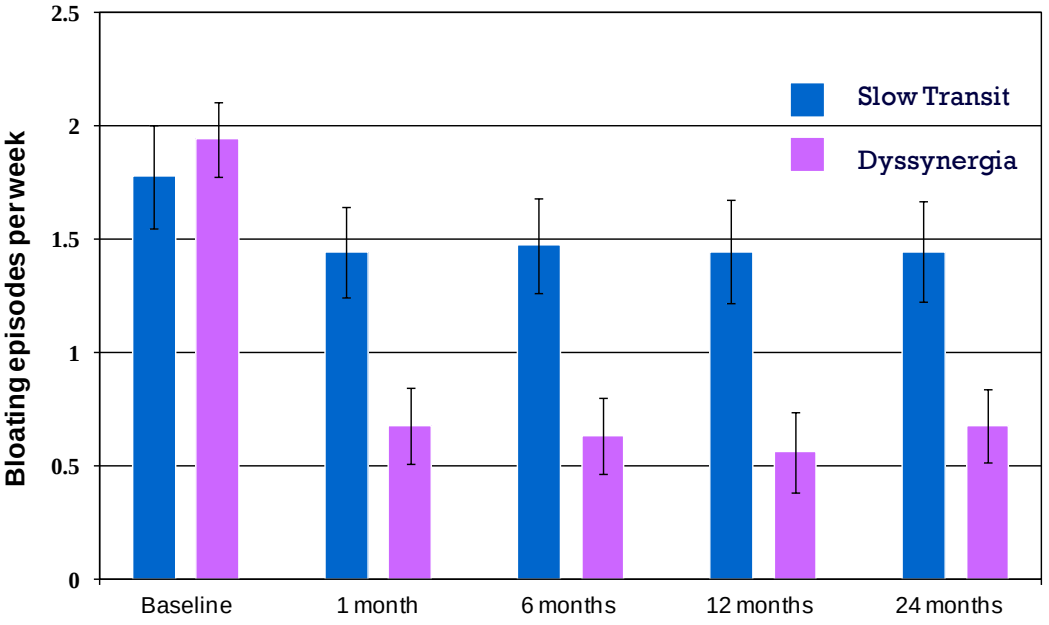
Biofeedback involves neuromuscular retraining of the pelvic floor muscles to improve evacuatory dysfunction in chronic constipation (Bassotti and Whitehead 1994; Koutsomanis, Lennard-Jones et al. 1995). There is evidence of long-term response (Chiotakakou-Faliakou, Kamm et al. 1998) with a measurable response in physiological parameters as well (Emmanuel and Kamm 2001). Patients with pelvic floor dyssynergia have been shown to receive long-term benefit from biofeedback with improvements in straining, bloating, intestinal transit and stool (Chiarioni, Salandini et al. 2005) (Figure 1-2, Figure 1-3). A recent study has shown biofeedback to be effective in patients with MS with improvements in symptoms and squeeze pressures (Preziosi, Raptis et al. 2011). However, uncontrolled series are not able to differentiate therapeutic response and natural regression of symptoms.

Figure 1-2: Straining after biofeedback



*(Chiarioni, Salandini and Whitehead 2005)

Figure 1-3: Bloating after biofeedback



*(Chiarioni, Salandini and Whitehead 2005)

1.4.4 Surgery

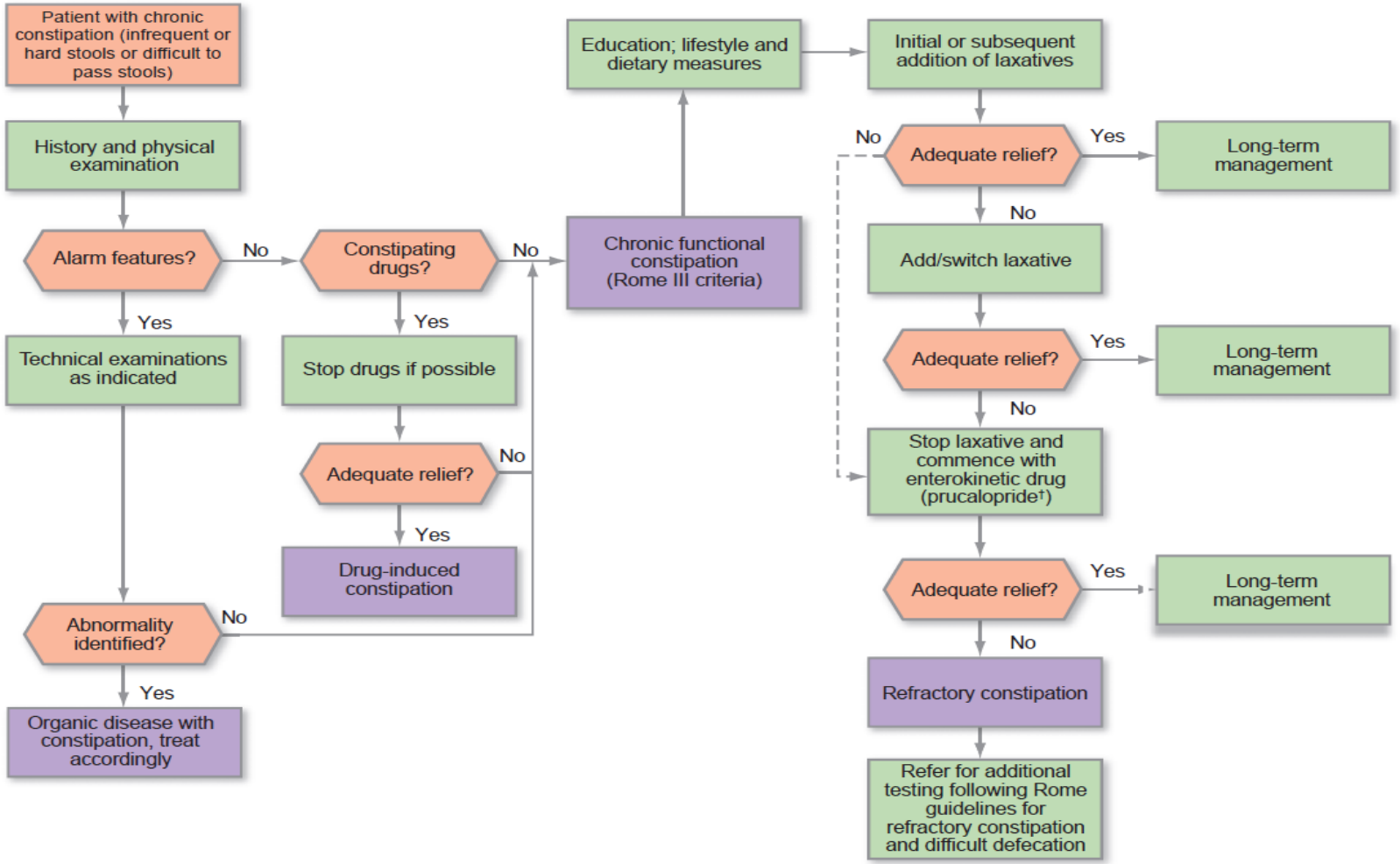
Surgery is a last resort for patients with chronic constipation and significant symptoms affecting their quality of life. Antegrade Continence Enema (ACE Procedure) can be performed in younger patients, providing effective symptomatic relief in up to 90% of patients (King, Sutcliffe et al. 2005). Some patients with severe refractory constipation finally face major surgery involving colectomy and ileorectal anastomosis. Some prefer undergoing surgery to having a stoma, which provides relief from their symptoms and can be reversed.

1.4.5 Novel therapies

Sacral nerve stimulation is a novel treatment with established efficacy in faecal incontinence. It has shown promising early results in trials for idiopathic constipation thus far: a formal NICE approval is still awaited for its use in idiopathic constipation.

In overview, a multidimensional approach is required in managing constipation with a progressive increase in treatment to formulate an appropriate bowel regimen according to the type and severity of constipation. See Figure 1-4: Treatment Algorithm for management of constipation.

Figure 1-4: Treatment Algorithm for management of constipation



**Reproduced from* (Tack et al. 2011)

1.5 Neurogenic bowel dysfunction

The enteric nervous system (ENS) is made up of neurons with cell bodies either in the submucosal layer (Meissner's Plexus) or in the myenteric layer beneath the muscular coat of the bowel (Auerbach's Plexus). These two are interconnected through inter-neurons and work in unison through physiological mechanisms that are unclear. ENS mediates reflexes that control internal sphincter relaxation during defaecation.

The extrinsic nerve supply to the gut is partly controlled by the autonomic nervous system (ANS). The ANS consists of both parasympathetic and sympathetic innervation. The parasympathetic nerve fibres innervating the proximal gut arise from the vagus nerve and the left colon, sigmoid colon and the rectum are supplied by the outflow from the ventral sacral roots (S2-S4). Parasympathetic innervation is mainly excitatory and accelerates transit and controls propulsion during defaecation. Sympathetic outflow arises from the spinal cord (T9-L2) via the lumbar ventral roots and lumbar splanchnic nerves. These provide an inhibitory input to the colon and excitatory fibres to the internal anal sphincter (IAS).

Pudendal nerves provide the somatic innervation to the external anal sphincter (EAS). The motor neuron cell bodies reside in the Onuf's nucleus in the spinal cord. The somatic innervation is both sensory and motor. Rectal afferent fibres terminate in the dorsal horn of the lumbosacral cord. Unmyelinated C fibre afferents express neuropeptides and carry the noxious and painful stimuli from the rectum. Myelinated Aδ fibres carry the sensations of rectal fullness and discomfort from the rectal mechanoreceptors. See Figure 1-5.

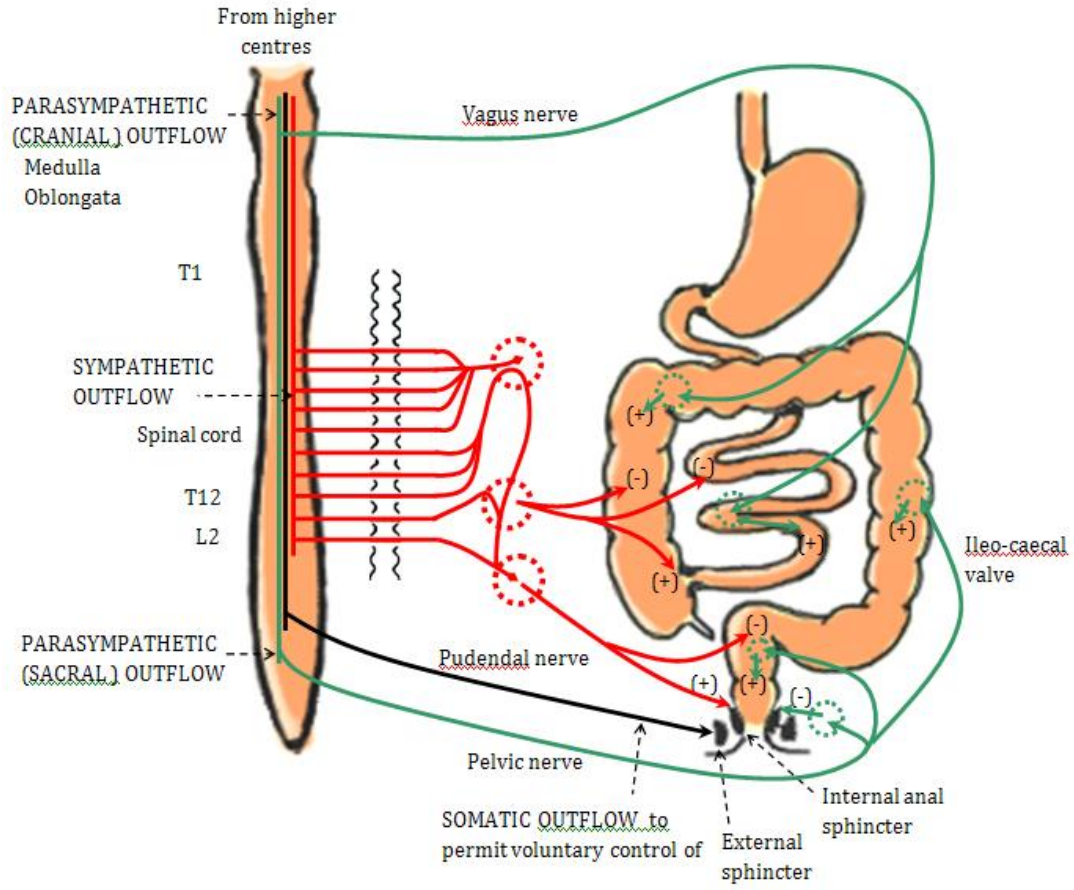
In spinal cord disease or injury the distal colon is the most affected segment of the large bowel. In lesions above the L2 segment (supraconal) sympathetic inhibition is lost. The injury pattern is similar to an upper motor neuron lesion and causes hyper-reflexia and hypertonia of the rectum (Lynch, Anthony et al. 2000). The whole gut transit is slowed. This can cause reflex defaecation and can lead to incontinence.

In cauda equina lesions, there is a lower motor neurone type presentation as the sacral reflex arc is disturbed leading to hypotonia and hyporeflexia (Krogh, Olsen et al. 2003). Both suparconal and conal injuries lead to faecal loading and impaction. This results in severe constipation leading to faecal incontinence and soiling. The most severe

dysfunction is seen in complete SCI. In incomplete SCI the level of the lesion does not correlate with the bowel dysfunction as the ENS plays some part in moderating the bowel function after the injury. The inhibitory parasympathetic input and excitatory sympathetic innervation to the IAS is lost. In complete SCI voluntary control is lost as the somatic innervation to the EAS via the pudendal nerves is disturbed.

In multiple sclerosis (MS), the pathophysiology is similar to spinal cord disease but the lesions can occur at multiple levels resulting in variable presentations in patients with MS. Previous studies have described colonic dysfunction in severe MS patients (Glick, Meshkinpour et al. 1982) and patients with spinal cord injury (Glick, Meshkinpour et al. 1984; Vallès, Vidal et al. 2006) secondary to visceral neuropathy causing severe constipation. According to one study, constipation, incontinence and nausea are all very common in spinal cord injury patients(Glickman and Kamm 1996).

Figure 1-5: Nerve supply of the Alimentary tract



1.6 Neuroconstipation

The term neuroconstipation refers to constipation due to neurological disease in the brain, spinal cord or the nerves supplying the bowel. Constipation is a major physical and psychological problem in patients with spinal cord disease and Multiple Sclerosis (MS). The prevalence of MS is 100 to 120 per 100,000 of the population; approximately 52,000 to 62,000 people in England and Wales (NICE 2003). The prevalence of constipation is between 43% and 58% in patients with MS or spinal cord injury (SCI)(Hinds, Eidelman et al. 1990; De Looze, Van Laere et al. 1998), being a significant cause of physical and emotional distress in these patients. According to a study by Glickman, 95% of patients require some form of treatment for their constipation and more than half have psychological distress caused by their symptoms (Glickman and Kamm 1996).

Neuroconstipation is a difficult condition to treat because of the complex pathological mechanisms involved. Thus, there are a number of factors contributing to constipation in patients with neurological disorders. A large proportion of these patients are either bed-bound or wheel chair bound. This reduced mobility has an adverse effect on their bowel habit causing severe constipation and faecal impaction. A poor diet with insufficient fluid intake and the lack of exercise, often compounds these problems. Patients are usually on long-term medication that can cause constipation as a side effect thus worsening their already poor bowel habit. Some patients on laxatives start experiencing diarrhoea which can cause incontinence.

1.6.1 Treatment Options for neuroconstipation.

Managing neuroconstipation is difficult in this heterogeneous group of patients with multiple aetiologies. The goal of therapy is to provide effective symptom relief while maintaining patient dignity and independence. The treatment also has to be cost-effective for it to be sustainably provided.

The options for managing neuroconstipation include manual evacuation with digital stimulation, pharmacological management with laxatives, suppositories and/or enemas, transanal irrigation and faecal diversion by formation of stomas.

Patients with SCI suffer from unplanned evacuations leading to faecal incontinence and urinary tract infections. Presence of hard stools leads to prolonged toileting times in patients with SCI. In a multi-centre cross-sectional study of 837 patients with SCI, Haas

et al found manual evacuation to be effective in patients with hard stools (Haas, Geng et al. 2005). Manual evacuation also decreased the frequency of unplanned bowel movements and duration of toileting time. There was no evidence of injury to the anal canal sustained during manual evacuation. Although effective in patients with SCI, manual evacuation is very labour intensive and takes several hours to complete. The procedure has to be repeated every two to three days and carries a significant carer associated cost.

Laxatives are associated with significant unplanned evacuations resulting in faecal incontinence. Soft or liquid stools result from laxative use and may lead to increased toileting time as well. Patients taking laxatives over a period of time often require increasing amounts of laxatives which may cause more difficulty in bowel evacuations. However, some patients with incomplete SCI having some control over their bowel function do seem to benefit positively form laxative therapy. (Harari, Sarkarati et al. 1997; Lynch, Wong et al. 2000)

For those patients undergoing surgery, a systematic review published in 2008 did not identify any functional or QOL related advantages in patients undergoing a colostomy when compared to SCI patients with an ileostomy. Toileting time was shown to significantly reduce in patients with a stoma (colostomy or ileostomy) and patients were satisfied with their stomas. (Hocevar and Gray 2008)

Surgery for diversion carries a significant risk of early or late complications. A retrospective study in 32 patients with SCI recorded increased patient satisfaction and a decrease in toileting time (from 10.3 hrs/week to 1.9 hrs/week). However, 44% of patients suffered from complications (6% early, 37.5% late). These included diversion colitis, faecal fistula, parastomal hernias and adhesional bowel obstruction. (Branagan, Tromans et al. 2003)

Transanal irrigation (TAI) is another treatment modality which has been shown to be effective and safe in patients with neuroconstipation. There is no standard protocol for TAI and treatment depends on individual response. TAI involves using a pump for irrigating the large bowel with tap water which results in evacuation of large bowel. Scintigraphic studies during TAI have shown that patients with SCI manage to evacuate most of their left colon and that TAI is more effective in patients with SCI (Christensen, Olsen et al. 2003).

A randomized controlled trial in 87 patients with SCI and neurogenic bowel dysfunction compared ten weeks of TAI with ten weeks of conservative management. The patients with SCI had both complete and incomplete spinal injuries. Subjective scoring methods were used to analyze the outcomes (Cleveland clinic constipation scoring system, St. Mark's FI score, NBD score). Patients receiving TAI reported improved QOL, a decrease in toileting time (from 74 mins/day to 47 mins/day), a decrease in the frequency of urinary infections and improved overall satisfaction. The study period was extended to include another 20 patients in the TAI group but the investigators did not identify any predictors of response to TAI (Christensen, Bazzocchi et al. 2006). The evidence for TAI in patients with MS is limited to observational studies with mixed reports.

In a 10 year follow-up study carried out in Denmark in 348 patients with different aetiologies, TAI was successful in 47% (145/348) of patients and treatment failure occurred in 53% (203/348) of patients. Patients with neurogenic bowel dysfunction had a better response to TAI than patients with other aetiologies. TAI was effective in 62% of patients with SCI (n=68) and 50% of patients with MS (n=10). The reported frequency of TAI was daily (36%), every other day (35%), two to three times per week (25%) and once per week (14%). A significant number of treatment failures ended up having surgery (23%, n=81) with 18 patients undergoing SNS. TAI was shown to be very safe with a perforation rate of 1 per 55000 irrigations (0.002%). Other side effects included abdominal pain, sweating and general discomfort but overall TAI was well tolerated. (Christensen, Krogh et al. 2009)

TAI is a safe and effective treatment option but requires a high frequency of treatment (every 2nd day in the Christensen study) and significant duration of toileting time. In contrast sacral nerve stimulation (SNS) offers a potential minimally invasive but unevaluated alternative.

1.7 Sacral Nerve Stimulation

Although not assessed in neuro-constipation, sacral nerve stimulation (SNS) has been extensively evaluated as a minimally invasive treatment option for patients with idiopathic constipation and/or faecal incontinence who have failed maximal conservative therapy. It involves continuing low-level stimulation of the sacral nerves to affect the hindgut, pelvic floor and the anal sphincters. It is a two-stage procedure

with a temporary (diagnostic) and permanent (therapeutic) stage and has been directly adapted from its use in treating urinary dysfunction (Figure 1-6).

Figure 1-6: Sacral Nerve Stimulation

1.7.1 Background

The origin of SNS lies in the 1950s when research work was carried out to find new treatment modalities for urinary dysfunction. Early studies involved direct stimulation of the spinal cord, followed by work on the detrusor muscle and the striated sphincter. Results of these studies were unsatisfactory, so the focus shifted towards SNS. It was observed that bowel function improved in patients undergoing SNS for urinary dysfunction, prompting interest in treating functional bowel disorders with SNS (Pettit, Thompson et al. 2002). The first permanent implant for SNS was reported in 1981 by E.

Tanagho and R. Schmidt, for the treatment of bladder dysfunction such as urge incontinence and non-obstructive urinary retention (Tanagho and Schmidt 1982).

1.7.2 Technique

Diagnostic or temporary SNS (TSNS) involves percutaneous placement of a needle inside the sacral foramina followed by the use of a stimulator to evaluate muscle responses in the pelvic floor. This helps to identify the sacral foramen offering the most appropriate response. The procedure requires a short general anaesthetic and has no major complications.

After evaluation and identification of an adequate response, the needle is substituted with a temporary nerve electrode, which is connected to an external stimulator for a short evaluative period typically two to three weeks. Functional response can then be assessed using objective measures such as transit time and subjectively by patient symptoms. Temporary SNS provides a diagnostic and screening stage and helps to identify patients who may benefit from a permanent implant. The temporary electrode can later be replaced with a permanent electrode placed surgically (under a general anaesthetic) inside the foramen of choice (usually S3) with an implantable pulse generator (IPG) placed subcutaneously. See Figure 1-7, Figure 1-8, Figure 1-9, Figure 1-10.

Figure 1-7: S3 foramen electrode placement for SNS

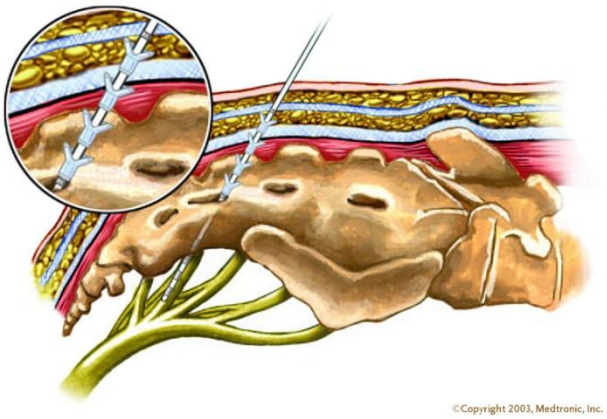
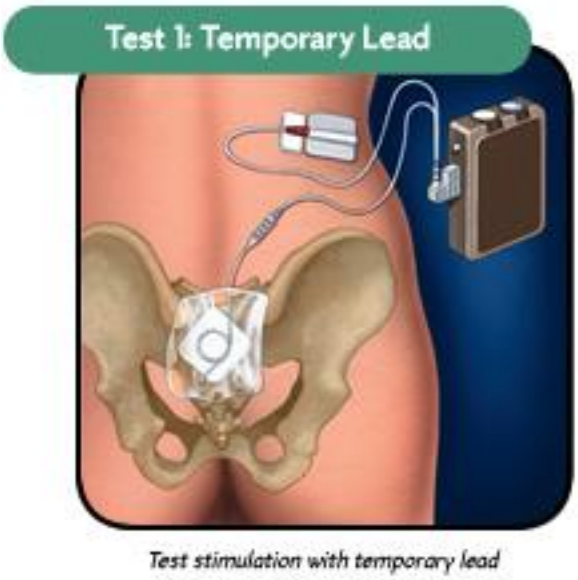


Figure 1-8: TSNS with helical lead



Test stimulation with temporary lead

Figure 1-9: TSNS with tined lead

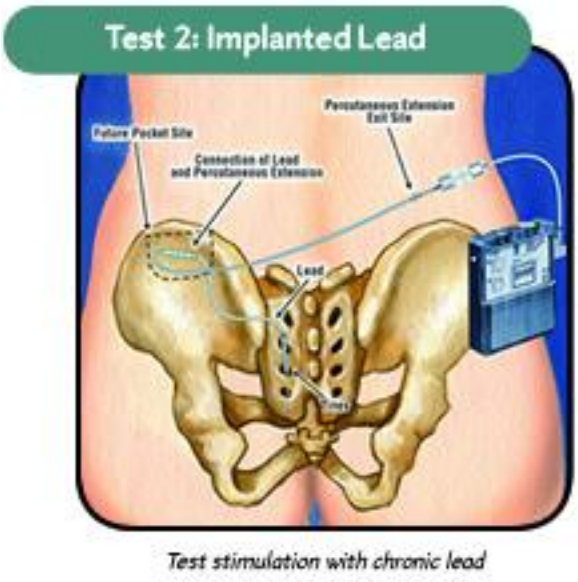


Figure 1-10: Implantable pulse generator (IPG)

1.7.3 Mechanism of Action

SNS is thought to modulate the sacral outflow thus affecting the bowel through mechanisms which are still not clear. It is thought to have its effect at local, central and even molecular levels. Somatic efferent nerves of S2, S3 and S4 innervate the external sphincters and pelvic floor. It appears that the effects of SNS on the pelvic floor are due to afferent fibre activation and by a sacral reflex arc which leads to better pelvic control. This in turn improves bladder and bowel function.

SNS may act on the central cortico-anal pathways to modulate bowel activity. It has been shown to have an inhibitory effect on motor cortical pathways to the external anal sphincter in incontinent patients after two weeks of stimulation(Sheldon, Kiff et al. 2005). Also, SNS seems to have some effect on cerebral somatosensory evoked potentials in both incontinence and constipation(Giani, Novelli et al. 2011; Griffin, Pickering et al. 2011). This suggests that in addition to the localized effect on spinal cord pathways, SNS may bring about dynamic changes in cortico-anal excitability via a central mechanism of action influencing the motor cortex.

Neurotransmitters like 5-HT and substance P interact with the enteric nervous system at mucosal and submucosal levels, affecting gut sensitivity, peristalsis and secretion. Recent studies have shown increased rectal mucosal levels of Substance P in incontinent patients and conversely decreased rectal mucosal levels in patients with slow transit constipation(Gooneratne, Facer et al. 2008). It is possible that SNS modulates neurotransmitter activity at a molecular level thus bringing about its effects on the gut.

1.7.4 SNS in neuroconstipation

The National Institute of Clinical Excellence has approved SNS for use in faecal incontinence and voiding dysfunction. In addition to the extensive work on SNS in relation to faecal incontinence, there is a limited body of evidence for the role of SNS in constipation.

A pan-European multi-centre study of SNS in functional constipation has now been completed with preliminary results presented at conference showing efficacy in two thirds of patients in terms of symptom improvement (Kamm, Dudding et al. 2010). No study to date has involved constipation due to neurological disease alone, though

theoretically this would seem the most obvious cohort to study, since the treatment may restore the compromised parasympathetic supply to the hindgut.

1.7.5 Rationale for SNS work in neuro-constipation

McDonagh et al demonstrated that complete control of defaecation is possible in spinal injury patients after sacral nerve stimulation by an intradural catheter(MacDonagh, Sun et al. 1990). This was reported in a series of 12 consecutive spinal injury patients with a success rate of 50%. The investigators employed a technique that stimulated the anterior roots of the sacral nerves by surgically placing an intradural catheter. However, this was a very invasive surgical procedure involving implantation of a Brindley-Finetech root stimulator along the anterior sacral nerve roots along with deafferentation of the posterior sacral nerve roots. The operative time was long and the patients underwent a complex procedure requiring significant surgical exposure. The rate of morbidity and complications from the procedure was high.

In contrast, SNS is a minimally invasive and very safe procedure with promising results. Theoretically speaking, SNS augments the extrinsic nerve supply to the bowel which is impaired in patients with neurogenic bowel dysfunction. Recent results have been promising: a recently concluded study of SNS for faecal incontinence has shown that patients with a neurological cause had the best outcome (Gourcerol, Gallas et al. 2007).

Autonomic Dysreflexia (AD) was a concern in patients with spinal cord injury. Noxious and non-noxious stimuli can lead to AD in patients with SCI above T5-T6 segments. It can cause headache, dysrhythmias, flushing and sweating above the lesion and vasoconstriction below the lesion. This may be associated with a sudden bout of hypertension. Patients can also experience piloerection, stuffy nose, anxiety, malaise and diaphoresis. This is due to widespread activation of sympathetic activity below the lesion and release of catecholamines. This can occur several times a day and can be asymptomatic.

Patients with high cord injuries had been thoroughly assessed at the regional spinal injury unit before referral to the constipation clinic. All patients with SCI had stable injuries older than at least six months. All patients with SCI were asked about symptoms and signs of AD at their first clinic visit. None of the patients recruited had a previous history of AD and they were advised to inform the clinical team in case of any adverse event. At the University Hospital of North Durham, SNS was offered to five

patients with neurogenic bowel dysfunction and four of them responded positively to the test stage of SNS. Three out of these four patients had a permanent stimulator implanted and reported marked improvement in their symptoms. Based on these experiences a formal study was planned to assess SNS and develop further knowledge in this field.

1.7.6 Rationale for this PhD

Neuroconstipation is a significant problem. This thesis brings together existing knowledge on SNS in neuroconstipation to assess the construct validity of this approach to care. It reports a trial of the efficacy of SNS in neurological constipation after temporary and permanent implantation. It substantially advances knowledge regarding SNS in neuroconstipation informing the future research agenda and future application in clinical practice. In the Chapter 2 a systematic review of the available literature on SNS is provided. In Chapter 3 the protocol and the methods used to conduct the trial are described. Chapters 4, 5 and 6 provide and explore the trial findings. An interpretation of trial findings, strengths, weaknesses and future direction are provided in Chapter 7.

2. Systematic Literature Review

2.1 Aim

This review summarises current published evidence addressing the use and efficacy of sacral nerve stimulation (SNS) in constipation.

2.2 Methods for review

2.2.1 Search Strategy

Electronic systematic literature searches were carried out using the databases provided by the National Library for Health website. Searching identified studies evaluating SNS used in constipation. Search terms utilizing Boolean logic were used to retrieve citations from the databases. Duplicates were removed. All studies were searched individually and relevant references were identified and retrieved. MEDLINE, EMBASE, CINAHL, OVID and Cochrane databases were searched for relevant studies.

Mesh terms included constipation, defecation, anorectal disorders, rectal diseases, anus diseases, anal canal, rectum, stimulation, electric stimulation, electrostimulation, electric stimulation therapy, neuromodulation, sacral spinal cord, lumbosacral spine, sacrum and lumbosacral plexus.

2.2.2 Inclusion criteria for the studies

Types of studies included were randomised controlled trials, case series, case reports, systematic reviews and narrative reviews.

Participants included were adults with constipation. The primary purpose of this review was to determine the efficacy and safety of SNS in a subgroup of patients with spinal cord disease or central neurological disease suffering from constipation by identifying studies describing the use of SNS in adults with neuroconstipation. Due to the paucity of adequate data, all studies of SNS in constipation were included regardless of underlying pathology or cause.

The only type of intervention considered is sacral nerve stimulation for constipation. Studies solely addressing SNS only in faecal incontinence were excluded. Reports

containing data on patients with both faecal incontinence and constipation were included.

Outcomes were considered in the following categories.

Improvement in Constipation: This was demonstrated by the proportion of participants who were cured or improved symptomatically, a decrease in use of laxatives, an increase in bowel movements, a decrease in episodes of straining and decrease in time with pain and bloating.

Quality of life: Both disease-specific and generic measures were considered.

Physiological measures: measures of anorectal physiology (resting pressure, maximal squeeze pressure, rectal sensory threshold to balloon distension, sensation of urgency to balloon distension and maximal tolerated rectal volume to balloon distension) were included in addition to transit studies.

Adverse effects: infection at the electrode site, pain at the implant site, electrode dislodgement, and technical failure of the device.

2.2.3 Exclusion criteria for the studies

Studies not meeting the inclusion criteria and non-English studies were excluded. Studies including patients with faecal incontinence only were excluded; as were studies on magnetic or cutaneous sacral nerve stimulation.

2.2.4 Data Extraction

The titles and abstracts of all the relevant studies were screened and then full text copies were requested for studies that were considered to be relevant. The references of the retrieved papers were checked to identify further relevant reports.

2.2.5 Analysis

If sufficient trials of a certain methodological quality were available (for example randomized controlled trials), these were analysed without reference to weaker study designs. In the absence of adequate high quality data, all evidence was described, analysing improvements in the context of whatever reference or control assessments are available. Since patients are offered SNS after a long period of chronic constipation, then persistent benefit from SNS treatment is likely to be an attributable treatment effect.

2.2.6 Data synthesis

Where studies of similar design and method reported comparable outcomes these were pooled using fixed effects methods, reporting findings and interpreting indicators of heterogeneity and consistency of treatment effect with study size.

2.3 Results

Number of studies found was as follows:

MEDLINE (1950 to date): Forty-eight citations on SNS and bowel disorders, which were reduced to nine studies addressing SNS and constipation.

EMBASE (1974 to date): Ten studies were found addressing SNS and bowel disorders.

CINAHL (1982 to date): Two studies found.

OVID: none.

COCHRANE: There were no relevant reviews or reports found.

A detail of the search strategy is attached in the appendix B (Page 171-173).

2.3.1 Studies predating SNS

Three papers were more than ten years old and described different techniques for stimulating either the spinal cord or the anterior sacral nerve roots. The results and techniques reported in these papers describe the origins underpinning the development of SNS. Both procedures preceded the modern technique of sacral nerve stimulation.

A study published in 1982 (Pescatori and Meglio 1982) presented data on two patients with neuroconstipation who were treated with spinal cord stimulation for chronic constipation. This was achieved by placing epidural electrodes under local anaesthesia at the level of T8 and T9 respectively. Low frequency electrical current stimulated these electrodes and the patients were assessed using physiological and clinical parameters. There was improvement in the transit time after the procedure and both patients achieved spontaneous defaecation without the use of laxatives within 12 hours of stimulation. The authors suggested that neuro-stimulation was improved propulsion in the distal colon in addition to activating neural pathways leading to improvement in bowel frequency.

Shafik demonstrated that controlled defaecation was possible in a canine model after stimulation of S2 ventral nerve root with electric current (Shafik 1995). The use of electrical stimulation of sacral roots was suggested for both incontinence and neuro-constipation.

Binnie and colleagues implanted a Brindley Fine-tech catheter, stimulating the S234 anterior sacral nerve roots, in seven patients with spinal cord injury (SCI) (Binnie, Smith et al. 1991). Data from a control group of SCI patients was compared with the group with SCI and Brindley implants. When compared to the control group, patients with the Brindley stimulator had more frequent bowel movements and decreased colonic transit time. This was attributed to the motor influence of the sacral root stimulation on the left colon and rectum. These studies were instrumental in developing the basic knowledge on nerve stimulation and led to further work that has shaped the way SNS is being utilized in modern clinical practice.

2.3.2 Number and type of studies and enrolled patients

Fourteen studies matched the inclusion criteria for this review. There was one double-blind placebo controlled trial, ten case series, one abstract, and two reviews. The two reviews included the studies covered in this chapter and did not identify any new studies (Jarrett, Mowatt et al. 2004; Kenefick 2006)

Overall one hundred and ninety eight patients were enrolled with a median age of 45.8 years and a range between 17-79 years, and including one hundred and seventy women and twenty eight men. The symptom duration ranged between 2-47 years, but this finding was only reported in 3 studies. The patients recruited in these studies were followed up over a period of time ranging from 2 weeks to 2 years. Six patients were reported as being lost to follow-up. The characteristics of these patients are shown in Table 2-1.

Table 2-1: Demographics

Study id	No.	Age (range)	Gender	Symptom Duration	Follow-up (m,w,d)	FU range (m,w,d)	Lost to FU
Dinning 2007	8	43(20-59 y)	8 F	24 (2-45 y)	3 w	0	2
E Ganio 2001	12	47(27-75 y)	9 F 3M	-	9.9 d	7 - 30 d	2
E Ganio 2002	16	49.2(30-72y)	13 F 3M	-	12 m	-	-
Hetzer et al. 2006	2	68(60-74y)	2 F	-	2 w	-	-
Holzer 2008	19	-	19F	-	11 m	2-20 m	-
Maeda et al. 2010	38	45.6(21-66)	32F 6M	-	25.7 m	0-70	-
Malouf 2002	8	47(35-68 y)	8 F	31 (9-47 y)	3 w	0	0
Kamm 2010	62	40(17-79y)	55F 7M	-	28 m	1 – 55 m	-
Naldini et al. 2010	15	45.7(25-64)	13F 2M	-	42 m	24-60 m	-
Kenefick, C Vaizey 2002*	2	36 y	2 F	-	2+2 w	-	-
Kenefick, Nicholls 2002**	4	33.5(27-36y)	4 F	22 (8-32 y)	8 m	1-11 m	2
Lombardi et al. 2010	12	39 +/- 10y	5F 7M	-	38 m	-	-
Total	198	45.8 (17-79)	170 F 28 M	-	-	-	6

**Unclear if patients from previous studies were included (Malouf, Kenefick)*

*** Included 2 patients from the Malouf study, going forward to P-SNS*

For the 198 patients, there were 146 cases of temporary SNS and 134 cases of permanent SNS. Kenefick enrolled four patients who all received a permanent implant after temporary stimulation (Kenefick, Nicholls et al. 2002) . In this study, two patients out of the four enrolled were lost to follow-up and did not complete the six-month assessment. Maeda reported 38 patients receiving a permanent implant although the number receiving temporary SNS was not reported (Maeda, Lundby et al. 2010). Similarly, Lombardi reported 12 patients with constipation receiving permanent SNS out of a total of 23 (11 FI patients)(Lombardi, Del Popolo et al. 2010). See Table 2-2.

Table 2-2: Permanent and temporary SNS in neuroconstipation

Study id	Enrolled	T-SNS	P-SNS
Dinning 2007	8	8	-
E Ganio 2001	12	12	-
E Ganio 2002	16	16	16
Hetzer et al. 2006	2	2	-
Holzer 2008	19	19	8
Maeda et al. 2010	38	-	38
Malouf,2002	8	8	-
Kamm 2010	62	62	45
Naldini et al. 2010	15	15	9
Kenefick, C J Vaizey 2002	2	-	2
Kenefick, R J Nicholls 2002	4	4	4
Lombardi et al. 2010	12	-	12
Total	198	146	134

Where estimates were consistently reported, meta-analysis was attempted to describe changes in measures of constipation. A fixed effect model was utilised, describing heterogeneity and vulnerability to bias.

2.3.3 SNS in neuroconstipation

One retrospective case series for neurogenic bowel dysfunction was identified. Lombardi and colleagues performed temporary SNS in 39 patients with incomplete spinal cord injury (SCI) suffering from neurogenic bowel dysfunction(Lombardi, Del Popolo et al.). Patients suffered from both faecal incontinence and constipation. Twenty three of the thirty nine patients received a permanent implant. Of these, only 12 patients suffered from constipation. The median number of bowel movements per week increased from 1.65 (1.5-2) to 4.98 (4.5-7) per week. The Wexner score improved from 19.91 (17-23) to 6.55 (4-9). The toileting time per defaecation also improved from 45.85 min (20-80 min) to 10.81 (5-15 min).

A European multi-centre study enrolled the largest number of cases (Kamm, Dudding et al. 2010), with 62 patients undergoing T-SNS and 45 subsequently receiving P-SNS. A case-series of sixteen patients presented at a conference in Italy in 2002 (Ganio 2002), has not subsequently been published in detail.

A double-blind placebo controlled crossover design included two women who received an SNS implant 12 months previously (Kenefick, Vaizey et al. 2002). Both the investigators and the patients were blinded by giving sub-sensory stimulation in "on" or "off" mode for two 2-week intervals. Diary cards were kept during those weeks and anorectal physiology was assessed.

Naldini performed SNS in 15 patients with slow transit constipation. Nine of the fifteen patients had a good response with a sustained improvement in constipation symptom scores and quality of life (SF-36)(Naldini, Martellucci et al. 2010).

There were two further reports of SNS that were considered relevant and are included. Hetzer described the technique of video-assisted SNS on six patients by using a fibre optic camera to monitor pelvic responses at the time of electrode insertion(Hetzer, Hahnloser et al. 2006). This enabled them to completely separate the pelvic area with a drape and potentially decrease the chance of infection. Two of the six patients recruited in this study had idiopathic constipation. Dinning demonstrated that SNS produces pan-colonic propagating pressure waves in patients with refractory constipation, which are essential for defaecation. This coincided with symptomatic improvement in six of the eight participants in the trial(Dinning, Fuentealba et al. 2007).

2.3.4 Improvement in constipation

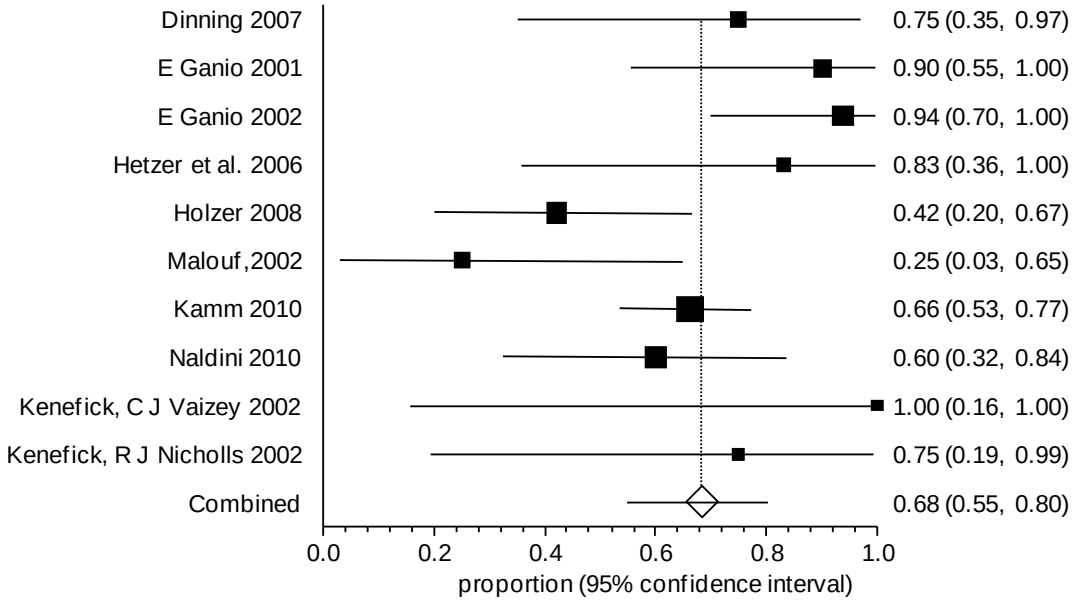
There were no standardized assessment criteria to define improvement and different tools were employed in each study. For example, 'response' rates were variously assessed using visual analogue scores, bowel frequency, percentage time with abdominal bloating/pain and use of laxatives. Patient responses assessed as an improvement in symptoms were recorded for one hundred and fifty three patients in these studies. A response to SNS occurred in one hundred and two of one hundred and thirty eight patients (67%), documented by symptoms scores and diaries. This is similar to the finding from the largest study: 45 out of the 62 patients within the multicentre trial (73%) had satisfactory clinical improvement defined as a >50%

improvement in symptoms(Kamm, Dudding et al. 2010). These patients went on to receive a permanent implant. See Table 2-3.

Table 2-3: Response rates

Study id	Improved
Dinning 2007	6/8 (75%)
E Ganio 2001*	9/10(90%)
E Ganio 2002	15/16(94%)
Hetzer et al. 2006**	5/6 (83%)
Holzer 2008	8/19(42%)
Malouf,2002	2/8 (25%)
Kamm 2010	45/62(73%)
Naldini 2010	9/15(60%)
Kenefick, C J Vaizey 2002	2/2(100%)
Kenefick, R J Nicholls 2002	3/4 (75%)
10 of the 12 patients completed the necessary period of stimulation* * Results were given collectively, only 2 patients had constipation*	

Figure 2-1: Analysis of Reported Response Rates to SNS (Random Effects)



These findings can be shown visually on a forest plot (see Figure 2.1). Using a fixed effects model the pooled proportion was 0.677 (95% CI = 0.600 to 0.750). However there was substantially heterogeneity between studies Q, p=0.005; I^2= 63.4%. A random effects model (DerSimonian-Laird) assumes that the true underlying value is distributed rather than taking a single value and is a more appropriate summary when heterogeneity is present: proportion [DL] = 0.696 (95% CI = 0.547 to 0.827). Unfortunately it does not identify the reason for heterogeneity and the studies are too few and small to meaningfully explore the variations in design and conduct. Although the number of studies is small, there was no evidence that the response rate varied with study size (Egger: bias p = 0.86), which might occur due to publication bias or study quality varying with study size. Malouf recorded a response rate of 25% in eight patients with longstanding slow-transit constipation undergoing T-SNS (Malouf, Wiesel et al. 2002). Thus, these patients might be considered more severe than other patient groups.

2.3.5 Outcomes

2.3.5.1 Bowel Frequency

There was evidence of improvement in frequency of bowel movements. At latest follow-up the bowel frequency improved from a baseline of 3.3 (0.5-28) before stimulation to 8.04 (1-21) after SNS. There was good correlation between temporary and permanent stages of SNS. Crude average rates are reported as it was not possible to abstract measures of variance consistently to permit meta-analysis of findings. See Table 2-4

Table 2-4: Bowel frequency

Study id	Pre SNS BMs/wk (Range)	After SNS (Range)
Dinning 2007	0.8	7.4 +/- 2.7
E Ganio 2001	9.5(2-28)	6.4(2-14)
E Ganio 2002	2.1(0.5-10)	3.5 (1-9)
		11.5 (5-21)
Malouf,2002	4.5(1-9)	6(2-13)
Kamm 2010	2.3	6.6
Naldini et al. 2010	1.7	3.3
Kenefick, R J Nicholls 2002 PSNS	3.25(1-6)	23(20-26)
Kenefick, R J Nicholls 2002TSNS	3.25(1-6)	8.25(9-13)
Lombardi et al. 2010	1.65 (1.5-2)	5.40 (4.5-7)

The data from the double-blind placebo controlled trial suggests that SNS has an effect greater than placebo (Kenefick, Vaizey et al. 2002). The two women received the implant 12 months before the study and the number of bowel movements during the inactive period was less than the number of defaecations during the stimulation period. See Table 2-5

Table 2-5: Bowel frequency

N J Kenefick, C J Vaizey, et al. 2002	BM/week (range)	Stimulation off	Stimulation On
	3.5(1-6)	3(2-4)	9(8-10)

Hetzer reported the safety of Video-assisted SNS and did not provide detailed outcome information (Hetzer, Hahnloser et al. 2006). Two patients in the Kenefick trial were lost to follow-up and the long-term figures were only available for two patients (Kenefick, Vaizey et al. 2002).

2.3.5.2 Constipation Scores

A variety of scores were reported in studies. The Wexner scale [6 studies] and Visual analogue score (VAS) [3 studies] were used variously before and after stimulation. Each score had its own scale: VAS 0: severe symptoms, 100: no symptoms; Wexner 0: best, 30: worst. Kenefick used both Wexner and VAS scores (Kenefick, Vaizey et al. 2002): both scores showed an improvement after TSNS in all four patients. Six month follow-up data after receiving implants was only available for two patients showing improvement in both Wexner and VAS. There was improvement in VAS and Wexner scores in all studies. One study utilized weekly laxative use as a score showing a reduction in the use of laxatives (Dinning, Fuentealba et al. 2007). See Table 2-6,Table 2-7.

The change in Wexner score is shown visually on a forest plot (see Figure 2.2). Using a random effects model the change in score was 12.03 (95% CI = 10.05 to 14.00). There was substantially heterogeneity between studies Q= 25.22; I^2= 80.17%. A random effects model (DerSimonian-Laird) assumes that the true underlying value is distributed rather than taking a single value and is a more appropriate summary when heterogeneity is present.

Figure 2-2 Change in Wexner score (random effects model)

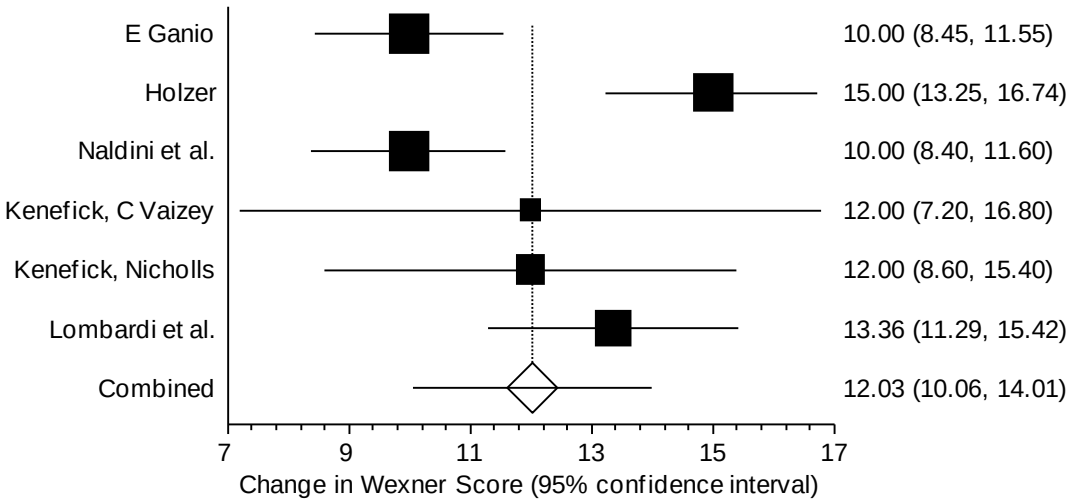


Table 2-6: Constipation scores

Study id	Constipation scores	Baseline (Range)	After SNS (mean)
Dinning 2007	Laxative use (days/week)	4.7+/- 3	1.5 +/- 1.9
E Ganio 2001	-	-	-
E Ganio 2002	Wexner (0-30)	14.6 (8-20)	4.6 (0-14) @3mths
			2.7 (3-16)@12 mths
Holzer 2008	Wexner (0-30)	23 (18-27)	8(4-13))@12 mths
Malouf 2002	VAS	15 (4-33)	30.3(2-88)
Kamm 2010	Wexner (0-30)	18	10.2
	VAS	18	66
Naldini et al. 2010	Wexner (0-30)	21(11-27)	11 (3-20)
Kenefick, R J Nicholls 2002 PSNS	Wexner (0-30)	16 (8-24)	5.5 (1-10)
	VAS [0-100]	16.5 (10-21)	90 (80-100)
Kenefick, R J Nicholls 2002 PSNS	Wexner (0-30)	21.5 (20-23)	13.7 (7-14)
	VAS [0-100]	22.5 (15-30)	67 (35-88)
Lombardi et al. 2010	Wexner (0-30)	19.91 (17-23)	6.55 (4-9)

VAS, 0=severe symptoms 100= no symptoms;

Wexner 0= Best 30= Worst;

In the double-blind crossover trial there was considerable difference in the Wexner and VAS scores during the two periods. There was a visible improvement in both scores while the stimulation was “on”.

Table 2-7: Constipation scores

	Score	Baseline (range)	Stimulation off	Stimulation On
Kenefick, C J Vaizey 2002	**Wexner**	21 (22 & 30)	14 (15&13)	9(5&13)
	VAS	30 (32 &28)	31.5(30 & 33)	74 (88 & 60)

2.3.5.3 Anorectal physiology

Recent studies have not emphasised anorectal physiology. Seven studies in this review reported data on anorectal physiology. Generally there was a reduction in both the sensory threshold and sensation of urgency due to balloon distension across all studies but findings were generally not statistically significant. The sphincter pressures at rest and on squeezing improved as well. This suggests a change in rectal sensitivity during SNS preventing an excessive rise in endorectal pressure. There was poor symptom correlation with Anorectal physiology findings. See Table 2-8 and Table 2-9.

Table 2-8: Anorectal Physiology

Study id	E Ganio 2001	E Ganio 2002	Malouf 2002	Kamm 2010	Kenefick, R J Nicholls 2002 PSNS	Lombardi et al. 2010
RP mean BL	73 mm Hg	-	-	-	75 cm H2O	31.58 cm H_2O
BL range		-	-	-	52-99	25-42
After SNS mean	80	-	-	-	91	32.25
After SNS range	29.3	-	-	-	72-114	27-45
MSP BL	120	-	-	-	42 cm H_2O	57.41 cm H_2O
BL range	33.1	-	-	-	32-102	45-70
After SNS mean	126	-	-	-	63	58.25
After SNS range	33.8	-	-	-	40-119	45-70
Sens. Threshold Vol. BL	106 mls	106 mls	47 mls	-	59 mls	68.58 mls
BL range	33.5	-	10-110	-	45-71	40-90
After SNS mean	89 mls	10 mls	25 mls	-	38 mls	67.33 mls
After SNS range	39	-	10-30	-	30-45	40-90
Urgency Vol BL	189 mls	214 mls	-	Reduced	115 mls	111.66 mls
BL range	52.99	0	-	-	90-185	90-140
After SNS mean	139 mls	95 mls	-	-	85 mls	105 mls
After SNS range	52.3	-	-	-	50-95	80-130
Max. Tolerated Vol BL	-	-	-	Reduced	157 mls	158.30 mls
BL range	-	-	-	-	130-245	135-190
After SNS mean	-	-	-	-	125	156.91 mls
After SNS range	-	-	-	-	63-130	135-180

BL: Baseline; RP: Resting pressure; MSP:Maximum squeeze pressure

Table 2-9: Anorectal physiology

Kenefick, C J Vaizey 2002	Baseline (Range)	Stimulation off (Range)	Stim. On
Anal Resting Pressure (cms H20)	74.5 (65 & 84)	51 (63 & 69)	76 (68 & 84)
Anal Squeeze pressure (mls)	39 (32 & 46)	54 (51 &57)	93 (41 &145)
Sens. Threshold to balloon distension (mls)	46 (45 & 47)	35 (30 & 40)	17.5 (2 & 15)
Urgency to balloon distension (mls)	130 (185 & 75)	70 (60 & 80)	34 (33 & 35)
Max. tolerated Volume to distension (mls)	194 (245 & 143)	102.5 (85 &120)	67.5 (65 & 70)

2.3.5.4 Other outcomes

2.3.5.4.1 Time needed for toileting

Time spent on toilet decreased from 17.6 to 9.3 minutes in one study (Kamm, Dudding et al. 2010) and from 12.5 minutes (5-20 min) to 9.3 minutes (5-30 min) for each bowel movement in another(Ganio, Masin et al. 2001). Lombardi reported an improvement from 45.85 (20-80) minutes per week to 10.41(5-15) minutes per week after SNS(Lombardi, Del Popolo et al. 2010). Other studies did not record this data.

2.3.5.4.2 Abdominal pain and bloating

Three studies provided findings. Malouf et al reported improvement in abdominal pain and bloating together with improvement in the VAS score although they failed to publish the data (Malouf, Wiesel et al. 2002). Kenefick documented percentage time with bloating before and after SNS (Kenefick, Vaizey et al. 2002) while Kamm recorded the number of days with abdominal pain and bloating during the week (Kamm, Dudding et al. 2010).

2.3.5.4.3 Unsuccessful evacuation

Both studies by Ganio documented numbers of unsuccessful visits to the toilet before and after SNS. In the 2001 study the episodes of unsuccessful visits to the toilet decreased from 29.2 (7-24) per week before stimulation to 6.7 (0-23) per week after SNS(Ganio, Masin et al. 2001). Similarly there was improvement noted in the 2002 study from 4.5 (2-14) episodes every week to 2.1 (0-7) at 3 months following SNS (Ganio 2002). There was no available data in other studies did not report changes in unsuccessful evacuations.

2.3.5.4.4 Difficulty with rectum emptying

Improvement in difficult evacuation was reported in three studies. Kamm et al reported a reduction in the proportion of straining from 75% of successful bowel movements to 46% of all successful evacuations at last follow-up. There was also an improvement in perception of incomplete evacuation. (Kamm, Dudding et al. 2010). See also Table 2-10.

Table 2-10: Improvements in evacuation

Study id	Difficult evacuation Pre-SNS	After SNS
E Ganio 2001	7 (2-21) episodes	2.1(0-6) episodes
Kenefick, R J Nicholls 2002	4 (0-4)*	1 (0-4)*

* evacuation score

2.3.5.4.5 Transit Time

Only three studies addressed transit time before and after SNS. Malouf et al included eight patients with slow-transit constipation. Only 2 out of the eight patients responded positively to T-SNS. The transit time did not normalize in the responders and stayed prolonged (Malouf, Wiesel et al. 2002). Kenefick documented prolonged transit time in two out of the four participants before permanent SNS that normalized in one after stimulation (Kenefick, Vaizey et al. 2002). In the European multi-centre trial, transit time normalized in half of patients who had slow transit before SNS (Kamm, Dudding et al. 2010).

2.3.5.4.6 Quality of Life (QOL)

The reporting of quality of life data was minimal across all studies. Several studies mentioned documenting QOL data but findings were not adequately reported. The double blind placebo-controlled cross-over trial utilized Short Form 36 to measure quality of life before and a year after stimulation. It reported marked improvement in both participants but no specific numbers were given. In their second report, Kenefick et al recorded improvement in all subscales of SF-36 except health transition after temporary and permanent SNS (Kenefick, Vaizey et al. 2002). Similar improvements in subsets of SF-36 were noticed in the multi-centre trial (Kamm, Dudding et al. 2010).

2.3.5.4.7 Safety/ Adverse Effects

Ganio enrolled 40 patients with functional anorectal and urinary disturbances. There were no infections but four patients had electrode displacement within the first 24 hours (Ganio, Masin et al. 2001). Two of these patients had repositioning of the electrodes. Kenefick and Malouf did not report any infections. There were no reported adverse events in the crossover trial (Kenefick, Vaizey et al. 2002).

Hetzer et al performed video-assisted SNS in six patients. They suggested that by separating the operative field with the help of a camera between the patient's legs, to observe stimulation responses in the pelvic floor, infection rates could be reduced for SNS. There was no infection in any of the six patients and five of the six screenings were successful. In their four-year experience of 36 SNS procedures, explantation was necessary in only one patient.(Hetzer, Hahnloser et al. 2006)

Table 2-11: Complications

Study id	Enrolled	Infection	Electrode Displacement	Implant Removal
E Ganio 2001	40	No infection	4 (10.8 %)	-
Hetzer et al. 2006	36	No infection	-	1 (2.8%)
Malouf 2002	8	None	None	None
Kenefick, C J Vaizey 2002	2	None	None	None
Kenefick, R J Nicholls 2002 PSNS	4	-	-	None
Kenefick, R J Nicholls 2002 TSNS	4	None	-	-

2.3.6 A critique of the Kamm Study

The largest study (with 62 patients) of the use of SNS in idiopathic constipation was published by Kamm and colleagues in 2010. It is the only study with a (clearly) prospective design, following 62 patients who underwent temporary SNS and 45 patients who proceeded to permanent SNS, with follow-up ranging from 1 to 55 months. Long term clinical outcomes are analysed using the last recorded observation carried forward. The study reported a 73% response from temporary SNS and an 87% response from permanent SNS. However there are several limitations within the analysis that reduce the quality of inference that can be made from the study. Firstly the primary endpoint of response to treatment depends on meeting one of three conditions: increased defecation frequency (≤2/wk to ≥3/wk), decreased straining (≥50% reduction) or decreased sensation of incomplete evacuation (≥50% reduction). This presents a very low bar for success, e.g. a patient might improve defecation frequency from 2 to 3 per week but experience worse straining and sensation of incomplete evacuation but still be marked as a success. Unfortunately this study provides no patient reported outcomes which can be correlated against the clinical assessments. When different definitions are applied then treatment response looks very variable. For example only 33% of patients reported improvement in all three components of the primary endpoint. Another concern is the uncritical use of a last observation carried forward analysis. The paper does not report whether the duration of follow-up for subjects was determined by censoring (running out of time) or loss to follow-up (which might be outcome related). This could have been explored by

reporting outcomes by duration of follow-up, e.g. outcomes for those patients with 1,2 and 3 years of follow-up.

2.4 Discussion

There are few studies in the literature which evaluate SNS for constipation and these studies are small. The data from the pan-European trial is the most significant having the largest number of patients (Kamm, Dudding et al. 2010). This review identified no adequate randomised controlled trials on use of SNS in constipation or faecal incontinence. Most studies are retrospective case-series reports with relatively few patients.

In some studies it was not apparent whether the data collection was prospective or retrospective. Furthermore, the small number of patients and absence of long-term data for some patients due to loss to follow-up raises the issue of selective reporting.

This systematic review is unable to provide definitive findings due to the lack of sufficient quality data. There was a different case-mix of patients in each study but the results were aggregated collectively within each. The outcome measures vary between reports, which in turn used different assessment criteria. As a result, there was little value in aggregated results within a meta-analysis.

2.4.1 Efficacy results

About half of patients having SNS respond to temporary stimulation and go on to receive a permanent implant. The only reliable reported data comes from the pan-European study in which 45 of the 62 participants (73%) received a permanent implant (Kamm, Dudding et al. 2010). Across all studies, there was no reliable information on cure rates but 67% of all participants receiving temporary SNS improved symptomatically.

The range of outcome measures showed consistent improvement in bowel frequency after SNS. Almost every study utilized bowel frequency as an outcome measure. Overall, about seventy percent of the patients showed improvement in bowel frequency from an average of three movements/week before stimulation to eight bowel movements/week during stimulation. This effect of SNS was reproducible during both temporary and permanent stages. The small double-blind placebo controlled trial included patients who had an implant for almost 12 months (Kenefick,

Vaizey et al. 2002). These patients had a significant decrease in number of bowel movements during the off phase that rapidly improved in frequency when the stimulation was turned on. This suggests a genuine treatment effect for SNS.

A range of constipation scores including VAS, Wexner and CCCS were used inconsistently in these studies making it difficult to combine results. There was an improvement in constipation scores during stimulation in all studies regardless of the type of score used or duration or type of stimulation.

When reported, there was reduction in time with bloating and abdominal pain as well as in time required for toileting. SNS improved the number of unsuccessful evacuation and straining and squeezing episodes during defaecation.

SNS may improve transit times in constipation but the mechanism of action is not clear yet. Of the ten patients with prolonged transit reported by Malouf and Kenefick, transit normalized in only one patient (Kenefick, Vaizey et al. 2002; Malouf, Wiesel et al. 2002). In the pan-European trial half of the patients with prolonged transit had improved transit times after SNS (Kamm, Dudding et al. 2010). Long-term data for a larger number of patients is required to characterise the impact of SNS on transit times. SNS appears to improve QOL in patients with constipation but more studies are needed to examine this more closely. Anorectal physiology results were inconclusive although these suggest improvements in sphincter pressures, reduction in sensory threshold and sensation of urgency to balloon distension during SNS. Anorectal physiology does not affect patient selection for SNS.

2.4.2 Safety results

Due to the small number of patients in the studies and inconsistent reporting, the extent and severity of adverse events is poorly understood. However, in the literature the reported infection rate for temporary electrodes is between 2-5%. In this review there were no reports of electrode infection. In case of permanent implants common adverse effects include infection and pain at implant site (2%), lead pain (4%), lead migration or displacement (5%).(NICE 2004)

As use and understanding of SNS has progressed, pain at the site of implantation has been reduced or avoided all together by placing the implant in the buttock instead of the abdominal wall. Lead migration and displacement has been improved by introduction of a helical lead design. The lead is also easier to remove, without sedation

or anaesthetic, in cases of superficial skin infections at the electrode site. There are no reported long-term problems from temporary or permanent stimulation.

2.5 Conclusions/ Limitations

Limited evidence from this review suggests that SNS may be an effective treatment for constipation based on short term improvements in symptoms and quality of life from case-series data. Firm conclusions are not possible in an absence of adequate randomised trial evidence and long term data. Furthermore, there are no comparisons with other forms of treatment that may be effective in constipation. Each patient in these case-series acted as their own control with improvements over baseline readings suggesting a positive effect. This raises the possibility of bias and selective reporting as well as the scope for a placebo response to SNS (particular in the short term). However, the persistence of improvement over time and good correlation between temporary and permanent stimulation makes it very unlikely that just a simple placebo response is being observed. Studies included different subgroups of patients in varying proportions and these have been reported collectively: it is possible that different subgroups may benefit more or less from SNS. This thesis will specifically cover the efficacy of SNS in patients with neuroconstipation and advance current understanding of the use of SNS in constipation caused by neurological diseases.

Table 2-12: Study Summary

Authors	Year	Methods	Sample	Interventions	Outcomes	Results/Notes
Dinning	2007	Type of study: Case series Follow-up: 3 weeks Setting: Single centre	Enrolled: 8 Gender: 8 F Age:43 +/-14.6 yrs (Range 20-59)	T-SNS at S2 and S3 over 3 weeks	Colonic Manometry: pan-colonic antegrade and retrograde propagating sequence (PS), Bowel Frequency, Laxative use	S3 stimulation significantly increased PS frequency (5.4 ± 4.2 *vs* 11.3 ± 6.6 PS/h, p= 0.01). S2 Stimulation significantly increased retrograde PS (basal 2.6 ± 1.8 *vs* SNS 5.6 ± 4.8 PS/h, p= 0.03). Six of eight enrolled: improved bowel frequency with a reduction in laxative usage.
Ganio	2001	Type of study: Case series Follow-up: 3 weeks Setting: Single centre Lost to follow-up: 2	Enrolled: 40 (12 with constipation) Gender: 9M 3F Age: 50.2 yrs (Range 26-79)	T-SNS at S3 or S4 over 3 weeks	Anorectal Manometry Bowel Diary	Reduction in difficult evacuations from 7 (range, 2-21) episodes/week to 2.1 (range, 0-6) episodes/week, P < 0.01). Reduction in unsuccessful evacuations from 29.2 (7-24) to 6.7 (0-28) per week (p = 0.01). Manometric findings: increase in maximum squeeze pressure during SNS (from 63 +/- 0 mm Hg to 78 +/- 1 mm Hg; p=0.009). Reduction in urge threshold (from 189 +/- 52 ml to 139 +/- 45 ml; p=0.004).
Ganio	2002	Type of study: Case series Follow-up: 1 yr. Setting: Single centre	Enrolled: 16 Gender: 3M 13F Age: 49.2 yrs (Range 30-72)	P-SNS at S3	Anorectal Manometry Transit study Wexner Score	One treatment failure (15/16 responded) Wexner's score improved from 14.6 (range 8-20) to 4.6 at 3 months (range 0-14) and to 2.7 at 12 months (range 3-16, p<0.01) Voluntary bowel movements/week increased 2.1 (range 0.5-10) to 3.5 (range 1-9) at 3 months and to 11.5 (range 5 – 21) at one year. Unsuccessful evacuations/week decreased from 4.5 (range 2-14) to 2.1 (range 0-7) at 3 months. Anorectal manometry: Rectal sensitivity improved. Sensory threshold to balloon distension decreased from 106 to 10 cc at 12 months. Urge volume decreased from 214 to 95 cc.
Hetzer et al.	2006	Type of study: Case series Follow-up: 8 weeks Setting: Single centre	Enrolled: 6 Gender: 6F Age: 68 yrs(Range 60-72). 2 (constipation)	Video assisted P-SNS	Wound infection	Combined success rate of 5 out of 6 patients reported. Bowel symptoms not reported.
Holzer	2008	Type of study: Case series Follow-up: 11 mths (Range 2-20) Setting: Single centre	Enrolled: 19 Gender: 6F Patients with STC and FDD	T-SNS over 3 weeks: 19 pts. P-SNS: 8 pts.	Wexner score QOL scores (SF-36) at 1 and 6 mths.	8/19 (42%) received permanent implants. Wexner score: improved from 23 (range 18-27) to 8(range 4-13) at 12 mths. Significant improvement in quality of life.
Maeda et al.	2010	Type of study: Retrospective case series Follow-up: 25.7 mths	Enrolled: 38 Gender: 32F 6M Age: 45.6 yrs (Range 21-66)	P-SNS	Suboptimal outcome Adverse events Failure of treatment	22/38 (58%) patients experienced at least one reportable event. 58 events in total including loss of efficacy, pain, and undesired change of sensation. Most managed by reprogramming 28/58(48%).

		(Range 0-70) Setting: Single centre				19/58 (33%) required surgery. 3 treatment failures.
Malouf	2002	Type of study: Case series Follow-up: 3 weeks Setting: Single centre	Enrolled: 8 Gender: 8F Age: 47 yrs (Range 35-68)	T-SNS for 3 weeks	Anorectal manometry Colonic Transit Bowel Diary	2/8 (25%) patients showed a response. Bowel frequency: from 4.5(1-9) per week to 6(2-13) per week. VAS: from 15 (4-33) to 30.3(2-88). Rectal threshold to distension decreased. Colonic transit did not improve.
Kamm et al.	2010	Type of study: Prospective Follow-up: 28mths.(Range 1-55) Setting: Multi-centre	Enrolled:62 Gender: 55F 7M Age: 40 yrs. (Range 17-79)	T-SNS: 62 P-SNS: 45	Defaecation frequency Straining Incomplete evacuation	45/62 (73%) had P-SNS. 39/45 (87%) treatment success. Defaecation frequency: From 2.3 to 6.6/week (p<0.001) Straining: From 75 to 46% of evacuations. Incomplete evacuation: From 71.5 to 46% of successful evacuations. Colonic transit normalized in half with STC at 6 mths (p=0.014) QOL improved significantly.
Naldini et al.	2010	Type of study: Retrospective case series Follow-up: 42 mths. (Range 24-60) Setting: Single centre	Enrolled:15 Gender: 13F 2M Age: 45.7 yrs. (Range 25-64)	T-SNS over 3 weeks: 15 pts. P-SNS: 9 pts.	Defaecogram Colonic transit Wexner score QOL score (SF-36)	9/15 had P-SNS (60%) Wexner score improved from 21 (range 11–27) to 11 (range 3–20) at one month. SF-36 increased from 95.8 (range 88–104) to 102 (range 96–113) at six months. Bowel frequency increased from 1.7 to 3.3 per week, p=0.003, at 6 months. Transit times not reported.
Kenefick, C Vaizey	2002	Type of study: Double-blind placebo-controlled crossover trial (On/Off design) Follow-up: 12 mths Setting: Single centre	Enrolled:2 Gender: 2F Age: 36 yrs. P-SNS implanted 12months before the study	P-SNS for two 2-week intervals with subsensory stimulation either on or off.	Anorectal manometry QOL assessment (SF-36) Wexner score Bowel diary Symptom analogue score (0-100)	Anorectal manometry inconclusive. SF-36 improved at 12 months. Marked difference in bowel frequency, pain and bloating, and the symptom analogue score in the 'on' compared with 'off'. No change in Wexner score in both 'on' and 'off' phase.
Kenefick, Nicholls	2002	Type of study: Case series Follow-up: 8 mths. (Range 1-11) Setting: Single centre	Enrolled:4 Gender: 4F Age: 33.5 (Range 27-36).	T-SNS: 4 P-SNS: 4	Anorectal manometry QOL assessment (SF-36) Wexner score Bowel diary Symptom analogue score (0-100)	3/4 showed marked improvements with P-SNS Bowel frequency: From 1-6 to 6-28 evacuations/3 weeks. Evacuation score: From 4 (0-4) to 1 (0-4) at 8 mths. Time with abdominal pain: From 98 (95-100)to 12 (0-100) % Time with bloating: From 100 (95-100) to 12 (5-100) % at 8 mt. Wexner score: From 21 (20-22) to 9 (1-20) at 8 mths. Analogue score: From 22 (16-32) to 80 (20-98) at 8mths. Maximum anal resting and squeeze pressures increased. Transit time normalized in one patient.
Lombardi et al.	2010	Type of study: Case series Follow-up: 38 mths. Setting: Single centre	Enrolled:39 with incomplete SCI. Gender: 5F 7M Age: 39 +/- 10 yrs. 12 (constipation)	P-SNS	Neurogenic bowel symptoms Wexner score	Bowel movements per week: from 1.65 (1.5-2) to 4.98 (4.5-7)/ week. Wexner score: from 19.91 (17-23) to 6.55 (4-9). Toileting time /defaecation: from 45.85 (20-80 min) to 10.81 (5-15 min).
STC: slow transit constipation, FDD: Functional defaecation disorder VAS: visual analogue scale						

3. Materials and methods

3.1 Study objectives

3.1.1 Primary

The primary objective was to investigate short-term efficacy of temporary (test) SNS in neurological constipation, using a global measure of constipation symptom severity.

3.1.2 Secondary

Secondary objectives were to

Assess the severity of constipation and incontinence before and during and after treatment using disease specific symptom and QOL measures.

Profile changes in generic health status of the participants by using standardized self-completion questionnaires (EuroQOL EQ-5D and EQ-VAS).

Quantify changes in intestinal transit before and during SNS.

Quantify changes in parasympathetic stimulation of the hindgut using laser Doppler flow cytometry before and during treatment.

Record side effects of SNS.

Establish the long-term efficacy in the subgroup of patients receiving permanent SNS.

3.1.3 Design

A within group off-on-off trial design was selected divided into three consecutive periods with patients acting as their own controls. Firstly, pre-treatment severity of constipation was assessed over a period of six weeks before SNS insertion. The participants then had the SNS wire placed bilaterally and were assessed over a period of three weeks. Finally the wires were removed and the participants underwent a final assessment period of three weeks post-SNS.

3.1.3.1 Rationale for the study design

Careful consideration was given to the most appropriate study design to explore the value of SNS in constipation of neurological origin. It was concluded that a controlled

trial was not feasible at this stage in the development of the use of SNS in this patient group. Patients were unlikely to be willing to be allocated to, and remain in, a treatment as usual group that continued to provide a failed pattern of care. The possibility of a controlled trial comparing active and sham SNS was considered but considered technically out of scope for the current study. When it is not possible to get an adequate control group, the attribution of treatment outcome can be improved by manipulating the use of the intervention over time. In this instance it was possible to demonstrate the chronic stability of the condition using a six-week run in period. The off-on-off design thus allows a high level of attribution where the temporal symptoms pattern follows the SNS stimulation pattern, and when the impact of SNS upon patient symptoms is anticipated to be large.

3.1.3.2 Patient involvement in the design

The trial was developed after discussion with four patients in the specialist constipation clinic who have neurological constipation, two of whom have already had insertion of an implant. The opinions of patients who have neurological disorders were canvassed to determine those investigations and interventions that would be acceptable to potential participants.

3.1.4 Number of subjects

The study involved planned prospective data collection from 30 patients with severe constipation caused by neurological disorders. A sample size of 30 had 94% power to detect a difference in means of 2.0 in a global symptom assessment scale (change from baseline), assuming a standard deviation of the differences of 3.0, using a two-group paired t-test with a 0.05 two-sided significance level.

3.1.5 Duration of Study

Participants were recruited over a two-year period. For each participant the total duration of the temporary SNS study was twelve weeks, from the point when consent was confirmed.

3.1.6 Primary outcome

The primary outcome was a weekly global assessment of symptoms using a five-point Likert scale. This recorded any changes in both constipation and faecal incontinence on a weekly basis.

3.1.7 Secondary outcomes

Secondary outcome measures included i) a daily defaecation and laxative diary; ii) weekly self-administered questionnaires to measure symptoms (PAC-SYM); iii) weekly self-administered questionnaires to assess quality of life (PAC-QOL); iv) self-administered questionnaires to assess generic status of patient health (EuroQOL EQ-5D and EQ-VAS) v) transit study; and vi) laser Doppler flowcytometry. Copies of all measures are reported in Appendix A.

3.1.8 Definitions

Multiple Sclerosis (MS): A progressive diffuse neurological disease characterised by areas of demyelination in the central nervous system. These lesions produce a variety of sensory and neurological disorders including constipation. Diagnosis of MS was made on clinical, radiological and electrophysiological grounds. All patients seen in the clinic were under the care of neurologists.

Spinal Cord Disease: Referring to damage to the spinal cord following trauma, surgical intervention, diseases of the spinal cord or as a result of abnormalities of the bony spine including congenital defects that result in spinal cord dysfunction.

Spina Bifida: A congenital defect that causes hydrocephalus and other neurological problems. These arise because of protrusion of the spinal cord or it's covering (meninges) through a defect caused by incomplete closure of the bony spinal column.

Constipation: For research purposes the "**Rome III Criteria**" were accepted and used in the study (Longstreth, Thompson et al. 2006).

The diagnosis of constipation required at least 2 of the following:

- Straining during at least 25% of defaecations
- Lumpy or hard stools in at least 25% of defaecations
- Sensation of incomplete evacuation for at least 25% of defaecations

- Sensation of anorectal obstruction/blockage for at least 25% of defaecations
- Manual manoeuvres to facilitate at least 25% of defaecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than 3 defaecations per week

3.2 Subject selection and withdrawal

3.2.1 Inclusion criteria

All of the following criteria had to be met to qualify the patient for inclusion:

- Males and females age 16 years or older
- Neurological disorder (MS or spinal disease)

  SCI injury patients had been seen at the regional spinal injury unit at James Cook University Hospital. The level of the lesion had been graded using the American Spinal Injury Association (ASIA) impairment scale. MS patients were referred from the regional neurology service to the constipation clinic. They had been diagnosed and classified before being seen at the constipation clinic by a neurologist. Only patients with significant bowel dysfunction and failed conservative management were referred.

- Constipation according to the above definition
- At least 6-month-old SCI at any level with at least one of the following
    - Spending 30 minutes or more attempting defaecation everyday or every other day
    - Faecal Incontinence episodes once or more a month
    - Abdominal discomfort before or during defaecation
    - Symptoms not adequately relieved by standard treatments (lifestyle modification, laxative, suppository, enema and rectal irrigation)

3.2.2 Exclusion criteria

The presence of any of the criteria disqualified the patient for inclusion:

- Age less than 16 years

- Unfit for general anaesthetic
- Severe psychiatric disease
- Persistent diarrhoea (except when due to laxative use)
- Uncontrolled or decompensated cardiac, respiratory, endocrine, renal, or hepatic diseases
- Rapid progression of neurological disease
- Active systemic infection
- Known pregnancy, suspected pregnancy or trying to conceive
- Subjects currently (or within one month) of any other study
- Severe incapacity of higher mental function such that informed consent can not be achieved
- Severe incapacity of higher mental function or physical abilities such that questionnaires cannot accurately be completed.

3.2.3 Recruitment

Potential subjects for recruitment were patients with neurological disorders (MS, spina bifida and spinal disease) causing severe constipation refractory to treatment with diet changes, laxatives, suppositories, enemas and rectal irrigation. Participants were recruited from the Specialist Constipation Clinic at the University Hospital North Durham. This clinic receives referrals from a wide area in the North-East (150 new patients per year; 350 under follow-up, 10-15 neuro referrals per year), and we anticipated adequate numbers to allow recruitment of the required number of patients over a two-year period. Aside from the presence of neurological disorders, these patients represent an unselected group of individuals with symptoms severe enough to justify specialist referral. Those considered suitable, according to standard definitions and the inclusion/exclusion criteria, were asked to participate.

3.2.3.1 The consent process

Participants were required to give written consent where possible. The investigators explained verbally and in writing if needed, the nature of the study. A copy of the information sheet (See Appendix B) was given for consideration by the patient before

consent was obtained. Patients were allowed to deliberate for at least 24 hours after the initial discussions before the consent process was completed. Patients were advised that they were free to withdraw from the study at their own request. It was explained that the study had been designed in line with the International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) and that they were protected by the 2000 Declaration of Helsinki ensuring their rights, safety and well being. Arrangements were made to ensure adequate consent for participants who may have had difficulty understanding English or who had impairments (e.g. visual or hearing) that could influence the consent process. Independent witnesses were available to confirm consent in those unable to do so in writing.

3.2.3.2 Patient subgroups

Patient subgroups included multiple sclerosis (MS), spinal cord injury (SCI) and others (including patients with polio and spinal myoclonus).

After recruitment, all the participants with SCI were classified according to international standards for classification of spinal cord injury based on the affected spinal segments. Patients were roughly divided into three groups according to their affected segments.

- High supraconal injury (T9 & above)
- Low supraconal injury (T10- S1)
- Conal or cauda equina lesion (S2-S4)

These were further subdivided into those with complete and incomplete injuries. All patients had been seen at the regional spinal injury unit and were classified according to the American spinal injury association (ASIA) impairment scale.

Patients with neurological disorders were not a heterogeneous group and a subgroup analysis was planned based on the groups described. Differences between subgroups might help inform hypotheses for future studies of SNS.

3.2.4 Patient withdrawal

Patients were provided with contact details allowing them to contact one of the investigators if they were considering withdrawal. Participants were able to terminate participation immediately at any point. Participants were offered the opportunity to meet an investigator within 48hrs if they wished, following withdrawal. Data gathered

from patients who withdrew were kept; this fact was included in the patient information sheet.

3.2.5 Study monitoring

The study was monitored by a monthly audit of adherence to protocol and review of participants. Additionally, a six monthly interim report was made to the Project Review Board at the University Hospital of North Durham as well as an annual report to Regional Ethics Committee.

The purpose of these arrangements was to identify any significant developments as the research proceeded that may necessitate alterations to the protocol and to protect the safety and wellbeing of participants. Although it was not expected, the arrangements were there to identify hazards to research participants. Complications, adverse events, adverse reactions occurring as a result of participation could be used as criteria to terminate the study.

3.3 Study procedures

3.3.1 Standard patient assessment in the Constipation Clinic

The Durham Constipation Clinic is a regional referral centre for patients with refractory disease. The ability of the clinic to find solutions where others have failed is partly dependent on pursuing detailed assessment of patient symptoms, lifestyle and physiology. The intensity of this assessment is discussed with patients at the outset, though we usually find that patients attending this clinic (often from some distance away) are highly motivated and very keen to have these assessments.

The following are standard for patients attending with neurological constipation:

- History taking
- Physical examination including PR examination
- Blood test including full blood count, urea and electrolytes, calcium, blood sugar and thyroid function tests.
- Symptom and Quality of Life (QOL) assessment is performed in all patients referred to the Constipation Clinic using self-administered questionnaires

- Transit Study. This is recommended in all patients and is part of standard clinical practice. Transit time is determined following a single plain abdominal X-ray taken after ingestion of radio-opaque markers. The markers are inert, easy to swallow and are taken on days 1, 2 and 3. The X-ray is taken on day 4 (Metcalf, Phillips et al. 1987). This method allows a reduction in the number of x-ray exposures compared to previous techniques.
- Flexible Sigmoidoscopy is recommended in nearly all patients. It helps in ruling out or diagnosing any structural pathology causing constipation in these patients. Random rectal mucosal biopsies are taken and assessed histologically to further rule out any pathology.

3.3.2 Standard management in the Constipation Clinic

The individual needs of patients with neurological disorders were taken into account when planning management. Standard approaches like dietary manipulation, laxatives, suppository and enema therapy were used as required. Should these therapies fail to control symptoms, a trial of rectal irrigation was considered. However, patients usually had symptoms that were refractory to all these interventions. In these difficult cases SNS was offered.

3.3.3 Assessments

The patients were assessed using the following measures:

3.3.3.1 Global Assessment of Symptoms

This addressed changes in symptoms of constipation and/or faecal incontinence. Weekly assessments were recorded throughout the 12-week study period. This helped quantify any changes in participants' symptoms before, during or after SNS. At the end of each week participants answered the following questions.

Table 3-1: Global assessment of symptoms

How has your constipation been this week? *Tick the appropriate box*		**How has your faecal incontinence been this week?** *Tick the appropriate box.*	
1. No problem		1. No problem	
2. Mild problem *(Can be ignored with effort)*		2. Mild problem *(Can be ignored with effort)*	
3. Moderate problem *(Cannot be ignored but does not influence my daily activities)*		3. Moderate problem *(Cannot be ignored but does not influence my daily activities)*	
4. Severe problem *(Cannot be ignored and often limits my concentration on daily activities)*		4. Severe problem *(Cannot be ignored and often limits my concentration on daily activities)*	
5. Very severe problem *(Cannot be ignored and markedly limits my daily activities and often requires rest)*		5. Very severe problem *(Cannot be ignored and markedly limits my daily activities and often requires rest)*	

3.3.3.2 Diary

In addition to weekly global assessments of symptoms, participants were asked to fill in daily diary cards on a weekly basis from week four to week nine (covering three weeks of pre-treatment assessment and 3 weeks of treatment). The diary included daily stool frequency, episodes and type of faecal incontinence, laxative intake and laxative score.

Patients with neurological constipation often suffer from faecal incontinence due to lack of sphincter control. Inability to open the bowels for a long period of time will lead to a more than average laxative use by the patient causing episodic faecal incontinence due to runny stools. Documentation of incontinence in the diary was based on a standardized scoring system (Wexner score).

3.3.3.2.1 Laxatives and laxative score

Each participant documented the intake of laxatives in the diary on a daily basis. Use of new laxative agents was limited in order to preserve continuity during the trial.

In our experience the dosage and type of laxatives vary in patients with neurological constipation and it is very difficult to quantify the laxative intake over a period of time. To account for this, weekly laxative use was averaged out for each participant and then documented with the help of a simple daily laxative score. Patients recorded in their diaries whether their laxative intake was more, same or less than their average use with the help of a simple scale.

3.3.3.3 PAC-SYM and PAC-QOL

The Patient Assessment of Constipation (PAC) tool consists of two separate scales, PAC-SYM (12 item measure of symptom severity) and PAC-QOL (28-item measure of health related quality of life). The questionnaire could be administered by patients or by investigators. This tool was designed to specifically assess constipation. The robust psychometric properties of the system have been demonstrated in community dwelling younger adults(Frank, Kleinman et al. 1999; Marquis, De La Loge et al. 2005). Both of theses questionnaires were administered on a weekly basis throughout the trial.

3.3.3.4 EuroQOL

EuroQOL is a standardized instrument for measurement and valuation of health status. It is used to determine the global or generic status of a person's health and health related quality of life. It is designed for self-completion and has been applied widely to a variety of health conditions and treatments(Rabin and de Charro 2001). It can be easily completed in a few minutes and has five dimensional (EQ-5D) descriptive profile (each dimension has 3 levels) and a visual analogue scale (EQ-VAS). EuroQOL has been applied in clinical, economical and population-based studies. The performance of EuroQOL in IBS and inflammatory bowel disease has been evaluated previously(König, Ulshöfer et al. 2002; Bushnell, Martin et al. 2006). As an outcome measure it can also help conduct an economic valuation of treatments by calculating quality adjusted life years (QALY) (estimating differences between treatments in quality of life over time). The EuroQOL tool was repeated before, during and after the treatment at three-week intervals. The potential differences in the profiles over this time period were to help assess changes in patients. A copy of EuroQOL is included in Appendix B. Although it

was recognised that neither EQ-5D nor EQ-VAS would be sensitive enough to detect changes in a small number of patients it was included to obtain estimates of variance to help design future studies.

3.3.3.5 Transit study

Transit time was one of the physiological parameters tested during this study and was also part of standard assessment in the constipation clinic. In addition to subjective assessments of the effect of SNS (QOL and symptoms), objective measures are helpful in ascertaining the effectiveness of treatment and extending understanding of who benefits from treatment. Findings may help advise future patients when they are making a decision regarding SNS treatment. Patients participating in the study underwent a further abdominal radiograph. This additional radiation exposure was however minimal and was not felt to constitute a significant risk to participants in either the short or long term. The issue of radiation exposure was carefully discussed with participants and an explanation of the justification for repeating the transit study given. Special attention was paid to certain groups to minimize radiation exposure.

3.3.3.6 Laser Doppler flowcytometry

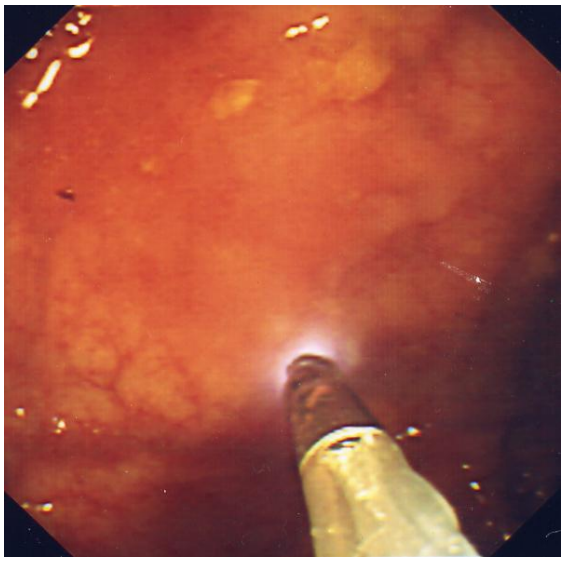
Laser Doppler flow cytometry (LDFC) measures the change in frequency of light reflected off moving objects: in this instance red blood cells flowing within capillaries. The equipment consists of a fibre optic probe producing a low intensity coherent monochromatic light beam. This light is reflected off moving blood cells and the frequency shift is measured and evaluated by a photocell and computer software. This measured frequency shift gives the volume flow (flux) through the respective tissue in millilitres of blood per minute per 100 grams of tissue.

A DRT4 laser Doppler flow meter (Moor Instruments, Devon, UK) with a bandwidth of 14.9 Hz was used. The area of measurement corresponds to 1 mm^2 of rectal mucosa up to a depth of 1 mm from the tip of the probe. Readings were taken with the help of a sigmoidoscope approximately 10 cm from the anal verge with the patient in a left lateral position. The first reading was taken after 30 seconds when the trace becomes more stable and was recorded over 3 minutes. Built-in software limits any movement artefacts. Four circumferential readings, 90 degrees apart, were taken at the same level in order to reduce the variability coefficient to less than 10%, thus making the measurements reliable (Emmanuel and Kamm 1999). Two separate measurements

were taken at 3 weeks and 9 weeks. There was one measurement before SNS and one during SNS.

LDFC provides a validated quantitative measure of extrinsic autonomic nerve activity of the GI tract. Patients with slow-transit constipation have less mucosal flux assessed by LDFC when compared to normal controls (Emmanuel and Kamm 2000). Laser Doppler measurements of rectal mucosa have shown improvement in blood flow after SNS suggesting a potentially positive autonomic neuromodulatory role for SNS. It has been suggested that sacral parasympathetic efferents, in response to direct stimulation, activate a cholinergic mediated vasodilator response that improves mucosal blood flow (Emmanuel and Kamm 1999). The use of LDFC may help quantify any potential changes in the autonomic input of the gut by performing LDFC before and during treatment.

Figure 3-1: LDFC Probe in rectum during measurement



3.3.3.7 Selection for Permanent implant (P-SNS)

Criteria for receiving a permanent implant after T-SNS included the following

- GA Constipation: An improvement of 2.0 on the GA scale for constipation
- PAC-SYM: improvement in overall score of PAC-SYM from baseline
- Patients were also asked to report any associated subjective improvements in their symptoms and quality of life.
- Absence of any adverse events associated with T-SNS.

Patients were considered for permanent implants if they fulfilled any of the above criteria and both the investigator and the patient felt that there was a significant improvement during T-SNS.

3.3.4 Adverse events

All untoward events that arose from participation in the study (whether or not they were considered serious or related to participation) were recorded. The following information was entered in the medical notes and in an adverse event database.

- Description of the event
- Severity
- Date
- Relationship to participation in the study
- Outcome

3.4 Analysis Plan

3.4.1 Baseline Data

Demographic data including, but not limited to age, race, gender and ethnicity and baseline characteristics were recorded for each subject. In addition, diagnosis, stage of the disease and effects on mobility were also included in the baseline data.

3.4.2 Grouping of measurements and analysis

Observations were grouped within SNS study phases (pre: weeks 1-6; during: weeks 7-9 and post: weeks 10-12) and included primary and secondary outcomes measured on

a weekly basis. Pre-intervention baseline scores were averaged for the first six weeks, forming the pre-SNS measure. The scores from week 8 and week 9 were used for the intervention phase, forming the SNS intervention measure. Week 12 scores were used for the post-stimulation of phase. Weeks 7, 10 and 11 were excluded from the planned analysis because of the prior expectation that changes in SNS stimulation would have a transient effect before change was stable. The scores for the pre-intervention period were compared with scores during and after temporary SNS, using a paired Student's t-test. The validity of parametric testing was explored by non-parametric testing usingbootstrapped estimates. Non-parametric findings were reported when they were divergent from parametric findings. The Mann Whitney U test was applied to compare responders and non-responder rates to SNS. Non-parametric findings were reported when they were divergent from parametric findings.

3.4.3 Primary outcome

3.4.3.1 Global assessment of Constipation (GA Constipation)

This was measured once weekly over the course of twelve weeks during the trial. The GA score for constipation is a 5 point Likert scale ranging from 1-5 (1= no symptoms, 5= very severe symptoms). For a description see Table 3-1.

3.4.4 Secondary Outcomes

3.4.4.1 Global Assessment of Faecal Incontinence (GA F.I.)

The GA score for faecal incontinence, like the constipation measure, is a 5 point Likert scale ranging from 1-5 (1= no symptoms, 5= very severe symptoms).

3.4.4.2 Patient Assessment of Constipation Symptoms (PAC-SYM)

The PAC-SYM questionnaire was used on a weekly basis during each trial phase. It is a 12 item measure of symptom severity. A sub domain analysis of measured changes in the three sub domains of PAC-SYM questionnaire was planned.

3.4.4.3 Patient Assessment of Constipation (PAC-QOL)

PAC-QOL score was measured weekly throughout the trial. PAC-QOL is a 28 point questionnaire self-administered by patients. This quantified constipation specific QOL for each patient during the trial. PAC-QOL has five sub domains. A sub domain analysis

of measured changes was planned.

3.4.4.4 Euro QOL Health Questionnaire (EQ-5D)

EQ-5D is a five domain health questionnaire designed to measure the general quality-of-life (QOL) of recruited patients. It was measured during weeks 3 and 6 (pre-intervention), week 9 (during SNS) and week 12 (post intervention). Responses were converted to a single health-related quality-of-life score using the social tariffs provided by the EuroQol group. Weeks 3 and 6 were combined to form the pre-intervention measure and compared with week 9 and week 12 using a paired student's t-test.

3.4.4.5 EuroQOL Visual Analogue Score (EQ-VAS)

EQ-VAS is a self administered score between 0 and 100 (0 poor state of health, 100 best state of health). This was administered at the same time as EQ-VAS and was analysed accordingly.

3.4.4.6 Daily Dairy

During weeks 4 to 9 patients completed a daily diary. This daily diary included bowel frequency, episodes of faecal incontinence, type of incontinence (flatus, liquid or solid), time spent during toileting in minutes and laxative score. This entailed documenting in the diary whether their laxative intake was more, the same or less than average use with the help of a simple scale.

Manual manoeuvres during toileting such as abdominal massage, digital stimulation and manual evacuation of rectum were measured on a daily basis as well. The average pre-intervention and during intervention scores were compared for each variable of the diary utilizing a paired t-test.

3.4.4.7 Stimulation Thresholds

The Stimulation thresholds were recorded at the time of insertion of the temporary electrodes. These were also measured at the end of the temporary trial. Differences between responders and non-responders were estimated using an unpaired Student's t-test.

3.4.4.8 Physiological Outcomes

3.4.4.8.1 Laser Doppler Flowcytometry (LDFC)

LDFC is a determinant of the autonomic innervation of the hindgut (Emmanuel and Kamm 2000) and has been shown to improve during SNS. LDFC was measured pre and during intervention. This was done by sigmoidoscopy at four sites in the rectum 10 cms from the anal verge. The average LDFC score for each site was analysed during and before treatment to measure any improvements in the autonomic innervation of the hindgut.

3.4.4.8.2 Colonic Transit time

As part of standard assessment of constipation each patient underwent a transit marker study at the start of the trial utilizing a previously described modified technique (Metcalf, Phillips et al. 1987). Patients underwent a repeat transit study during temporary SNS and any changes from the pre-intervention phase were analysed.

3.4.4.9 Correlation between outcomes

Correlation coefficients between primary and secondary trial endpoints were estimated. The purpose was to understand the relationship between outcomes.

3.4.5 Permanent SNS implantation

Patients who had a successful trial of bilateral SNS received an implantable pulse generator (IPG). The medium to long-term data from these patients was collected and compared to their pre-intervention baseline scores to quantify the extent to which the effect of SNS was sustained.

The longer term follow-up data included GA scores for constipation, PAC-SYM scores and PAC-QOL scores.

3.4.6 Predictors of Outcome

A linear regression analysis was planned, to explore the determinants of response to SNS during the temporary and permanent phases. This included exploration of stimulation thresholds at the time of procedure, baseline characteristics including the

diagnosis and mobility criteria and long-term data. The dependent variables included primary and secondary outcomes.

3.4.7 Other Analyses

3.4.7.1 Subgroup analyses

A subgroup analysis was planned for patients with Multiple Sclerosis (MS) recruited to the trial. MS patients have a different aetiology and presentation than spinal cord diseases or injuries and may respond differently to SNS. We anticipated a majority of participants would have MS.

3.4.8 Missing Data

Patients not commencing SNS or having a failed trial at the time of wire placement did enter the treatment phase (weeks 7-9) of the study. These patients were documented and reported separately from the main analyses.

For each outcome, any patient with missing data was omitted from the analysis of that outcome without imputation.

3.5 Ethical Considerations

The decision to offer SNS was made on clinical grounds and did not form part of the study protocol. However, the ethics of SNS are considered here. SNS for neurological constipation is a novel therapy and experience is still limited. Therefore, patients were counselled and consented in a rigorous fashion so that they were fully aware of the issues surrounding the procedure. The alternatives to SNS for patients with refractory symptoms are invasive surgical interventions with recognized complications and without guarantee of success. By actively studying the effect of SNS in this group we hoped to improve our understanding of how best to manage these patients who are severely disabled by their symptoms.

Following the decision to offer SNS, patients were free to choose whether to participate in the study without prejudice to their routine care. Ethical questions could be raised regarding repeat transit study and laser Doppler: two investigations that would not normally be routinely performed. However, it was felt that subjects would find these tests acceptable and tolerate them well. The additional radiation exposure of the

transit study was minimal and was not considered to contribute to long-term problems. These tests were crucial to improve our understanding of the efficacy of SNS.

3.5.1 Confidentiality

Identification within the study was by a pseudonymous coded number effectively ensuring anonymisation. However, using this number the principle investigators were able to identify subjects rapidly to react to research related information that may influence a patient's management or involvement in the study. A subject's inclusion in the study was made clear in their medical notes. Other medical practitioners involved with the non-research related care of the subjects (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 the investigators if needed.

3.5.2 Information to GPs

General Practitioners were informed of their patient's decision to participate. The letter to GPs provided information about the study. The GP was invited to contact the investigators at the University of North Durham if they had questions or objections.

3.5.3 Information to carers

Carers (both formal and informal) were made aware of the patient's decision to participate. An information leaflet for carers was available (see Appendix B). This letter provided information about the study. Carers were invited to contact the investigators at the University Hospital of North Durham if they had enquires or objections.

3.5.4 Radiological Procedures

Patients with constipation due to neurological disorders required radiological investigation including a Transit Study. This forms part of the standard approach. In this study there was a research need to repeat the Transit Study following SNS insertion. We believe that the additional radiation exposure was small and carried negligible risk to the individual. Using the current technique at the University Hospital of North Durham (Metcalf, Phillips et al. 1987). Only one abdominal radiograph per transit study was required thus reducing radiation exposure. To avoid exposure in any individual who maybe pregnant certain precautions were observed:

- All patients were warned verbally and in writing of the potential risk of radiation exposure to a developing foetus
- Patients were excluded from the study at the initial assessment if they were pregnant; thought they might be pregnant or were trying to conceive.
- All women of childbearing age were asked to give written consent to for each individual radiological procedure in the study.
- Subjects at high risk included pre-menopausal women who were sexually active and were not using regular reliable contraception. All such patients had radiological procedures timed to coincide with the first 10 days of their menstrual cycle. Patients who had irregular periods were offered the option of a pregnancy test on the day of the procedure.

3.5.5 Additional Radiation exposure as part of the study

Study participants underwent an additional abdominal X ray as part of the second Transit Study three weeks after SNS insertion (at week nine of the study). The additional exposure had been calculated as 0.5mSv.

The dose constraint (ED) set for this research exposure by the Radiation Protection Officer was 1.0 mSv. The associated additional excess lifetime mortality risk was therefore approximately 1 in 13,000. The radiation dose was comparable with the annual dose from natural sources in the United Kingdom. The risk was less than the annual risk of a fatal road accident and at least 25 times less than the natural annual cancer risk. An ED of 1.0 mSv equates to approximately 4.5 months natural background radiation in the UK. This represented a very small additional risk. The written patient information included reference to this additional radiation exposure, with the risk put into context for the patient.

3.5.6 Magnetic Resonance Imaging (MRI) following SNS

Patients with an established diagnosis of multiple sclerosis may require further MRI scans in case of disease progression. They may require brain and/or spine MRI scans depending on the site of lesions in each patient.

MR scanning in patients with implanted pulse generators (IPG) for SNS can cause excessive and painful stimulation and heating during the MR exam as well as decreased function of the IPG after the MRI. Medtronic have published guidelines regarding the

interstim system of implants for patients undergoing MRI scans. Patients implanted with the MR conditional type of pulse generators can have head scans providing that certain conditions have been met. They recommend using MR scanners up to 1.5Tesla with the stimulator turned off and the magnetic switch disabled. They also recommend withholding sedation during the MR to get reliable patient feedback.(Medtronic)

There have been a number of papers published on the safety of MRI scans in patients with neurostimulators. In a series of 15 patients with P-SNS, Chermansky et al. reported device failure in only one patient after MRI scans. They followed the manufacturer's guidelines and did not have any adverse events in the rest of the patients after re-programming (Chermansky, Krlin et al. 2010). Elkelini reported similar findings in another series of patients with interstim implants (Elkelini and Hassouna 2006). Kainz et al. reported a temperature rise of 2.1 degree Celsius at the lead tip and only 1.8 degree Celsius over the implant casing during MRI. This was reproduced with both 1.5Tesla and 3Tesla MR scanners (Kainz, Neubauer et al. 20022).

However, most of the patients with stable MS may not require any MR scans after implantation. The field of view of MR scans in MS is the brain and/or the spinal cord which is away from the pelvis where the leads and the implant are sited. The threshold for irreversible thermal injury is more than 45 degree Celsius and a change of 2-3 degree Celsius during MR seems to be clinically safe in these patients. The functionality issue can be managed by switching the IPG off for the scan and re-programming after scanning.

3.6 Study schedule

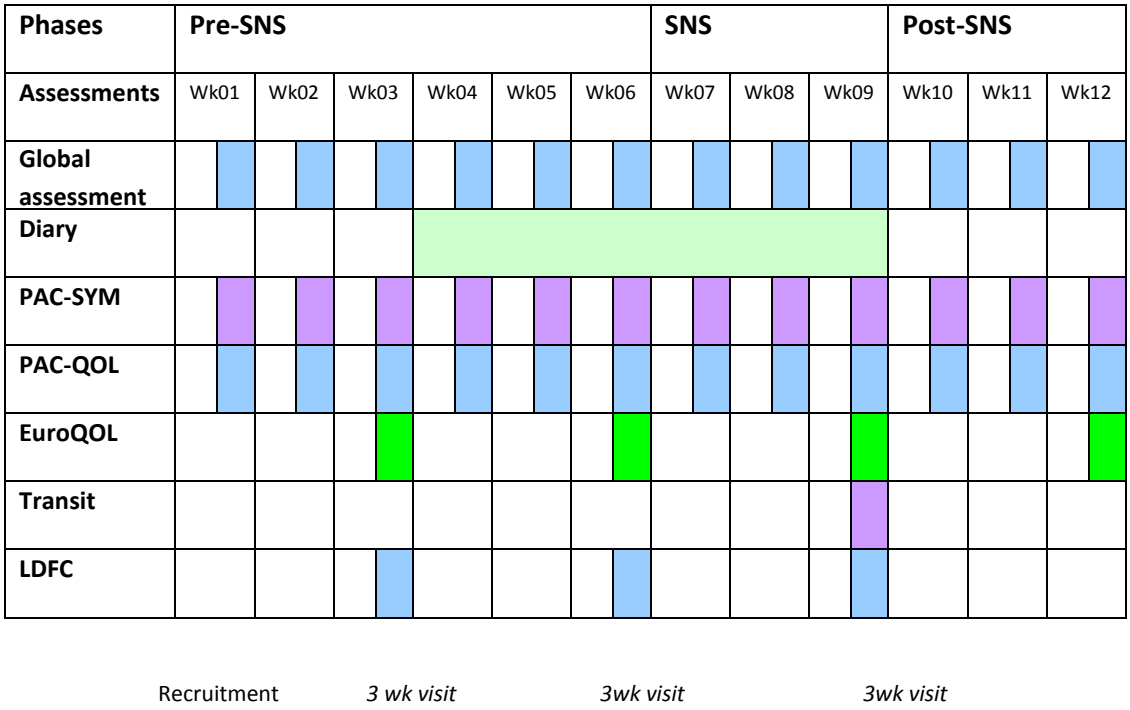
The study schedule is set out in Table 3-2 and assessment schedule in Figure 3-2.

Table 3-2: Study schedule

(Blue boxes denote research activity; Green boxes represent standard clinical management)

1. Patient referred to Constipation clinic at University Hospital of North Durham History, examination, Symptom & QOL assessment, Transit study, Flexible sigmoidoscopy. Standard treatments 2. Patients not responding offered SNS and referred to surgeons 3. Patients seen in surgical clinic by Consultant Surgeon 4. Patient consented to SNS and referred to constipation clinic	
5. Patient consents to inclusion in study & is recruited	Week 0
6. Patient fills weekly global symptom assessment (GA) diary, PAC-SYM and PAC-QOL	Week1-3
7. Patient fills EuroQOL and undergo laser Doppler flowmetry	Week 3
8. Daily stool and laxative diary cards *(Pre-SNS)*	Week 4-6
9. Repeat weekly GA, PAC-SYM & PAC-QOL	Week 4-6
10. Repeat EuroQOL in clinic	Week 6
11. Temporary SNS, 12-24 hour hospital admission	Week 7
12. Daily stool and laxative diary cards *(during SNS)*	Week 7-9
13. Repeat weekly GA, PAC-SYM & PAC-QOL	Week 7-9
14. Repeat EuroQOL, transit study and laser Doppler flowmetry in clinic	Week 9
15. Temporary SNS removed	Week 9
16. Repeat weekly GA, PAC-SYM & PAC-QOL	Week 10-12
17. Final reassessment of EuroQOL and end of trial appointment	Week 12
Monthly meetings of investigators to review and audit data Interim report to Project Review Board at 6 months following start of study Completion of result analysis and preparation of final report predicted at 30 months following start of study	

Figure 3-2: Assessment schedule



4. Findings

4.1 Recruitment and Baseline Data:

The trial recruited 22 patients over 2 years (December 2007 to December 2009) from one tertiary care centre: the specialist constipation clinic at the University Hospital North Durham. There were 8 men and 14 women with an average age of 51.5 years (Range 38-69 yrs.). Of 22 patients: 14 patients had Multiple Sclerosis; 5 had Spinal Cord Injury (2 cauda equina lesions, 1 incomplete lumbar spine injury, 1 complete thoracic spine injury and 1 incomplete cervical spine injury); 1 patient had autonomic dystonia; 1 had spinal myoclonus; and, 1 had a history of myelitis secondary to polio. During the study, 4 patients dropped out before temporary SNS; 18 patients completed the trial. Reasons for drop-out were not recorded. See Table 4-1.

The referral route for the majority of patients seen in the constipation clinic at the University hospital of North Durham is through local GP practices and regional hospitals. The trial aimed to recruit 30 patients with neuroconstipation, however during the second year the referral rates from local practices and hospitals dropped significantly. One major contributing factor was the retirement of a local collaborator which led to a decrease in the frequency of outpatient clinics at the local neurology unit. Hence, the trial was unable to meet the recruitment target within the two year trial time frame.

Table 4-1: Demographics and Participation

	Age	Sex	Diagnosis	Mobility	Successful trial	IPG implanted
SNS001	39	M	Autonomic Dystonia	RM	Dropped out	-
SNS002	61	M	SCI cervical	Normal	***Yes***	***Yes***
SNS003*	50	F	MS	WB	***Yes***	***Yes***
SNS004	69	M	MS	RM	***Yes***	***Yes***
SNS005	38	M	MS	RM	***Yes***	***Yes***
SNS006	58	F	SCI thoracic	WB	No	No
SNS007	63	M	MS	WB	***Yes***	***Yes***
SNS008	45	M	Cauda Equina	Normal	***Yes***	***Yes***
SNS009	40	F	MS	WB	***Yes***	***Yes***
SNS010	54	F	MS	WB	No	No
SNS011	50	F	MS	RM	No	No
SNS012	55	F	SCI	RM	No	No
SNS013	60	F	Spinal Myoclonus	WB	***Yes***	***Yes***
SNS014	67	F	MS	Normal	Dropped out	-
SNS015	64	F	MS	Normal	Dropped out	-
SNS 016	53	F	MS	WB	***Yes***	***Yes***
SNS 017	41	M	MS	Normal	***Yes***	***Yes***
SNS018	55	F	MS	WB	No	No
SNS019	47	F	MS	Normal	Dropped out	-
SNS020	64	F	Polio/ Hemiplegia	Normal	***Yes***	***Yes***
SNS021	58	F	MS	Normal	***Yes***	***Yes***
SNS022**	50	M	Cauda Equina	RM	No	No

Key:

* Sigmoid Volvulus; has loop colostomy now

** Patient died midtrial in RTA

MS= Multiple Sclerosis

SCI=Spinal cord Injury

IPG= Implantable pulse generator

Mobility= WB wheelchair bound, RM reduced mobility, N normal.

4.2 Primary outcome

4.2.1 Global assessment of Constipation

Table 4-2 shows the average scores for GA constipation from week 1 to week 12 of the trial. The Likert scale ranges from 1 (normal bowel habit) to 5 (very severe constipation). One of the patients failed to respond to SNS at the time of wire insertion; and the data were not included. Complete data were available for 15 patients as 2 patients did not report complete data.

The weekly mean scores and confidence intervals are reported in Table 4-2 and visualized in Figure 4-1.

Figure 4-1: Mean GA scores for constipation

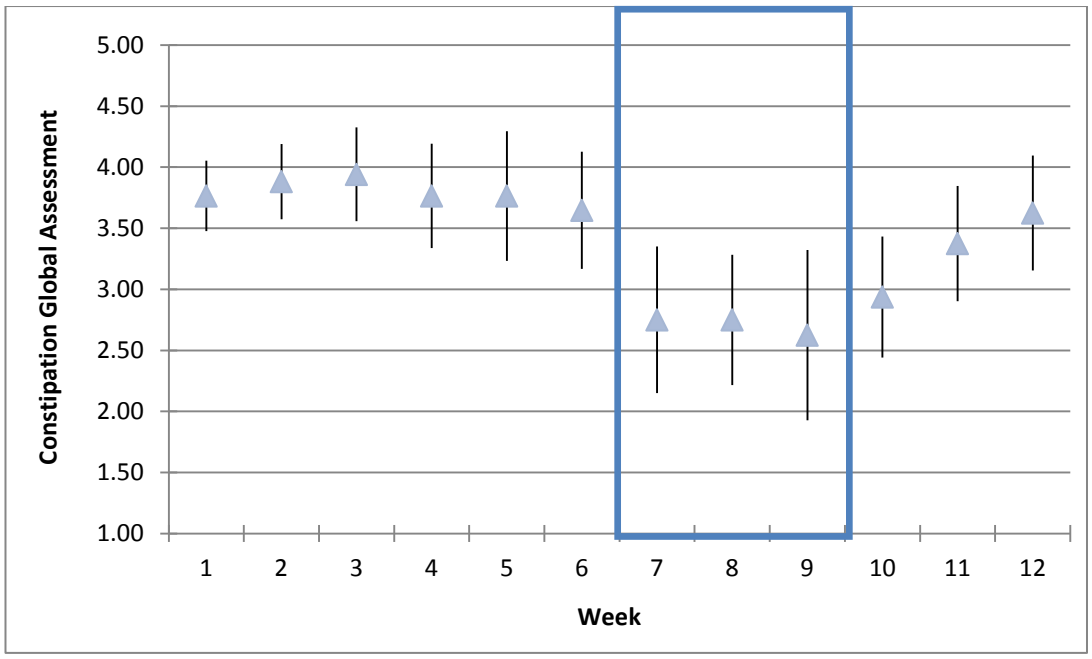


Table 4-2: Mean weekly scores for global assessment of constipation

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	3.75	3.88	3.94	3.75	3.75	3.63	2.75	2.75	2.63	2.94	3.38	3.63
95%CI-	3.44	3.55	3.53	3.29	3.18	3.11	2.15	2.22	1.93	2.44	2.90	3.15
95%CI+	4.06	4.20	4.35	4.21	4.32	4.14	3.35	3.28	3.32	3.43	3.85	4.10

The mean GA score for constipation during the first six weeks was 3.78 (95% CI 3.44 to 4.12). It improved during intervention (week 8-9) to 2.69 (95% CI 2.12 to 3.25) and post intervention (week 12) increased to 3.63 (95% CI 3.15 to 4.10).

There was an improvement in GA score for constipation during the intervention phase when compared to the pre-intervention stage (Table 4-3 p= 0.0003, paired t-test). Alternative use of the non-parametric Wilcoxon signed-rank test supported a statistically significant difference (p=0.001). There was a gradual washout of effect after the removal of stimulation (see Figure 4-1). At week 12 symptoms were similar to baseline (p=0.40). Individual patient data reported in appendix A.

Table 4-3: Changes in GA Constipation during each phase of the study

	Int-Pre	**End-Pre**
Mean	-1.09	-0.16
95% CI-	-1.59	-0.54
95% CI+	-0.59	0.23
p	0.0003	0.40
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.2.2 Permanent Implant Decision

All patients demonstrating a positive response (12 of 18, 67%) were offered and received a permanent implant (see Table 4-1). Four of the original sample of 22 patients did not proceed to temporary implant.

4.3 Secondary Outcomes

4.3.1 Global Assessment of Faecal Incontinence

The Likert scale ranged from 1 (no incontinence) to 5 (very severe incontinence). One of the patients failed to respond to SNS at the time of wire insertion and was not included in the final analysis. Complete data were available for 15 patients.

The mean GA score for faecal incontinence during the first six weeks was 1.29 (95% CI 0.61 to 1.97), during intervention (week 8-9) was 1.13 (95% CI 0.41 to 1.84) and post intervention was 1.25 (95% CI 0.35 to 2.15). The mean weekly scores and confidence intervals for GA FI are given in Figure 4-2 and Table 4-4.

Figure 4-2: GA of Faecal Incontinence

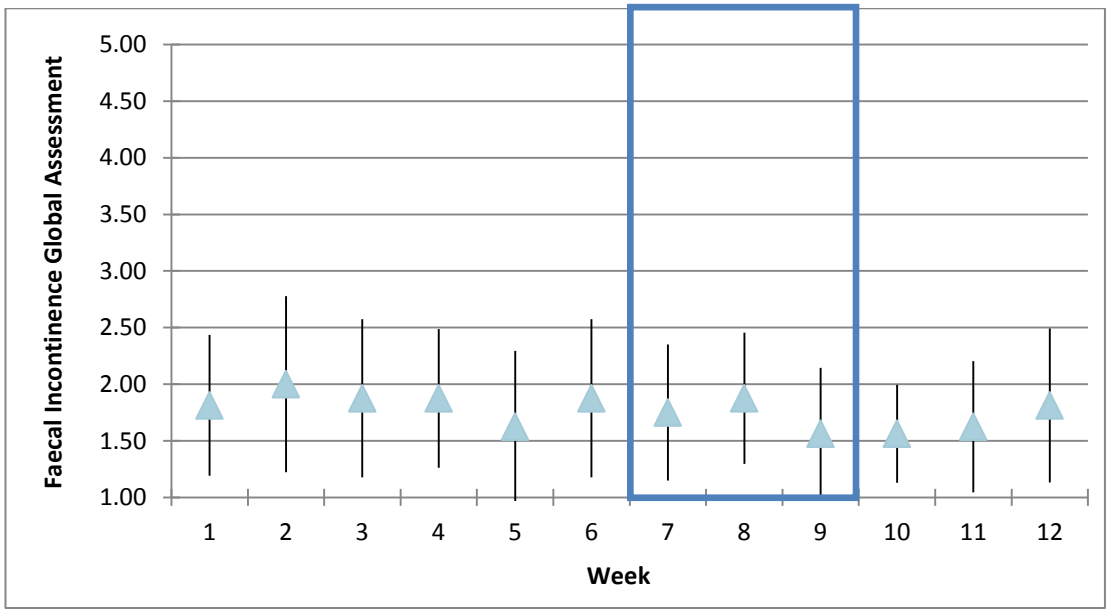


Table 4-4: Mean weekly scores for GA FI

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.81	2.00	1.88	1.88	1.63	1.88	1.75	1.88	1.56	1.56	1.63	1.81
95%CI-	1.19	1.22	1.18	1.26	0.95	1.18	1.15	1.30	0.98	1.13	1.05	1.13
95%CI+	2.43	2.78	2.55	2.49	2.30	2.57	2.35	2.45	2.12	2.00	2.18	2.49

The change in mean GA score of FI during the intervention phase of the study was neither clinically important nor statistically significant (p = 0.36, see Table **4-5**). The

lack of response in this measure was consistent with prior expectation, since FI was not an important symptom in this patient group.

Table 4-5: Changes in GA FI during each phase of the study

	Int-Pre	**End-Pre**
Mean	-0.13	-0.03
95% CI-	-0.41	-0.44
95% CI+	0.16	0.37
p	0.36	0.87
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.2 Patient Assessment of Constipation Symptoms (PAC-SYM)

The aggregate PAC-SYM score ranges from 0 (no constipation) to 4 (severe constipation). The overall score is calculated as the average of 12 items, each scored from 0 to 4. Missing values were subtracted from the denominator during the calculation of the overall score. Complete data were available for 15 patients.

The mean PAC-SYM score during the first six weeks was 1.83 (95% CI 1.49 to 2.17). It improved during intervention (week 8-9) to 1.10 (95% CI 0.67 to 1.54) and post intervention increased to 1.54 (95% CI 1.13 to 1.94). The mean weekly scores and confidence intervals for PAC-SYM are given in Figure 4-3 and Table 4-6.

Figure 4-3: PAC-SYM Score

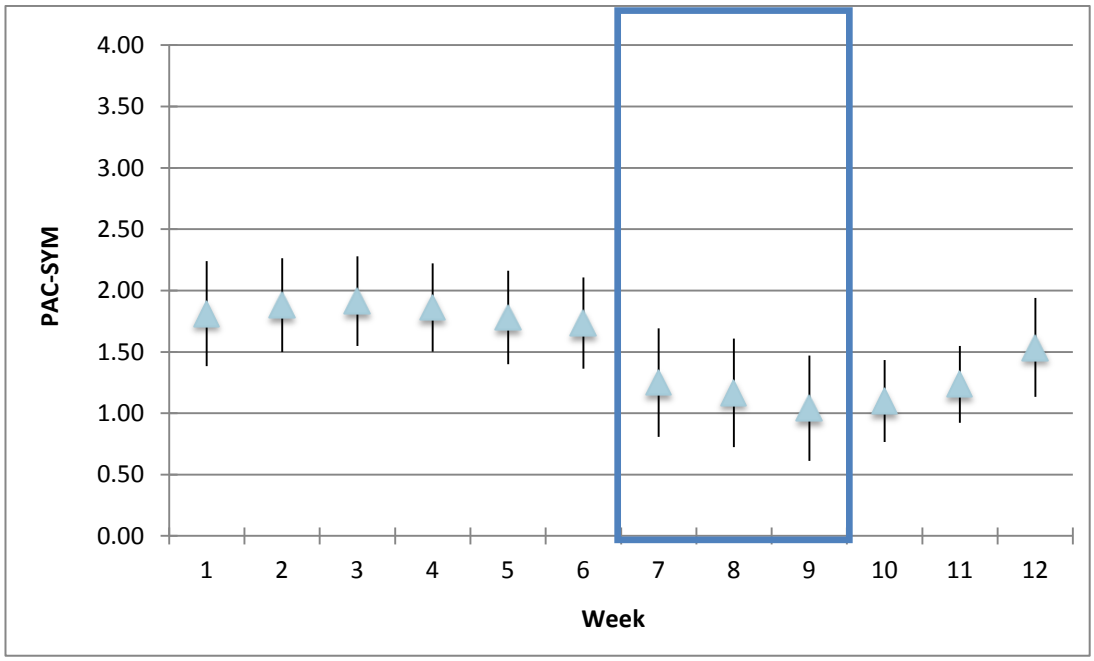


Table 4-6: Weekly mean scores for PAC-SYM

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.81	1.88	1.91	1.86	1.78	1.73	1.25	1.17	1.04	1.10	1.23	1.54
95%CI-	1.38	1.50	1.55	1.50	1.40	1.36	0.81	0.72	0.61	0.76	0.92	1.13
95%CI+	2.24	2.26	2.28	2.22	2.16	2.11	1.69	1.61	1.47	1.43	1.55	1.94

There was a clinically important improvement in PAC-SYM score during the intervention phase when compared to the pre-intervention stage (p=0.003). There was a gradual diminution of effect after the removal of stimulation (see Table 4-7 and Figure 4-3), although symptoms had not fully returned to baseline at week 12 (p=0.04).

Table 4-7: Change in PAC-SYM during each phase of the study

	Int-Pre	**End-Pre**
Mean	-0.73	-0.29
95% CI-	-1.06	-0.58
95% CI+	-0.39	-0.01
p	0.0003	0.04
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.2.1 PAC-SYM Domain Analysis

The PAC-SYM12-item self-report measure is divided into three symptom subscales (i.e. abdominal, rectal and stool). Items are scored on a four-point Likert scale, with 4 indicating the worst symptom severity. A sub-domain analysis was carried out to check variations in each domain during each phase of the trial. In summary, over the 12 week period, each sub-domain qualitatively reflected the pattern found in the overall PAC-SYM score.

4.3.2.1.1 Abdominal Domain

There are four items in the abdominal domain which include abdominal discomfort, abdominal pain, abdominal cramping and abdominal bloating. Table 4-7 shows the average scores for the abdominal domain of PAC-SYM from week 1 to week 12 of the trial. The mean score during the first six weeks was 2.00 (95% CI 1.60 to 2.41). It improved during intervention (week 8-9) to 1.16 (95% CI 0.65 to 1.67) and post intervention increased to 1.64 (95% CI 1.16 to 2.13). The weekly mean scores and confidence intervals are given in Table 4-8 and visualized in Figure 4-4.

Figure 4-4: PAC-SYM Abdominal score

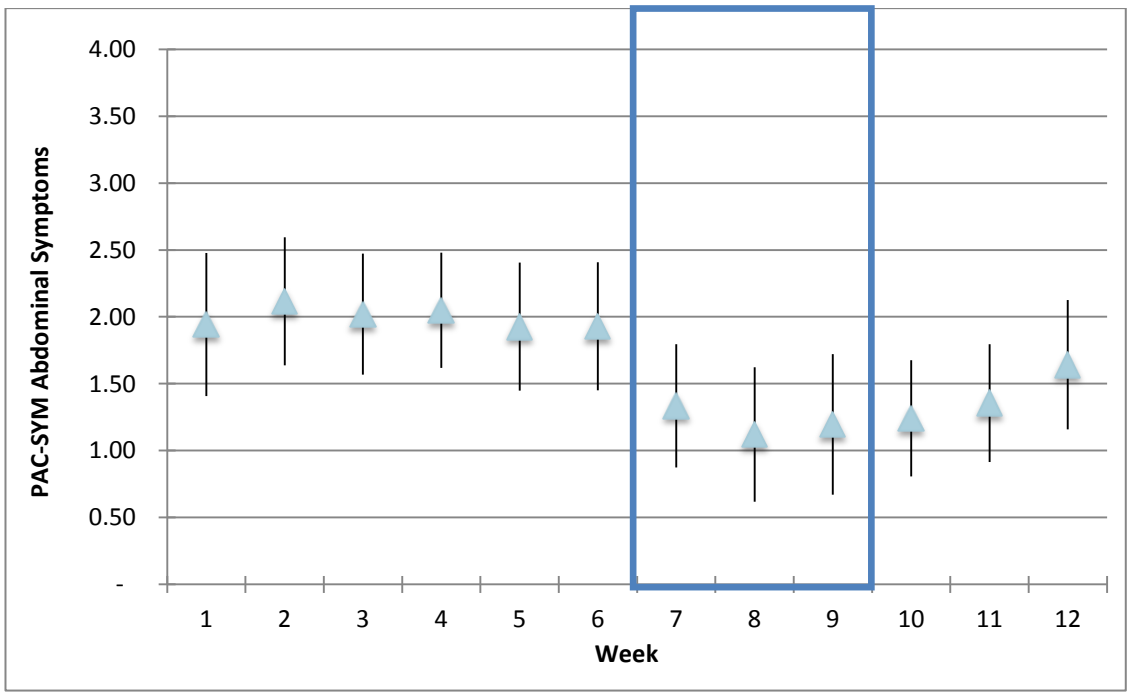


Table 4-8: Weekly mean scores for PAC-SYM abdominal domain

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.94	2.12	2.02	2.05	1.93	1.93	1.34	1.12	1.20	1.24	1.36	1.64
95%CI-	1.41	1.64	1.57	1.62	1.45	1.45	0.88	0.62	0.67	0.81	0.92	1.16
95%CI+	2.48	2.59	2.47	2.48	2.41	2.41	1.80	1.62	1.72	1.68	1.79	2.13

There was an improvement in the PAC-SYM abdominal domain score during the intervention phase when compared to the pre-intervention stage (Table 4-9, p=0.0009). There was a trend from week 10 to 12 of the score returning to baseline after removal of wires (see Figure 4-4).

Table 4-9: Change in PAC-SYM abdominal domain

	Int-Pre	End-Pre
Mean	-0.84	-0.36
95% CI-	-1.27	-0.77
95% CI+	-0.41	0.06
p	0.0009	0.09
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.2.1.2 Rectal domain

There are 3 items related to the rectal domain. These include painful bowel movements, rectal burning and bleeding or tearing during or after bowel movements. Table 4-10 shows the average scores for the rectal domain of PAC-SYM from week 1 to week 12 of the trial. The mean score during the first six weeks was 1.42 (95% CI 1.06 to 1.78). It improved during intervention (week 8-9) to 0.78 (95% CI 0.42 to 1.14) and post intervention increased to 1.15 (95% CI 0.70 to 1.60). The weekly mean scores and confidence intervals are given in Figure 4-5.

Figure 4-5: PAC-SYM Rectal score

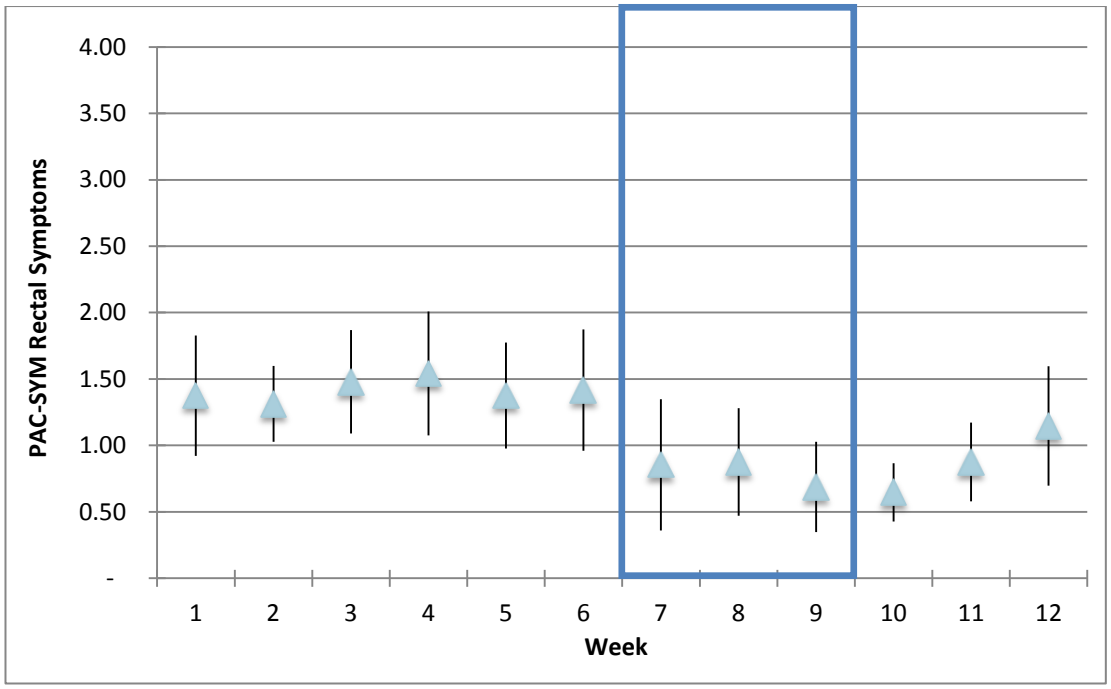


Table 4-10: Mean scores for rectal domain of PAC-SYM

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.38	1.31	1.48	1.54	1.38	1.42	0.85	0.88	0.69	0.65	0.88	1.15
95%CI-	0.92	1.03	1.09	1.07	0.98	0.96	0.36	0.47	0.35	0.43	0.58	0.70
95%CI+	1.83	1.60	1.87	2.01	1.77	1.87	1.35	1.28	1.03	0.87	1.17	1.60

There was an improvement in PAC-SYM rectal domain score during the intervention phase when compared to the pre-intervention stage (p=0.003). There was a trend from week 10 to 12 of the score returning to baseline after removal of wires (see Figure 4-5 and Table 4-11).

Table 4-11: Change in Rectal domain of PAC-SYM

	Int-Pre	End-Pre
Mean	-0.64	-0.27
95% CI-	-1.03	-0.75
95% CI+	-0.24	0.21
p	0.003	0.25
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.2.1.3 Stool Domain

The stool domain has five items which include bowel movements that require straining or squeezing, bowel movements that are too hard, bowel movements that are too small, bowel movements that result in a sensation of incomplete evacuation and having false alarms.

The mean score during the first six weeks was 1.94 (95% CI 1.48 to 2.40). It improved during intervention (week 8-9) to 1.27 (95% CI 0.76 to 1.77) and post intervention increased to 1.67 (95% CI 1.16 to 2.18). The weekly mean scores and confidence intervals are given in Figure 4-6 and Table 4-12.

Figure 4-6: PAC-SYM Stool score

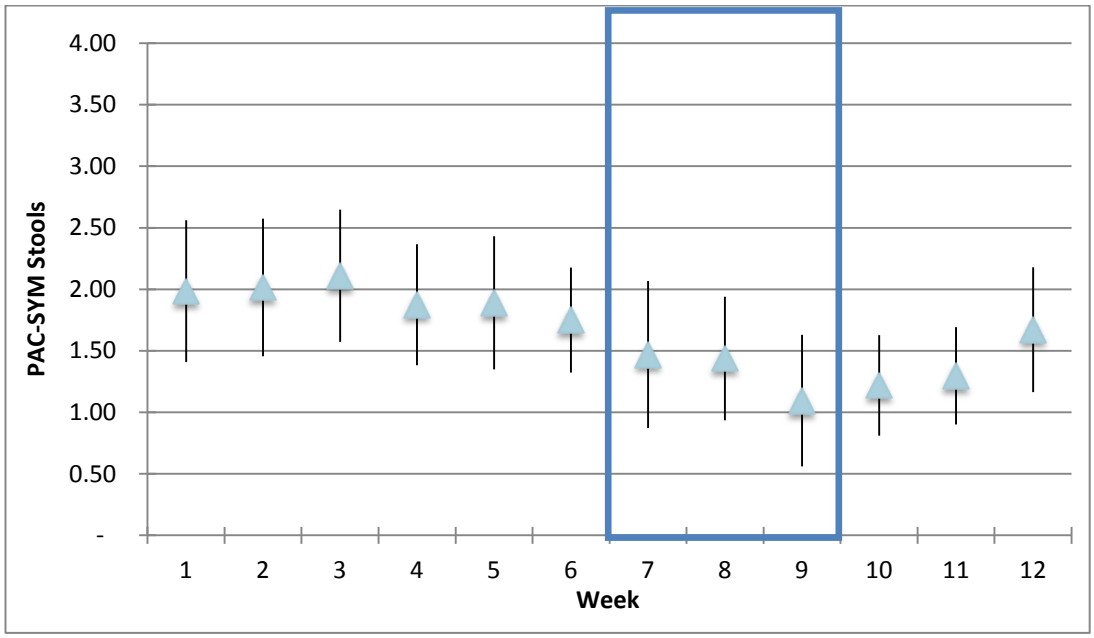


Table 4-12: Mean scores for Stool domain of PAC-SYM

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.98	2.02	2.11	1.88	1.89	1.75	1.47	1.44	1.09	1.22	1.30	1.67
95%CI-	1.41	1.46	1.57	1.38	1.35	1.32	0.87	0.94	0.56	0.81	0.90	1.16
95%CI+	2.56	2.58	2.65	2.37	2.43	2.18	2.07	1.94	1.63	1.63	1.69	2.18

There was an improvement in the stool domain of PAC-SYM during intervention. This was statistically significant ($p<0.0001$). There was a gradual diminution of benefit after the removal of wires and the symptoms reverted towards the pre-treatment stage (Table 4-13 $p=0.12$).

Table 4-13: Change in Stool domain of PAC-SYM

	Int-Pre	End-Pre
Mean	-0.67	-0.27
95% CI-	-0.92	-0.61
95% CI+	-0.43	0.08
p	<0.01	0.12
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.3 Patient Assessment of Constipation (PAC-QOL)

The PAC-QOL is a 28-item subject self-administered instrument that measures the severity of constipation-related quality of life. Items are rated on a 5-point scale: 0=not at all/none of the time, 1=a little bit/a little of the time, 2=moderately/some of the time, 3=quite a bit/most of the time and 4=extremely/all of the time.

The aggregate average score similarly ranges from 0 (best QOL) to 4 (Worst QOL). Missing values are subtracted from the denominator during the calculation of overall score. Complete data were available for 15 patients.

The mean PAC-QOL score during the first six weeks was 2.26 (95% CI 1.96 to 2.55). It improved during intervention (week 8-9) to 1.58 (95% CI 1.11 to 2.05) and post intervention increased to 2.16 (95% CI 1.82 to 2.51) almost returning to baseline value by the end of week 12. The mean weekly scores and confidence intervals for PAC-QOL are given in Figure 4-7 and Table 4-14.

Figure 4-7: PAC-QOL Score

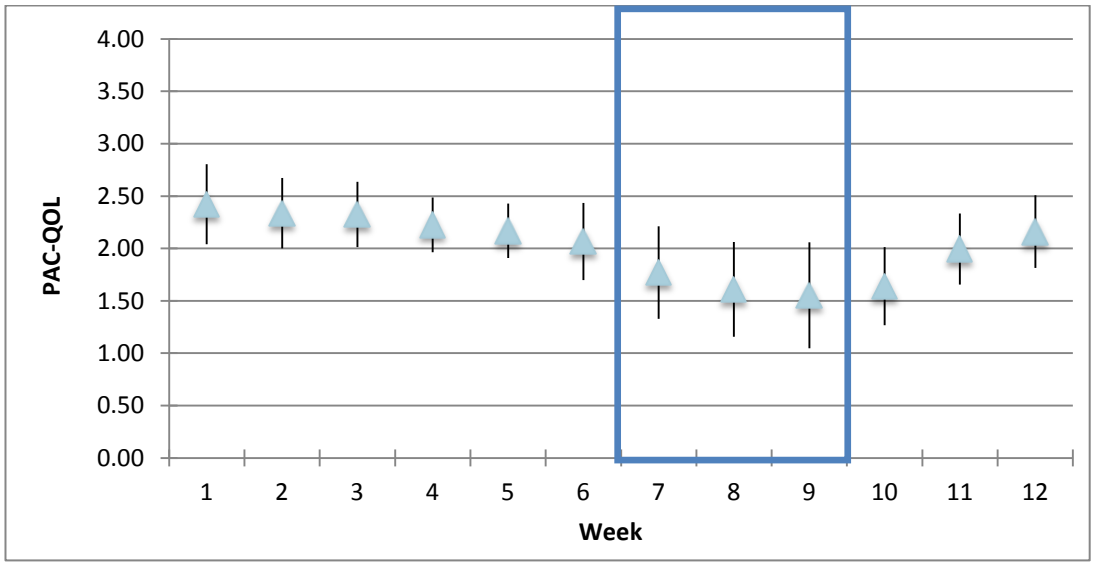


Table 4-14: Weekly mean score for PAC-QOL

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	2.42	2.34	2.32	2.23	2.17	2.07	1.77	1.61	1.55	1.64	1.99	2.16
95%CI-	2.04	2.00	2.01	1.96	1.91	1.70	1.33	1.16	1.05	1.27	1.66	1.82
95%CI+	2.80	2.67	2.64	2.49	2.43	2.44	2.21	2.06	2.06	2.01	2.33	2.51

The improvement in PAC-QOL during SNS was statistically significant during the intervention phase (p=0.0008) and was similar to baseline by week 12 (p=0.43), after cessation of SNS (Table 4-15).

Table 4-15: Change in PAC-QOL during intervention

	Int-Pre	End-Pre
Mean	-0.68	-0.10
95% CI-	-1.02	-0.35
95% CI+	-0.33	0.16
p	0.0008	0.43
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.3.1 PAC-QOL Domain Analysis

PAC-QOL has four subscales which include physical, psychosocial, worries and concerns and satisfaction domains.

4.3.3.1.1 Physical Discomfort

Physical discomfort has 4 items which include the following: bloated to the point of bursting, felt heavy because of constipation, felt any physical discomfort and false alarms.

The mean score during the first six weeks was 2.51 (95% CI 2.09 to 2.92). It improved during intervention (week 8-9) to 1.59 (95% CI 1.03 to 2.15) and post intervention increased to 2.31 (95% CI 1.80 to 2.83). The weekly mean scores and confidence intervals are given in Figure 4-8 and Table 4-16.

Figure 4-8: PAC-QOL Physical discomfort domain

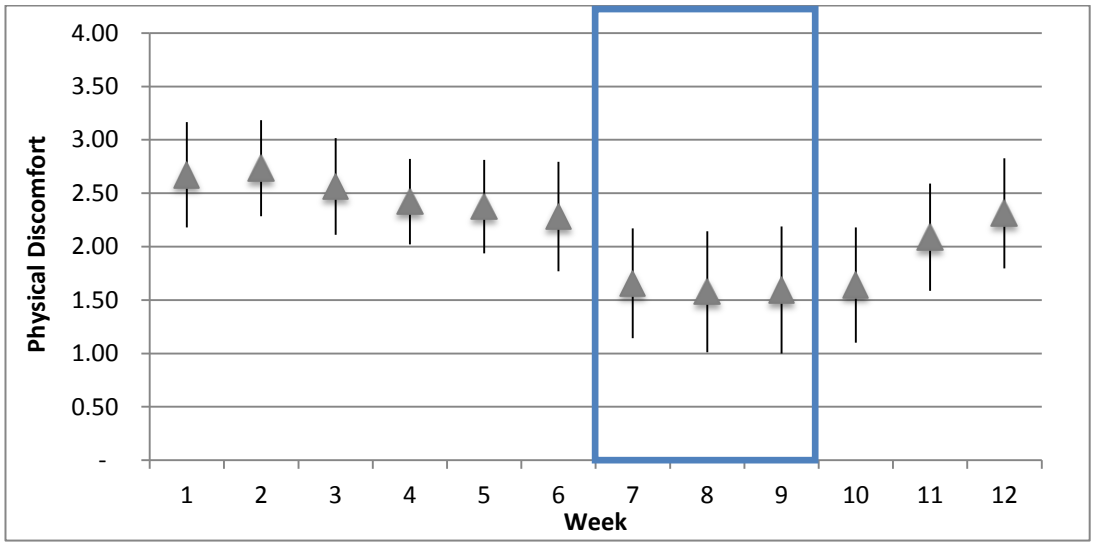


Table 4-16: Mean weekly score for PAC-QOL physical discomfort

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	2.67	2.73	2.56	2.42	2.38	2.28	1.66	1.58	1.59	1.64	2.09	2.31
95%CI-	2.18	2.28	2.11	2.02	1.94	1.77	1.14	1.01	1.00	1.10	1.59	1.80
95%CI+	3.16	3.18	3.01	2.82	2.81	2.79	2.17	2.14	2.19	2.18	2.59	2.83

There was an improvement in the PAC-QOL physical discomfort domain score during the intervention phase when compared to the pre-intervention stage (p value <0.01), which had largely disappeared by week 12 (Table 4-17, p=0.41)

Table 4-17: Change in PAC-QOL physical discomfort

	Int-Pre	End-Pre
Mean	-0.92	-0.20
95% CI-	-1.41	-0.68
95% CI+	-0.43	0.29
p	0.0012	0.41
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.3.1.2 Psychosocial Discomfort

Psychosocial discomfort has 8 items which include the following:

1. been embarrassed to be with other people
2. been eating less and less because of not being able to have bowel movements
3. had to be careful about what you eat
4. had a decreased appetite
5. been worried about not being able to choose what you eat
6. been embarrassed about staying in the toilet for so long when you were away from home
7. been embarrassed about having to go to the toilet so often when you were away from home
8. been worried about having to change your daily routine

The mean score during the first six weeks was 1.40 (95% CI 1.02 to 1.79). It improved during intervention (week 8-9) to 1.10 (95% CI 0.58 to 1.62) and post intervention

increased to 1.34 (95% CI 0.79 to 1.79). The weekly mean scores and confidence intervals are given in Figure 4-9 and Table 4-18.

Figure 4-9: PAC-QOL Psychosocial discomfort

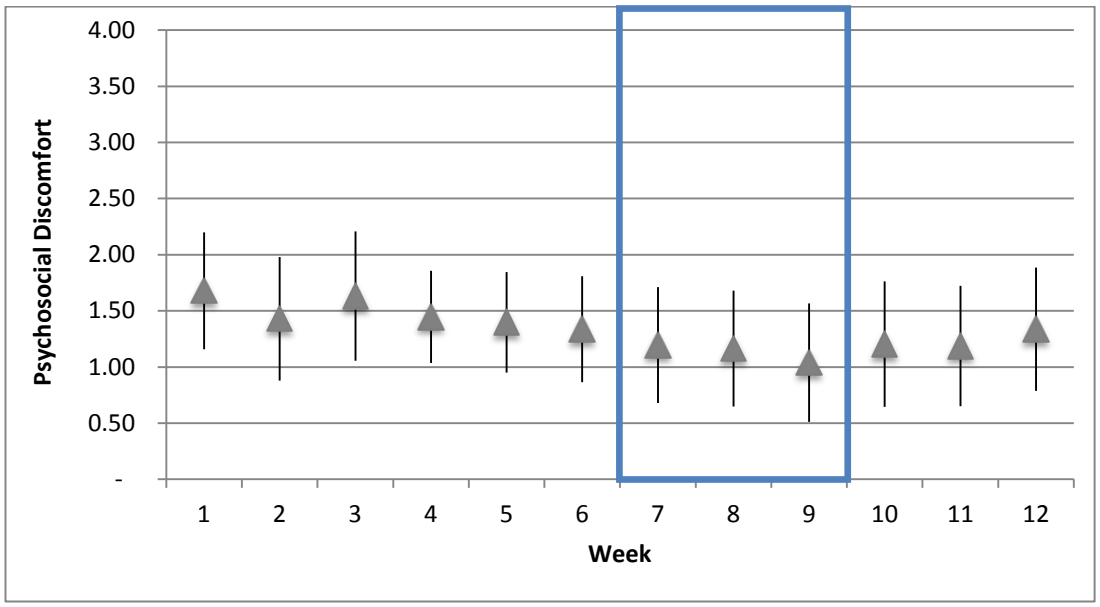


Table 4-18: Weekly scores PAC-QOL Psychosocial domain

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.81	2.00	1.81	1.88	1.63	1.88	1.75	1.88	1.50	1.56	1.56	1.81
95% CI-	1.16	0.88	1.06	1.03	0.95	0.86	0.68	0.65	0.51	0.64	0.65	0.79
95% CI+	2.20	1.98	2.21	1.86	1.85	1.81	1.71	1.68	1.57	1.76	1.72	1.89

There was an improvement in PAC-QOL psychosocial discomfort domain score during the intervention phase when compared to the pre-intervention stage (Table 4-19, p=0.039). The score returned to baseline after removal of wires.

Table 4-19: Change in PAC-QOL Psychosocial domain

	Int-Pre	End-Pre
Mean	-0.30	-0.07
95% CI-	-0.58	-0.36
95% CI+	-0.02	0.23
p	0.039	0.63
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.3.1.3 Worries and Concerns

Within the PAC-QOL measure, worries and concerns has 11 items which include the following:

1. felt irritable because of your condition
2. been upset by your condition
3. felt obsessed by your condition
4. felt stressed by your condition
5. felt less self-confident because of your condition
6. felt in control of your situation
7. been worried about not knowing when you are going to be able to open your bowels
8. been worried about not being able to open your bowels when you needed to
9. been more and more bothered by not being able to open your bowels
10. been afraid that your condition will get worse
11. felt that your body was not working properly

The mean score during the first six weeks was 2.35 (95% CI 1.96 to 2.74). It improved during intervention (week 8-9) to 1.69 (95% CI 1.15 to 2.23) and post intervention

increased to 2.20 (95% CI 1.79 to 2.62). The weekly mean scores and confidence intervals are given in Figure 4-10 and Table 4-20.

Figure 4-10: PAC-QOL Worries and Concerns

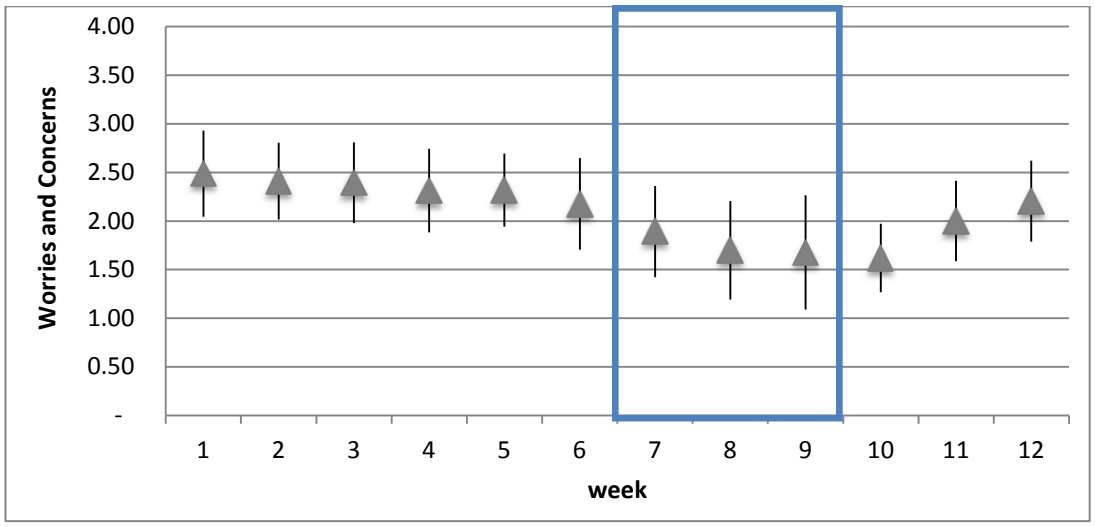


Table 4-20: Weekly scores for PAC-QOL worries and concerns

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	2.49	2.41	2.39	2.31	2.32	2.18	1.89	1.70	1.68	1.62	2.00	2.20
95%CI-	2.05	2.01	1.98	1.88	1.94	1.71	1.42	1.19	1.09	1.27	1.59	1.79
95%CI+	2.93	2.80	2.81	2.74	2.69	2.65	2.36	2.20	2.26	1.97	2.41	2.62

There was a statistically significant improvement during the intervention phase (p=0.002), that did not persist to week 12 (Table 4-21, p=0.36), after cessation of SNS.

Table 4-21: Change in PAC-QOL worries and concerns

	Int-Pre	End-Pre
Mean	-0.66	-0.15
95% CI-	-1.04	-0.47
95% CI+	-0.29	0.18
p	0.002	0.36
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.3.1.4 Dissatisfaction

The dissatisfaction domain has 5 items:

1. fewer bowel movements than you would like
2. satisfied with how often you open your bowels
3. satisfied with the regularity with which you open your bowels
4. satisfied with your bowel function
5. satisfied with your treatment

The mean score during the first six weeks was 3.09 (95% CI 2.81 to 3.36). It improved during intervention (week 8-9) to 2.11 (95% CI 1.49 to 2.73) and post intervention increased to 3.26 (95% CI 3.01 to 3.51). The weekly mean scores and confidence intervals are given in Figure 4-11 and Table 4-22.

Figure 4-11: PAC-QOL Dissatisfaction domain score

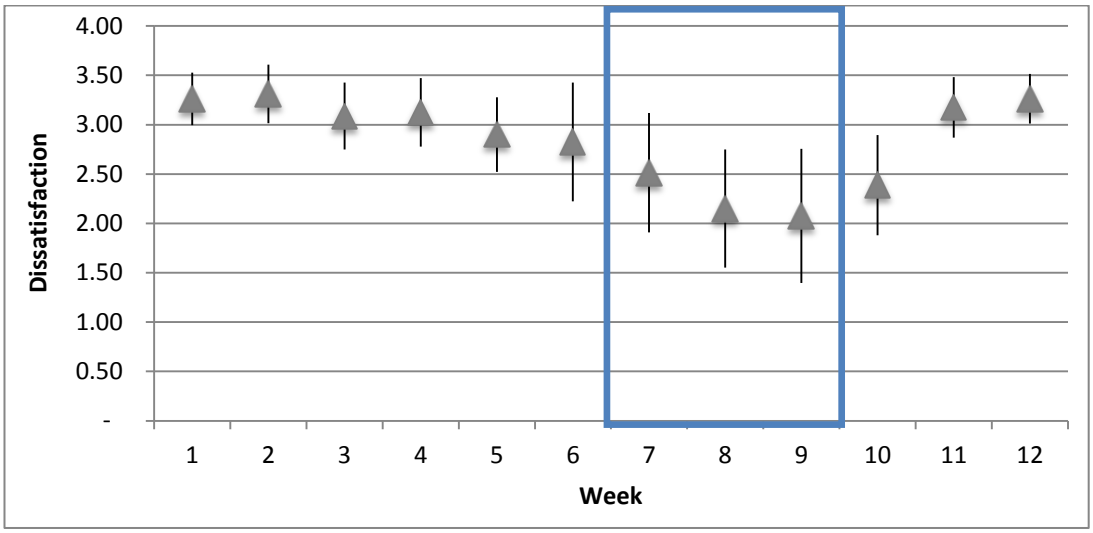


Table 4-22: Weekly score for PAC-QOL dissatisfaction score

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	3.26	3.31	3.09	3.13	2.90	2.83	2.51	2.15	2.08	2.39	3.18	3.26
95%CI-	3.00	3.02	2.75	2.78	2.52	2.22	1.91	1.55	1.40	1.88	2.87	3.01
95%CI+	3.53	3.61	3.43	3.47	3.28	3.43	3.12	2.75	2.75	2.90	3.48	3.51

There was a statistically significant improvement during the intervention phase (p=0.005), that did not persist to week 12 (Table 4-23, p=0.19), after cessation of SNS.

Table 4-23: Change in PAC-QOL Dissatisfaction score

	Int-Pre	End-Pre
Mean	-0.97	0.18
95% CI-	-1.60	-0.10
95% CI+	-0.35	0.46
p	0.005	0.19
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

4.3.4 Euro QOL Health Questionnaire (EQ5D)

EQ5D is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (1=no problems 2=some or moderate problems, 3=extreme problems) within each EQ-5D dimension. Responses are converted to 'utility' scores (0-1) using a lookup algorithm provided by the EuroQoL group and based on societal values. Assessments were made pre-intervention phase (week 3, 6), one during SNS (week 9) and one after SNS (week 12).

The average EQ5D pre-intervention score was 0.22 (95% CI 0.07 to 0.37). It increased during intervention to 0.32 (95% CI 0.15 to 0.49) and post intervention decreased to 0.25 (95% CI 0.08 to 0.43). The mean scores and confidence intervals are given in Fig 4-12 and Table 4-24.

Figure 4-12: EQ5D Scores

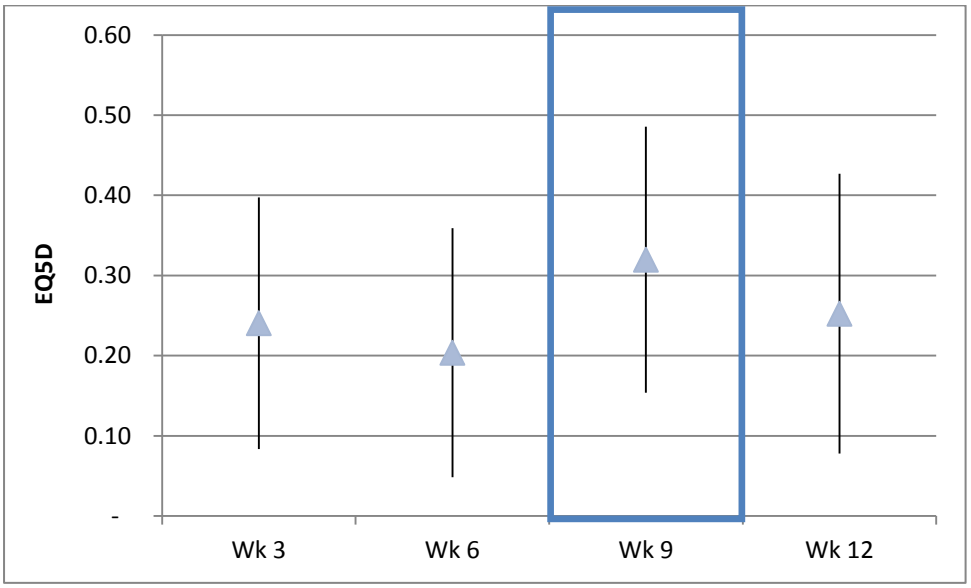


Table 4-24: Mean scores for EQ5D

	Week 3	Week 6	Week 9	Week 12
Mean	0.22	0.22	0.32	0.25
95%CI-	0.06	0.06	0.15	0.08
95%CI+	0.39	0.38	0.49	0.43

Although qualitatively there seems to be an improvement during intervention this was not a statistically significant change from baseline (Table 4-25, p=0.16).

Table 4-25: Change in EQ5D during each phase

	Int-Pre	End-Pre
Mean	0.10	0.03
95% CI-	-0.04	-0.12
95% CI+	0.24	0.18
p	0.16	0.68
Int: Intervention (wk 9) Pre: Pre-intervention (wks3,6) End: Post-intervention (wk 12)		

4.3.5 EuroQOL Visual Analogue Score (EQ-VAS)

EQ-5D is a standardised instrument for use as a proxy measure of health. It uses a standard vertical 20 cm visual analogue scale (similar to a thermometer) for recording an individual's rating for their current health-related quality of life. The maximum score is 100 (best state of health) and the minimum score is 0 (worst state of health). Two readings were taken in the pre-intervention phase (week 3, 6); one during SNS (week 9) and the last measurement was taken after SNS (week 12).

The average pre-intervention score was 45.5 (95% CI: 38.5 to 52.4). It increased marginally during intervention to 47.7 (95% CI: 35.8 to 59.5) and post intervention the score was 45.0 (95% CI: 38.4 to 51.6). The weekly mean scores and confidence intervals are given in Figure 4-13 and Table 4-26.

Figure 4-13: EQ-VAS scores

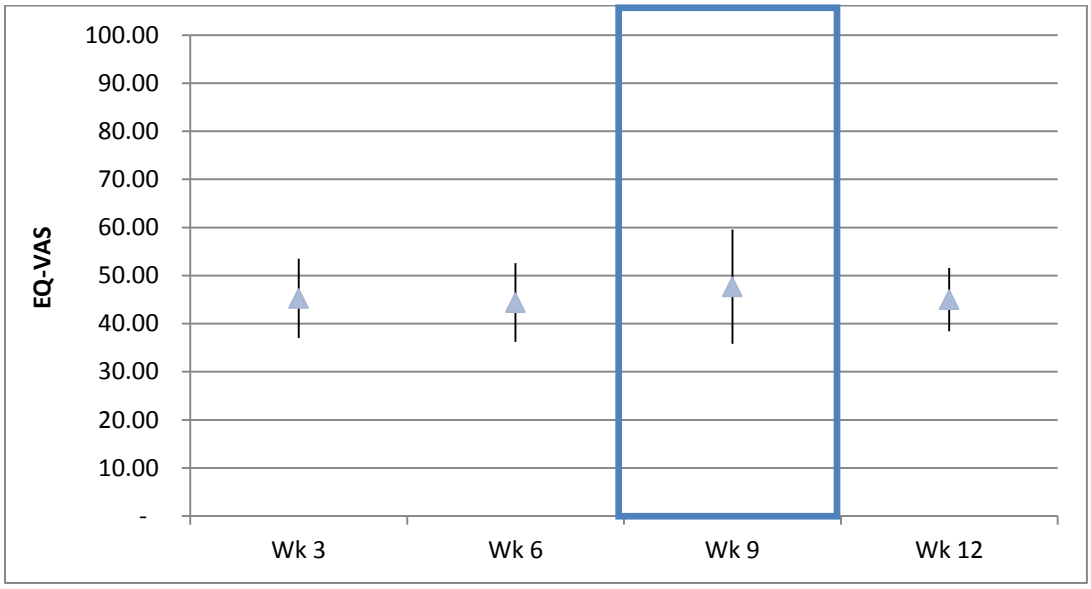


Table 4-26: Mean weekly EQ-VAS score

	Week 3	Week 6	Week 9	Week 12
Mean	45.6	45.3	47.7	45.0
95%CI-	36.8	36.8	35.8	38.4
95%CI+	54.4	53.9	59.5	51.6

There was no change in the overall EQ-VAS scores during the intervention phase (Table 4-27, p >0.05) or subsequently.

Table 4-27: Change in EQ-VAS

	Int-Pre	End-Pre
Mean	2.2	-0.47
95% CI-	-9.2	-6.1
95% CI+	13.6	5.2
p	0.69	0.86
Int: Intervention (wk 9) Pre: Pre-intervention (wks3,6) End: Post-intervention (wk 12)		

4.3.6 Daily Diary

A daily dairy was administered during the pre-intervention phase (week 4 to week 6) and the intervention phase (week 7 to week 9) of the study.

Patients kept a daily record of their bowel movements, episodes of faecal incontinence, time spent toileting and laxative score: these were aggregated to weekly averages for the analysis.

4.3.6.1 Bowel Movements

Complete diary data were available for 15 subjects. The mean number of pre-intervention bowel movements was 1.46 per week (95% CI 0.78 to 2.33) and during intervention was 1.15 per week (95% CI 0.73 to 1.78). The mean scores and confidence intervals are given in Figure 4-14 and Table 4-28.

Figure 4-14: Bowel Movements

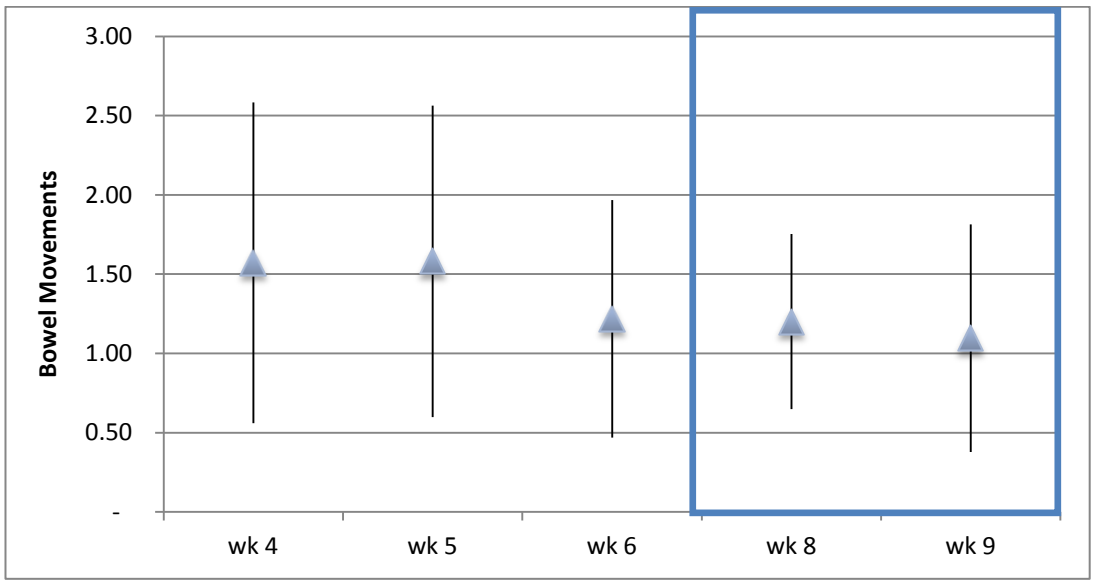


Table 4-28: Mean weekly bowel movements

	Week 4	Week 5	Week 6	Week 8	Week 9
Mean	1.57	1.58	1.22	1.20	1.10
95%CI-	0.78	0.82	0.68	0.77	0.63
95%CI+	2.57	2.56	1.99	1.75	1.84

Comparing intervention and pre-intervention phases, changes in bowel movement were not statistically significantly different (Table 4-29, p=0.29).

Table 4-29: Change in bowel movement during intervention

	Int-Pre
Mean	-0.31
95% CI-	-0.77
95% CI+	0.01
p	0.29
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks 4,5,6)	

4.3.6.2 Faecal Incontinence Episodes

Complete diary data were available for 15 subjects. Patients with neuropathic constipation may suffer from faecal incontinence (FI) as well. The median FI score was zero, being reported in 9 patients consistently throughout the diary period. A related samples Wilcoxon signed rank test comparing intervention and pre-intervention found no statistically significant change in FI: p=0.345.

4.3.6.3 Time spent toileting

Complete diary data were available for 15 subjects. Before SNS, an average of 20 minutes per visit (95% CI 11 to 31) was spent on toileting. This decreased during intervention to 13 minutes per visit (95% CI 8 to 19). The mean scores and confidence intervals are given in Figure 4-15 and Table 4-30.

Figure 4-15: Time spent toileting (minutes)

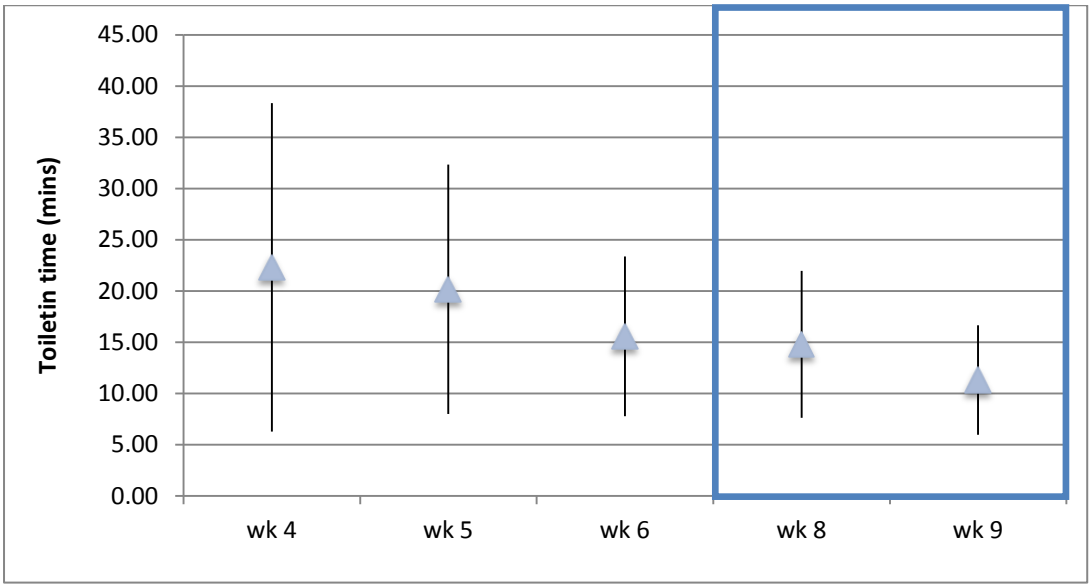


Table 4-30: Mean time spent toileting (minutes)

	Week 4	Week 5	Week 6	Week 8	Week 9
Mean	22.3	20.2	15.6	14.8	11.3
95%CI-	10.5	10.7	9.6	9.5	7.0
95%CI+	38.0	32.1	23.1	21.7	16.3

There was a suggested (non-statistically significant) mean reduction of 6 minutes in the time spent toileting per visit during intervention (p=0.126, Table 4-31).

Table 4-31: Change in time spent toileting (minutes)

	Int-Pre
Mean	-6.5
95% CI-	-13.3
95% CI+	1.5
p	0.126
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks 4,5,6)	

4.3.6.4 Laxative Score

Complete diary data were available for 16 subjects. The dosage and type of laxatives vary in patients with neurological constipation and it is very difficult to quantify the laxative intake over a period of time. Weekly laxative use was averaged for each participant and then documented with a daily laxative score. The participants documented whether their laxative intake was more, same or less than their average daily use on a scale (0=same, +1 =more, -1=less than the usual dose).

The pre-intervention laxative score was 0.10 (95% CI -0.03 to 0.22). It decreased during intervention to -0.06 (95% CI -0.24 to 0.10). The mean scores and confidence intervals are given in Figure 4-16 and Table 4-32.

Figure 4-16: Mean Laxative score

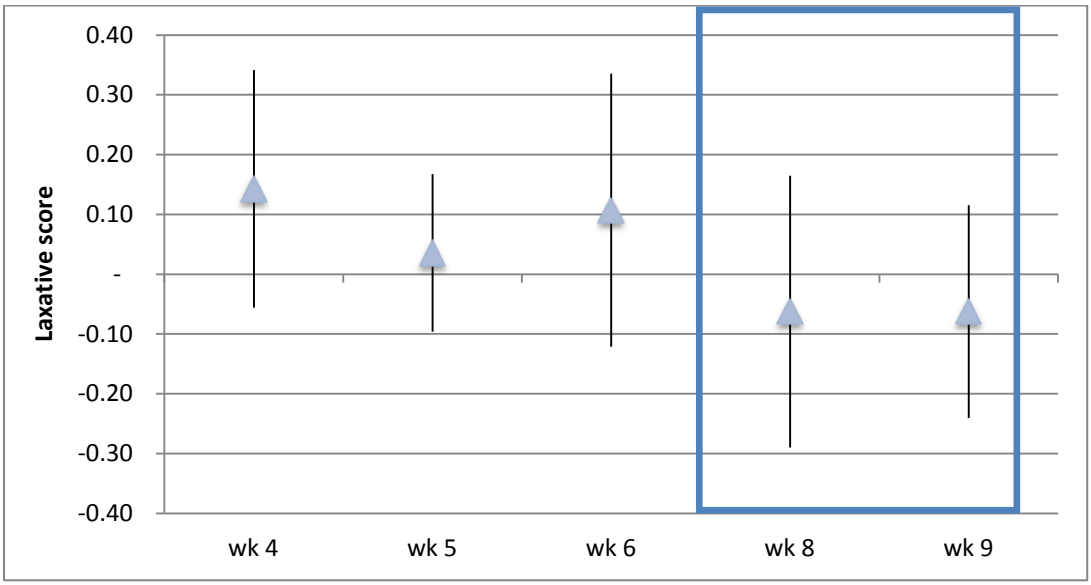


Table 4-32: Mean weekly laxative score

	Week 4	Week 5	Week 6	Week 8	Week 9
Mean	0.14	0.04	0.11	-0.06	-0.06
95%CI-	-0.28	-0.09	-0.10	-0.27	-0.23
95%CI+	0.32	0.14	0.30	0.13	0.08

Laxative score decreased during intervention: the mean decrease in use was 0.16 (Table 4-33, p=0.032).

Table 4-33: Change in Laxative score

	Int-Pre
Mean	-0.16
95% CI-	-0.29
95% CI+	-0.04
p	0.032
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks 4,5,6)	

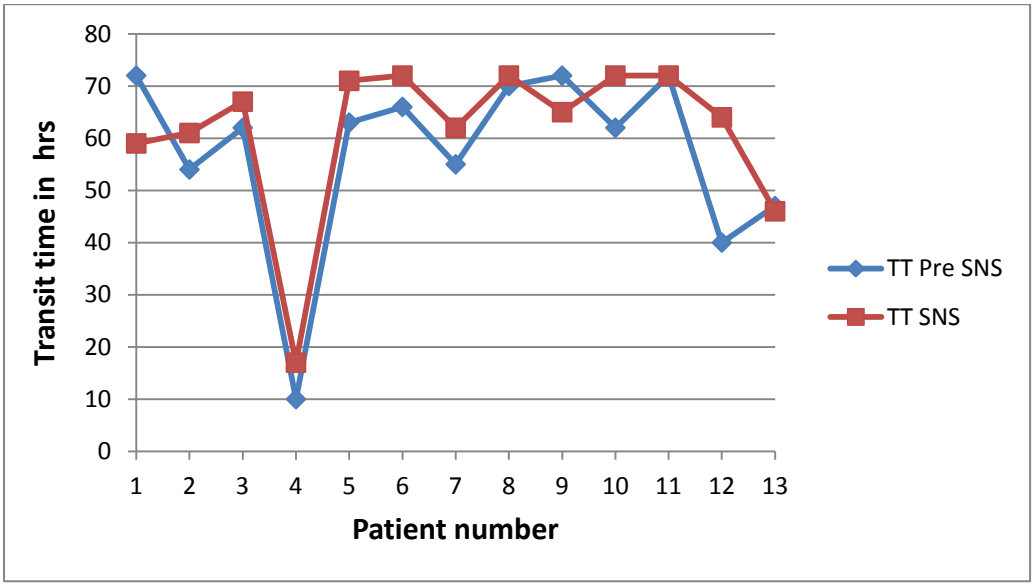
4.3.7 Physiological Outcomes

Two physiological measures were included in the study: the colonic transit time and laser Doppler flow cytometry. For an explanation of these methods see sections 3.3.3.5 and 3.3.3.6.

4.3.7.1 Transit Study

Transit time measurements were completed at recruitment and towards the end of the intervention phase. Transit studies were completed by 13 patients, with transit times shown in Fig 4-17.

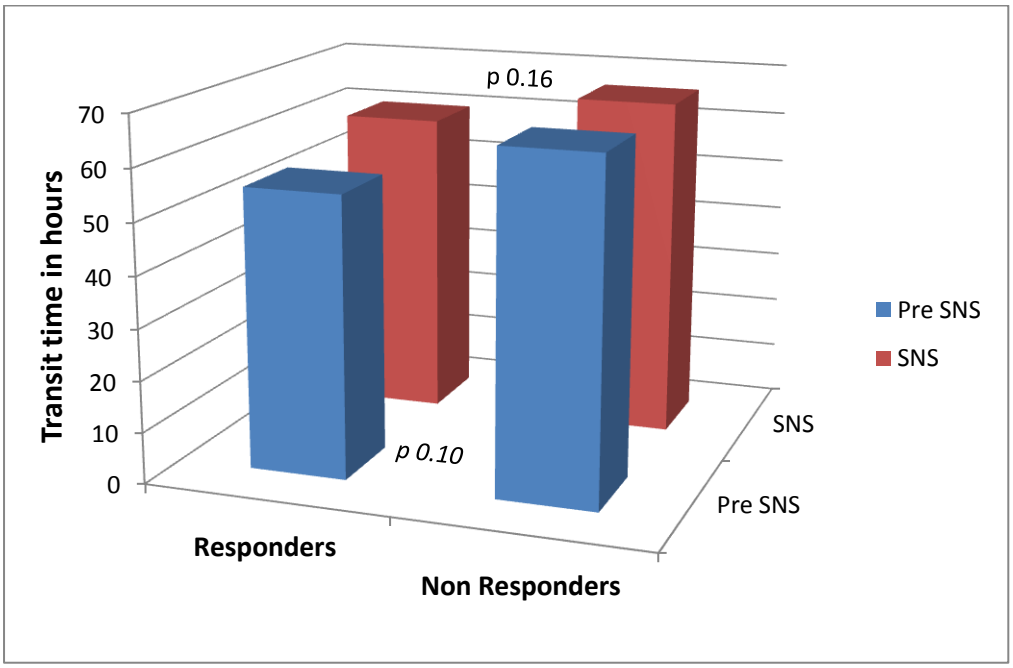
Figure 4-17 Transit times



The pre-intervention transit time (TT) was 58.5 hours (95% CI 49.4 to 67.6). During SNS intervention the transit time was 62.1 hours (95% CI 53.5 to 70.6). The transit times were not significantly different: SNS – Pre SNS = 4.23 hours (95% CI -1.11, 9.57, p=0.11).

Patients who had a positive response during SNS (responders) were offered permanent stimulation. Patients who failed to respond during temporary stimulation were identified as non-responders. At baseline both groups had delayed transit times. The mean transit time before SNS was lower in responders when compared to the non-responders, although not statistically significantly different (p= 0.10). During SNS, although the transit times of both groups increased, there were no significant differences between the two groups (p=0.16, Figure 4-18.

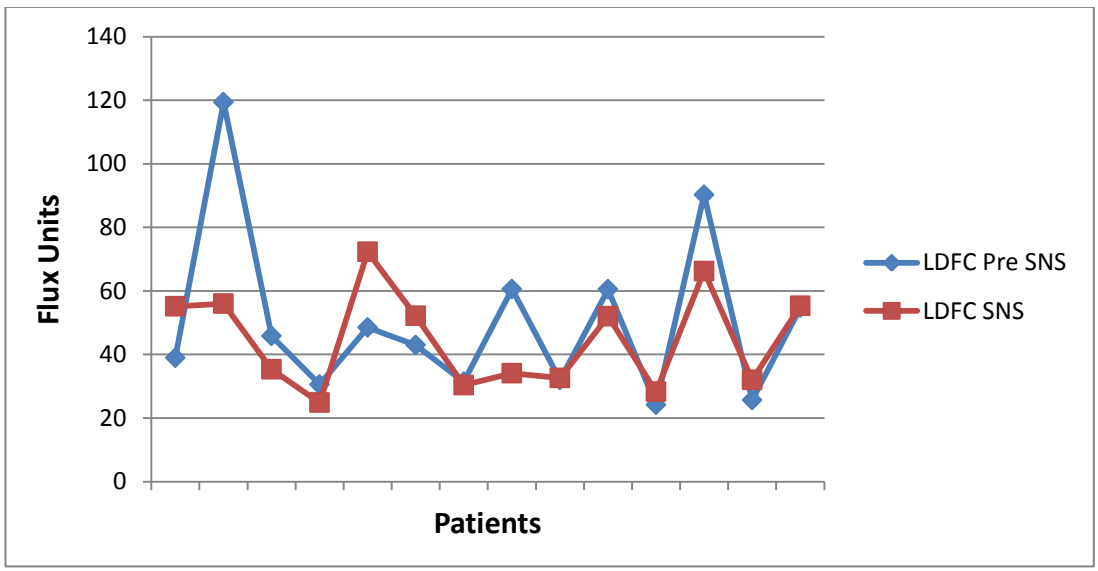
Figure 4-18: Transit time in responders and non-responders



4.3.7.2 Laser Doppler Flowcytometry (LDFC)

LDFC provides a direct measure of the autonomic innervation (nerve activity) of the hind gut, which should be improved by SNS. Two separate measurements were taken at 3 weeks and 9 weeks, before and during SNS. LDFC was completed by 14 patients, with scores shown in Figure 4-18.

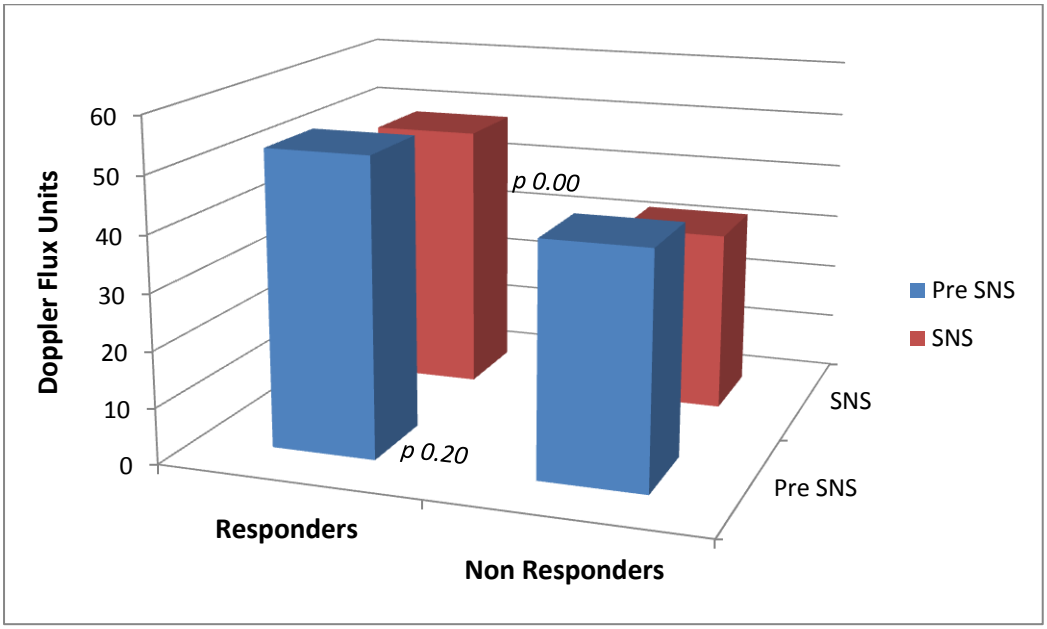
Figure 4-19: LDFC Scores



The mean cumulative LDFC score was 50.4 flux units (95% CI 35.1 to 65.7) before intervention and 44.8 flux units (95% CI 35.9 to 53.6) during SNS: the reduction of 5.6 flux units (95% CI -18.1 to 6.8) was not statistically significant. LDFC scores were expected to improve during stimulation in response to an expected increase in the rectal mucosal blood flow. However, the cumulative flux was similar before and during treatment. This might be explained by the different pathophysiological processes involved in neuroconstipation when compared to idiopathic disease.

The LDFC score for responders decreased during intervention but was comparably higher than the non-responders. See below.

Figure 4-20: LDFC in responders and non-responders



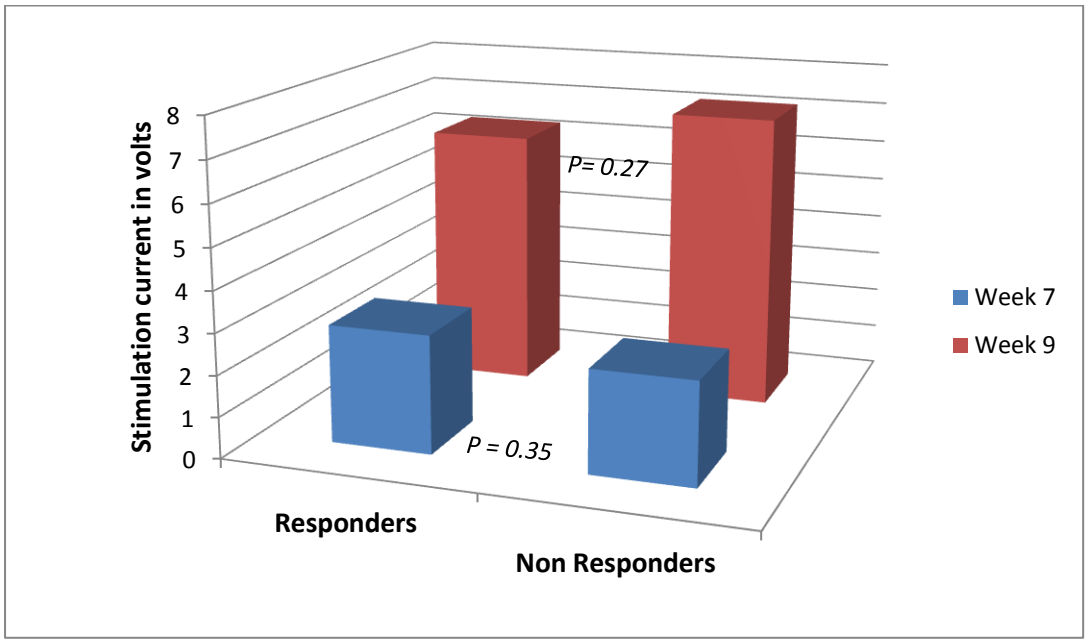
4.3.8 Stimulation Thresholds

The temporary pulse generator can produce a maximum current of 10 volts during the first temporary stage of SNS. The correct positioning of the electrode is confirmed by observable anal sphincter contraction and toe dorsiflexion at the time of the operation. The current threshold at which this occurs was found to be variable across different patients. Dudding reported that a low motor threshold at the time of wire insertion is a predictive factor for better long-term response. This was reported in a cohort of patients treated with faecal incontinence who received SNS (Dudding, Parés et al. 2008).

The motor stimulation threshold of the participants was measured at the time of insertion of the electrodes at week 7 and at the time of removal at the end of week 9. At the time of insertion the mean threshold on the right side was 2.90 volts (95% CI 1.81 to 4.01) and 6.54 volts (95% CI 4.17 to 8.92) at the time of removal. On the left side, the mean threshold was 2.64 volts (95% CI 1.46 to 3.81) and 6.55 volts (95% CI 3.90 to 9.19) at the time of removal.

The motor stimulation threshold at the time of electrode siting was 2.87 volts (95% CI 1.56 to 4.16) in the responders and 2.50 volts (95% CI -0.36 to 6.21) in the non-responders (p=0.35). At the time of removal, this increased to 6.31 volts (95% CI 3.90 to 8.73) in the responders and to 7.16 volts (95% CI 0.07 to 15.04) in the non-responders. Although the current at the time of electrode removal was lower in responders when compared to non-responders, this difference was statistically not significant (p= 0.27). See Figure 4-19.

Figure 4-21 Stimulation Thresholds in responders and non-responders



The motor response observed during T-SNS at the time of electrode placement under general anaesthetic is due to afferent fibre activation within the sacral nerve root. This acts as a valuable assessment tool for electrode placement but its value in predicting a successful outcome is uncertain. The stimulation threshold was noted to change from week 7 to week 9 for all patients. There was a gradual increase in the current value required for a satisfactory sensation of stimulation between weeks 7 and 9. This change in amplitude could be due to the neuroplasticity of the sacral roots, asymmetric innervation of the pelvic floor muscles, mechanical and/or patient factors.

The distance of the electrode tip from the nerve is crucial. Ideally, the tip should be just anterior to the sacral cortex during placement and confirmed with an image intensifier during the procedure. There is a strong case for placing these leads under local anaesthetic to get valuable patient feedback during placement. Lead migration during T-SNS can change the stimulation requirements as the distance between the electrode and the nerve root increases. Loose connections and breakage of electrode fibres are other important factors which affect the helical single leads used for T-SNS in this trial. Future research trials are utilizing tined leads with a 4-electrode tip which should be more reliable when compared to helical leads. Patient factors such as change in perception of stimulation and behavioural changes also affect the stimulus threshold for a sustained response.

4.3.9 Correlation of outcomes

The relatedness of outcome measures was explored by examining bivariate correlations. The purpose is to demonstrate that conceptually related outcomes report similar trends, thus providing supporting evidence about the principle findings. Each variable is analysed as its change score comparing the intervention and pre-intervention period. It is recognised that the numbers of patients contributing data is small and the correlations tentative.

It should be noted that a lower global assessment scores (incontinence, constipation), PAC-SYM, PAC-QOL, laxative score, bowel movement and toileting time denote improvement, whereas higher EQ-5D and EQ-VAS denote improvement.

The global assessment of constipation was strongly and positively correlated with the PAC-QOL measure but was only weakly positively correlated with PAC-SYM. Interestingly EQ-VAS was strongly negatively correlated with the global assessment of constipation (lower constipation score, higher quality of life) although EQ-VAS did not independently record a benefit from intervention (see 4.3.5). There were few other significant correlations, although in line with expectation frequency of bowel movement and toilet time were positively correlated.

Table 4-34 Correlation Matrix

		GA constipation	GA incontinence	PAC-sym	PAC-Qol	EQ 5D	EQ VAS	Laxative Score	Bowel Movement	Toilet Time
GA constipation	Pearson Correlation	1	.355	.357	.868**	-.097	-.715**	-.492	-.366	-.081
	Sig. (2-tailed)		.177	.174	.000	.730	.003	.053	.179	.775
	N	16	16	16	16	15	15	16	15	15
GA incontinence	Pearson Correlation	.355	1	-.055	.247	-.180	-.172	-.100	-.309	.100
	Sig. (2-tailed)	.177		.839	.356	.522	.540	.712	.263	.722
	N	16	16	16	16	15	15	16	15	15
PAC-sym	Pearson Correlation	.357	-.055	1	.626**	.381	-.393	-.058	-.116	.070
	Sig. (2-tailed)	.174	.839		.010	.161	.147	.832	.680	.803
	N	16	16	16	16	15	15	16	15	15
PAC-Qol	Pearson Correlation	.868**	.247	.626**	1	-.050	-.705**	-.450	-.273	-.010
	Sig. (2-tailed)	.000	.356	.010		.859	.003	.080	.324	.971
	N	16	16	16	16	15	15	16	15	15
EQ 5D	Pearson Correlation	-.097	-.180	.381	-.050	1	.234	.200	.012	-.112
	Sig. (2-tailed)	.730	.522	.161	.859		.401	.475	.966	.703
	N	15	15	15	15	15	15	15	14	14
EQ VAS	Pearson Correlation	-.715**	-.172	-.393	-.705**	.234	1	.470	.172	-.222
	Sig. (2-tailed)	.003	.540	.147	.003	.401		.077	.556	.446
	N	15	15	15	15	15	15	15	14	14
Laxative Score	Pearson Correlation	-.492	-.100	-.058	-.450	.200	.470	1	.453	.191
	Sig. (2-tailed)	.053	.712	.832	.080	.475	.077		.090	.496
	N	16	16	16	16	15	15	16	15	15
Bowel Movement	Pearson Correlation	-.366	-.309	-.116	-.273	.012	.172	.453	1	.723**
	Sig. (2-tailed)	.179	.263	.680	.324	.966	.556	.090		.002
	N	15	15	15	15	14	14	15	15	15
Toilet Time	Pearson Correlation	-.081	.100	.070	-.010	-.112	-.222	.191	.723**	1
	Sig. (2-tailed)	.775	.722	.803	.971	.703	.446	.496	.002	
	N	15	15	15	15	14	14	15	15	15

Correlations estimated using the change score estimate (during – pre-intervention) **. Correlation is significant at the 0.01 level (2-tailed).

4.4 Exploration of the determinants of temporary response

A range of baseline variables were explored as potential determinants of response due to temporary stimulation. Simple univariate analysis revealed no statistically significant differences in responders and non-responders to any of the baseline parameters. However, the study is underpowered to identify potentially important factors. For example the response rate was 86% for men and 55% for women: a 30% change. To have adequate study power to detect this change would require 40 men and 40 women. Consequently regression modelling of determinants was not attempted.

Table 4-35 Determinants of temporary response

		Response		
	N	**No**	**Yes**	**P**
Gender: Male:Female	18	1:5	6:6	0.32
Age	18	53.7	53.3	0.82
GA Constipation (pre)	16	4.08	3.68	0.33
PAC SYM (pre)	16	1.37	1.26	0.81
PAC QOL (pre)	16	2.18	1.71	0.33
Laxative Score (pre)	15	0.31	1.99	0.76
Bowel Movement (pre)	15	0.89	1.66	0.90
Toilet Time (pre)	15	11.86	22.86	0.36
Stimulation Threshold at insertion (V)	11	2.33	2.88	0.51
Transit time (pre) (hours)	13	53.5	59.00	0.82

* Continuous variables estimated using Mann-Whitney U; Gender estimated using an exact test on counts

4.5 Summary

Findings show a consistent pattern of positive response during temporary SNS, as seen with the global assessment of constipation, PAC-SYM and PAC-QOL measures. Improvement during the SNS phase was followed by consistent diminution towards baseline scores apparent 3 weeks after cessation of stimulation. There was a consistent

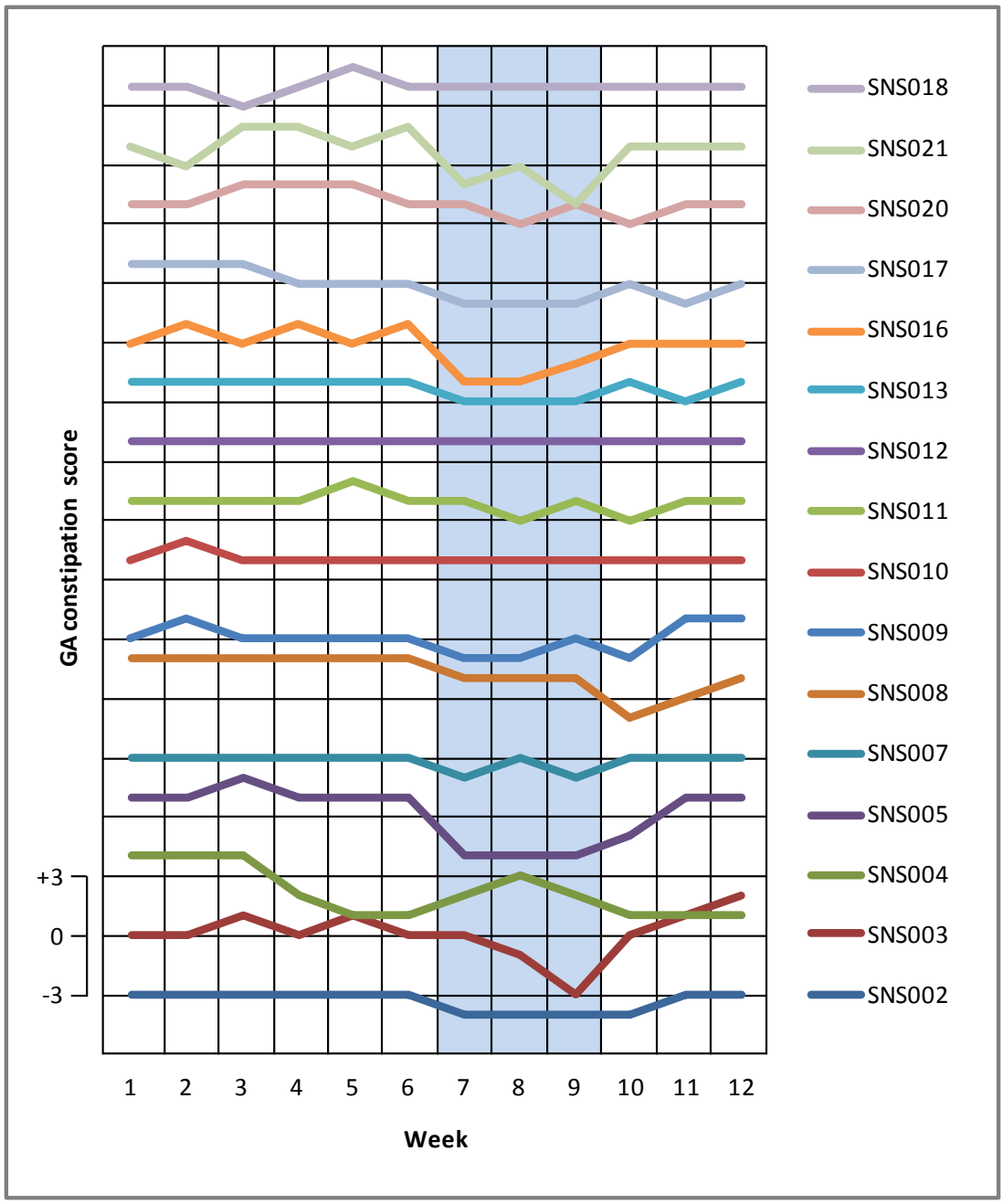
lack of response to measures of incontinence (global assessment of incontinence, diary and physiological measures); an unsurprising finding since less than half of patients had any incontinence at baseline.

The coincidence of response and stimulation provides high attribution of improvement to the SNS process. However, it is not able to differentiate between response due to active stimulation and the broader process of being treated which might include some form of placebo response. Any placebo response is likely to be transient and diminishing, consequently only long term SNS can definitively differentiate active and placebo response and this is explored in Chapter 5. However, the chronic and stable nature of disease and substantial treatment history, together with consistent (rather than random) response in these patients provides some support in favour of active response. (See Figure 4-20).

The potential for placebo response could be minimized by exploring the use of sham stimulation either within or between patients. The use of sham treatment was considered during the trial design. After discussion with all the stakeholders, it was decided that providing sham treatment for these patients was problematic because of: unnecessary procedures and use of anaesthetic; unwillingness of patients to participate; financial limitations in the use of expensive equipment; and, difficulty obtaining the relevant ethical approvals. Due to the small number of patients to be recruited, a within group off-on-off study design with multiple observations during each phase of the study was agreed upon as most efficient method to take the next step in understanding.

The results from this study have helped inform subsequent trial design. A multi-centre study design has being developed to further improve the predictive long term performance of test stimulation and minimize placebo response**.** Using a tined lead for test stimulation (not available when conducting the research for this thesis) allows a longer period of testing (up to six weeks). This can allow for identifying placebo responses, by using intermittent real or sham stimulation. The stimulation can be provided using subsensory settings so that the patient will not be able to differentiate between real and sham stimulation.

Figure 4-22: GA constipation: individual responses during temporary SNS



5. Long-term Data

Twelve of the 18 patients (67%), who completed the trial, received an implantable pulse generator (IPG). These patients had a good temporary response after bilateral temporary SNS. There were 6 men and 6 women with an average age of 54 years (Range 38-69 years). Patients were assessed clinically for ongoing response to SNS, categorised as successful or unsuccessful. Categorisation took into account patient progression of symptoms, changes in laxative use, questionnaire scores and the clinician and patient overall assessment.

We arranged follow-up appointments with these patients and asked them to complete additional questionnaires. We were not able to contact three patients to provide long term follow-up data, see Table 5-1 . Two further patients provided unusable questionnaire data but were clinically assessed for ongoing response.

Table 5-1: Long term follow-up data

	Pre-SNS Scores			During SNS			Long term SNS			Follow up in months	Disease Progression	IPG Effective
Trial Number	GA	PAC-SYM	PAC-QOL	GA	PAC-SYM	PAC-QOL	GA	PAC-SYM	PAC-QOL			
SNS002	3.00	1.18	1.63	2.00	0.63	1.04	3.00	1.00	1.50	27	No	Yes
SNS003	3.33	2.51	2.43	1.00	0.71	0.98	-	-	-	27	Yes	No*
SNS004	2.67	1.86	1.98	2.50	0.33	1.18	1.00	0.00	0.54	24	Yes	Yes
SNS005	4.17	1.75	2.15	1.00	0.25	0.14	1.00	0.25	0.43	27	Yes	Yes
SNS007	3.00	0.89	1.52	2.50	0.33	1.18	1.00	0.17	0.32	27	No	Yes
SNS008	5.00	2.50	2.77	4.00	2.00	2.43	-	-	-	24	No	No
SNS009	3.17	1.13	1.28	2.50	0.46	1.02	-	-	-	11	Yes	Yes
SNS013	4.00	2.13	2.48	3.00	1.25	1.75	4.00	2.25	2.64	18	Yes	No
SNS016	3.50	1.25	2.27	1.50	0.29	0.46	-	-	-	22	No	Yes
SNS017	3.50	1.92	1.82	2.00	1.67	1.52	3.00	2.00	1.28	12	Yes	No
SNS020	4.50	2.17	3.27	3.50	2.83	3.07	5.00	1.50	2.50	10	No	No
SNS021	4.33	1.29	2.18	2.00	0.50	0.75	-	-	-	8	No	No

Key: * Pt. underwent colostomy for Sigmoid Volvulus

5.1 Response to permanent SNS

The average length of follow-up was 20 months (range 8-27 months). Six of the 12 patients (50%) who received IPGs failed to respond to the permanent implant. One patient suffered from sigmoid volvulus almost a year after receiving the permanent implant and proceeded to a colostomy. This patient had a good continuous response from her IPG until her operation. The overall response during long-term follow-up as determined by clinical assessment was 6/12 (50%, 95%CI: 21% to 79%).

In subjects undergoing long term stimulation, there was a persistent improvement in the cumulative GA score for constipation, PAC-SYM and PAC-QOL scores when compared to the pre-intervention phase, although it had become borderline statistical significant, with some diminution of effect when compared to the early response recorded in the temporary SNS phase (see Table 5-2). In subjects reporting long term response, there was a pattern of retaining or improving upon test phase scores, with one exception (patient SNS002). The pattern of long term scores in patients reporting cessation of response, showed a consistent return to baseline (pre-intervention) scores.

Table 5-2: Long term outcome scores

	GA		PAC-SYM		PAC-QOL	
	Int-Pre	**LT-Pre**	**Int-Pre**	**LT-Pre**	**Int-Pre**	**LT-Pre**
Mean	-1.29	-0.98	-0.69	-0.67	-0.85	-0.80
95% CI-	-2.08	-2.21	-1.29	-1.38	-1.42	-1.44
95% CI+	-0.50	0.26	-0.10	0.04	-0.27	-0.17
p	0.006	0.10	0.028	0.060	0.010	0.022
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) LT: Long-term (Post IPG) 7 subjects						

5.2 Exploration of the determinants of long term response

A range of baseline variables were explored as potential determinants of response due to permanent stimulation, following the approach used in 4.4. Given the lack of study power to determine response it was not-anticipated that any predictors of permanent implant response could be identified. Nonetheless potential variables are tabulated in Table 5-3. Consequently regression modelling of determinants was not attempted.

Table 5-3 Determinants of permanent SNS response.

		Response		
	N	**No**	**Yes**	**P**
Gender: Male: Female	12	2:3	4:3	>0.99
Age	12	53.6	53.4	0.94
GA Constipation (int-pre)	10	-1.44	-1.26	0.48
PAC SYM (int-pre)	10	-0.72	-0.85	0.73
PAC QOL (int-pre)	10	-0.83	-0.80	0.82
Laxative Score (int-pre)	10	-0.04	-0.12	0.91
Bowel Movement (int-pre)	9	-0.50	-0.47	0.36
Toilet Time (int-pre) (min)	9	-15.13	-9.30	0.30
Stimulation Threshold at removal (V)	8	7.40	7.33	0.87
Stimulation Threshold change (V)	8	4.2	5.00	0.65

* Continuous variables estimated using Mann-Whitney U; Gender estimated using an exact test on counts

6. Subgroup Analyses

A subgroup analysis was carried out on patients suffering from Multiple Sclerosis (MS). There were 14 patients with MS recruited to the study, including 4 men and 10 women with an average age of 53 years (38-70 years). Of these, 3 patients dropped out and did not complete the trial. Bilateral SNS was carried out in 11 patients. Temporary SNS was successful in 8 of 11 patients (73%) in the MS subgroup. These patients went on to have a permanent implant.

6.1 Primary Outcome

6.1.1 Global Assessment of Constipation

The mean GA score for constipation during the first six weeks was 3.64 (95% CI 3.26 to 4.01). It improved during intervention (week 8-9) to 2.41 (95% CI 1.69 to 3.13) and post intervention increased to 3.55 (95% CI 2.85 to 4.24). The weekly mean scores and confidence intervals are given in Figure 6-1 and Table 6-21.

There was an improvement in GA score for constipation during the intervention phase when compared to the pre-intervention stage (Table 6-2, p=0.004, paired t-test). There was a gradual washout of effect after the removal of stimulation. Symptoms returned to baseline at week 12.

Figure 6-1: GA Constipation (MS)

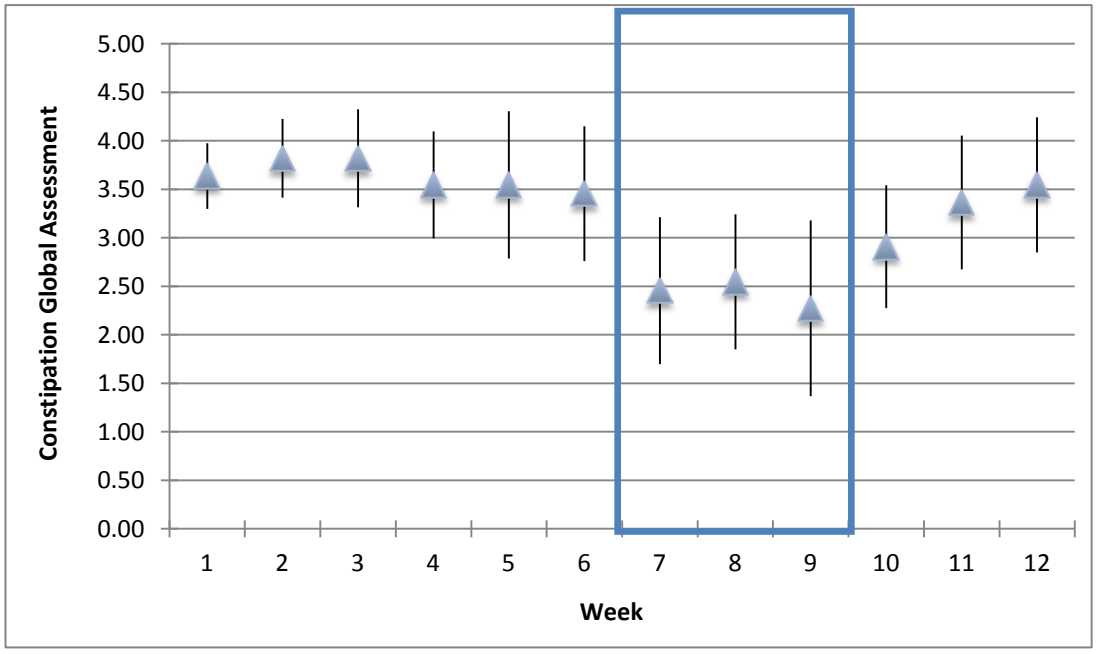


Table 6-1: Weekly GA Scores (MS)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	3.64	3.82	3.82	3.55	3.55	3.45	2.45	2.55	2.27	2.91	3.36	3.55
95%CI-	3.30	3.41	3.31	2.99	2.79	2.76	1.70	1.85	1.37	2.27	2.67	2.85
95%CI+	3.98	4.22	4.32	4.10	4.30	4.15	3.21	3.24	3.18	3.54	4.05	4.24

Table 6-2: Mean GA Scores (MS)

	Int-Pre	End-Pre
Mean	-1.23	-0.09
95% CI-	-1.96	-0.65
95% CI+	-0.50	0.47
p	0.004	<0.001
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

6.2 Secondary Outcomes

6.2.1 Global Assessment of Faecal Incontinence

The mean GA score for faecal incontinence during the first six weeks was 0.91 (95% CI 0.16 to -1.66, during intervention (week 8-9) was 0.73 (95% CI -0.03 to 1.48) and post intervention was 0.45 (95% CI -0.17 to 1.09). The mean weekly scores and confidence intervals for GA FI are given in Figure 6-12 and Table 6-3.

The mean GA score of FI slightly improved during the intervention phase of the study. There was no pattern of improvement that could be related to the intervention (Table 6-3). There is a reduction in FI at week 12, but this may be a chance finding. The change in GA FI score for this subgroup was not expected to be significant as most of the patients did not suffer from any incontinence at baseline.

Figure 6-2: GA Faecal Incontinence (MS)

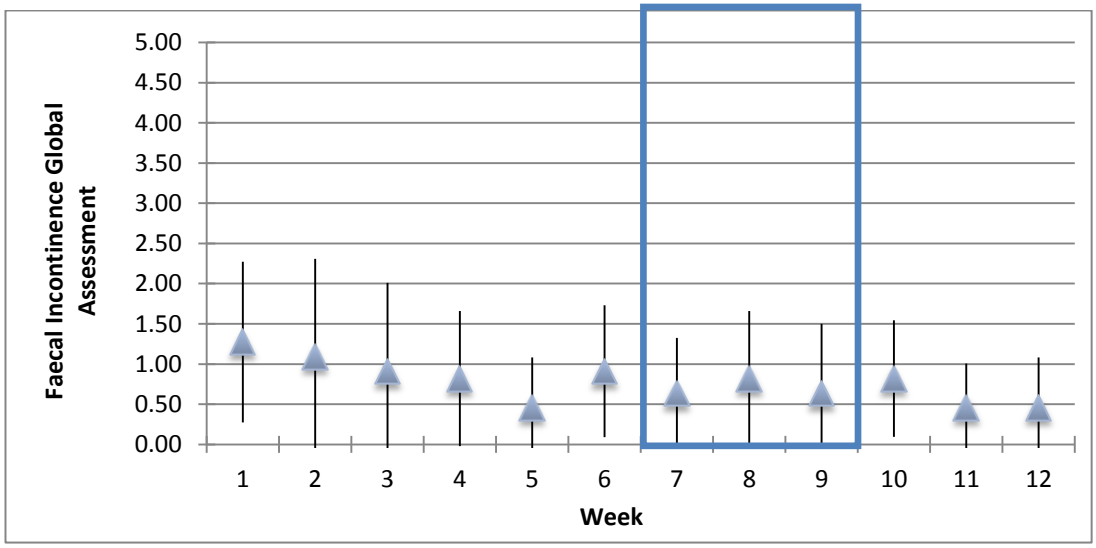


Table 6-3: Weekly GA FI (MS)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.27	1.09	0.91	0.82	0.45	0.91	0.64	0.82	0.64	0.82	0.45	0.45
95%CI-	0.27	- 0.13	- 0.19	- 0.02	- 0.17	0.09	- 0.05	- 0.02	-0.23	0.09	- 0.10	-0.17
95%CI+	2.27	2.31	2.01	1.66	1.08	1.73	1.33	1.66	1.50	1.54	1.01	1.08

Table 6-4: Mean scores for GA FI (MS)

	Int-Pre	End-Pre
Mean	-0.18	-0.45
95% CI-	-0.50	-0.86
95% CI+	0.14	-0.05
p	0.23	0.03
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

6.2.2 Patient Assessment of Constipation Symptoms (PAC-SYM)

The mean PAC-SYM score during the first six weeks was 1.64 (95% CI 1.30 to 1.97). It improved during intervention (week 8-9) to 0.80 (95% CI 0.39 to 1.20) and post intervention increased to 1.23 (95% CI 0.84 to 1.63). The mean weekly scores and confidence intervals for PAC-SYM are given in Figure 6-3 and Table 6-65.

There was an improvement in PAC-SYM score during the intervention phase when compared to the pre-intervention stage (Table 6-6, p=0.001). PAC-SYM scores tended towards pre-stimulation values after removal of SNS.

Figure 6-3: PAC-SYM (MS)

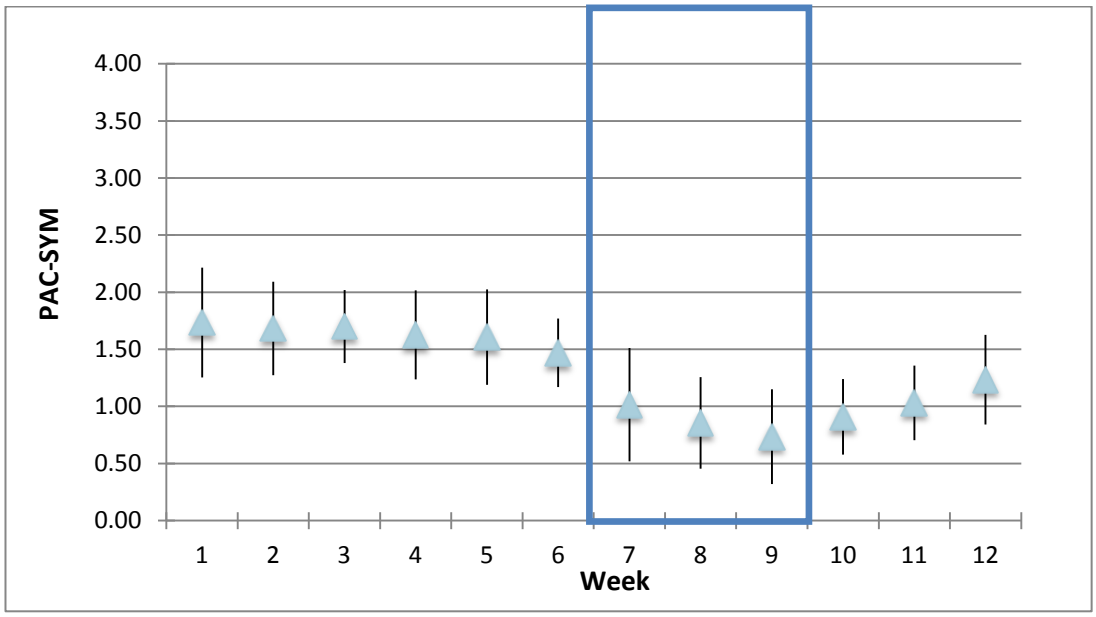


Table 6-5: Weekly PAC-SYM (MS)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	1.73	1.68	1.70	1.63	1.61	1.47	1.02	0.86	0.73	0.91	1.03	1.23
95%CI-	1.25	1.27	1.38	1.24	1.19	1.17	0.52	0.46	0.32	0.58	0.71	0.84
95%CI+	2.22	2.09	2.02	2.02	2.02	1.77	1.51	1.26	1.15	1.24	1.36	1.63

Table 6-6: Mean PAC-SYM Scores (MS)

	Int-Pre	End-Pre
Mean	-0.84	-0.40
95% CI-	-1.25	-0.66
95% CI+	-0.44	-0.14
p	0.001	0.007

Int: Intervention (wks 8,9)
Pre: Pre-intervention (wks1-6)
End: Post-intervention (wk 12)

6.2.3 Patient Assessment of Constipation (PAC-QOL)

The mean PAC-QOL score during the first six weeks was 2.07 (95% CI 1.80 to 2.33). It improved during intervention (week 8-9) to 1.27 (95% CI 0.78 to 1.76) and post intervention increased to 2.01 (95% CI 1.60 to 2.41) almost returning to baseline value by the end of week 12. The mean weekly scores and confidence intervals for PAC-QOL are given in Figure 6-34 and Table 6-7. The improvement in PAC-QOL during SNS was statistically significant (Table 6-8, p=0.006).

Figure 6-4: PAC-QOL (MS)

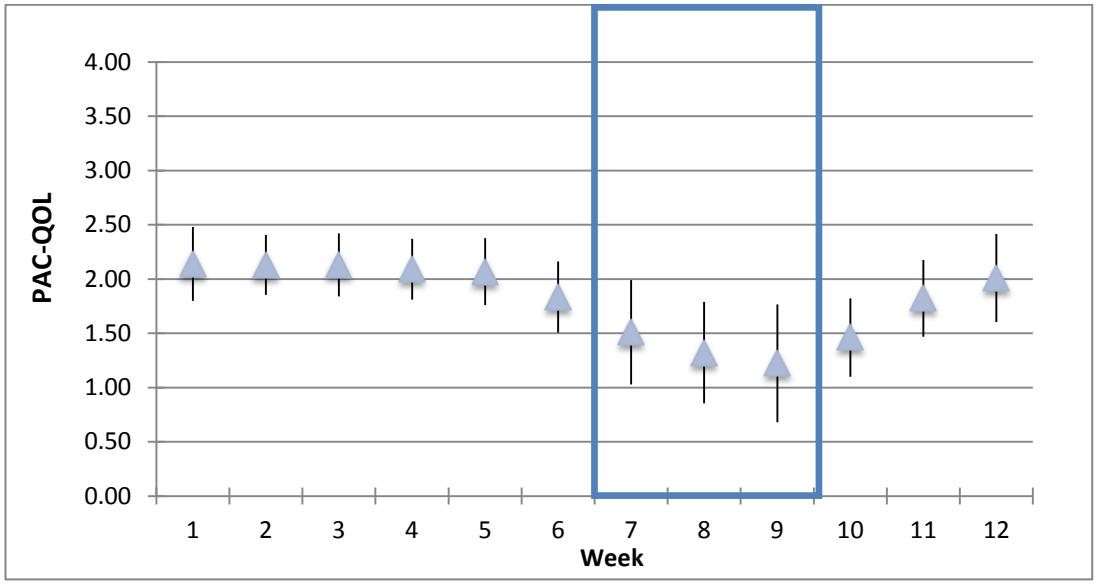


Table 6-7: Weekly PAC-QOL (MS)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Mean	2.14	2.13	2.13	2.09	2.07	1.83	1.51	1.32	1.22	1.46	1.82	2.01
95%CI-	1.80	1.85	1.84	1.81	1.76	1.51	1.03	0.85	0.68	1.10	1.47	1.60
95%CI+	2.48	2.41	2.42	2.37	2.38	2.16	1.99	1.79	1.77	1.82	2.18	2.41

Table 6-8: Mean PAC-QOL (MS)

	Int-Pre	End-Pre
Mean	-0.79	-0.06
95% CI-	-1.30	-0.42
95% CI+	-0.29	0.31
p	0.006	0.74
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

6.2.4 Euro QOL Health Questionnaire (EQ5D)

The EQ5D pre-intervention score was 0.31 (95% CI 0.13 to 0.48), during intervention was 0.35 (95% CI 0.16 to 0.55) and post intervention was 0.36 (95% CI 0.16 to 0.56). The mean scores and confidence intervals are given in Figure 6-5and Table 6-9. There was no change apparent in EQ5D scores during the trial (Table 6-10).

Figure 6-5: EQ5D (MS)

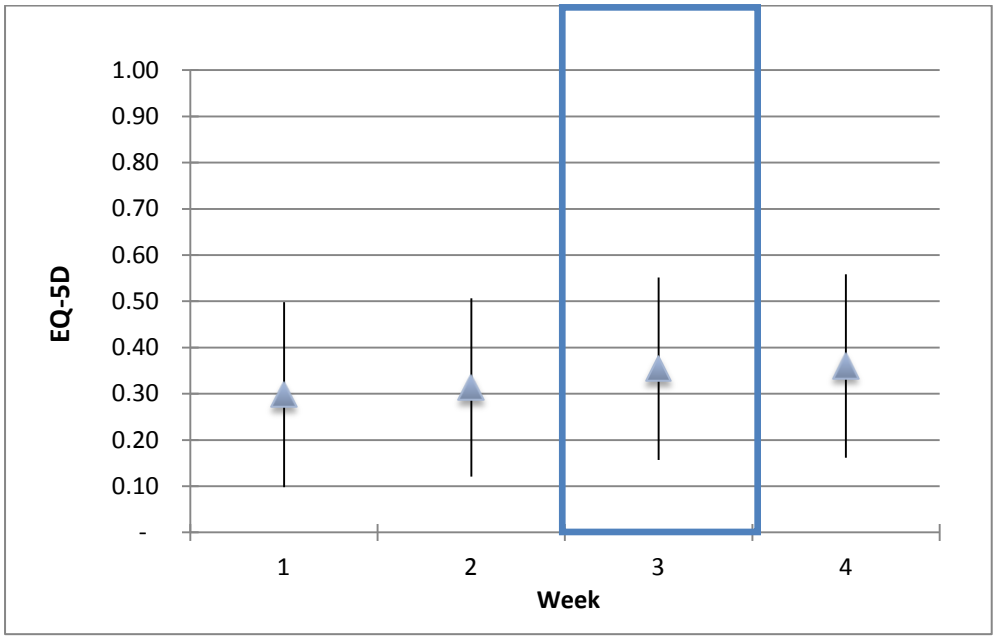


Table 6-9: Weekly EQ5D (MS)

Week	3	6	9	12
Mean	0.30	0.31	0.35	0.36
95%CI-	0.10	0.12	0.16	0.16
95%CI+	0.50	0.51	0.55	0.56

Table 6-10: Mean EQ5D (MS)

	Int-Pre	End-Pre
Mean	0.05	0.05
95% CI-	-0.11	-0.16
95% CI+	0.21	0.27
p	0.51	0.59
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

6.2.5 EuroQOL Visual Analogue Score (EQ-VAS)

The pre-intervention score was 45.4 (95% CI 36.7 to 54.2) during intervention was 47.3 (95% CI 32.2 to 62.3) and post intervention the score was 47.7 (95% CI 40.8 to 54.7). The weekly mean scores and confidence intervals are given in Figure 6-6 and Table 6-11. There was no change apparent in EQ-VAS scores during the trial (Table 6-12).

Figure 6-6: EQ-VAS (MS)

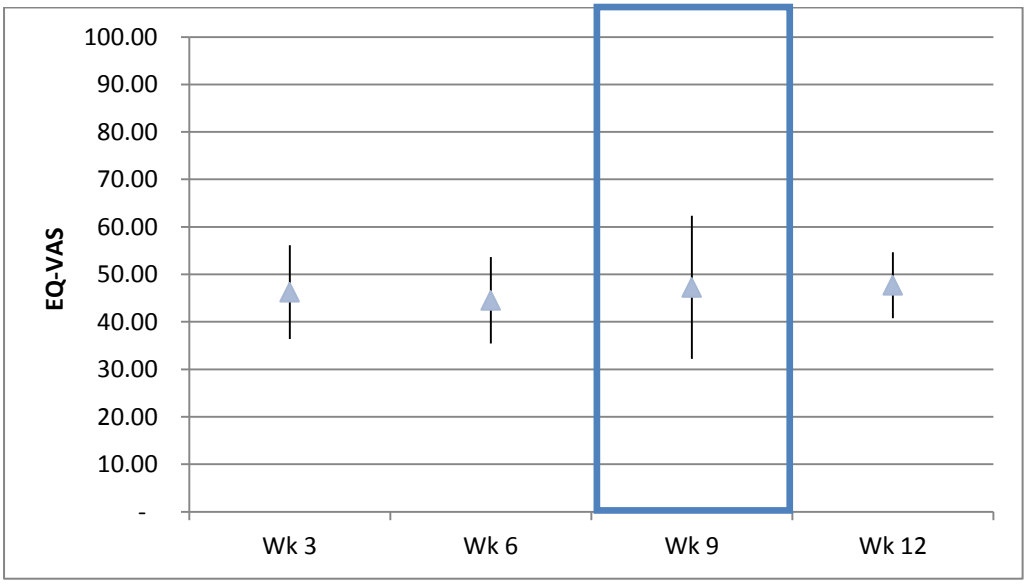


Table 6-11: Weekly EQ-VAS (MS)

Week	3	6	9	12
Mean	46.3	44.5	47.3	47.7
95%CI-	36.4	35.5	32.2	40.8
95%CI+	56.2	53.6	62.3	54.7

Table 6-12: Mean EQ-VAS (MS)

	Int-Pre	End-Pre
Mean	1.9	2.3
95% CI-	-12.9	-4.1
95% CI+	16.6	8.8
p	0.78	0.44
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) End: Post-intervention (wk 12)		

6.3 Long-term Follow-up (MS)

Eight of the 11 MS patients (73%) completing the trial received an implantable pulse generator (IPG). This section provides subgroup analyses of all patients reported in Chapter 5. Although it was possible to assess long term response in all patients, 4 patients declined to provide questionnaire data.

The average length of follow-up was 21 months (Range 11-27 months). Three of the 8 patients (37.5%) who received IPGs failed to respond after the implant. One patient suffered from sigmoid volvulus almost a year after receiving the permanent implant and ended up having a colostomy. The overall response for long-term follow-up in the MS subgroup was 62.5% (5/8) as determined by patient symptom scores and overall clinical assessment.

Table 6-13: Long-term Follow-up (MS)

	Pre-SNS Scores			During SNS			Long term SNS			FU (mths)	Disease progression	IPG Effective
Trial Number	GA	PAC-SYM	PAC-QOL	GA	PAC-SYM	PAC-QOL	GA	PAC-SYM	PAC-QOL			
SNS003	3.33	2.51	2.43	1.00	0.71	0.98	-	-	-	27	yes	no
SNS004	2.67	1.86	1.98	2.50	0.33	1.18	1.00	0.00	0.54	24	yes	yes
SNS005	4.17	1.75	2.15	1.00	0.25	0.14	1.00	0.25	0.43	27	yes	yes
SNS007	3.00	0.89	1.52	2.50	0.33	1.18	1.00	0.17	0.32	27	no	yes
SNS009	3.17	1.13	1.28	2.50	0.46	1.02	-	-	-	11	yes	yes
SNS016	3.50	1.25	2.27	1.50	0.29	0.46	-	-	-	22	no	yes
SNS017	3.50	1.92	1.82	2.00	1.67	1.52	3.00	2.00	1.28	12	Yes	no
SNS021	4.33	1.29	2.18	2.00	0.50	0.75	-	-	-	-	no	no

Constipation GA, PAC-SYM and PAC-QOL scores were similar when comparing improvements from temporary SNS and long term with permanent SNS, although this comparison is limited by the small numbers completing long term questionnaire data.

The overall long-term response (5 of 8, 63%) suggests that patients with MS receiving permanent SNS may do better than other types (1 of 4, 25%), but small numbers preclude firm conclusions (p=0.30).

Despite disease progression the response has been consistent in patients with MS over a period of time. A few minor adjustments in electrode settings were required for some patients during follow-up. Informal feedback during follow-up visits has shown that the improvement in quality of life has made a vast difference in the daily routines of patients responding to permanent SNS.

Table 6-14: Mean Outcome Score (MS)

	GA		PAC-SYM		PAC-QOL	
	Int-Pre	**LT-Pre**	**Int-Pre**	**LT-Pre**	**Int-Pre**	**LT-Pre**
Mean	-1.58	-1.83	-1.01	-1.00	-1.05	-1.22
95% CI-	-2.47	-3.58	-1.46	-2.38	-1.64	-2.02
95% CI+	-0.70	-0.09	-0.55	0.38	-0.46	-0.42
p	0.003	0.04	0.001	0.10	0.004	0.01
Int: Intervention (wks 8,9) Pre: Pre-intervention (wks1-6) LT: Long-term (Post IPG)						

7. Discussion

7.1 Principal Findings

7.1.1 Temporary SNS

Patient-assessed global assessment of constipation (GA-constipation), PAC-SYM and PAC-QOL scores improved significantly during temporary SNS, with 29%, 40% and 30% improvements respectively. There was a clear pattern of diminishing benefit after removal of the electrodes. There was no pattern of change in faecal incontinence GA scores, consistent with prior expectation (faecal incontinence was largely absent from the group). There was no change in the EQ-VAS or EQ-5D scores during intervention: these measures were included to provide estimates of variance to help design future studies. They were not anticipated to be adequately sensitive to show change within this trial.

The majority of patients in the trial had ongoing mobility or independence issues due to the disabling nature of their disease, reflected in low EQ-VAS and EQ-5D scores.

The use of SNS was expected (when decreasing constipation) to increase the frequency of bowel movements, although this was not found in this trial. A characteristic of patients with neuroconstipation is the experience of a high number of failed and incomplete evacuations. It is possible that SNS caused patients to have improved (and thus fewer) bowel movements, although diary data from this trial did not record the completeness of the bowel movements. In support of this hypothesis, a number of patients reported verbally experiencing an improvement in their bowel function with better evacuations and less frequent toilet visits.

Patients with neuroconstipation spend a significant amount of time in the toilet and have to use large amounts of laxatives to achieve a bowel movement. There was a significant reduction in toilet time per visit (33%) and use of laxatives during temporary SNS intervention.

Neuroconstipation causes reduced colonic activity thus delaying transit times, as seen in the study patients (58.5 hours [mean] compared with less than 38 hours in a normal population). It would be anticipated to that colonic transit times would decrease with

SNS. However transit times were not altered during the intervention phase of this study. The pathological processes affecting gut motility in neuroconstipation are different to idiopathic constipation which may explain the absence of any improvement in transit times in our patients. Kamm and colleagues reported an improvement in transit times after permanent SNS in idiopathic constipation (Kamm, Dudding et al. 2010). The number of patients in our study may be inadequate to quantify the effect of SNS on colonic transit, or the temporary SNS period may be too short to capture change. Another limitation may be in the method of assessing transit times. Snapshot X-rays (rather than real-time scintigraphic studies) may be inadequately refined to capture the non-linear progress of stools through the bowel. A recent paper by Cowlam reported that segmental colonic transit studies were not reliable in assessing idiopathic constipation (Cowlam, Khan et al. 2008). Another recent report on the effect of SNS on gastrointestinal motor function did not show any change in gastric emptying, small intestinal and colonic transit (Damgaard, Thomsen et al.).

Laser Doppler mucosal flowmetry (LDFC) is a gut specific, quantitative measure of extrinsic autonomic nerve activity. Emmanuel and Kamm showed that patients with idiopathic constipation have impaired extrinsic gut nerve activity, and have a lower than normal rectal mucosal flux (Emmanuel and Kamm 2000). The mucosal circulation has been shown to increase and reach a plateau in response to voltage increments in patients with SNS. This was reported in sixteen patients with permanent SNS implants who were suffering from faecal incontinence (Kenefick, Emmanuel et al. 2003). We did not increase the voltage during LDFC measurement in our patients as LDFC was recorded at the end of the three week period of temporary stimulation and all patients were at the maximum temporary SNS voltage. In this study there was no apparent change in LDFC flux during treatment instead of the expected increase. However, the patients in our study suffered from constipation rather than faecal incontinence. The different pathophysiology in our patients, a low number of subjects in this study and the lack of study power may explain the lack of any change in the scores of rectal mucosal flux during SNS.

7.1.2 Permanent SNS

The initial response rate according to the global assessment of constipation during temporary SNS was 67% (12/18): these patients received a permanent implant and were followed-up long term (mean follow-up 20 months). Six of 12 patients implanted

reported a long-term response. Thus the response rate was 50% (6/12 patients) for patients progressing to permanent SNS and from the initial cohort 33% (6/18) of patients overall were able to benefit. A formal exploration of the determinants of response was not feasible due to small numbers. Sub-group analyses suggested that patients with MS receiving permanent SNS may do better than other types (63% vs. 25%, p=0.30) and that men may do better than women (86% vs. 55%, p=0.32) but the numbers are small and inconclusive.

7.1.3 Patients with Multiple Sclerosis (MS)

The global assessment of constipation, PAC-SYM and PAC-QOL scores for the patients with MS improved significantly during the intervention phase of the trial. There was a 25% improvement in the GA score during SNS and 20 % improvement in both PAC-SYM and PAC-QOL. The initial response rate for improvement during temporary SNS was 73%. These patients received a permanent implant and long term follow-up over 21 months revealed a persistent effect in 63% (5/8 patients). There was a no change in the EQ-VAS and EQ-5D scores, although these were not anticipated to be sensitive to changes in bowel function in small numbers of patients.

When compared with neurological constipation due to other or undefined causes there is a suggestion of a much higher response from permanent SNS although this needs to be confirmed in adequately powered studies. For example an adequately powered study to demonstrate response rates of 63% (MS) and 25% (non-MS), recruiting at a ratio of 2:1, with 90% power and α=0.05 would require 60 MS patients and 30 non-MS patients, bigger than any current study of SNS in neuroconstipation.

There were a few incidents when patients reported a decrease in the effect of SNS during an exacerbation of MS. This was rectified in most of the cases with reprogramming the stimulator by changing the electrode settings. Patients, who did not improve after re-programming, noticed a significant diminution in effect and ended up with failure of treatment. Despite disease progression there was generally a sustained response in patients with MS.

MS offers an association plausibly related to better long-term response. It is likely that in most patients there are still functional ascending spinal pathways which might explain the better response in MS than in spinal cord injury patients. One patient in this study with a complete spinal cord injury did not have any motor response to

stimulation despite an intact bulbospongiosus reflex (signifying sacral sparing). Previously, it has been postulated that the effect of SNS may involve modulation of spinal pathways (Sheldon, Kiff et al. 2005) and vagal afferents leading to cortical activation (Lundby, Møller et al. 2011): the results from this study support this hypothesis.

7.2 Patient perspectives

Although a formal qualitative analysis of the patient's experience during the trial was not performed, it was possible to note patient perspectives and experiences within routine follow-up visits. Multi-source feedback from the principal investigators, research nurses and the patients over the course of two years has been helpful in providing the core of patient experience described.

Patients experienced neuroconstipation as a chronic disabling condition which had proved refractory to most available therapies. The quality of life of these patients was very poor; having a non-functional gut exacerbated overall suffering caused by neurological disease. Patients reported having to adhere to a strict bowel regime on a daily basis. This could take up a significant amount of time every day and was one of the main issues that patients brought up during their initial consultation at the time of recruitment.

Since the trial, patient feedback has been largely positive. Patients with a functioning IPG were followed up in clinic and reviewed on an annual basis. Patients assessed as responding to treatment reported a general improvement in their physical and psychological quality of life. One of the participants who worked as a psychotherapist was actively involved in our patient advisory group since receiving his implant. He noticed a significant improvement in his daily work life as he did not have to worry about his bowel function while working. He has provided advice and a narrative of his own experience to other patients considering SNS. One of the other patients who was wheelchair bound reported a significant improvement in her bowel function. She had severe refractory disease and was being considered for a stoma before receiving SNS.

Conversely, patients who failed initial testing stage were disappointed and patients who failed to respond to permanent SNS after initial response were perhaps the most despondent. Generally, these patients were not prepared to accept any further surgical interventions and are being managed conservatively.

7.3 Relationship between current and previous findings

7.3.1 Published evidence

The National Institute of Clinical Excellence has approved SNS for use in faecal incontinence and voiding dysfunction (NICE 2002; NICE 2004) but has not considered its use in constipation. There is a limited body of evidence for the role of SNS in neurological bowel disease relating to neuroconstipation (Lombardi, Del Popolo et al. 2010).

There have been a number of small uncontrolled, mostly retrospective studies exploring the efficacy of SNS in idiopathic constipation (see Chapter 2 and Table 2-1). These studies suggest a significant response rate in idiopathic constipation although these case series are uncontrolled and patients are often poorly characterised. A randomized sham-controlled study in idiopathic constipation is underway in Australia but is likely to show similar results, i.e. SNS is effective in an as yet undefined sub-group of patients with chronic constipation and that a two-week test stimulation is a poor predictor of long-term response (personal communication: P Dinning).

7.3.2 Contribution of new findings

This is the first prospective study reporting the efficacy of SNS in patients of varying aetiology with neuropathic constipation. The potential value of treating patients with neuroconstipation has been demonstrated, although further research is needed to understand the mechanisms of benefit and influence of aetiology.

The study by Kamm et al found a permanent response rate varying from 33% to 87% depending upon the definition of treatment success and is thus broadly in line with study findings reported here. Similarly, an audit of patients with chronic constipation treated in our clinics at Durham and Hull, found that 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.

The one patient with complete spinal cord injury and thus no afferent response showed no response to SNS at the initial test stage, supporting the hypothesis that SNS requires an afferent pathway to work. Consequently SNS may be a misnomer: SNS works by stimulating the local nervous system and by modulating the local response by

stimulating afferent spinal pathways. Thus it is not (local) sacral nerve stimulation per se that is causing a treatment effect.

Physiological assessments during temporary SNS (laser Doppler flow cytometry and transit time) were not informative in this study. This may be a consequence of an under powered study, the duration of temporary SNS being too short to capture change or because SNS modifies neuroconstipation through a different mechanism of action to than is understood to occur in idiopathic constipation.

Temporary SNS correctly predicted 50% (95%CI: 21% to 79%) of subjects who reported long-term response. Further research is needed to refine this estimate and identify patient sub-groups who benefit most, if this treatment to be economically viable. The tariff for permanent SNS is typically around £15,000 and use in neuro constipation does not generate the cost savings that occur when used in faecal incontinence (primarily due to reduced nursing care).

The study has demonstrated the stability and responsiveness of a number of key outcome measures. The global assessment of constipation, PAC-SYM and PAC-QOL produced consistent findings and correlated with clinical assessments of response. Thus these measures would be useful and appropriate in future research. Because of its simplicity and sensitivity, the global assessment of constipation measure appears most appropriate for clinical assessment of the temporary SNS phase.

The off-on-off design permitted an exploration of the duration of, and time to response of, starting and ceasing stimulation. The study design reported in this thesis was chosen to permit all subjects to receive SNS, but could not differentiate genuine and placebo response during the temporary phase. If it were possible to do this then long-term response to permanent stimulation might be achievable in a much higher proportion of patients. Knowledge of the time to response from changing stimulus, has informed the design of a crossover temporary SNS evaluation phase with washout period, where patients receive actual or sham stimulation in blinded sequence. Thus in future research it may be possible to differentiate sham and genuine response. On the basis of findings reported here a washout period of two weeks appears optimal.

7.4 Strengths and weaknesses of the study

7.4.1 Study Design

The performance of SNS has not been compared with a control, instead repeated measures have been made over time to improve the attribution of findings. Patients entering the study were characterised by long-term chronic constipation and this was verified in the six week pre-intervention phase (see Figure 4-20). Thus changes observed during and after temporary stimulation are likely to be due to the process of SNS treatment but can't differentiate placebo and genuine response (i.e. the effect of needle insertion and signal versus the process of needle insertion). Theoretically, this problem could be managed by exposing patients to periods of both real and sham stimulation during the temporary phase. This was not possible within the study because the response and washout times were previously unknown. For the process to be viable the temporarily inserting needles need to be in place throughout the entire real-washout-sham period, although the risk of infection or lead migration increases with time. In the light of the new findings presented in this thesis it would be realistic to have two-week stimulation period separated by a two-week washout (6 weeks in total) as a viable design. Although limited in its attribution and examination of aetiology, this study has substantially augmented current understanding of SNS in neuroconstipation and informed the design of a subsequent larger trial using crossover temporary SNS to explore the determinants of response to permanent SNS.

7.4.2 Why bilateral SNS?

Unilateral lead placement is usually sufficient for treating faecal incontinence and idiopathic constipation. Expert opinion was sought regarding the optimum placement of electrodes for study patients. Bilateral wire placement was performed in all patients to reduce the chance of electrode displacement and laterality bias in the final analysis. There was no available evidence addressing this specific issue, therefore, this decision was reached after consensus within the clinical team. In a proof of concept study it was decided it was important to maximise the potential to demonstrate a therapeutic response. Two patients received a unilateral lead as they did not have any motor response in the contralateral sacral foramina during electrode placement.

7.4.3 Selection of outcome measures

There are no universally accepted severity assessments for constipation. Most measures used have been validated in chronic constipation. It is likely, though not certain, that they will be sensitive to changes in neuroconstipation.

We decided to use the global assessment of constipation as the primary outcome measure. This has been used in many randomized controlled trials in functional bowel disease and has shown been shown to be reliable (Camilleri et al. 2000; Kellow et al. 2003; Nyhlin et al. 2004; S A Müller-Lissner et al. 2001). A validation analysis compared to a visual analogue scale has been reported (Müller-Lissner et al. 2003). Although the scale has been shown to be reliable in functional constipation, it has not been used in patients with neuroconstipation before.

PAC-SYM and PAC-QOL have been well validated and show considerable stability and responsiveness (Frank et al. 1999; Marquis et al. 2005). This has been observed in this study as well (see 4.3.2 and 4.3.3). Despite being reliable and stable during the study, PAC scores have not been used in this patient subgroup before. Further work is needed to formally validate these scores in neuro-constipation.

Secondary outcome measures like transit times and LDFC were selected to explain the mechanism of action and the anticipated physiological effects during the intervention (Blanchard, Schwarz, et al. 1992; Blanchard, Scharff, et al. 1992). Others (stimulation thresholds, EuroQOL) provided the data for exploratory analyses and estimation of variance in these patients.

The diary cards did not record spontaneous complete bowel movements (SCBM) during the study. The completeness of the bowel movements was also difficult to record. The lack of reporting SCBMs during intervention is a potential weakness of the study. The diary cards during week 4 to week 9 included items for frequency, incontinence, time spent toileting and laxative use.

7.5 Comparison with other interventions

Most patients with neuroconstipation are managed conservatively. This includes establishing a scheduled pattern for bowel movements, dietary and lifestyle modification, use of laxatives and/or suppositories. These measures work in a majority of patients and only a few require intervention. The options for intervention in

neuroconstipation include transanal irrigation (TAI), percutaneous endoscopic colostomy (PEC), antegrade continence enema (appendicostomy, ACE) or faecal diversion through stomas.

Faaborg et al. reported the outcome of TAI in a series of 211 patients with neurogenic bowel dysfunction(Faaborg, Christensen et al. 2009). The authors reported a success rate of 46% at 19 months follow-up which decreased to 35% at 3 years. TAI was considered safe (risk of perforation: 1 in 50000) but side effects were seen in up to 48% of patients. TAI is effective but a labour intensive modality for treatment. Studies reporting the outcome after ACE procedures have shown a success rate of 80% in children but evidence in neuroconstipation is limited. The stenosis rate is high (30%) requiring further surgery (Malone 2004).

A case series of 31 patients (6 with neurogenic aetiology) receiving PEC was reported in 2007. There was significant morbidity associated with PEC (infection rate 77%) and two deaths due to faecal peritonitis. A high percentage of patients (44%) ended up having the PEC removed (Cowlam, Watson et al. 2007). Similarly, surgery for diversion carries a significant risk of early or late complications. A retrospective study in 32 patients with SCI recorded increased patient satisfaction and a decrease in toileting time (from 10.3 hrs/week to 1.9 hrs/week). However, 44% of patients suffered from complications (6% early, 37.5% late). These included diversion colitis, faecal fistula, parastomal hernias and adhesional bowel obstruction. (Branagan, Tromans et al. 2003)

In contrast, SNS offers a minimally invasive and safe alternative. This study has shown that 67% of patients have a good response after T-SNS. Long term response is limited (33%) but patients with MS seem to respond better (63%) than patients with other aetiology.

7.6 Dissemination of findings

To date, response and physiological findings have been presented at two major international conferences in the form of a poster. Details in Appendix B. Thesis findings will be disseminated through peer-reviewed publication.

7.7 Future Research Directions

The main challenge faced in this field of research is the need to identify those patients who will benefit from permanent SNS. The initial response to temporary stimulation was 67% but only half of patients demonstrated persistent benefit (after a mean of 27 months follow-up).

The standard method of predicting response, across all studies of SNS for incontinence and constipation, has been to use 2 or 3-week test stimulation. However, this approach does not seem as effective in neuroconstipation as in faecal incontinence and bladder dysfunction. Within the research reported here, simple helical leads were used during the temporary phase but some recent studies have used the same tined leads used in permanent SNS.

The success rate for subsequent permanent implantation when using quadripolar or tined leads during the diagnostic phase has been reported to be between 63% to 80% when compared to 50% for conventional testing (Donato F Altomare et al. 2009; Seif et al. 2006; Sievert et al. 2007; Spinelli et al. 2003). Consequently, the future planned study with active sham temporary phase stimulation will also employ tined leads.

The lack of an accurate test phase to reliably predict long term benefit poses a major barrier to the viability of the treatment in this condition, both from a patient perspective and an economic one. It is probable that the current predictive value of test stimulation is inadequate to allow any consensus for approval of SNS in constipation. The reasons for the poor predictive performance of the temporary-wire test stimulation in constipation are unknown. A placebo effect, if present, is most likely to be strongest following commencement of treatment, and reduce with time (Bland and Altman 1994). There is a possibility that the lead position may be more critical in chronic constipation, thus a test procedure is only effective at predicting the outcome of a lead in that specific position, but once that lead is changed for a permanent (tined) lead the small change in position results in a change in efficacy.

7.8 Conclusions

Temporary SNS may accurately predict about half of patients who will benefit long term from permanent SNS. Nonetheless, in patients in whom other management options have been exhausted, SNS offers a potentially valuable alternative to invasive

surgical procedures. Further research is needed to refine estimates of long term benefit, prediction of which patients and sub-groups benefit most and develop understanding of the underlying physiological mechanism of benefit. Findings from this study provide important insights in the design of future research.

8. References

Bassotti, G. and W. E. Whitehead (1994). "Biofeedback as a treatment approach to gastrointestinal tract disorders." The American Journal of Gastroenterology 89(2): 158-164 %U http://www.ncbi.nlm.nih.gov/pubmed/8304295.

Bingham, S. A. and J. H. Cummings (1989). "Effect of exercise and physical fitness on large intestinal function." Gastroenterology 97(6): 1389-1399 %U http://www.ncbi.nlm.nih.gov/pubmed/2583406.

Binnie, N. R., A. N. Smith, et al. (1991). "Constipation associated with chronic spinal cord injury: the effect of pelvic parasympathetic stimulation by the Brindley stimulator." Paraplegia 29(7): 463-469 %U http://www.ncbi.nlm.nih.gov/pubmed/1784513.

Branagan, G., A. Tromans, et al. (2003). "Effect of stoma formation on bowel care and quality of life in patients with spinal cord injury." Spinal Cord 41(12): 680-683 %U http://www.ncbi.nlm.nih.gov/pubmed/14639447.

Bushnell, D. M., M. L. Martin, et al. (2006). "Performance of the EQ-5D in patients with irritable bowel syndrome." Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research 9(2): 90-97 %U http://www.ncbi.nlm.nih.gov/pubmed/16626412.

Campbell, A. J., W. J. Busby, et al. (1993). "Factors associated with constipation in a community based sample of people aged 70 years and over." Journal of Epidemiology and Community Health 47(1): 23-26 %U http://www.ncbi.nlm.nih.gov/pubmed/8382251.

Chermansky, C., R. Krlin, et al. (2010). "Magnetic resonance imaging following InterStim®: an institutional experience with imaging safety and patient satisfaction." Neurourology and Urodynamics 30(8): 1486-8.

Cheskin, L. J., N. Kamal, et al. (1995). "Mechanisms of constipation in older persons and effects of fiber compared with placebo." Journal of the American Geriatrics Society 43(6): 666-669 %U http://www.ncbi.nlm.nih.gov/pubmed/7775727.

Chiarioni, G., L. Salandini, et al. (2005). "Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation." Gastroenterology 129(1): 86-97 %U http://www.ncbi.nlm.nih.gov/pubmed/16012938.

Chiotakakou-Faliakou, E., M. A. Kamm, et al. (1998). "Biofeedback provides long-term benefit for patients with intractable, slow and normal transit constipation." Gut 42(4): 517-521 %U http://www.ncbi.nlm.nih.gov/pubmed/9616314.

Christensen, P., G. Bazzocchi, et al. (2006). "A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord-injured patients." Gastroenterology 131(3): 738-747 %U http://www.ncbi.nlm.nih.gov/pubmed/16952543.

Christensen, P., K. Krogh, et al. (2009). "Long-term outcome and safety of transanal irrigation for constipation and fecal incontinence." Diseases of

the Colon and Rectum 52(2): 286-292 %U http://www.ncbi.nlm.nih.gov/pubmed/19279425.

Christensen, P., N. Olsen, et al. (2003). "Scintigraphic assessment of retrograde colonic washout in fecal incontinence and constipation." Diseases of the Colon and Rectum 46(1): 68-76 %U http://www.ncbi.nlm.nih.gov/pubmed/12544524.

Cowlam, S. (2008). Quality of life, physiological evaluation, and novel treatment, in refractory constipation. Newcastle, University of Newcastle.

Cowlam, S., U. Khan, et al. (2008). "Validity of segmental transit studies used in routine clinical practice, to characterize defaecatory disorder in patients with functional constipation." Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 10(8): 818-822 %U http://www.ncbi.nlm.nih.gov/pubmed/18462230.

Cowlam, S., C. Watson, et al. (2007). "Percutaneous endoscopic colostomy of the left side of the colon." Gastrointestinal Endoscopy 65(7): 1007-14.

Damgaard, M., F. G. Thomsen, et al. "The influence of sacral nerve stimulation on gastrointestinal motor function in patients with fecal incontinence." Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society 23(6): 556-e207 %U http://www.ncbi.nlm.nih.gov/pubmed/21385289.

De Looze, D., M. Van Laere, et al. (1998). "Constipation and other chronic gastrointestinal problems in spinal cord injury patients." Spinal Cord: The Official Journal of the International Medical Society of Paraplegia 36(1): 63-66 %U http://www.ncbi.nlm.nih.gov/pubmed/9471141.

Dinning, P. G., S. E. Fuentealba, et al. (2007). "Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation." Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 9(2): 123-132 %U http://www.ncbi.nlm.nih.gov/pubmed/17223936.

Dudding, T. C., D. Parés, et al. (2008). "Predictive factors for successful sacral nerve stimulation in the treatment of faecal incontinence: a 10-year cohort analysis." Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 10(3): 249-256 %U http://www.ncbi.nlm.nih.gov/pubmed/17655722.

Elkelini, M. and M. Hassouna (2006). "Safety of MRI at 1.5Tesla in patients with implanted sacral nerve neurostimulator." European Urology 50(2): 311-6.

Emmanuel, A. V. and M. A. Kamm (1999). "Laser Doppler measurement of rectal mucosal blood flow." Gut 45(1): 64-69 %U http://www.ncbi.nlm.nih.gov/pubmed/10369706.

Emmanuel, A. V. and M. A. Kamm (2000). "Laser Doppler flowmetry as a measure of extrinsic colonic innervation in functional bowel disease." Gut 46(2): 212-217 %U http://www.ncbi.nlm.nih.gov/pubmed/10644315.

Emmanuel, A. V. and M. A. Kamm (2001). "Response to a behavioural treatment, biofeedback, in constipated patients is associated with improved gut transit and autonomic innervation." Gut 49(2): 214-219 %U http://www.ncbi.nlm.nih.gov/pubmed/11454797.

Faaborg, P. M., P. Christensen, et al. (2009). "Long-term outcome and safety of transanal colonic irrigation for neurogenic bowel dysfunction." Spinal Cord 47(7): 545-549 %U http://www.ncbi.nlm.nih.gov/pubmed/19104513.

Frank, L., L. Kleinman, et al. (1999). "Psychometric validation of a constipation symptom assessment questionnaire." Scandinavian Journal of Gastroenterology 34(9): 870-877 %U http://www.ncbi.nlm.nih.gov/pubmed/10522604.

Ganio, E. (2002). Sacral nerve modulation for chronic outlet obstruction. Saint Vincent, Italy.

Ganio, E., A. Masin, et al. (2001). "Short-term sacral nerve stimulation for functional anorectal and urinary disturbances: results in 40 patients: evaluation of a new option for anorectal functional disorders." Diseases of the Colon and Rectum 44(9): 1261-1267 %U http://www.ncbi.nlm.nih.gov/pubmed/11584196.

Gattuso, J. M. and M. A. Kamm (1993). "Review article: the management of constipation in adults." Alimentary Pharmacology & Therapeutics 7(5): 487-500 %U http://www.ncbi.nlm.nih.gov/pubmed/8280817.

Giani, I., E. Novelli, et al. (2011). "The effect of sacral nerve modulation on cerebral evoked potential latency in fecal incontinence and constipation." Annals of Surgery 254(1): 90-96 %U http://www.ncbi.nlm.nih.gov/pubmed/21494120.

Glick, M. E., H. Meshkinpour, et al. (1982). "Colonic dysfunction in multiple sclerosis." Gastroenterology 83(5): 1002-1007 %U http://www.ncbi.nlm.nih.gov/pubmed/6288506.

Glick, M. E., H. Meshkinpour, et al. (1984). "Colonic dysfunction in patients with thoracic spinal cord injury." Gastroenterology 86(2): 287-294 %U http://www.ncbi.nlm.nih.gov/pubmed/6690355.

Glickman, S. and M. A. Kamm (1996). "Bowel dysfunction in spinal-cord-injury patients." Lancet 347(9016): 1651-1653 %U http://www.ncbi.nlm.nih.gov/pubmed/8642958.

Gooneratne, M. L., P. Facer, et al. (2008). "Normalization of substance P levels in rectal mucosa of patients with faecal incontinence treated successfully by sacral nerve stimulation." The British Journal of Surgery 95(4): 477-483 %U http://www.ncbi.nlm.nih.gov/pubmed/18256993.

Gourcerol, G., S. Gallas, et al. (2007). "Sacral nerve stimulation in fecal incontinence: are there factors associated with success?" Diseases of the Colon and Rectum 50(1): 3-12 %U http://www.ncbi.nlm.nih.gov/pubmed/17080278.

Griffin, K. M., M. Pickering, et al. (2011). "Sacral nerve stimulation increases activation of the primary somatosensory cortex by anal canal stimulation in an experimental model %U http://www.ncbi.nlm.nih.gov/pubmed/21590761." The British Journal of Surgery.

Haas, U., V. Geng, et al. (2005). "Bowel management in patients with spinal cord injury -- a multicentre study of the German speaking society of paraplegia (DMGP)." Spinal Cord 43(12): 724-730 %U http://www.ncbi.nlm.nih.gov/pubmed/16010276.

Harari, D., M. Sarkarati, et al. (1997). "Constipation-related symptoms and bowel program concerning individuals with spinal cord injury." Spinal Cord 35(6): 394-401 %U http://www.ncbi.nlm.nih.gov/pubmed/9194264.

Heaton, K. W. and H. A. Cripps (1993). "Straining at stool and laxative taking in an English population." Digestive Diseases and Sciences 38(6): 1004-1008 %U http://www.ncbi.nlm.nih.gov/pubmed/8508693.

Hetzer, F. H., D. Hahnloser, et al. (2006). "Video-assisted sacral nerve stimulation." Techniques in Coloproctology 10(2): 121-123; discussion 123-124 %U http://www.ncbi.nlm.nih.gov/pubmed/16773288.

Higgins, P. D. R. and J. F. Johanson (2004). "Epidemiology of constipation in North America: a systematic review." The American Journal of Gastroenterology 99(4): 750-759 %U http://www.ncbi.nlm.nih.gov/pubmed/15089911.

Hinds, J. P., B. H. Eidelman, et al. (1990). "Prevalence of bowel dysfunction in multiple sclerosis. A population survey." Gastroenterology 98(6): 1538-1542 %U http://www.ncbi.nlm.nih.gov/pubmed/2338192.

Hocevar, B. and M. Gray (2008). "Intestinal diversion (colostomy or ileostomy) in patients with severe bowel dysfunction following spinal cord injury." Journal of Wound, Ostomy, and Continence Nursing: Official Publication of The Wound, Ostomy and Continence Nurses Society / WOCN 35(2): 159-166 %U http://www.ncbi.nlm.nih.gov/pubmed/18344790.

Infantino, A., A. Masin, et al. (1990). "Role of proctography in severe constipation." Diseases of the Colon and Rectum 33(8): 707-712 %U http://www.ncbi.nlm.nih.gov/pubmed/2376228.

Jarrett, M. E. D., G. Mowatt, et al. (2004). "Systematic review of sacral nerve stimulation for faecal incontinence and constipation." The British Journal of Surgery 91(12): 1559-1569 %U http://www.ncbi.nlm.nih.gov/pubmed/15455360.

Johanson, J. F. (2007). "Review of the treatment options for chronic constipation." MedGenMed: Medscape General Medicine 9(2): 25 %U http://www.ncbi.nlm.nih.gov/pubmed/17955081.

Kainz, W., G. Neubauer, et al. (20022). "Temperature measurement on neurological pulse generators during MR scans." Biomedical Engineering Online 12(1).

Kamm, M. A., T. C. Dudding, et al. (2010). "Sacral nerve stimulation for intractable constipation." Gut 59(3): 333-340 %U http://www.ncbi.nlm.nih.gov/pubmed/20207638.

Kenefick, N. J. (2006). "Sacral nerve neuromodulation for the treatment of lower bowel motility disorders." Annals of the Royal College of Surgeons of England 88(7): 617-623 %U http://www.ncbi.nlm.nih.gov/pubmed/17132307.

Kenefick, N. J., A. Emmanuel, et al. (2003). "Effect of sacral nerve stimulation on autonomic nerve function." The British Journal of Surgery 90(10): 1256-1260 %U http://www.ncbi.nlm.nih.gov/pubmed/14515296.

Kenefick, N. J., R. J. Nicholls, et al. (2002). "Permanent sacral nerve stimulation for treatment of idiopathic constipation." The British Journal of Surgery 89(7): 882-888 %U http://www.ncbi.nlm.nih.gov/pubmed/12081738.

Kenefick, N. J., C. J. Vaizey, et al. (2002). "Double-blind placebo-controlled crossover study of sacral nerve stimulation for idiopathic constipation." The British Journal of Surgery 89(12): 1570-1571 %U http://www.ncbi.nlm.nih.gov/pubmed/12445068.

King, S. K., J. R. Sutcliffe, et al. (2005). "The antegrade continence enema successfully treats idiopathic slow-transit constipation." Journal of Pediatric Surgery 40(12): 1935-1940 %U http://www.ncbi.nlm.nih.gov/pubmed/16338323.

König, H.-H., A. Ulshöfer, et al. (2002). "Validation of the EuroQol questionnaire in patients with inflammatory bowel disease." European Journal of Gastroenterology & Hepatology 14(11): 1205-1215 %U http://www.ncbi.nlm.nih.gov/pubmed/12439115.

Koutsomanis, D., J. E. Lennard-Jones, et al. (1995). "Controlled randomised trial of visual biofeedback versus muscle training without a visual display for intractable constipation." Gut 37(1): 95-99 %U http://www.ncbi.nlm.nih.gov/pubmed/7672690.

Krogh, K., N. Olsen, et al. (2003). "Colorectal transport during defecation in patients with lesions of the sacral spinal cord." Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society 15(1): 25-31 %U http://www.ncbi.nlm.nih.gov/pubmed/12588466.

Larkin, P. J., N. P. Sykes, et al. (2008). "The management of constipation in palliative care: clinical practice recommendations." Palliative Medicine 22(7): 796-807 %U http://www.ncbi.nlm.nih.gov/pubmed/18838491.

Lombardi, G., G. Del Popolo, et al. "Clinical outcome of sacral neuromodulation in incomplete spinal cord-injured patients suffering from neurogenic bowel dysfunctions." Spinal Cord 48(2): 154-159 %U http://www.ncbi.nlm.nih.gov/pubmed/19668257.

Lombardi, G., G. Del Popolo, et al. (2010). "Clinical outcome of sacral neuromodulation in incomplete spinal cord-injured patients suffering from neurogenic bowel dysfunctions." Spinal Cord: The Official Journal of the International Medical Society of Paraplegia 48(2): 154-159 %U http://www.ncbi.nlm.nih.gov/pubmed/19668257.

Longstreth, G. F., W. G. Thompson, et al. (2006). "Functional bowel disorders." Gastroenterology 130(5): 1480-1491 %U http://www.ncbi.nlm.nih.gov/pubmed/16678561.

Lundby, L., A. Møller, et al. (2011). "Relief of fecal incontinence by sacral nerve stimulation linked to focal brain activation." Diseases of the Colon and Rectum 54(3): 318-323.

Lynch, A. C., A. Anthony, et al. (2000). "Anorectal physiology following spinal cord injury." Spinal Cord 38(10): 573-580 %U http://www.ncbi.nlm.nih.gov/pubmed/11093318.

Lynch, A. C., C. Wong, et al. (2000). "Bowel dysfunction following spinal cord injury: a description of bowel function in a spinal cord-injured population and comparison with age and gender matched controls." Spinal Cord 38(12): 717-723 %U http://www.ncbi.nlm.nih.gov/pubmed/11175370.

MacDonagh, R. P., W. M. Sun, et al. (1990). "Control of defecation in patients with spinal injuries by stimulation of sacral anterior nerve roots." BMJ

(Clinical Research Ed.) 300(6738): 1494-1497 %U http://www.ncbi.nlm.nih.gov/pubmed/2372600.

Maeda, Y., L. Lundby, et al. (2010). "Sacral nerve stimulation for constipation: suboptimal outcome and adverse events." Diseases of the Colon and Rectum 53(7): 995-999 %U http://www.ncbi.nlm.nih.gov/pubmed/20551750.

Malone, P. S. J. (2004). "The antegrade continence enema procedure." BJU international 93(3): 248-249.

Malouf, A. J., P. H. Wiesel, et al. (2002). "Short-term effects of sacral nerve stimulation for idiopathic slow transit constipation." World Journal of Surgery 26(2): 166-170 %U http://www.ncbi.nlm.nih.gov/pubmed/11865344.

Marquis, P., C. De La Loge, et al. (2005). "Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire." Scandinavian Journal of Gastroenterology 40(5): 540-551 %U http://www.ncbi.nlm.nih.gov/pubmed/16036506.

Medtronic "MRI guidelines for InterStim Therapy neurostimulation systems." Volume, 1-18 DOI:

Metcalf, A. M., S. F. Phillips, et al. (1987). "Simplified assessment of segmental colonic transit." Gastroenterology 92(1): 40-47 %U http://www.ncbi.nlm.nih.gov/pubmed/3023168.

Muller-Lissner, S. A., M. A. Kamm, et al. (2005). "Myths and misconceptions about chronic constipation." The American Journal of Gastroenterology 100(1): 232-242 %U http://www.ncbi.nlm.nih.gov/pubmed/15654804.

Naldini, G., J. Martellucci, et al. (2010). "Treatment of slow-transit constipation with sacral nerve modulation." Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 12(11): 1149-1152 %U http://www.ncbi.nlm.nih.gov/pubmed/19843118.

NICE (2002). IPG64 Sacral nerve stimulation for urge incontinence and urgency-frequency: guidance.

NICE (2003) "Multiple Scelrosis. National clinical guideline for diagnosis and management in primary and secondary care." Volume, DOI:

NICE (2004). IPG99 Sacral nerve stimulation for faecal incontinence: guidance.

O'Keefe, E. A., N. J. Talley, et al. (1995). "Bowel disorders impair functional status and quality of life in the elderly: a population-based study." The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 50(4): M184-189 %U http://www.ncbi.nlm.nih.gov/pubmed/7614239.

Papachrysostomou, M., A. N. Smith, et al. (1994). "Obstructive defaecation and slow transit constipation: the proctographic parameters." International Journal of Colorectal Disease 9(3): 115-120 %U http://www.ncbi.nlm.nih.gov/pubmed/7814982.

Pare', P., R. Bridges, et al. (2007). "Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment." Canadian Journal of Gastroenterology = Journal Canadien De Gastroenterologie 21 Suppl B: 3B-22B %U http://www.ncbi.nlm.nih.gov/pubmed/17464377.

Pepin, C. and U. Ladabaum (2002). "The yield of lower endoscopy in patients with constipation: survey of a university hospital, a public county

hospital, and a Veterans Administration medical center." Gastrointestinal Endoscopy 56(3): 325-332 %U http://www.ncbi.nlm.nih.gov/pubmed/12196767.

Pescatori, M. and M. Meglio (1982). Colonic motility in two constipated neurological patients treated by spinal cord stimulation. Motility of the Digestive Tract. New York, Raven Press: 541-6.

Pettit, P. D. M., J. R. Thompson, et al. (2002). "Sacral neuromodulation: new applications in the treatment of female pelvic floor dysfunction." Current Opinion in Obstetrics & Gynecology 14(5): 521-525 %U http://www.ncbi.nlm.nih.gov/pubmed/12401982.

Preziosi, G., D. A. Raptis, et al. (2011). "Bowel biofeedback treatment in patients with multiple sclerosis and bowel symptoms." Dis Colon Rectum 54(9): 1114-21.

Rabin, R. and F. de Charro (2001). "EQ-5D: a measure of health status from the EuroQol Group." Annals of Medicine 33(5): 337-343 %U http://www.ncbi.nlm.nih.gov/pubmed/11491192.

Ramkumar, D. and S. S. C. Rao (2005). "Efficacy and safety of traditional medical therapies for chronic constipation: systematic review." The American Journal of Gastroenterology 100(4): 936-971 %U http://www.ncbi.nlm.nih.gov/pubmed/15784043.

Sarna, S. K. (1991). "Physiology and pathophysiology of colonic motor activity (1)." Digestive Diseases and Sciences 36(6): 827-862 %U http://www.ncbi.nlm.nih.gov/pubmed/1674470.

Shafik, A. (1995). "Sacral root stimulation for controlled defecation." European Surgical Research. EuropÃ¤ische Chirurgische Forschung. Recherches Chirurgicales EuropÃ©ennes 27(1): 63-68 %U http://www.ncbi.nlm.nih.gov/pubmed/7890007.

Sheldon, R., E. S. Kiff, et al. (2005). "Sacral nerve stimulation reduces corticoanal excitability in patients with faecal incontinence." The British Journal of Surgery 92(11): 1423-1431 %U http://www.ncbi.nlm.nih.gov/pubmed/16044426.

Stewart, W. F., J. N. Liberman, et al. (1999). "Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features." The American Journal of Gastroenterology 94(12): 3530-3540 %U http://www.ncbi.nlm.nih.gov/pubmed/10606315.

Sun, W. M., N. W. Read, et al. (1990). "Sensory and motor responses to rectal distention vary according to rate and pattern of balloon inflation." Gastroenterology 99(4): 1008-1015 %U http://www.ncbi.nlm.nih.gov/pubmed/2394323.

Tanagho, E. A. and R. A. Schmidt (1982). "Bladder pacemaker: scientific basis and clinical future." Urology 20(6): 614-619 %U http://www.ncbi.nlm.nih.gov/pubmed/7179629.

The, N. H. S. I. C. Prescription Cost Analysis, England - 2009 %U http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england--2009.

Vallès, M., J. Vidal, et al. (2006). "Bowel dysfunction in patients with motor complete spinal cord injury: clinical, neurological, and pathophysiological associations." The American Journal of

Gastroenterology 101(10): 2290-2299 %U http://www.ncbi.nlm.nih.gov/pubmed/17032195.

Wald, A., C. Scarpignato, et al. (2008). "A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation." Alimentary Pharmacology & Therapeutics 28(7): 917-930 %U http://www.ncbi.nlm.nih.gov/pubmed/18644012.

Wester, C. and L. Brubaker (1998). "Normal pelvic floor physiology." Obstetrics and Gynecology Clinics of North America 25(4): 707-722, v %U http://www.ncbi.nlm.nih.gov/pubmed/9921552.

Womack, N. R., N. S. Williams, et al. (1985). "New method for the dynamic assessment of anorectal function in constipation." The British Journal of Surgery 72(12): 994-998 %U http://www.ncbi.nlm.nih.gov/pubmed/4084758.

Appendix A

Table_Apx 1: Weekly GA Constipation scores

	con1	con2	con3	con4	con5	con6	con7	con8	con9	con10	con11	con12
SNS002	3	3	3	3	3	3	2	2	2	2	3	3
SNS003	3	3	4	3	4	3	3	2	0	3	4	5
SNS004	4	4	4	2	1	1	2	3	2	1	1	1
SNS005	4	4	5	4	4	4	1	1	1	2	4	4
SNS006	4	4	4	4	4	4	-	-	-	-	-	-
SNS007	3	3	3	3	3	3	2	3	2	3	3	3
SNS008	5	5	5	5	5	5	4	4	4	2	3	4
SNS009	3	4	3	3	3	3	2	2	3	2	4	4
SNS010	4	5	4	4	4	4	4	4	4	4	4	4
SNS011	4	4	4	4	5	4	4	3	4	3	4	4
SNS012	4	4	4	4	4	4	4	4	4	4	4	4
SNS013	4	4	4	4	4	4	3	3	3	4	3	4
SNS016	3	4	3	4	3	4	1	1	2	3	3	3
SNS017	4	4	4	3	3	3	2	2	2	3	2	3
SNS020	4	4	5	5	5	4	4	3	4	3	4	4
SNS021	4	3	5	5	4	5	2	3	1	4	4	4
SNS018	4	4	3	4	5	4	4	4	4	4	4	4

Table_Apx 2: Weekly GA FI scores

	con1	con2	con3	con4	con5	con6	con7	con8	con9	con10	con11	con12
SNS002	0	0	0	0	0	0	0	0	0	0	0	0
SNS003	0	0	0	0	0	2	0	0	0	0	0	0
SNS004	2	2	0	2	1	1	2	3	0	2	0	1
SNS005	3	1	2	1	1	1	1	1	1	1	1	1
SNS006	0	0	0	2	2	1	-	-	-	-	-	-
SNS007	0	0	0	0	0	0	0	0	0	1	0	0
SNS008	0	0	0	3	4	5	3	3	4	2	1	4
SNS009	0	0	0	3	0	0	0	0	0	0	0	0
SNS010	0	0	0	0	0	0	0	0	0	0	0	0
SNS011	0	0	0	0	0	0	0	0	0	0	0	0
SNS012	4	4	4	4	0	4	4	4	3	0	3	3
SNS013	3	3	2	2	2	3	2	3	0	3	4	4
SNS016	3	0	0	0	0	0	0	0	0	0	0	0
SNS017	4	4	4	3	3	3	1	3	2	3	2	3
SNS020	0	4	4	4	5	0	4	3	0	3	4	4
SNS021	1	0	0	0	0	0	0	0	0	0	0	0
SNS018	1	5	4	0	0	3	3	2	4	2	2	0

Table_Apx 3: Weekly scores for PAC-SYM

	pacsym1	pacsym2	pacsym3	pacsym4	pacsym5	pacsym6	pacsym7	pacsym8	pacsym9	pacsym10	pacsym11	pacsym12
SNS002	1.00	1.33	1.25	1.33	0.92	1.25	1.17	0.58	0.67	0.42	1.08	1.08
SNS003	3.17	2.50	2.36	2.64	2.50	1.92	2.17	0.83	0.58	0.92	1.09	2.00
SNS004	2.17	2.08	1.58	2.17	2.25	0.92	0.50	0.42	0.25	0.92	0.67	0.83
SNS005	1.50	2.00	1.67	1.92	1.75	1.67	0.33	0.33	0.17	0.58	1.75	1.67
SNS006	1.33	1.00	1.00	1.08	0.92	1.08	-	-	-	-	-	-
SNS007	0.83	0.83	0.92	1.00	0.83	0.92	0.50	0.42	0.25	0.42	0.67	0.83
SNS008	2.33	2.25	2.58	2.50	2.67	2.67	1.67	2.08	1.92	1.25	1.08	2.17
SNS009	1.00	0.92	2.00	1.17	0.83	0.83	0.75	0.50	0.42	0.33	0.92	0.83
SNS010	1.75	2.25	1.92	1.25	1.17	1.67	0.75	0.92	0.67	1.33	1.25	1.50
SNS011	2.58	2.08	2.42	2.33	2.33	2.08	2.17	1.75	1.67	1.83	1.92	2.33
SNS012	3.58	3.42	3.50	2.83	3.08	3.50	2.83	2.50	1.92	2.42	2.17	2.17
SNS013	1.83	1.83	1.75	2.83	2.25	2.25	0.75	1.25	1.25	1.75	2.33	2.67
SNS016	1.25	1.17	1.33	1.17	1.25	1.33	0.17	0.17	0.42	0.42	0.42	0.42
SNS017	2.17	2.17	1.92	1.17	2.08	2.00	1.75	1.67	1.67	0.75	0.50	0.92
SNS020	1.17	2.75	2.83	2.42	1.92	1.92	2.42	2.83	2.83	1.75	1.75	2.92
SNS021	1.33	1.00	1.17	1.92	1.00	1.33	0.58	0.67	0.33	0.92	0.92	0.92
SNS018	1.33	1.50	1.42	1.17	1.67	1.50	1.50	1.75	1.67	1.58	1.25	1.33

Table_Apx 4: PAC-SYM Abdominal domain

	pacsym1	pacsym2	pacsym3	pacsym4	pacsym5	pacsym6	pacsym7	pacsym8	pacsym9	pacsym10	pacsym11	pacsym12
SNS002	0.80	0.80	0.80	1.20	0.60	0.80	0.80	0.40	0.40	0.20	0.80	0.80
SNS003	3.40	2.80	1.25	2.40	2.60	1.60	2.60	0.40	0.40	0.80	0.50	3.20
SNS004	2.80	2.40	1.60	2.80	2.40	0.80	0.40	0.20	0.20	0.80	0.40	0.60
SNS005	1.40	2.00	1.80	2.00	1.60	1.40	0.60	0.20	0.20	0.60	1.60	1.40
SNS006	1.40	1.00	1.20	1.40	1.20	1.40	-	-	-	-	-	-
SNS007	0.80	0.80	1.00	0.80	0.60	0.80	0.40	0.20	0.20	0.20	0.40	0.60
SNS008	2.40	2.20	2.60	2.80	2.80	2.80	1.60	1.80	1.60	1.20	1.00	2.20
SNS009	1.40	1.80	2.20	1.40	1.20	1.40	1.80	0.80	0.80	0.40	1.40	1.40
SNS010	2.00	3.20	3.20	2.00	1.80	2.40	0.80	1.00	1.00	1.60	1.60	1.60
SNS011	2.20	1.40	2.20	2.20	2.40	1.80	2.20	1.40	1.20	2.00	2.00	2.40
SNS012	3.80	4.00	3.80	3.40	3.40	4.00	3.00	2.60	3.20	2.60	2.80	2.20
SNS013	3.00	2.80	2.60	3.60	3.20	2.80	1.20	1.40	1.60	2.40	2.80	3.00
SNS016	1.60	1.60	1.60	1.60	1.60	1.60	0.40	0.40	1.00	0.60	0.60	0.60
SNS017	2.80	2.60	2.40	1.60	2.80	2.80	2.40	2.00	2.20	1.40	1.20	1.00
SNS020	0.80	2.80	2.80	1.80	0.80	2.60	1.40	3.20	3.20	2.60	2.60	3.00
SNS021	0.80	1.20	1.20	2.20	1.40	1.80	0.40	0.20	0.40	1.00	0.80	1.00
SNS018	1.09	1.45	1.27	1.00	1.64	1.45	1.36	1.73	1.55	1.45	1.18	1.27

Table_Apx 5:PAC-SYM Rectal domain

	pacsym1	pacsym2	pacsym3	pacsym4	pacsym5	pacsym6	pacsym7	pacsym8	pacsym9	pacsym10	pacsym11	pacsym12
SNS002	0.67	1.00	1.00	1.00	0.67	1.00	0.67	0.33	0.33	0.33	0.67	0.67
SNS003	3.00	2.00	3.33	3.00	3.00	3.00	1.33	1.33	0.67	1.00	1.00	-
SNS004	3.00	1.67	1.67	3.00	2.33	0.67	0.67	0.33	0.33	0.33	1.00	1.00
SNS005	2.00	2.00	1.67	2.00	2.33	2.00	-	0.33	0.33	-	1.67	2.33
SNS006	1.00	1.00	0.67	0.67	0.67	0.67	-	-	-	-	-	-
SNS007	0.67	0.67	1.00	1.00	1.00	0.67	0.67	0.33	0.33	0.33	1.00	1.00
SNS008	1.33	1.33	2.00	1.00	1.67	2.00	0.67	1.33	1.00	0.67	1.00	2.00
SNS009	0.33	0.33	1.33	0.67	0.33	0.33	-	-	-	0.33	-	-
SNS010	1.00	1.00	1.00	0.67	1.00	0.67	0.67	0.67	0.33	0.67	0.67	0.67
SNS011	1.33	1.33	1.00	1.33	1.00	1.00	1.00	1.00	1.00	0.67	0.67	1.00
SNS012	2.67	1.67	2.67	2.00	1.67	3.33	3.00	1.67	0.67	1.33	1.00	2.00
SNS013	1.00	1.00	1.33	2.67	1.33	1.67	0.33	1.00	1.00	1.33	2.33	3.00
SNS016	1.33	1.33	1.33	1.33	1.33	1.33	-	-	-	0.67	0.67	0.67
SNS017	0.67	1.33	0.67	0.67	1.00	1.00	0.67	0.67	1.00	-	-	0.33
SNS020	1.33	2.33	2.00	2.67	2.00	2.00	3.00	3.00	2.67	1.00	1.00	1.67
SNS021	1.00	0.67	0.67	1.00	0.33	1.00	-	0.67	0.33	0.67	0.67	1.00
SNS018	0.67	1.33	1.00	0.67	1.00	1.00	1.00	1.33	1.00	1.00	0.67	1.00

Table_Apx 6: PAC-SYM stool domain

	pacsym1	pacsym2	pacsym3	pacsym4	pacsym5	pacsym6	pacsym7	pacsym8	pacsym9	pacsym10	pacsym11	pacsym12
SNS002	1.50	2.25	2.00	1.75	1.50	2.00	2.00	1.00	1.25	0.75	1.75	1.75
SNS003	3.00	2.50	2.75	2.75	2.00	1.50	2.25	1.00	0.75	1.00	1.75	2.00
SNS004	0.75	2.00	1.50	0.75	2.00	1.25	0.50	0.75	0.25	1.50	0.75	1.00
SNS005	1.25	2.00	1.50	1.75	1.50	1.75	0.25	0.50	-	1.00	2.00	1.50
SNS006	1.50	1.00	1.00	1.00	0.75	1.00	-	-	-	-	-	-
SNS007	1.00	1.00	0.75	1.25	1.00	1.25	0.50	0.75	0.25	0.75	0.75	1.00
SNS008	3.00	3.00	3.00	3.25	3.25	3.00	2.50	3.00	3.00	1.75	1.25	2.25
SNS009	1.00	0.25	2.25	1.25	0.75	0.50	-	0.50	0.25	0.25	1.00	0.75
SNS010	2.00	2.00	1.00	0.75	0.50	1.50	0.75	1.00	0.50	1.50	1.25	2.00
SNS011	4.00	3.50	3.75	3.25	3.25	3.25	3.00	2.75	2.75	2.50	2.75	3.25
SNS012	4.00	4.00	3.75	2.75	3.75	3.00	2.50	3.00	1.25	3.00	2.25	2.25
SNS013	1.00	1.25	1.00	2.00	1.75	2.00	0.50	1.25	1.00	1.25	1.75	2.00
SNS016	0.75	0.50	1.00	0.50	0.75	1.00	-	-	-	-	-	-
SNS017	2.50	2.25	2.25	1.00	2.00	1.75	1.75	2.00	1.50	0.50	-	1.25
SNS020	1.50	3.00	3.50	3.00	3.25	1.00	3.25	2.25	2.50	1.25	1.25	3.75
SNS021	2.25	1.00	1.50	2.25	1.00	1.00	1.25	1.25	0.25	1.00	1.25	0.75
SNS018	2.25	1.75	2.25	1.75	2.00	2.25	2.50	2.00	2.00	1.50	1.00	1.25

Table_Apx 7: Weekly PAC-QOL Scores

	pacqol1	pacqol2	pacqol3	pacqol4	pacqol5	pacqol6	pacqol7	pacqol8	pacqol9	pacqol10	pacqol11	pacqol12
SNS002	1.89	1.68	1.68	1.71	1.46	1.32	1.29	1.00	1.07	0.71	1.32	1.36
SNS003	2.79	2.11	2.79	2.36	2.29	2.25	1.50	1.39	0.57	1.54	2.22	3.04
SNS004	2.14	2.07	2.33	2.14	2.14	1.04	1.54	1.29	1.07	1.14	1.25	1.54
SNS005	1.79	2.25	2.18	2.39	2.18	2.11	0.29	0.14	0.14	0.75	1.54	1.75
SNS006	2.57	2.32	2.43	2.43	2.71	2.68	-	-	-	-	-	-
SNS007	1.71	1.75	1.61	1.57	1.43	1.04	1.54	1.29	1.07	1.14	1.25	1.54
SNS008	3.00	2.96	3.00	2.50	2.61	2.54	2.39	2.57	2.29	1.54	2.04	2.46
SNS009	1.04	1.32	1.43	1.32	1.29	1.29	1.39	1.14	0.89	0.71	2.14	2.18
SNS010	2.04	2.93	2.61	2.21	2.25	2.39	2.43	2.14	2.64	2.57	2.57	2.61
SNS011	2.82	2.54	2.43	2.64	2.89	1.96	2.64	2.18	2.07	1.61	2.50	2.64
SNS012	3.82	3.61	3.21	2.89	2.71	3.25	2.89	2.86	3.18	2.61	2.71	2.68
SNS013	2.86	2.21	2.46	2.32	2.68	2.32	1.79	1.71	1.79	2.36	2.46	2.79
SNS016	2.50	2.18	2.14	2.18	2.50	2.14	0.68	0.32	0.61	1.29	1.29	1.29
SNS017	2.18	2.04	1.57	1.57	1.75	1.82	1.43	1.43	1.61	1.68	1.25	1.18
SNS020	3.64	3.50	3.39	3.18	2.46	3.46	3.36	3.07	3.07	2.96	3.32	3.18
SNS021	2.32	1.96	2.18	2.39	2.11	2.14	0.96	0.96	0.54	1.68	1.86	2.14
SNS018	2.21	2.29	2.18	2.21	1.93	2.00	2.21	2.25	2.25	1.96	2.18	2.21

Table_Apx 8: PAC-QOL Physical discomfort domain

	pacqol1	pacqol2	pacqol3	pacqol4	pacqol5	pacqol6	pacqol7	pacqol8	pacqol9	pacqol10	pacqol11	pacqol12
SNS002	2.25	2.25	2.25	2.25	1.75	2.00	1.25	1.00	1.00	0.50	1.75	1.75
SNS003	2.75	2.75	2.00	2.50	2.25	1.50	1.50	1.00	0.50	1.50	0.67	3.75
SNS004	2.50	2.75	2.00	2.50	2.25	1.00	0.75	0.75	0.50	0.50	0.75	1.00
SNS005	1.75	3.50	3.25	3.00	2.75	2.75	0.25	-	-	0.50	2.25	2.50
SNS006	2.00	2.25	1.75	2.25	2.75	2.50	-	-	-	-	-	-
SNS007	0.75	1.00	0.75	0.75	0.50	1.00	0.75	0.75	0.50	0.50	0.75	1.00
SNS008	2.50	2.25	2.25	1.50	1.50	1.75	1.50	1.75	1.50	1.00	1.25	1.75
SNS009	1.25	1.50	1.50	1.75	1.75	1.75	2.00	1.50	0.75	0.25	2.75	2.50
SNS010	3.00	3.50	3.50	2.75	2.75	3.25	2.25	2.25	2.50	3.00	3.00	3.00
SNS011	3.75	2.75	2.50	3.00	3.00	1.75	3.25	2.75	2.75	2.00	2.75	3.25
SNS012	4.00	4.00	4.00	3.00	3.75	4.00	3.00	3.75	3.25	3.25	3.50	3.25
SNS013	3.00	2.75	2.75	2.50	2.50	3.00	1.50	1.75	2.25	2.75	2.50	3.25
SNS016	2.75	3.50	3.00	3.50	2.75	3.00	0.25	-	1.50	2.25	2.25	2.25
SNS017	3.75	3.25	3.00	2.00	2.50	1.75	2.25	1.75	2.50	2.25	1.00	0.25
SNS020	3.75	3.75	3.50	3.25	3.75	4.00	3.25	3.25	3.25	2.75	3.25	2.75
SNS021	3.00	2.50	3.00	3.00	2.50	2.50	1.00	1.00	0.25	1.50	2.25	2.75
SNS018	2.00	1.75	1.75	1.50	1.75	1.50	1.75	2.00	2.50	1.75	2.75	2.00

Table_Apx 9: PAC-QOL Psychosocial discomfort domain

	pacqol1	pacqol2	pacqol3	pacqol4	pacqol5	pacqol6	pacqol7	pacqol8	pacqol9	pacqol10	pacqol11	pacqol12
SNS002	0.50	0.13	-	0.63	0.25	0.25	-	-	-	-	0.13	0.13
SNS003	2.25	0.63	2.13	1.25	1.38	1.13	1.00	1.00	0.38	1.13	2.00	2.00
SNS004	1.75	0.88	1.63	1.75	1.38	1.13	1.13	1.38	1.13	1.13	0.75	1.13
SNS005	0.63	0.75	0.38	0.75	0.63	0.50	-	-	-	-	-	-
SNS006	2.50	2.38	2.50	3.00	3.13	2.88						
SNS007	1.13	1.13	1.13	1.25	1.13	1.13	1.13	1.38	1.13	1.13	0.75	1.13
SNS008	2.50	2.50	2.75	2.00	2.13	2.25	2.13	2.13	2.13	2.00	1.63	2.25
SNS009	0.25	0.50	0.50	-	0.25	0.13	0.38	0.13	-	0.25	0.38	0.25
SNS010	1.38	2.63	3.00	2.38	2.88	2.25	2.63	2.50	2.38	2.63	2.63	2.63
SNS011	1.00	0.63	0.75	1.00	1.50	0.50	0.88	0.63	0.38	0.25	0.75	1.00
SNS012	3.38	3.13	2.63	1.88	1.88	2.00	2.00	2.00	2.00	2.63	1.63	1.50
SNS013	3.00	1.75	2.88	2.50	2.88	2.50	2.13	1.50	1.38	2.50	3.00	3.25
SNS016	1.50	1.38	1.50	1.38	1.50	1.50	-	-	0.25	-	-	-
SNS017	0.88	0.25	-	0.25	-	-	-	-	-	-	-	0.38
SNS020	3.25	3.38	3.13	2.50	1.25	2.75	2.75	2.88	2.88	2.75	2.50	2.38
SNS021	1.50	1.13	1.75	1.75	1.75	1.50	1.00	1.13	0.50	1.38	1.00	1.13
SNS018	2.00	2.13	2.00	1.88	1.63	1.88	2.00	2.00	2.13	1.50	1.88	2.25

Table_Apx 10: PAC-QOL Worries and concerns domain

	pacqol1	pacqol2	pacqol3	pacqol4	pacqol5	pacqol6	pacqol7	pacqol8	pacqol9	pacqol10	pacqol11	pacqol12
SNS002	2.18	2.09	2.18	1.82	1.64	1.36	1.73	1.36	1.36	0.82	1.45	1.55
SNS003	2.73	2.36	3.18	2.64	2.64	2.82	2.09	1.36	0.64	1.45	2.36	3.36
SNS004	2.18	2.09	2.50	2.18	2.55	1.27	1.55	1.00	0.82	1.00	1.18	1.45
SNS005	2.18	2.09	2.36	2.64	2.36	2.27	0.64	0.36	0.36	1.09	1.36	2.09
SNS006	2.73	2.45	2.45	2.27	2.55	2.64						
SNS007	1.82	1.91	1.73	1.55	1.36	1.27	1.55	1.00	0.82	1.00	1.18	1.45
SNS008	3.27	3.27	3.18	2.64	2.82	2.55	2.36	2.64	2.09	1.91	2.09	2.55
SNS009	0.73	1.09	1.09	1.00	0.91	0.91	1.18	0.91	0.82	0.55	2.36	2.64
SNS010	1.73	2.55	1.91	1.73	1.64	2.00	1.91	1.64	2.36	1.91	1.91	2.00
SNS011	3.36	3.27	3.00	3.09	3.36	2.27	3.09	2.45	2.27	2.64	3.09	3.00
SNS012	4.00	3.73	3.82	3.45	3.36	3.91	3.36	3.00	3.82	1.91	3.00	3.18
SNS013	2.27	1.73	1.55	1.91	2.27	1.55	1.18	1.36	1.36	1.73	1.55	1.82
SNS016	2.82	1.55	1.64	1.55	2.82	1.64	0.91	0.64	0.64	1.09	1.09	1.09
SNS017	2.00	2.36	2.00	1.45	2.00	2.36	1.82	2.18	2.36	1.91	1.36	1.27
SNS020	3.82	3.64	3.64	4.00	3.09	3.91	3.64	3.82	3.82	2.91	3.73	3.64
SNS021	2.45	2.45	2.27	2.55	2.27	2.82	1.00	1.09	0.82	1.82	2.27	2.09
SNS018	2.27	2.36	2.27	2.82	2.00	1.91	2.27	2.36	2.45	2.18	2.00	2.09

Table_Apx 11: PAC-QOL dissatisfaction domain

	pacqol1	pacqol2	pacqol3	pacqol4	pacqol5	pacqol6	pacqol7	pacqol8	pacqol9	pacqol10	pacqol11	pacqol12
SNS002	3.20	2.80	2.80	2.80	2.80	2.40	2.40	1.80	2.20	1.80	2.60	2.60
SNS003	3.80	3.40	3.60	3.40	3.00	3.40	1.00	2.40	0.80	2.40	3.20	3.40
SNS004	2.40	3.40	3.40	2.40	2.40	0.40	2.80	2.20	2.00	2.00	2.60	2.80
SNS005	2.80	4.00	3.80	4.00	3.80	3.80	-	-	-	1.40	3.80	3.20
SNS006	2.80	2.00	2.80	2.00	2.40	2.60	-	-	-	-	-	-
SNS007	3.20	3.00	2.80	2.80	2.80	0.40	2.80	2.20	2.00	2.00	2.60	2.80
SNS008	3.60	3.60	3.60	3.80	3.80	3.60	3.60	3.80	3.60	0.40	3.20	3.20
SNS009	2.80	3.00	3.60	3.80	3.40	3.60	3.00	3.00	2.60	2.20	4.00	4.00
SNS010	3.00	3.80	2.80	2.60	2.20	2.80	3.40	2.60	3.80	3.60	3.60	3.60
SNS011	3.80	3.80	3.80	4.00	4.00	3.80	4.00	3.60	3.80	1.20	3.80	4.00
SNS012	4.00	3.80	2.20	3.20	1.80	3.20	3.20	3.20	3.60	3.60	3.20	3.00
SNS013	3.80	3.60	3.60	2.80	3.40	3.20	2.80	2.80	3.00	3.20	3.60	3.80
SNS016	3.20	3.80	3.60	3.80	3.20	3.60	1.60	0.40	0.40	3.00	3.00	3.00
SNS017	3.40	3.20	2.00	3.60	3.40	3.60	2.20	1.80	1.80	3.40	3.20	3.00
SNS020	3.80	3.20	3.20	2.40	2.00	3.20	3.80	1.60	1.60	3.60	3.80	3.80
SNS021	2.80	1.80	2.00	2.60	2.00	1.40	0.80	0.40	0.20	2.00	2.00	3.40
SNS018	2.60	2.80	2.60	2.00	2.40	2.80	2.80	2.60	1.80	2.40	2.60	2.60

Table_Apx 12: EQ-VAS scores

	eqvas3	eqvas6	eqvas9	eqvas12
SNS003	75	45	95	50
SNS004	50	50	50	60
SNS005	39	30	80	50
SNS006	40	30	-	-
SNS007	50	50	50	50
SNS008	70	40	70	55
SNS009	55	65	45	60
SNS010	30	40	20	30
SNS011	50	50	30	40
SNS012	20	70	20	40
SNS013	35	20	45	20
SNS016	20	20	40	40
SNS017	35	30	25	35
SNS020	50	60	60	35
SNS021	55	60	45	60
SNS018	50	50	40	50

0-100 (0 worst state of health, 100 best state of health)

Table_Apx 13: EQ-5D Scores

	eq5d3	eq5d6	eq5d9	eq5d12
SNS003	0.587	0.516	0.746	-0.181
SNS004	0.273	0.273	0.273	0.312
SNS005	0.587	0.623	0.587	0.691
SNS006	0.516	-0.056		
SNS007	0.620	0.691	0.691	0.691
SNS008	0.088	-0.135	0.030	0.088
SNS009	-0.037	0.073	0.073	0.587
SNS010	-0.086	0.159	-0.003	0.159
SNS011	0.516	0.516	0.088	0.516
SNS012	-0.181	0.082	-0.077	-0.181
SNS013	-0.074	-0.003	0.260	-0.003
SNS016	-0.095	-0.095	0.073	0.073
SNS017	0.088	0.620	0.159	0.691
SNS020	0.222	-0.077	0.689	-0.077
SNS021	0.620	0.088	0.691	0.159
SNS018	0.205	-0.016	0.516	0.260

Table_Apx 14: Weekly Bowel Movements

Bowel Movements	wk 4	wk 5	wk 6	wk 8	wk 9
SNS002	2.43	2.14	1.71	1.71	1.14
SNS003	0.43	0.29	0.57	0.71	0.71
SNS004	1.43	1.29	1.50	2.00	-
SNS005	0.29	0.29	0.29	0.71	0.57
SNS006	4.14	3.29	3.57	-	-
SNS007	6.14	5.71	1.71	1.43	1.71
SNS008	5.29	5.71	5.57	4.14	5.57
SNS009	0.29	0.43	0.29	0.43	0.29
SNS010	1.29	0.71	0.71	1.00	0.57
SNS011	0.43	0.86	0.43	0.71	0.43
SNS012	0.86	1.43	1.14	0.29	1.14
SNS013	2.00	1.71	2.00	2.43	0.57
SNS016	0.14	0.29	0.14	0.43	0.29
SNS017	0.29	0.71	0.29	0.71	0.71
SNS020	0.86	0.71	0.86	1.00	0.86
SNS021	1.86	1.71	1.71	1.57	1.14
SNS018	1.00	1.00	0.85	0.72	0.72

Table_Apx 15: Faecal Incontinence Episodes

FI	wk 4	wk 5	wk 6	wk 8	wk 9
SNS002	0	0	0	0	0
SNS003	0	0	0	0	0
SNS004	0	0	0	0	0
SNS005	0	0	0	0	0
SNS006	0	0	0	-	0
SNS007	0	0	0	0	0
SNS008	15	6	5	0	0
SNS009	0	0	0	0	0
SNS010	0	0	0	0	0
SNS011	0	0	0	0	0
SNS012	0	0	0	0	0
SNS013	0	0	0	0	0
SNS016	0	0	0	0	0
SNS017	0	9	8	0	0
SNS020	0	0	0	0	0
SNS021	0	0	0	0	0
SNS018	0	1	0	0	0

Table_Apx 16: Mean toileting time

Toileting Time	wk 4	wk 5	wk 6	wk 8	wk 9
SNS002	16.57	16.43	12.14	16.00	10.71
SNS003	11.43	8.57	11.43	12.14	5.71
SNS004	20.00	16.43	20.00	12.86	-
SNS005	12.86	18.57	18.57	10.00	8.57
SNS006	77.14	45.71	54.29	-	-
SNS007	72.14	76.43	26.43	25.00	16.43
SNS008	20.43	20.29	19.71	10.14	14.29
SNS009	26.43	30.00	24.29	22.14	21.43
SNS010	12.86	8.57	8.57	12.43	4.57
SNS011	6.57	6.71	5.71	8.57	3.57
SNS012	2.86	1.71	2.86	1.43	5.71
SNS013	107.14	65.00	58.57	55.00	32.14
SNS016	6.43	12.86	6.43	12.86	4.29
SNS017	1.00	3.00	2.86	4.71	4.43
SNS020	8.43	7.71	9.43	7.14	5.00
SNS021	9.57	6.86	6.86	4.43	2.86
SNS018	28.33	28.89	28.70	28.98	30.00

Table_Apx 17: Mean Laxative score

Laxative Score	wk 4	wk 5	wk 6	wk 8	wk 9
SNS002	0.14	0.00	0.00	0.00	-0.57
SNS003	0.57	0.29	0.43	0.71	0.43
SNS004	0.57	0.29	0.43	0.71	0.43
SNS005	0.00	0.00	0.00	0.00	0.00
SNS006	0.00	0.00	0.00	0.00	0.00
SNS007	0.29	-0.71	-1.00	-1.00	-1.00
SNS008	0.00	0.00	0.00	0.00	0.00
SNS009	0.29	0.29	0.29	0.00	0.00
SNS010	-0.14	0.29	1.00	-0.71	-0.14
SNS011	0.14	-0.14	-0.29	-0.29	0.00
SNS012	1.00	0.00	0.57	0.00	0.00
SNS013	0.14	0.00	0.00	0.00	-0.14
SNS016	0.00	0.00	0.29	0.00	0.00
SNS017	0.00	0.00	0.00	0.00	0.00
SNS020	0.00	0.00	0.00	0.00	0.00
SNS021	0.00	0.00	0.00	0.00	0.00
SNS018	-0.72	0.28	0	-0.43	0.00

Table_Apx 18: Transit times

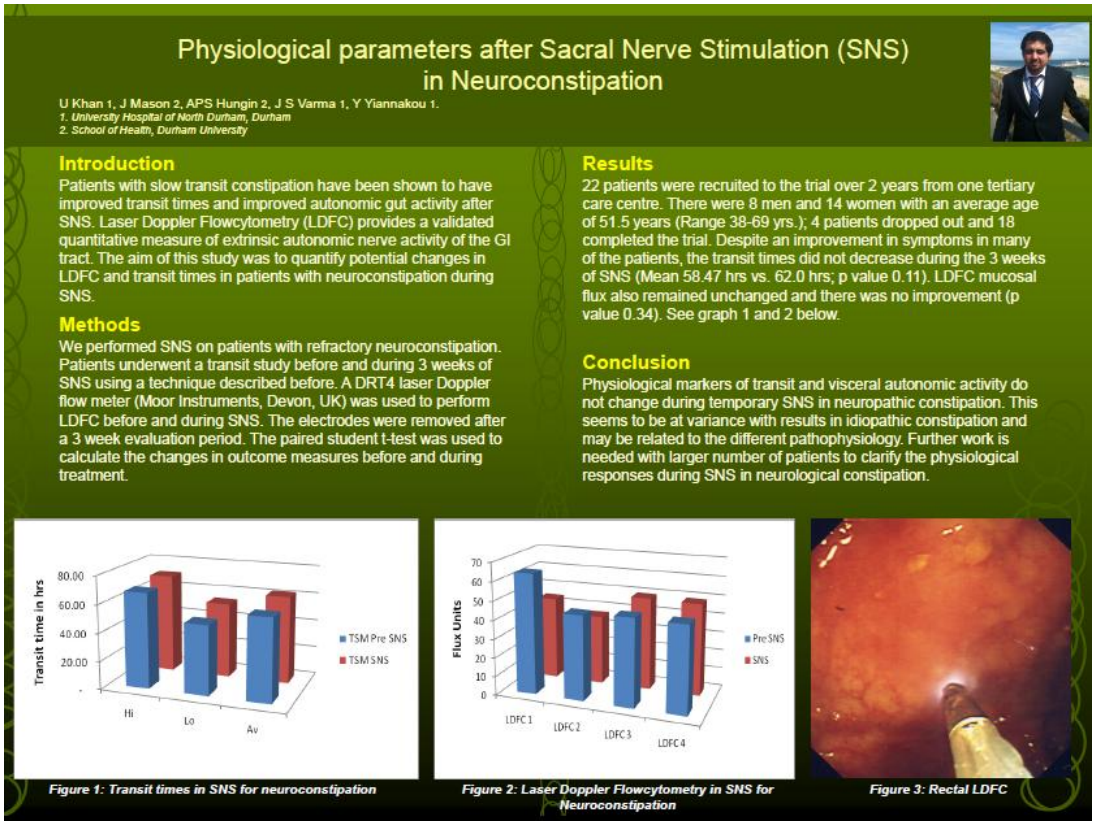
	TSM Pre SNS	TSM SNS
SNS002	-	69
SNS003	72	59
SNS004	54	61
SNS005	62	67
SNS006	69	-
SNS007	10	17
SNS008	63	71
SNS009	66	72
SNS010	55	62
SNS011	70	72
SNS012	72	65
SNS013	62	72
SNS016	72	72
SNS017	40	64
SNS020	63	-
SNS021	47	46

Table_Apx 19: LDFC Scores

	LDFC Pre SNS	LDFC SNS
SNS002	38.95	55.15
SNS003	119.375	56
SNS005	45.825	35.325
SNS007	30.55	24.875
SNS008	48.5	72.3
SNS009	42.975	52.175
SNS010	31.425	30.35
SNS011	60.575	34.1
SNS012	32	32.6
SNS013	60.525	52.025
SNS016	24.175	28.3
SNS017	90.25	66.225
SNS020	25.65	32
SNS021	54.75	55.3

Appendix B

Figure_Apx 1: Poster (ASGBI, Bournemouth 2011)



Figure_Apx 2: Poster (BSG, Birmingham 2011)

Sacral Nerve Stimulation (SNS) in Neuropathic Constipation

U Khan 1, J Mason 2, APS Hungin 2, J S Varma 1, Y Yiannakou 1.
1. University Hospital of North Durham, Durham
2. School of Health, Durham University

Introduction

The prevalence of constipation is between 43% and 58% in patients with either MS or spinal cord injury (SCI). Neuro-constipation is a very difficult to treat because of poor mobility, poor diet and side effects of long-term medication. Surgical options for intractable neuroconstipation involve prolonged operations with significant complications, and are unacceptable to many patients. In contrast sacral nerve stimulation (SNS) offers a potential minimally invasive and effective alternative.

Methods

Patients with refractory neuropathic constipation were recruited from a tertiary specialist unit and offered temporary SNS (TSNS). All patients were recruited prospectively and gave formal consent for inclusion. Appropriate ethical approvals were in place. The length of the study was twelve weeks for each patient and included a six week evaluation period before SNS during which the baseline assessments were made. Bilateral TSNS was performed under sedation and continued for three weeks. The electrodes were removed after the evaluation period during which patients completed diaries and questionnaires. Paired student t-test was used to calculate the changes in outcome measures before and during treatment.

Results

22 patients were recruited. There were 8 men and 14 women with an average age of 51.5 years (Range 38-69 yrs.). 4 patients dropped out and 18 completed the trial. 12 patients (67 %) had a successful response after three weeks of bilateral temporary stimulation and underwent permanent implant. The Global Assessment Score for constipation, PAC-SYM and PAC-QOL scores for these patients improved during treatment (p value <0.05). There was also an improvement in toileting time (p 0.04) and decrease in overall laxative use (p 0.03).

Conclusion

Short term treatment with SNS seems to help some patients with neuropathic constipation. There is good symptoms stability before treatment and rapid return to baseline after treatment.

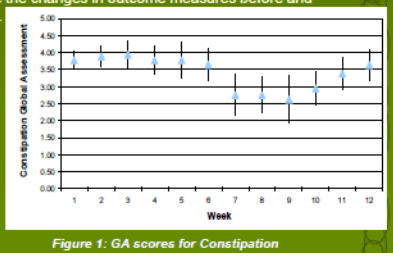


Figure 1: GA scores for Constipation

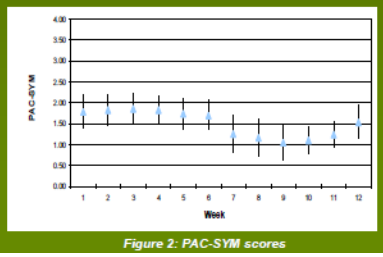


Figure 2: PAC-SYM scores

Figure_Apx 3: Search Strategy Medline

59	MEDLINE – 1950 to date	CONSTIPATION#.W..DE.	unrestricted	7455
60	MEDLINE – 1950 to date	STIMULATION	unrestricted	482439
61	MEDLINE – 1950 to date	ELECTRIC–STIMULATION#.DE.	unrestricted	104160
62	MEDLINE – 1950 to date	LUMBOSACRAL ADJ PLEXUS	unrestricted	1748
63	MEDLINE – 1950 to date	LUMBOSACRAL–PLEXUS#.DE.	unrestricted	25740
64	MEDLINE – 1950 to date	ELECTRIC ADJ STIMULATION ADJ THERAPY	unrestricted	12451
65	MEDLINE – 1950 to date	ELECTRIC–STIMULATION–THERAPY#.DE.	unrestricted	25916
66	MEDLINE – 1950 to date	59 AND 65 AND 63	unrestricted	8
67	MEDLINE – 1950 to date	59 AND 61 AND 63	unrestricted	1
68	MEDLINE – 1950 to date	combined sets 66, 67	unrestricted	9
69	MEDLINE – 1950 to date	dropped duplicates from 68	unrestricted	0
70	MEDLINE – 1950 to date	unique records from 68	unrestricted	9
71	MEDLINE – 1950 to date	ANORECTAL ADJ DISORDERS	unrestricted	167
72	MEDLINE – 1950 to date	RECTAL–DISEASES#.DE. OR ANUS–DISEASES#.DE. OR ANAL–CANAL#.DE. OR RECTUM#.W..DE. OR DEFECATION#.W..DE.	unrestricted	100617
73	MEDLINE – 1950 to date	72 AND 63 AND 65	unrestricted	45
74	MEDLINE – 1950 to date	combined sets 70, 73	unrestricted	54
75	MEDLINE – 1950 to date	dropped duplicates from 74	unrestricted	6
76	MEDLINE – 1950 to date	unique records from 74	unrestricted	48

Saved: 10–Apr–2007 18:26:53 MEST

No.	Database	Search term	Info added since	Results
59	MEDLINE – 1950 to date	CONSTIPATION#.W..DE.	unrestricted	7455
61	MEDLINE – 1950 to date	ELECTRIC–STIMULATION#.DE.	unrestricted	104160
63	MEDLINE – 1950 to date	LUMBOSACRAL–PLEXUS#.DE.	unrestricted	25740
65	MEDLINE – 1950 to date	ELECTRIC–STIMULATION–THERAPY#.DE.	unrestricted	25916
66	MEDLINE – 1950 to date	59 AND 65 AND 63	unrestricted	8
67	MEDLINE – 1950 to date	59 AND 61 AND 63	unrestricted	1
68	MEDLINE – 1950 to date	combined sets 66, 67	unrestricted	9
70	MEDLINE – 1950 to date	unique records from 68	unrestricted	9

Saved: 10–Apr–2007 18:20:19 MEST

Figure_Apx 4: Searh Strategy Embase

No.	Database	Search term	Info added since	Results
2	EMBASE – 1974 to date	CONSTIPATION#.W..DE.	unrestricted	22451
4	EMBASE – 1974 to date	ELECTROSTIMULATION#.W..DE. OR ELECTROSTIMULATION–THERAPY#.DE.	unrestricted	98060
23	EMBASE – 1974 to date	Sacrum.W..DE.	unrestricted	2399
25	EMBASE – 1974 to date	2 AND 4 AND 23	unrestricted	10

Saved: 11–Apr–2007 17:08:42 MEST

Figure_Apx 5: Search Strategy CINAHL

No.	Database	Search term	Info added since	Results
1	CINAHL (R) - 1982 to date	CONSTIPATION	unrestricted	2103
2	CINAHL (R) - 1982 to date	CONSTIPATION#.W..DE.	unrestricted	1204
3	CINAHL (R) - 1982 to date	DEFECATION	unrestricted	488
4	CINAHL (R) - 1982 to date	DEFECATION#.W..DE.	unrestricted	270
5	CINAHL (R) - 1982 to date	ANUS	unrestricted	595
6	CINAHL (R) - 1982 to date	ANUS#.W..DE. OR ANUS-DISEASES#.DE. OR RECTUM#.W..DE. OR RECTAL-DISEASES#.DE.	unrestricted	4645
7	CINAHL (R) - 1982 to date	ELECTRIC ADJ STIMULATION ADJ THERAPY	unrestricted	3
8	CINAHL (R) - 1982 to date	ELECTRIC-STIMULATION#.DE.	unrestricted	3299
9	CINAHL (R) - 1982 to date	NEUROMODULATION	unrestricted	124
10	CINAHL (R) - 1982 to date	ELECTRICAL-STIMULATION-FUNCTIONAL#.DE. OR ELECTRICAL-STIMULATION-NEUROMUSCULAR#.DE.	unrestricted	406
11	CINAHL (R) - 1982 to date	LUMBOSACRAL ADJ PLEXUS	unrestricted	141
12	CINAHL (R) - 1982 to date	LUMBOSACRAL-PLEXUS#.DE.	unrestricted	564
13	CINAHL (R) - 1982 to date	SACROCOCCYGEAL ADJ REGION	unrestricted	3
14	CINAHL (R) - 1982 to date	SACRAL ADJ SPINAL ADJ CORD	unrestricted	15
15	CINAHL (R) - 1982 to date	LUMBOSACRAL ADJ SPINE	unrestricted	205
16	CINAHL (R) - 1982 to date	SPINE#.W..DE. OR SACRUM#.W..DE.	unrestricted	6036
17	CINAHL (R) - 1982 to date	2 AND 8 AND 12	unrestricted	0
18	CINAHL (R) - 1982 to date	2 OR 4 AND 8 AND 12	unrestricted	1204

NHS

National Research Ethics Service

Northern and Yorkshire Research Ethics Committee

Room 215
TEDCO Business Centre
Viking Industrial Park
Jarrow
Tyne & Wear NE32 3DT

Telephone 0191 4283545/4283438 Fax 0191 4283303

Bill Hackett (Co-ordinator) e-mail: bill.hackett@suntpct.nhs.uk
Helen Wilson (Asst Co-ordinator) e-mail: helen.wilson@suntpct.nhs.uk

26 July 2007

Dr Yan Yiannakou
Consultant Physician and Gastroenterologist
University Hospital of North Durham
North Road
Durham
DH1 5TW

Dear Dr Yiannakou

Full title of study: **The short-term efficacy of Sacral Nerve Stimulation in patients with neurological constipation**
REC reference number: **07/H0903/45**

The Research Ethics Committee reviewed the above application at the meeting held on 13 July 2007. Thank you for attending to discuss the study.

Ethical opinion

1 The Committee was pleased to accept the assurances provided by the researcher in respect of questions which had been raised.
2 The Committee was satisfied that the researcher would add details to the information sheet about collection of data for a thesis and that terms such as "laser doppler" could be explained in a more meaningful way.
3 The Committee accepted the assurances provided by the researcher that the font size would be increased and that the flowchart was in colour.

Members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation.

Ethical review of research sites

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to submit the Site-Specific Information Form to any Research Ethics Committee. The favourable opinion for the study applies to all sites involved in the research.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Peter Carey
Vice Chair

Email: Helen.Wilson@suntpct.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions

Copy to: Dr Keith Holden
R & D Department
Co Durham & Darlington Acute Hospitals NHS Trust
Darlington Memorial Hospital
Hollyhurst Road
Darlington
DL3 6HX

LETTER TO THE GP

Dr Y Yiannakou Secretary, University Hospital North Durham Tel 0191 3332 889
Department of Gastroenterology, University Hospital North Durham Tel 0191 333 2248

Dear Doctor

Patient:

AFFIX ADDRESSOGRAPH

Date……..

Your patient has agreed to be included in a study to examine the effectiveness of sacral nerve stimulation (SNS) for the management of neurological constipation.

Patients referred to the Specialist Constipation Clinic at the University Hospital of North Durham will be invited to take part. The study involves assessment of subjective and objective measures pre and post SNS insertion to investigate the effectiveness of this procedure for the management of neuro-constipation. These measures involve Pre and Post Transit Study with Abdominal X-Ray (following ingestion of radio opaque markers), a daily defaecation and laxative diary, weekly self-administered questionnaires to measure symptoms (PAC-SYM) and quality of life (PAC-QOL); and laser Doppler flowcytometry.

The decision to insert SNS is made on compassionate grounds and offered to patients as an alternative to surgical management for their constipation. The decision to offer SNS to patients does not form part of the research protocol and inclusion in the study is completely voluntary. Information pertaining to SNS (irrespective of whether they are involved in the study or not) will be provided to GP's via the normal channels.

The results of the assessments made as part of the study will be available to the clinicians in Dr Yiannakou's Constipation Clinic who will correspond with the patient's GP in the usual manner.

Yours Faithfully

Mr U Khan and Dr Y Yiannakou
Principle Investigators

(*Form to be on headed paper*)

CONSENT FORM

Copies of this form must be a) supplied to the subject b) included in the medical notes

A study to examine the short-term efficacy of sacral nerve stimulation (SNS) in neurological constipation

Patient identification Addressograph

I understand the nature and the purpose of the proposed study as explained to me by the chief investigator, Dr Y Yiannakou.

I understand that I am free to ask any questions at any time during my participation in the study. I confirm that I have been given full written information (or equivalent non written information if required) about this study and have been informed of potential problems or side effects that might occur as part of my participation. I will report any problems or side effects that I experience as part of my involvement.

I am aware that I am free to withdraw from the study at any time and without stating a reason. This will not affect my future health care.

I am aware that in the event of health deteriorating in any way as a result of my taking part in this study, I may submit a claim to the County Durham and Darlington Acute Hospitals NHS Trust for compensation to be considered. I understand that I do not necessarily have to prove that anyone involved in the research project has been negligent before submitting a claim. If negligence can be established, I understand that my claim would be dealt with in accordance with the legal principles affecting claims for damages for personal injuries. If negligence cannot be established, the County Durham and Darlington Acute Hospitals NHS Trust will consider any claims on their merits and in appropriate circumstances, may decide to offer an ex-gratis payment.

I declare that I am not taking part in any other trials at this time.

(*Form to be on headed paper*)

CONSENT FORM

Patient Identification (addressograph):

Title of Project:

A study to examine the short-term efficacy of sacral nerve stimulation (SNS) in neurological constipation

Name of Researcher: Dr Y Yiannakou, Consultant Gastroenterologist

Please initial box

1) I confirm that I have read and understand the information sheet dated ..... (Version .....) for the above study and have had the opportunity to ask questions. ☐

2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3) I understand that sections of any medical notes may be looked at by responsible individuals from County Durham and Darlington Acute Hospitals NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4) I understand that the investigators would like to inform my GP of my participation in the study. I give permission for my GP to be informed. ☐

5) I agree to take part in the above study. ☐

_____	_____ ___	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

PROCEDURE INFORMATION SHEET
(Given to all patients undergoing SNS even if not participating in the study)

SACRAL NERVE STIMULATION (SNS)

Your symptoms of constipation are severe and have not responded to simple treatments like changes to diet, laxatives or enemas. For some of our patients other treatments can be offered but may involve surgery to remove part of the colon (large bowel).

This would involve a major operation with risks of complications that although infrequent, can be significant and serious.

You are invited to consider an alternative treatment called Sacral Nerve Stimulation (SNS). This is a minimally invasive procedure that should benefit patients with severe constipation.

SNS is a two-stage procedure with a test (diagnostic) stage and permanent (therapeutic) stage. It involves placement of wire inside the sacrum bone in the lower back of a patient, which is connected to an external stimulator worn on a belt for a short period of time. Over a period of two to three weeks the symptoms of the patient are assessed. This test stage helps in identifying patients who may potentially benefit from a permanent implant. This temporary wire can later be replaced with a permanent one and a stimulator placed in the buttocks (under a general anaesthetic).

The procedure to insert the test wire is relatively simple. The patient is put under a general anaesthetic in theatre. They are positioned face down on the table. The surgeon puts a needle into a small opening in the sacrum bone in the lower back. This is where the nerves supplying the bowel originate. After placing the needle its position is checked with x-rays. The wire is passed through the needle close to the nerves and the needle is removed. The wire is secured with tape and then connected to a stimulator, which the patient wears on a belt. The doctors who insert SNS in Durham are all experienced in this procedure and the whole procedure takes 10-15 minutes.

SNS involves the use of chronic low-level stimulation of sacral nerves by a small electrical current to produce a beneficial effect on the hindgut, pelvic floor and the anal sphincters. It has been shown to be safe and effective in faecal incontinence and bladder dysfunction. Using SNS to treat constipation is relatively new but it is being done more and more in the UK.

SNS is a very safe procedure but you should be aware that there are some small risks that can happen when test wire is inserted. These can include **bleeding** and **infection**. These risks are explained below.

At the time of wire insertion minor bleeding can occur due to the needle. The surgeon can easily control this bleeding during the operation.

Infection can sometimes develop at the site where the wire is inserted. Every necessary precaution including strict aseptic measures is taken to prevent infection. If the infection does not settle, it maybe necessary to remove the wire. After removal the infection will improve. There is a small chance of the wire falling out but every necessary precaution is taken to prevent that at the time of the procedure.

We plan for a hospital stay of 12 hours. The wire and stimulator settings will be set and explained by a representative from Medtronic (the company that makes this equipment) to the patients before discharge. Patients will be seen and assessed in clinic after three weeks of SNS.

Before SNS is inserted you will be able to discuss the procedure with the surgeons in the outpatient clinic. You will also have the opportunity to speak to some the patients who have already had SNS inserted. You will be able to talk to them about their experiences.

Before the procedure you will be asked by Mr Jag Varma or Ms Susan Green to sign a form to give consent. Should you have any questions at any time we will be happy to answer them.

Mr. Jag Varma
Consultant Colorectal Surgeon

Ms Susan Green
Consultant Colorectal Surgeon

University Hospital North Durham

Durham DH1 5TW

STUDY INFORMATION SHEET
(Given to patient participating in the study)

A STUDY TO EXAMINE THE SHORT-TERM EFFICACY OF SACRAL NERVE STIMULATION (SNS) IN NEUROLOGICAL CONSTIPATION

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. 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.

Introduction

Your Doctor (either a hospital specialist or your GP) has referred you to the Constipation Clinic at the University Hospital of North Durham. At the clinic tests are performed to understand why you have constipation and how severe the problem is.

In patients with neurological problems like multiple sclerosis (MS) or spinal cord diseases, constipation can be a severe predicament. Often treatment with laxatives or enemas is ineffective. For some of our patients other treatments can be offered but may involve surgery to remove part of the colon (large bowel).

An alternative to surgery is SNS, which stimulates the large bowel to improve constipation. Information is available about SNS from the doctors in the Constipation Clinic (Dr Yan Yiannakou and Mr Usman Khan).

SNS is being used more and more in the UK to treat constipation. The technique has been shown to be successful and is an alternative to surgery. We feel that it is important to gather detailed information about how useful SNS is to treat patients with neurological constipation.

What is the purpose of the study?

The purpose of the study is to look at how effective SNS is for treating neurological constipation in patients only during the testing stage. To do this we need to gather detailed information about how severe the constipation is before and after the SNS.

Why have I been chosen?

You have been invited to take part because you have severe neurological constipation that has not responded well to standard treatments (laxatives and enemas). Because your symptoms have not responded well to laxatives and enemas and you have agreed to have SNS you have been invited to take part.

Deciding that you would like to have SNS does not automatically mean that you will be involved in the study. To become part of the study you will have to make a separate decision to take part or not.

What will happen to me if I take part?

The study will last 12 weeks for each person taking part in the study. Each person taking part in the study will be asked to fill in a daily diary during the trial. For the first three weeks that will involve a weekly assessment of your constipation or faecal incontinence by filling in one box in the diary with the help of a rating scale that will be provided. During the next six weeks you will also have to provide information about your bowel habits and intake of laxatives in addition to the above and during the last three weeks you will revert back to filling one box weekly about your constipation or faecal incontinence. We will also ask you to fill in weekly short questionnaires about your symptoms and quality of life in addition to the diary.

We will ask everyone taking part in the trial to come to the hospital for a three weekly visit (at week three, six and nine) for a laser Doppler test of the back passage lasting 10-15 minutes. This will involve passing a small telescope in the back passage to take laser Doppler measurements. During that visit you will be asked to fill in a health related questionnaire and your diary cards will be collected and analysed.

At week nine during the period of stimulation you will be asked to have a Transit Study. This will involve swallowing small capsules full of markers and then having an X-ray of the abdomen. By counting the number of markers in the bowel we will be able to work out how fast the bowel is working. You will already have had a Transit Study done when you were first referred to Dr Yiannakou's clinic.

Will my taking part in the study be kept confidential?

The results and information collected in the study will not be disclosed outside of the hospital. Any information about you will have the name and address removed so that you cannot be recognised by it.

What will happen to the results of my tests?

The results of your investigations will be kept confidentially in your medical records. The results will be available to the doctors in the Constipation Clinic, your hospital doctor and GP. We will analyse the results of tests and questionnaires and discuss the results with you in clinic. We will provide you with a written summary of the project upon completion of the study.

We may write a report about our findings and attempt to publish this in a medical journal. In the report the results will be anonymous with no personal details such as name or address. If you decide to withdraw from the study, we will ask your permission to keep the results of your investigations. Any results from the study will

be kept securely and confidentially in the hospital for a maximum of three years. After this, the results will be destroyed.

What are the benefits of taking part in the study?

The experience in other hospitals around the world suggests that investigations such as these give extra information about neurological constipation. It is hoped that such information will help patients now and in the future who have similar problems.

What are the disadvantages of taking part in the study?

We understand that filling in diaries and questionnaires can be a little tedious but they are designed to be very simple and can be filled by marking off the boxes in a few minutes.

If you take part in the study you will have two transit studies done, one before the SNS and one after. This means that in addition to the routine abdominal X-ray that we request for all of our patients in the clinic, you will be asked to have another Abdominal X-ray as part of the study.

We do not believe that the extra radiation exposure during the second abdominal X-ray will cause any problems to our patients either now or in the future. This is because the amount of X-ray radiation used for the Transit study is minimal.

However, extra radiation is not recommended in special situations (such as pregnancy) and you are encouraged to discuss having the X-rays with the doctors in the clinic to make sure no special situations affect them. There are no reports in the medical literature that the markers we ask the patients to swallow for the transit study cause any side effects.

We believe that the only disadvantage of being involved is that you may have to spend a little longer visiting hospital during your three weekly visits for laser Doppler testing. The laser Doppler procedure is an additional but essential element of this study and is not part of standard treatment for patients coming to the constipation clinic.

Do I have to take part in the study?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep. You will be asked to sign a consent form.

If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive now or in the future. Being involved in the study is completely voluntary.

What if I am upset or inconvenienced by taking part in the study?

If you feel upset at any time during your involvement or you wish to complain about any aspect of the way you have been approached or treated during the study, the normal National Health Service complaints processes will be available to you.

In addition you will be able to discuss any concerns you have at any time before or after the tests with Dr Yan Yiannakou or Mr Usman Khan.

Who is co-ordinating the study?
Dr Yan Yiannakou and Mr Usman Khan are co-ordinating the study. Both are based at the University Hospital of North Durham. If you wish to ask questions please do not hesitate to telephone Dr Yiannakou's secretary on 0191 3332889.

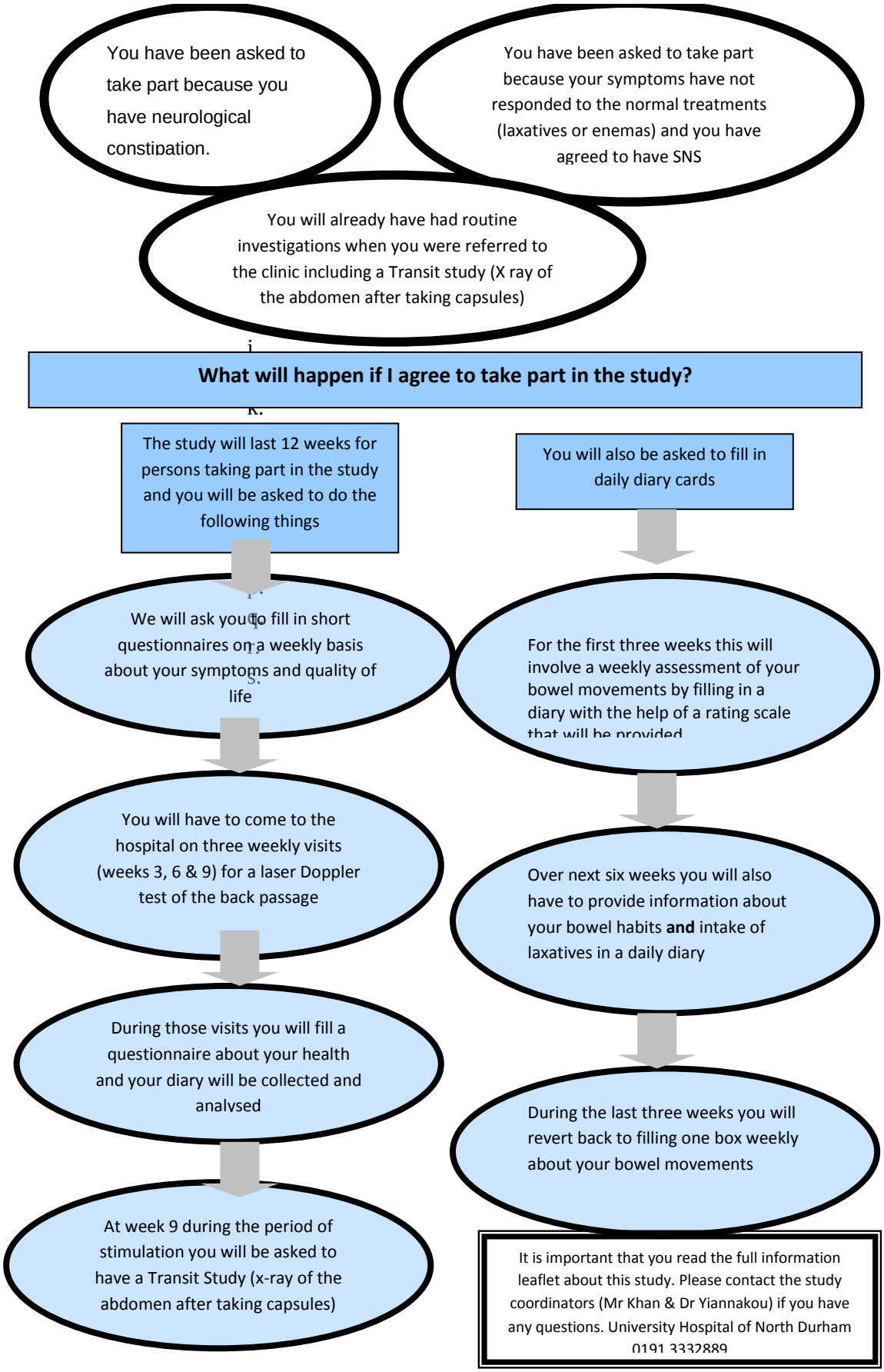
Has the design of this study been checked by other Doctors or Scientists?
Members of the Local Ethics Committee have checked the aims and design of this study. This committee is made up of doctors, scientists and lay people. Their job is to make certain that any studies involving patients in the UK are carried out safely and sensibly and in away that will be beneficial to patients now and in the future.

What do I do now?
If you would like to help with the study please sign the consent form. Please keep this information sheet.

Thank you for your cooperation.

V1 03/03/2007

A STUDY TO EXAMINE THE SHORT-TERM EFFICACY OF SACRAL NERVE STIMULATION (SNS) IN NEUROLOGICAL CONSTIPATION



V1 03/03/2007

CARER INFORMATION

A STUDY TO EXAMINE THE SHORT-TERM EFFICACY OF SACRAL NERVE STIMULATION (SNS) IN NEUROLOGICAL CONSTIPATION

The person you care for has been invited to take part in a research study. Their involvement in the study may have an effect on your role as a carer. It is important for you and the person you care for to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information.

Introduction

The person you care for has been referred by their Doctor (either a hospital specialist or your GP) to the Constipation Clinic at the University Hospital of North Durham. At the clinic tests are performed to understand why patients have constipation and how severe the problem is.

In patients with neurological problems like multiple sclerosis (MS) or spinal cord diseases, constipation can be a severe predicament. Often treatment with laxatives or enemas is ineffective. For some of our patients other treatments can be offered but may involve surgery to remove part of the colon (large bowel).

An alternative to surgery is SNS, which stimulates the large bowel to improve constipation. Information is available about SNS from the doctors in the Constipation Clinic (Dr Y Yiannakou and Mr U Khan).

SNS is being used more and more in the UK to treat constipation. The technique has been shown to be successful and is an alternative to surgery. We feel that it is important to gather detailed information about how useful SNS is to treat patients with neurological constipation.

What is the purpose of the study?

The purpose of the study is to look at how effective SNS is for treating neurological constipation in patients. To do this we need to gather detailed information about how severe the constipation is before and after the SNS.

Why has the person you care for been chosen?

The person you care for has been invited to take part because they have severe neurological constipation that has not responded well to standard treatments (laxatives and enemas). They have been invited to take part because they have agreed to have SNS.

Deciding that they would like to have SNS does not automatically mean that they will be involved in the study. To become part of the study the person you care for will have to make a separate decision to take part or not.

What will happen to the person you care for if they take part?

The study will last 12 weeks for each person taking part in the study. Each person taking part in the study will be asked to fill in a daily diary during the trial. For the first three weeks that will involve a weekly assessment of their constipation or faecal incontinence by filling in one box in the diary with the help of a rating scale that will be provided. During the next six weeks the person you care for will also have to provide information about their bowel habits and intake of laxatives in addition to the above and during the last three weeks they will revert back to filling one box weekly about your constipation or faecal incontinence. We will also ask them to fill in weekly short questionnaires about their symptoms and quality of life in addition to the diary.

We will ask everyone taking part in the trial to come to the hospital for a three weekly visit (at week three, six and nine) for a laser Doppler test of the back passage lasting 10-15 minutes. This will involve passing a small telescope in the back passage to take laser Doppler measurements. During that visit the person you care for will be asked to fill in a health related questionnaire and their diary cards will be collected and analysed.

At week 9 during the period of stimulation they will be asked to have a Transit Study. This will involve swallowing small capsules full of markers and then having an X-ray of the abdomen. By counting the number of markers in the bowel we will be able to work out how fast the bowel is working. The person you care for will already have had a Transit Study done when they were first referred to Dr Yiannakou's clinic.

What are the benefits of taking part in the study?

The experience in other hospitals around the world suggests that investigations such as these give extra information about neurological constipation. It is hoped that such information will help patients now and in the future who have similar problems.

What are the disadvantages of taking part in the study?

We understand that filling in diaries and questionnaires can be a little tedious but they are designed to be very simple and can be filled by marking off the boxes in a few minutes.

If the person you care for takes part in the study they will have two transit studies done, one before the SNS and one after. This means that in addition to the routine abdominal X-ray that we request for all of our patients in the clinic, they will be asked to have another Abdominal X-ray as part of the study.

We do not believe that the extra radiation exposure during the second abdominal X-ray will cause any problems to our patients either now or in the future. This is because the amount of X-ray radiation used for the Transit study is minimal.

However, extra radiation is not recommended in special situations (such as pregnancy) and the person you care for is encouraged to discuss having the X-rays with the doctors in the clinic to make sure no special situations affect them. There are no reports in the medical literature that the markers we ask the patients to swallow for the transit study cause any side effects.
We believe that the only disadvantage of being involved is that the person you care for may have to spend a little longer visiting hospital during their three weekly visits for laser Doppler testing. The laser Doppler procedure is an additional but essential element of this study and is not part of standard treatment for patients coming to the constipation clinic.

Does the person I care for have to take part in the study?
It is up to the person you care for to decide whether or not to take part. To help them make this decision they may want to talk to the doctors in the Constipation Clinic, their GP, friends, family and carers. If the person you take care of decides to take part you will be given this information sheet to keep.
The person you care for will be asked to sign a consent form. If they decide to take part they are still free to withdraw at any time and without giving a reason. This will not affect the standard of care they receive now or in the future. Being involved in the study is completely voluntary.

What if the person I care for is upset or inconvenienced by taking part in the study?
If the person you care for feels upset at any time during their involvement or they wish to complain about any aspect of the way they have been approached or treated during the study, the normal National Health Service complaints processes will be available to them. In addition they will be able to discuss any concerns they have at any time before or after the tests with Dr Yan Yiannakou or Mr Usman Khan.

Who is co-ordinating the study?
Dr Yan Yiannakou and Mr Usman Khan are co-ordinating the study. Both are based at the University Hospital of North Durham. If you or the person you care for wish to ask questions please do not hesitate to telephone Dr Yiannakou's secretary on 0191 3332889.

Thank you for your cooperation.

V1 03/03/2007

Date .....Patient's name **WEEKLY SYMPTOM DIARIES** Week 1-3 Subject No.

GLOBAL ASSESSMENT OF SYMPTOMS

Please choose the number that best describes how your symptoms have been over this week using the 5-point rating scale below and place a tick in the appropriate box.

How has your constipation been this week? *Tick the appropriate box*		**How has your faecal incontinence been this week?** *Tick the appropriate box. If none put = 0 in the first box*	
1. No problem		1. No problem	
2. Mild problem *(can be ignored with effort)*		2. Mild problem *(can be ignored with effort)*	
3. Moderate problem *(cannot be ignored but does not influence my daily activities)*		3. Moderate problem *(cannot be ignored but does not influence my daily activities)*	
4. Severe problem *(cannot be ignored and often limits my concentration on daily activities)*		4. Severe problem *(cannot be ignored and often limits my concentration on daily activities)*	
5. Very severe problem *(cannot be ignored and markedly limits my daily activities and often requires rest)*		5. Very severe problem *(cannot be ignored and markedly limits my daily activities and often requires rest)*	

Date .....Patient's name

SYMPTOM DIARY CARD

Week 4-9

Subject No.

DAY	DATE	No. Of bowel movements	Faecal Incontinence	Type of FI	Use of Pads	Time spent toileting	Laxative Score	Laxatives used
1	D/M							
2								
3								
4								
5								
6								
7								

How to complete the diary card *The diary card contains seven rows, which you need to fill for each day. Please choose the number that best describes how that symptom has been over the past 24 hours (listed below) and write this number in the box for today. Please fill in all boxes for each day and repeat the process for each day of the trial.*

1. **NO. OF BOWEL MOVEMENTS** (Number of times at which motions were passed today) = record total number. If no bowel movement = 0
2. **FAECAL INCONTINENCE** (Number of times of incontinence episodes today) = record total number. If no incontinence = 0
3. **TYPE OF FAECAL INCONTINENCE** (Solid=1, Liquid=2, Gas=3) If no incontinence =0
4. **USE OF PADS** (No=0, Yes=1)
5. **TIME SPENT TOILETING** (Total minutes spent in bowel care today)=record number of minutes in total. If no bowel movement = 0
6. **LAXATIVE SCORE** (Compared with your usual laxatives the amount you took today was More=+1, Same= 0, Less= -1)
7. **LAXATIVES** (Have you taken any laxative medication today) write the name and dose of each laxative taken today

GLOBAL ASSESSMENT OF SYMPTOMS

Please choose the number that best describes how your symptoms have been over this week using the 5-point rating scale below and place a tick in the appropriate box.

My agreed daily laxatives are

1.

2.

3.

4.

How has your constipation been this week? *Tick the appropriate box*		**How has your faecal incontinence been this week?** *Tick the appropriate box. If none put = 0 in the first box*	
1. No problem		1. No problem	
2. Mild problem *(can be ignored with effort)*		2. Mild problem *(can be ignored with effort)*	
3. Moderate problem *(cannot be ignored but does not influence my daily activities)*		3. Moderate problem *(cannot be ignored but does not influence my daily activities)*	
4. Severe problem *(cannot be ignored and often limits my concentration on daily activities)*		4. Severe problem *(cannot be ignored and often limits my concentration on daily activities)*	
5. Very severe problem *(cannot be ignored and markedly limits my daily activities and often requires rest)*		5. Very severe problem *(cannot be ignored and markedly limits my daily activities and often requires rest)*	

Please fill the questionnaires given below for your symptoms over this past one week

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)	☐	☐	☐	☐	☐

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 <u>intensity</u> 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 <u>daily life</u>. 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 <u>daily life</u>. 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	**None of**	**A little of**	**Some of**	**Most of**	**All of the**
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 <u>feelings</u>. 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 <u>life with constipation</u>. 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 <u>how satisfied</u> 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?	☐	☐	☐	☐	☐

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 statements best 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 ❑

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